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[Intervention Review]

Closed-system drug-transfer devices plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional hazardous drugs in healthcare staff

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ABSTRACT

Background

Occupational exposure to hazardous drugs can decrease fertility and result in miscarriages, stillbirths, and cancers in healthcare staff. Several recommended practices aim to reduce this exposure, including protective clothing, gloves, and biological safety cabinets ('safe handling'). There is significant uncertainty as to whether using closed-system drug-transfer devices (CSTD) in addition to safe handling decreases the contamination and risk of staff exposure to infusional hazardous drugs compared to safe handling alone.

Objectives

To assess the effects of closed-system drug-transfer of infusional hazardous drugs plus safe handling versus safe handling alone for reducing staff exposure to infusional hazardous drugs and risk of staff contamination.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, OSH-UPDATE, CINAHL, Science Citation Index Expanded, economic evaluation databases, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov to October 2017.

Selection criteria

We included comparative studies of any study design (irrespective of language, blinding, or publication status) that compared CSTD plus safe handling versus safe handling alone for infusional hazardous drugs.

Data collection and analysis

Two review authors independently identified trials and extracted data. We calculated the risk ratio (RR) and mean difference (MD) with 95% confidence intervals (CI) using both fixed-effect and random-effects models. We assessed risk of bias according to the risk of bias in non-randomised studies of interventions (ROBINS-I) tool, used an intracluster correlation coefficient of 0.10, and we assessed the quality of the evidence using GRADE.

Closed-system drug-transfer devices plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional hazardous drugs in healthcare staff (Review)

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Main results

We included 23 observational cluster studies (358 hospitals) in this review. We did not find any randomised controlled trials or formal economic evaluations. In 21 studies, the people who used the intervention (CSTD plus safe handling) and control (safe handling alone) were pharmacists or pharmacy technicians; in the other two studies, the people who used the intervention and control were nurses, pharmacists, or pharmacy technicians. The CSTD used in the studies were PhaSeal (13 studies), Tevadaptor (1 study), SpikeSwan (1 study), PhaSeal and Tevadaptor (1 study), varied (5 studies), and not stated (2 studies). The studies' descriptions of the control groups were varied. Twenty-one studies provide data on one or more outcomes for this systematic review. All the studies are at serious risk of bias. The quality of evidence is very low for all the outcomes.

There is no evidence of differences in the proportion of people with positive urine tests for exposure between the CSTD and control groups for cyclophosphamide alone (RR 0.83, 95% CI 0.46 to 1.52; $I^2 = 12\%$; 2 studies; 2 hospitals; 20 participants; CSTD: 76.1% versus control: 91.7%); cyclophosphamide or ifosfamide (RR 0.09, 95% CI 0.00 to 2.79; 1 study; 1 hospital; 14 participants; CSTD: 6.4% versus control: 71.4%); and cyclophosphamide, ifosfamide, or gemcitabine (RR not estimable; 1 study; 1 hospital; 36 participants; 0% in both groups).

There is no evidence of a difference in the proportion of surface samples contaminated in the pharmacy areas or patient-care areas for any of the drugs except 5-fluorouracil, which was lower in the CSTD group than in the control (RR 0.65, 95% CI 0.43 to 0.97; 3 studies, 106 hospitals, 1008 samples; CSTD: 9% versus control: 13.9%).

The amount of cyclophosphamide was lower in pharmacy areas in the CSTD group than in the control group (MD -49.34 pg/cm², 95% CI -84.11 to -14.56 , $I^2 = 0\%$, 7 studies; 282 hospitals, 1793 surface samples). Additionally, one interrupted time-series study (3 hospitals; 342 samples) demonstrated a change in the slope between pre-CSTD and CSTD (3.9439 pg/cm², 95% CI 1.2303 to 6.6576; $P = 0.010$), but not between CSTD and post-CSTD withdrawal (-1.9331 pg/cm², 95% CI -5.1260 to 1.2598; $P = 0.20$). There is no evidence of difference in the amount of the other drugs between CSTD and control groups in the pharmacy areas or patient-care areas.

None of the studies report on atmospheric contamination, blood tests, or other measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, or micronuclei induction.

None of the studies report short-term health benefits such as reduction in skin rashes, medium-term reproductive health benefits such as fertility and parity, or long-term health benefits related to the development of any type of cancer or adverse events.

Five studies (six hospitals) report the potential cost savings through the use of CSTD. The studies used different methods of calculating the costs, and the results were not reported in a format that could be pooled via meta-analysis. There is significant variability between the studies in terms of whether CSTD resulted in cost savings (the point estimates of the average potential cost savings ranged from (2017) USD $-642,656$ to (2017) USD 221,818).

Authors' conclusions

There is currently no evidence to support or refute the routine use of closed-system drug transfer devices in addition to safe handling of infusional hazardous drugs, as there is no evidence of differences in exposure or financial benefits between CSTD plus safe handling versus safe handling alone (very low-quality evidence). None of the studies report health benefits.

Well-designed multicentre randomised controlled trials may be feasible depending upon the proportion of people with exposure. The next best study design is interrupted time-series. This design is likely to provide a better estimate than uncontrolled before-after studies or cross-sectional studies. Future studies may involve other alternate ways of reducing exposure in addition to safe handling as one intervention group in a multi-arm parallel design or factorial design trial. Future studies should have designs that decrease the risk of bias and enable measurement of direct health benefits in addition to exposure. Studies using exposure should be tested for a relevant selection of hazardous drugs used in the hospital to provide an estimate of the exposure and health benefits of using CSTD. Steps should be undertaken to ensure that there are no other differences between CSTD and control groups, so that one can obtain a reasonable estimate of the health benefits of using CSTD.

PLAIN LANGUAGE SUMMARY

Closed-system drug-transfer devices for reducing exposure to infusional hazardous medicines in healthcare staff

Closed-system drug-transfer devices plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional hazardous drugs in healthcare staff (Review) 2

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Some medicines - whether given as tablets or as a drip through the veins - are hazardous to the healthcare staff who handle them. Patients receive infusional hazardous medicines through the veins as treatment for serious diseases like cancer. When healthcare staff are exposed to these medicines, they can decrease their fertility and result in miscarriages, stillbirths, and cancers. Several recommended practices can reduce healthcare staff exposure to these hazardous medicines. These include protective clothing, gloves, and special cabinets where staff can prepare the hazardous medicines prior to giving them to patients. Together, these practices constitute 'safe handling'. A closed-system drug-transfer device (CSTD) is a device system that mechanically prevents the escape of hazardous drug outside the system.

What is the aim of this review?

There is significant uncertainty as to whether using CSTD in addition to safe handling decreases the exposure and risk of staff contamination to hazardous medicines compared to safe handling alone. We sought to resolve this issue by searching for existing studies on the topic.

Key messages

Based on very low-quality evidence, there is currently no evidence for or against adding CSTD to safe handling of hazardous medicines. Further well designed studies are necessary.

What was studied in the review?

We included all types of studies that compared CSTD plus safe handling ('CSTD group') and safe handling alone ('control group').

What are the main results of the review?

We included 23 studies (358 hospitals) in this review, none of which used the gold standard study design (randomised controlled trials) or explored a treatment's value for money. In 21 studies, the people who used the CSTD and safe handling were pharmacists or pharmacy technicians. Nineteen studies provide information that could be included for this study.

There is no evidence of any benefit for using CSTD in the indirect measures of exposure such as the presence of the hazardous drug in the urine of the healthcare professionals. There is no evidence that the contamination of surfaces or the floor with most hazardous medicines was decreased by the use of CSTD. There is significant variability between the studies in terms of whether the use of CSTD resulted in cost savings, with some studies reporting increased costs and others reporting decreased costs after introducing CSTD. None of the studies report on health benefits such as reduction in skin rashes, infertility, miscarriage, development of any type of cancer, or adverse events.

The overall quality of evidence is very low for all the outcomes because all the studies had one or more significant limitation in their design. Therefore, the results may not be reliable.

How up-to-date is this review?

We searched for studies up until 26 October 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Closed-system transfer device safe handling versus safe handling alone for reducing healthcare staff exposure to infusional hazardous drugs: exposure and contamination					
Patient or population: healthcare staff who handle infusional hazardous drugs Settings: hospitals Intervention: closed-system transfer device plus safe handling Control: safe handling alone					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of hospitals (samples; studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Safe handling alone	Closed-system transfer device plus safe handling			
Exposure (urine tests for exposure)					
Cyclophosphamide alone	917 per 1000	761 per 1000 (422 to 1393)	RR 0.83 (0.46 to 1.52)	2 hospitals (20 participants; 2 studies)	⊕○○○ Very low ^{a,b,c}
Cyclophosphamide or ifosfamide	714 per 1000	64 per 1000 (0 to 1000)	RR 0.09 (0.00 to 2.79)	1 hospital (14 participants; 1 study)	⊕○○○ Very low ^{a,b,c}
Cyclophosphamide, ifosfamide, or gemcitabine	There were no participants with exposure in either group.			4 hospitals (36 participants; 1 study)	⊕○○○ Very low ^{a,b,c}
Other measures of exposure	None of the studies report on blood tests or other measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, or micronuclei induction				
Surface contamination (proportion of surfaces contaminated)					
<i>Pharmacy areas</i>					
<i>Cyclophosphamide</i>	507 per 1000	451 per 1000 (395 to 512)	RR 0.89 (0.78 to 1.01)	338 hospitals (2937 samples; 13 studies)	⊕○○○ Very low ^{a,b,d,e}

<i>Ifosfamide</i>	267 per 1000	251 per 1000 (197 to 317)	RR 0.94 (0.74 to 1.19)	304 hospitals (2332 samples; 9 studies)	⊕○○○ Very low ^{a,b,d}
<i>Methotrexate</i>	102 per 1000	85 per 1000 (59 to 124)	RR 0.84 (0.58 to 1.22)	280 hospitals (1781 samples; 6 studies)	⊕○○○ Very low ^{a,b,d}
<i>5-fluorouracil</i>	139 per 1000	90 per 1000 (60 to 135)	RR 0.65 (0.43 to 0.97)	106 hospitals (1008 samples; 3 studies)	⊕○○○ Very low ^{a,d,f}
<i>Cytarabine</i>	267 per 1000	192 per 1000 (48 to 762)	RR 0.72 (0.18 to 2.86)	84 hospitals (780 samples; 2 studies)	⊕○○○ Very low ^{a,b,d}
<i>Gemcitabine</i>	322 per 1000	309 per 1000 (193 to 496)	RR 0.96 (0.60 to 1.54)	84 hospitals (780 samples; 2 studies)	⊕○○○ Very low ^{a,b,d}
<i>Irinotecan, docetaxel, paclitaxel, vinorelbine, ganciclovir, multiple drugs</i> [†]	There is no evidence of difference in the proportion of samples contaminated with 5-fluorouracil, cytarabine, gemcitabine, irinotecan, docetaxel, paclitaxel, vinorelbine, ganciclovir, or multiple drugs in pharmacy areas between closed-system transfer device plus safe handling versus safe handling alone			Irinotecan, docetaxel, paclitaxel, vinorelbine: 83 hospitals (493 samples; 1 study) Ganciclovir: 1 hospital (287 samples; 1 study) Multiple drugs: 4 hospitals (109 samples; 1 study)	⊕○○○ Very low ^{a,b,d}
Patient-care areas					
<i>Cyclophosphamide</i>	440 per 1000	444 per 1000 (378 to 519)	RR 1.01 (0.86 to 1.18)	279 hospitals (1535 samples; 5 studies)	⊕○○○ Very low ^{a,b,d}
<i>Ifosfamide</i>	71 per 1000	102 per 1000 (64 to 161)	RR 1.44 (0.91 to 2.28)	279 hospitals (1535 samples; 5 studies)	⊕○○○ Very low ^{a,b,d}
<i>Methotrexate</i>	25 per 1000	25 per 1000 (14 to 46)	RR 1.00 (0.55 to 1.85)	279 hospitals (1535 samples; 5 studies)	⊕○○○ Very low ^{a,b,d}

<p>5-fluorouracil, cytarabine, gemcitabine, irinotecan, docetaxel, paclitaxel, vinorelbine, multiple drugs[†]</p>	<p>There is no evidence of difference in the proportion of samples contaminated with 5-fluorouracil, cytarabine, gemcitabine, irinotecan, docetaxel, paclitaxel, vinorelbine, multiple drugs in patient-care areas between closed-system transfer device plus safe handling and safe handling alone</p>		<p>5-fluorouracil, cytarabine, gemcitabine, irinotecan, docetaxel, paclitaxel, vinorelbine: 83 hospitals (493 samples; 1 study) Multiple drugs: 4 hospitals (33 samples; 1 study)</p> <p>⊕○○○ Very low^{a,b,d}</p>	
<p>Surface contamination (quantity of surface contamination (pg/cm²))</p>				
<p><i>Pharmacy areas</i></p>				
<p><i>Cyclophosphamide</i>[‡]</p>	<p>The mean cyclophosphamide in the control group is 124.30 pg/cm²</p>	<p>The mean cyclophosphamide in the intervention group is 49.34 pg/cm² lower (84.11 lower to 14.56 lower)</p>	<p>MD −49.34 pg/cm² (−84.11 to −14.56)</p>	<p>282 hospitals (1793 samples; 7 studies)</p> <p>⊕○○○ Very low^{a,b,f}</p>
<p><i>Ifosfamide</i></p>	<p>The mean ifosfamide in the control group is 10.8 pg/cm²</p>	<p>The mean ifosfamide in the intervention group is 0.32 pg/cm² lower (6.58 lower to 5.94 higher)</p>	<p>MD −0.32 pg/cm² (−6.58 to 5.94)</p>	<p>280 hospitals (1749 samples; 6 studies)</p> <p>⊕○○○ Very low^{a,b,d}</p>
<p><i>Methotrexate</i></p>	<p>The mean methotrexate in the control groups is 18.23 pg/cm²</p>	<p>The mean methotrexate in the intervention group is 3.09 pg/cm² lower (13.80 lower to 7.61 higher)</p>	<p>MD −3.09 pg/cm² (−13.80 to 7.61)</p>	<p>280 hospitals (1749 samples; 6 studies)</p> <p>⊕○○○ Very low^{a,b,d}</p>
<p><i>5-fluorouracil</i></p>	<p>The mean 5-fluorouracil in the control groups is 8720.5 pg/cm²</p>	<p>The mean 5-fluorouracil in the intervention group is 257.87 pg/cm² higher (459.65 lower to 975.38 higher)</p>	<p>MD 257.87 (−459.65 to 975.38)</p>	<p>84 hospitals (542 samples; 2 studies)</p> <p>⊕○○○ Very low^{a,b,d}</p>
<p><i>Cytarabine, gemcitabine, and irinotecan</i></p>	<p>There is no evidence of difference in the amount of cytarabine, gemcitabine, and irinotecan in pharmacy areas between closed-system transfer device plus safe handling and safe handling alone</p>		<p>83 hospitals (493 samples; 1 study)</p> <p>⊕○○○ Very low^{a,b,d}</p>	

Patient-care areas					
<i>Cyclophosphamide</i>	The mean cyclophosphamide in the control groups is 168 pg/cm²	The mean cyclophosphamide in the intervention group is 13.34 pg/cm² lower (36.01 lower to 9.32 higher)	MD –13.34 pg/cm² (–36.01 to 9.32)	279 hospitals (1535 samples; 5 studies)	⊕○○○ Very low ^{a,b,d,e}
<i>Ifosfamide</i>	The mean ifosfamide in the control group is 4.59 pg/cm²	The mean ifosfamide in the intervention group is 3.59 pg/cm² higher (3.45 lower to 10.63 higher)	MD 3.59 pg/cm² (–3.45 to 10.63)	279 hospitals (1535 samples; 5 studies)	⊕○○○ Very low ^{a,b,d}
<i>Methotrexate</i>	The mean methotrexate in the control groups is 1.42 pg/cm²	The mean methotrexate in the intervention group is 0.10 pg/cm² higher (0.57 lower to 0.78 higher)	MD 0.10 pg/cm² (–0.57 to 0.78)	279 hospitals (1535 samples; 5 studies)	⊕○○○ Very low ^{a,b,d}
<i>5-fluorouracil, cytarabine, gemcitabine, and irinotecan</i>	There is no evidence of difference in the amount of 5-fluorouracil, cytarabine, gemcitabine, and irinotecan in patient-care areas between closed-system transfer device plus safe handling and safe handling alone			83 hospitals (460 samples; 1 study)	⊕○○○ Very low ^{a,b,d}
Other measures of contamination	None of the studies report on atmospheric contamination.				

CI: confidence interval; MD: mean difference; RR: risk ratio

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Report contains multiple drugs with no outcome information on individual drugs.

‡In addition, one interrupted time-series study (three hospitals; 342 samples) provided data on the quantity of contamination with cyclophosphamide from surface samples in pharmacy areas during three phases, initial phase of no CSTD, followed by CSTD, and then by no CSTD, each phase lasting three weeks (Harrison 2006). The authors took biweekly measurements in all three phases. Between the first two phases, the change in the slope between pre-CSTD and CSTD was 3.9439 pg/cm² (95% CI 1.2303 to 6.6576; P = 0.01). Between the second and third phases, the slope and level were expected to rise again but the change in the slope between CSTD and post-CSTD withdrawal was –1.9331 pg/cm², 95% CI –5.126 to 1.2598 (P = 0.200) and the level was 14.167 pg/cm² (SD = 10.619)

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aThe study or studies was or were at serious risk of bias (downgraded one level for risk of bias).

^bThe confidence intervals were wide (downgraded one level for imprecision).

^cThe sample size was small (downgraded one level for imprecision).

^dThis is a surrogate measure of health benefit (downgraded one level for indirectness).

^eThere was possible evidence of publication bias (Egger's test P value < 0.05) (downgraded one level for publication bias).

^fThere is no evidence that this small difference in levels of cyclophosphamide leads to decreased exposure or tangible health benefits (downgraded one level for imprecision).

BACKGROUND

Description of the condition

Hazardous drugs include those used for cancer chemotherapy, antiviral drugs, hormones, some bioengineered drugs, and other drugs (NIOSH 2004). Although there is some variation in the definition of hazardous drugs, the National Institute for Occupational Safety and Health (NIOSH) describes hazardous drugs as those that have the potential to cause one or more of the following: carcinogenicity (inducing cancer), teratogenicity (causing birth defects), developmental toxicity (having an adverse impact on development), reproductive toxicity (interfering with normal reproduction), organ toxicity at low doses (damaging organs), or genotoxicity (causing mutations, i.e. alterations in the genetic structure) (NIOSH 2004). New drugs that have a structure and toxicity profile that mimics existing drugs considered hazardous according to the above criteria are also considered hazardous (NIOSH 2004). There is a subtle difference between cytotoxic drugs and hazardous drugs. Cytotoxic drugs are medicines that are toxic to human cells (NCBI 1978), while hazardous drugs include cytotoxic drugs and new drugs that have a structure and toxicity profile similar to cytotoxic drugs.

The various types of hazardous drugs include alkylating drugs (e.g. cyclophosphamide, chlorambucil), anthracyclines and other cytotoxic antibiotics (e.g. daunorubicin, doxorubicin), antimetabolites (e.g. methotrexate, fluorouracil, gemcitabine), vinca alkaloids and etoposide (e.g. vinblastine, vincristine), and some antineoplastic drugs (e.g. bevacizumab, denosumab, pertuzumab, rituximab, trastuzumab, mitotane) (BNF 2017). The mechanism of action varies between different types of cytotoxic drugs. In general, cytotoxic drugs interfere with cell replication by damaging DNA or by preventing normal cell division (BNF 2017).

Cytotoxic drugs have anticancer activity and immunosuppressive properties (Brogan 2000). Therefore, they are used in the treatment of many cancers (e.g. breast cancer, bowel cancer, stomach cancer, sarcoma, leukaemia) and non-cancerous conditions that require immunosuppression (e.g. polyarteritis nodosa, Wegener's granulomatosis, systemic lupus erythematosus, idiopathic nephrotic syndrome, inflammatory bowel disease, mixed connective tissue disease, scleroderma, multiple sclerosis, idiopathic inflammatory myopathy, sarcoidosis, primary membranous nephropathy, membranoproliferative glomerulonephritis, transplantation) (Awad 2009; BNF 2017; Brogan 2000; Cassidy 2011; Fernandes Moca Trevisani 2013; Ge 2015; Hartman 2001; Hazlewood 2016; Mulder 2015; Nunes 2015; Poormoghim 2012; Rodriguez-Peralvarez 2017; Zhu 2017).

Hazardous drugs can be administered orally, intravenously by infusions, or intrathecally (BNF 2017). When hazardous drugs are given by intravenous infusion, there is a risk of contamination, which means that staff handling the infusional hazardous drugs, particularly the pharmacy technicians who prepare the

drugs and the nurses who administer them, may come into contact with them. The hazardous drug aerosol, formed due to the spillage of drugs during preparation, transport, or administration, can be inhaled or absorbed through the skin (Chu 2012; Hon 2014; Poupeau 2016; Ramphal 2014; Schierl 2016; Sessink 2011; Sessink 2015; Sugiura 2011; Viegas 2014; Yoshida 2011; Yoshida 2013). Other staff (e.g. pharmacists, respiratory therapists, physicians, support staff) working in the hospital that administers hazardous drugs can also be exposed to the contamination, not just those who handle the hazardous drugs) (Hon 2014; Ramphal 2014).

Occupational exposure to hazardous drugs increases mutations that predispose the exposed staff to the development of cancer (HSE 2017; Mahmoodi 2017; McDiarmid 2010; McDiarmid 2014; Moretti 2015; NIOSH 2004; Skov 1992). Maternal occupational exposure to hazardous drugs during pregnancy can cause congenital abnormalities, miscarriages, stillbirths, and low birth-weight (Connor 2014; HSE 2017; NIOSH 2004). Occupational exposure to hazardous drugs can also decrease fertility in women (Connor 2014; HSE 2017; NIOSH 2004). Other adverse effects include skin rash, hair loss, light-headedness, abnormal blood counts, liver damage, abdominal pain, and vomiting (HSE 2017; NIOSH 2004).

Several methods have been proposed to decrease the risk of exposure to hazardous drugs. These include the use of biological safety cabinets with laminar airflow for drug preparation, robotic drug preparation, centralisation of priming of intravenous tubing, personal protective equipment, staff education for safe handling of hazardous drugs, and closed-system drug transfer devices (Guillemette 2014; Schierl 2016; Sessink 2011; Sessink 2015; Yoshida 2013). There are several guidelines for safe handling of hazardous drugs including those issued by the UK Health and Safety Executive (HSE), NHS Pharmaceutical Quality Assurance Committee, US NIOSH, US Pharmacopeial Convention (USP), Program in Evidence-Based Care guidelines, International Society of Oncology Pharmacy Practitioners Standards, American Society of Health-System Pharmacists, and Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASST-SAS) (ASSTSAS 2008; ASHP 2006; Bateman 2015; Easty 2015; HSE 2017; ISOPP 2007; NIOSH 2004; USP 2017). Broadly, these guidelines recommend the identification of the risk, use of biological safety cabinets, use of closed-system drug-transfer devices where reasonably practicable, and control of exposure at source (e.g. by using adequate extraction systems and appropriate organisational measures, issuing personal protective equipment, monitoring exposure at the workplace, providing health surveillance programmes, providing employee information and training, maintaining equipment appropriately, having appropriate procedures for dealing with spillages or contamination of people or work surfaces, and providing safe waste disposal) (ASSTSAS 2008; ASHP 2006; Bateman 2015; Easty 2015; HSE 2017; ISOPP 2007; NIOSH 2004; USP 2017).

Description of the intervention

A closed-system drug-transfer device is an apparatus that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour outside the system (NIOSH 2004). Some examples of closed-system drug-transfer devices are: PhaSeal system, ChemoClave system, Equashield system, and Chemo Safety system. These devices include a method to access the intravenous infusion (e.g. a spike designed to prevent leaks and spillages), and a leak-proof connection that attempts to transfer drugs without leaks or spillage, as a minimum (B Braun 2017a; BD 2017a; BD 2017b; Equashield 2017; ICUMED 2017). However, some devices used in compounding hazardous drugs are not fully considered closed-system drug-transfer devices, as they are not conceived or have not been demonstrated to capture aerosols such as hydrophobic-air-venting filters or chemotherapy transfer/reconstitution spikes (B Braun 2017b; Healthmark 2017). In this review, we will accept any device described as a closed-system drug-transfer device by the manufacturer.

How the intervention might work

Closed-system drug-transfer devices work by attempting to provide a leak-proof connection that prevents leaks and spills (B Braun 2017a; BD 2017a; BD 2017b; Equashield 2017; ICUMED 2017). This may decrease surface contamination and atmospheric contamination (with drug aerosol), thereby decreasing occupational exposure to infusional hazardous drugs. This in turn might result in fewer adverse events related to exposure. In addition, the systems also attempt to prevent microbiological contamination of the drug (BD 2017a; Equashield 2017; ICUMED 2017), potentially enabling reuse of vials and decreasing the costs.

Why it is important to do this review

There is significant variation in the way hazardous drugs are handled by staff. Legislation requires organisations to protect workers' health and safety (HSE 2017). All the staff working in hospitals that administer hazardous drugs are at potential risk of exposure to the drugs, which can result in the serious consequences described above (see [Description of the condition](#)). Even when staff handle hazardous drugs according to all instructions and as safely as possible, there is still the possibility of accidental contamination of surfaces around them, which exposes other staff members to the drugs and their serious consequences. Therefore, it is important to use the most effective methods to decrease the risk of staff contact with infusional hazardous drugs. Some studies have shown that closed-system drug-transfer devices may decrease surface contamination compared to current safe handling practices including biological safety cabinets and use of personal protective equipment (Harrison 2006; Sessink 2011). However, there are additional costs associated

with using closed-system drug-transfer devices compared to safe handling of infusional hazardous drugs, and it is unclear whether these devices provide good value for money (i.e. whether the cost-benefit ratio is favourable to using closed-system drug-transfer devices compared to conventional safe handling of infusional hazardous drugs). There is also major uncertainty about whether these devices are effective in reducing the risk of exposure. In one study, pharmacists considered that the use of a closed-system drug-transfer device increased technical issues, increased the risk of spillage, was slower and more cumbersome to use, and increased the risk of drug absorption through the skin and by inhalation (Guillemette 2014). In addition, there is concern that the observed differences in surface contamination attributed to the addition of closed-system drug-transfer devices to safe handling could actually be due to differences in the removal of previous drug residue. Further concerns include the possible contamination of the exterior of the hazardous drug vials at the manufacturing site (Connor 2005; Favier 2003; Fleury-Souverain 2014; Hedmer 2005; Mason 2003; Naito 2012), which may decrease the effectiveness of the closed-system drug-transfer devices in real-life situations compared to controlled laboratory situations. Several studies have shown high levels of drug vial exterior contamination (Connor 2005; Favier 2003; Fleury-Souverain 2014; Hedmer 2005; Mason 2003; Naito 2012), although there are exceptions to this (Power 2014). The risk of contamination may be dependent upon the manufacturing process used, for example due to different decontamination procedures and the encasing of the vials using protective sleeves (Connor 2005; Power 2014). Because of the uncertainty in the effectiveness of the closed-system drug-transfer devices, there is variation in the recommendations of different guidelines about the use of these devices. For example, USP recommends mandatory use of closed-system drug-transfer devices for administration when the dosage form allows, while NIOSH only recommends considering their use when transferring hazardous drugs (NIOSH 2004; USP 2017). Furthermore, the staff handling hazardous drugs may be anxious about the serious consequences and want to know how well these devices protect them. There is currently no systematic review on the effect of closed-system drug-transfer devices versus conventional safe handling for reducing the risk of staff contamination to infusional hazardous drugs. This Cochrane Review will provide the best available evidence regarding this issue.

OBJECTIVES

To assess the effects of closed-system drug-transfer of infusional hazardous drugs plus safe handling versus safe handling alone for reducing staff exposure to infusional hazardous drugs and risk of staff contamination.

METHODS

Criteria for considering studies for this review

Types of studies

Due to the complex nature of the intervention, which is applied at the group level in work situations rather than at the individual level, randomised controlled trials (RCTs) are not very feasible, which is one of the major reasons for including non-randomised studies in Cochrane Reviews (Ijaz 2014). Therefore, we included other study designs in addition to RCTs. We considered comparative studies that are commonly performed in this field, that is, uncontrolled before-after studies and cohort studies. We also included interrupted time-series, controlled before-after (CBA) studies, and case-control studies. This is because interrupted time-series may account for time trends in improvement of practices, and CBA studies may account for any interim changes in policies. We included case-control studies because the outcomes following exposure are rare.

Types of participants

We included studies conducted on adult healthcare staff (aged 18 years or above) involved in the preparation, transport, delivery, administration, and disposal of waste of infusional hazardous drugs. We also considered healthcare organisations where healthcare staff were exposed to infusional hazardous drugs as participants with regards to outcomes such as surface contamination and aerosol contamination.

Types of interventions

We included trials that evaluated the effectiveness of closed-system drug transfer of infusional hazardous drugs (e.g. PhaSeal system and ChemoClave system) plus safe handling of infusional hazardous drugs (e.g. including class II biological safety cabinet, isolator, and personal protective equipment) versus safe handling alone. We accepted any device whose manufacturer described it as a closed-system drug-transfer device. We included trials with any co-interventions provided they were not part of the randomised treatment or were applied equally in both arms in non-randomised studies.

Types of outcome measures

Primary outcomes

- Measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and micronuclei induction
- Environmental contamination measured with surrogate outcomes for exposure: surface samples, splashes, leakage tests, or atmospheric contamination

- Short-term health outcomes such as skin rashes
- Medium-term health outcomes such as infertility or miscarriage
- Long-term health outcomes such as cancer (any type of cancer)

We accepted any methods used by the study authors, for example, routine screening for the presence or absence of outcomes or assessment of these outcomes in only people with symptoms suggestive of the presence of these outcomes. The Board of the UK Oncology Nursing Society identified these outcomes as the most important outcomes for the target population by as part of their funding call.

Secondary outcomes

- Adverse events (e.g. personal injury due to the use of spikes or needles resulting in infections)
- Potential cost savings due to reuse of multi-dose vials

We considered follow-up times for primary and secondary outcome measurement as: short term (up to one year), medium term (one to five years), and long term (longer than five years).

Reporting one or more of the primary or secondary outcomes listed here is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We conducted a systematic literature search to identify all published and unpublished trials that were potentially eligible for inclusion in this review. We adapted the search strategy developed for MEDLINE (see Appendix 1) for use in the other electronic databases. We imposed no restrictions on language of publication and translated the key sections of potentially eligible non-English language papers to assess them fully for potential inclusion in the review as necessary.

We searched the following electronic databases from inception to 26 October 2017 to identify potential studies. The only exception was the databases searched through OSH-UPDATE search platform, which we searched on 3 October 2017.

- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library) (Appendix 2).
- MEDLINE (OvidSP) (Appendix 1).
- Embase (OvidSP) (Appendix 3).
- NIOSHTIC (OSH-UPDATE) (Appendix 4).
- NIOSHTIC-2 (OSH-UPDATE) (Appendix 4).
- HSELINE (OSH-UPDATE) (Appendix 4).
- CISDOC (OSH-UPDATE) (Appendix 4).
- CINAHL (EBSCO) (Appendix 5).
- Science Citation Index Expanded (including Conference Proceedings) (Appendix 6).

- NHS Economic Evaluation Database (NHS EED) (Appendix 7).
- Cost-Effectiveness Analysis Registry (CEA) at Tufts University (Appendix 7).

We also conducted a search for unpublished trials in ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/) (Appendix 8) on 26 October 2017.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references and contacted experts in the field to identify additional unpublished material.

Data collection and analysis

Selection of studies

We conducted the selection of eligible studies in two stages. First, two review authors (KG and LB) independently screened titles and abstracts of all potentially relevant studies found with our systematic search to exclude studies that clearly did not fulfil the criteria for inclusion. CT identified additional studies by reviewing bibliographies to identify further full-text records for potential inclusion. The same review authors coded records as 'include' (eligible or potentially eligible/unclear) or 'exclude'. We excluded all references that clearly did not fulfil our inclusion criteria or that fulfilled our exclusion criteria. Second, we retrieved the full-text study reports/publications, and two review authors (KG and LB) independently assessed the full-text to identify studies for inclusion. At this stage, we included all references that fulfilled our inclusion criteria. We recorded reasons for excluding studies based on assessment of the full text and reported these in a 'Characteristics of excluded studies' table. We resolved any disagreements through discussion. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA study flow diagram.

Data extraction and management

We used an Excel-based data collection form for study characteristics and outcome data that was piloted on two studies in the review. Two review authors (KG and LB) extracted the following study characteristics from included studies.

- Methods: study design, duration of study, study location, study setting, withdrawals, and date of study.
- Participants: number of participants, number of clusters (hospitals or wards), mean age or age range, sex, inclusion criteria, and exclusion criteria.

- Interventions: description of intervention, comparison (elements included in safe handling in the control group), and co-interventions.

- Outcomes: description of primary and secondary outcomes specified and collected, and at which time points reported.

- Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (KG and LB) independently extracted outcome data from included studies. We noted in the 'Characteristics of included studies' table if authors did not report outcome data in a usable way. We resolved disagreements by consensus. One review author (KG) transferred data into Review Manager 5 (RevMan 2014). We double-checked the data entry by comparing the data presented in the systematic review with the study reports. A third review author (CT) spot-checked study characteristics and data for accuracy against the trial report. The author team was proficient in all languages of the studies included in the review (English and French).

Assessment of risk of bias in included studies

For each RCT, two review authors (KG and LB) independently planned to assess risk of bias using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to resolve any disagreements by discussion. We planned to assess the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias (including source of funding and whether the duration of exposure to hazardous drugs in the intervention group and control group was measured reliably after ensuring that the participants were free from the outcome at the beginning of the study).

We planned to grade each potential risk of bias as high, low, or unclear, and we provided a quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We planned to summarise the risk of bias judgements across different studies for each of the domains listed. We planned to consider blinding separately for different key outcomes where necessary. To classify studies as being at low risk of bias in measurement of outcome, we required them to have carried out blinded assessment of all outcomes except for contamination of surface samples, where we accepted samples obtained and analysed by an automated machine as being at low risk of bias regardless of blinding. For urinary levels, we accepted this outcome as being at low risk of bias regardless of blinding. Where information on risk of

bias relates to unpublished data or correspondence with a trialist, we planned to note this in the 'Risk of bias' table.

For each non-randomised study, the same two review authors (KG and LB) assessed the risk of bias independently using the risk of bias in non-randomised studies of interventions (ROBINS-I) tool (Sterne 2016). We considered the following as possible sources of confounding.

- Changes or differences in other factors for genetic and chromosomal damage such as stress from work, working long hours, and smoking that might lead to fewer genetic and chromosomal abnormalities compared to the intervention.
- Differences in drug residue on a surface prior to contamination (e.g. thorough cleaning before the study in only one group).
- Changes or differences in drug residue on the drug vials because of different batches or different manufacturers of the drug.

In terms of bias due to classification of interventions, we considered studies to be at low risk of bias when it was clear that the intervention group was CSTD and the control group was no CSTD. We considered the following co-interventions.

- Changes or differences in layout, ventilation, fume cupboards, etc., that might lead to less contamination compared to the intervention.
- Changes or differences in policies that might lead to less contamination compared to the intervention.
- Education, training, and experience of healthcare staff that might lead to less contamination compared to the intervention.
- Differences in the supervision for drug preparation or drug administration that might lead to less contamination compared to the intervention.

We planned to assess the risk of bias in the included economic evaluations using either the Consensus Health Economic Criteria (CHEC) list for assessment of methodological quality of economic evaluations, described in Evers 2005, or the Philips 2004 checklist. We considered all domains other than blinding of healthcare providers to be key domains. We judged a study to be at high risk of bias overall when we judged one or more key domains to be at high risk of bias. Conversely, we judged a study to be at low risk of bias when we assigned a low risk of bias for all key domains. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in Differences between protocol and review.

Measures of treatment effect

We entered the outcome data for each study into the data tables in RevMan 5 to calculate the treatment effects unadjusted for clustering (RevMan 2014). As we did not find any case-control studies, we used the risk ratio (RR) for dichotomous outcomes (this is because RRs are much easier to interpret; however, they cannot be calculated in case-control studies without the use of risk from another study), and mean differences (MDs) for continuous outcomes. If studies reported only effect estimates and their 95% confidence intervals (CIs) or standard errors, we planned to enter these data into RevMan 5 using the generic inverse variance method (RevMan 2014). We ensured that higher scores for continuous outcomes have the same meaning for the particular outcome. When the results could not be entered in either way, we entered the data into additional tables.

For interrupted time-series studies, we extracted data from the original papers and reanalysed them according to the recommended methods for analysing interrupted time-series designs for inclusion in systematic reviews (Ramsay 2003). We planned to use the standardised change in level and change in slope as effect measures.

Unit of analysis issues

For studies that employed a cluster-design and reported sufficient data to be included in the meta-analysis but did not make an allowance for the design effect, we calculated the design effect based on a fairly large assumed intracluster correlation coefficient (ICC) of 0.10. We based this assumption of 0.10 being a realistic estimate by analogy with studies about implementation research (Campbell 2001). We followed the methods stated in the *Cochrane Handbook for Systematic Reviews of Interventions* for the calculations, and we entered the data adjusted for clustering as generic inverse variance data (Higgins 2011). This involved calculating the average cluster size 'M' (by dividing the total number of samples by the total number of hospitals) and calculating the design effect by using the formula $1 + (M - 1) ICC$. We multiplied the standard error for each cluster study by the square root of the design effect to obtain a standard error adjusted for clustering. This adjusted standard error was then used to calculate the confidence intervals.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was reported as abstract only). Where this was not possible, and if the missing data were thought to introduce serious bias, we would have explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data were missing, such as standard deviations or correlation coefficients, and they could not be obtained

from the authors, we planned to calculate them from other available statistics such as P values, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We assessed the clinical homogeneity of the results of included studies based on similarity of population, intervention, outcome, and follow-up. We considered populations as similar when they were staff who were exposed to infusional hazardous drugs, for example, oncology nurses, pharmacy technicians, or pharmacists who handled infusional hazardous drugs. We considered interventions as similar when it was clear that the system was a closed-system drug transfer device. We combined results data produced by each of the measures of contamination separately (e.g. urine tests, surface contamination, and atmospheric contamination), and we planned to combine cancer- and fertility-related outcome data separately. We considered short-term (up to one year), medium-term (one to five years), and long-term (more than five years) follow-up times as different.

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (above 50%, as described in Higgins 2011), we planned to report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we were able to pool more than five trials in any single meta-analysis, we created and examined a funnel plot to explore possible small-study biases. We used Egger's test to identify reporting biases (Egger 1997). We considered a P value of less than 0.05 as statistically significant reporting bias.

Data synthesis

We pooled data from studies we judged to be clinically homogeneous using RevMan 5 software (RevMan 2014). If two or more studies provided usable data in any single comparison, we performed meta-analyses. However, we did not plan to pool data from different study designs (i.e. RCT and non-randomised studies). We analysed different drugs in separate analyses since drugs are reconstituted differently, administered differently (for example, some are intravenous only while others can be used intravenously, subcutaneously, or orally), used in different quantities, and can lead to different levels of exposure and contamination. Furthermore, these are dangerous at different dosages. In addition, we analysed the pharmacy areas and patient-care areas separately since the levels of exposure and contamination vary between them.

For costs, we used an international exchange rate based on purchasing power parities (PPP) to convert cost estimates to US dollars (USD), and we used the gross domestic product (GDP) deflators (or implicit price deflators for GDP) to convert cost estimates

to 2017 USD using PPP conversion rates and GDP deflator values available from the International Monetary Fund in the World Economic Outlook Database (updated biannually: see www.imf.org/external/data.htm). We used both a fixed-effect model and a random-effects model to perform the meta-analyses and reported the more conservative model. When the I^2 statistic was higher than 75%, we did not plan to pool results of studies in meta-analysis. Where a single trial reported multiple trial arms, we included only the relevant arms. If two comparisons (e.g. device A versus safe handling and device B versus safe handling) were combined in the same meta-analysis, we planned to halve the control group to avoid double-counting.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

- Study design: CBA studies versus other non-randomised study designs; individual versus cluster unit of analysis. These were planned subgroup analyses. We also performed a post hoc subgroup analysis of uncontrolled before-after studies versus cross-sectional studies, as these were the two types of studies that contributed data for the analysis. This analysis can assess the impact of trend in improving safe handling practices that could be problematic in uncontrolled before-after studies.
- Professional role: pharmacy technician versus chemotherapy nurse versus other healthcare staff.
- Duration of possible exposure.
- Intervention: any closed-system drug-transfer device.
- Control: safe handling following UK HSE standards.

We planned to perform subgroup analyses for primary outcomes (i.e. immediate to short-term contamination, short-term health benefits, long-term reproductive health benefits, and development of any type of cancers). We planned to use the Chi^2 test to test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We planned to perform a sensitivity analysis involving studies with low risk of bias versus studies with high risk of bias defined a priori to assess the robustness of our conclusions.

We performed a post hoc sensitivity analysis to assess the impact of the influence of different intracluster correlation coefficients on the results to determine if the differences in conclusions between our systematic review and primary research studies could be due to the lack of adjusting for cluster effect in primary research studies.

Summary of findings table

We created a 'Summary of findings' table using all outcomes (i.e. exposure, environmental contamination, health outcomes, adverse events, and potential cost savings). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body

of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade or upgrade the quality of studies using footnotes.

Since we described all the decisions to downgrade or upgrade the quality of studies using the footnotes and described the reason in detail under each outcome in the text, we did not compile an additional GRADE table showing all our decisions about the quality of evidence and their justifications.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We avoided making recommendations for practice based on more than just the evidence, such as values and available resources. Our implications for research suggest priorities for future research and outline what the remaining uncertainties are in the area.

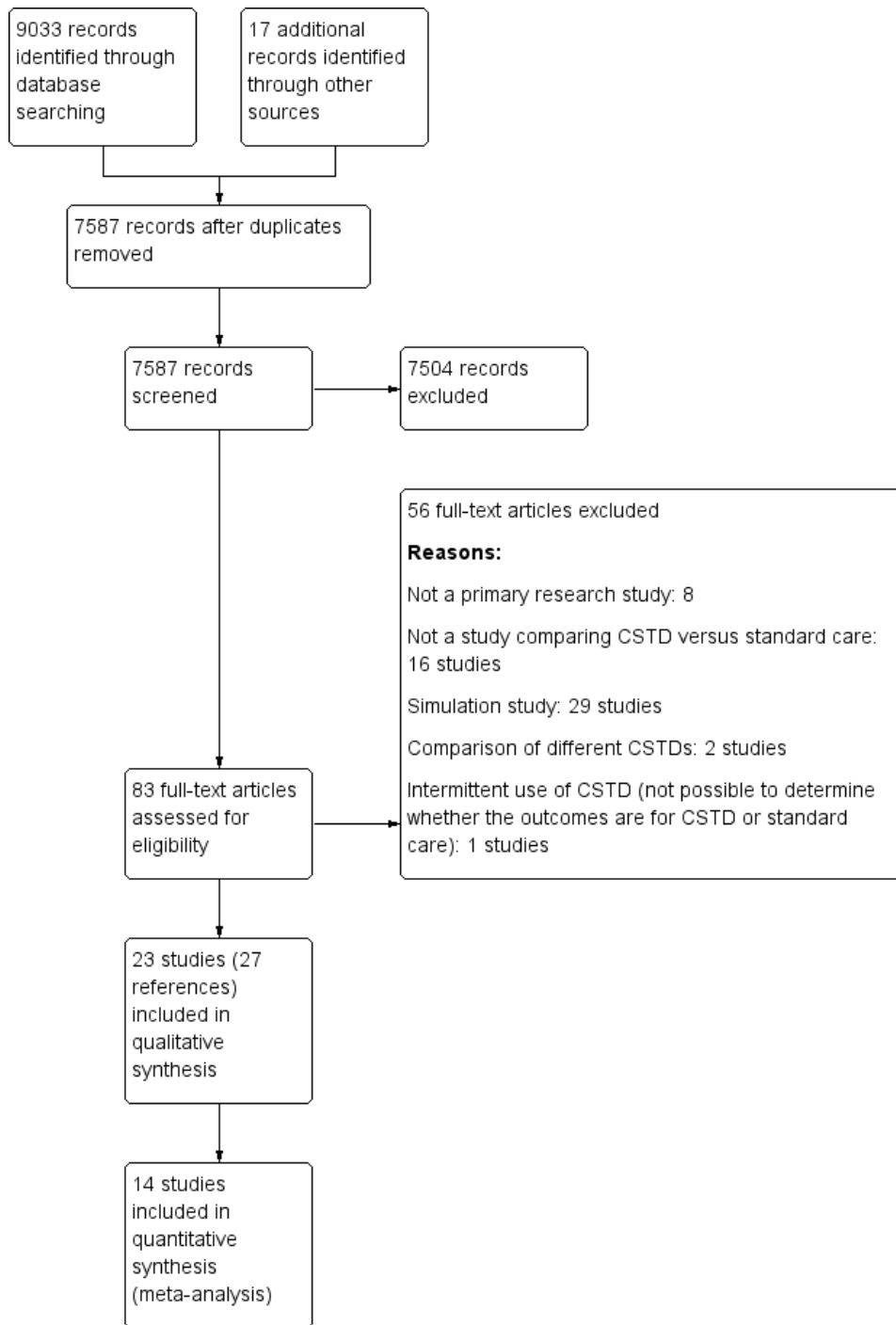
RESULTS

Description of studies

Results of the search

We identified a total of 9033 records from CENTRAL (70 references), MEDLINE (695 references), Embase (1043 references), OSH-UPDATE (8 references), CINAHL (253 references), Science Citation Index Expanded (including Conference Proceedings) (6830 references), NHS EED (0 references), CEA at Tufts University (0 references), ClinicalTrials.gov (131 references), and the World Health Organization (WHO) trials portal (3 references). After excluding 1463 duplicate records and seeking 17 other references based on handsearching, we screened the titles and abstracts of 7587 records. We obtained full texts for 83 potentially eligible studies. Of these, we excluded 56 references for the reasons detailed in [Characteristics of excluded studies](#) and summarised in [Excluded studies](#). In total, we included 23 studies (27 references). See the study inclusion process explained in [Figure 1](#).

Figure 1. PRISMA study flow diagram. CSTD: closed-system transfer device



Included studies

All 23 included studies are cluster studies, that is, the comparison is between hospitals that used CSTD versus those that did not (cross-sectional studies) or between the period in which CSTD was used versus the period in which it was not (interrupted time-series or uncontrolled before-after studies). Of the 23 included studies, 1 study (3 hospitals) is an interrupted time-series (Harrison 2006), 13 (65 hospitals) are uncontrolled before-after studies (Chan 2016; Edwards 2013; Guillemette 2014; Hama 2012; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Sessink 2011; Sessink 2013; Siderov 2010; Wick 2003; Yoshida 2009), and 9 (290 hospitals) are cross-sectional studies (Berruyer 2015; Chauchat 2017; Forges 2011; Janes 2015; Poupeau 2016; Roland 2017; Simon 2016; Sottani 2012; Yoshida 2011). In one cross-sectional study, a hospital used the same isolators during the same period to prepare drugs using CSTD and no CSTD (Forges 2011). In another, the same hospital used two different isolators to prepare drugs over the same period: CSTD in one isolator and no CSTD in the other (Simon 2016). In the remaining seven cross-sectional studies, 91 hospitals used CSTD and 197 hospitals did not (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017; Sottani 2012; Yoshida 2011). We did not find any randomised controlled trials or formal economic evaluations. Overall, 358 hospitals in Australia, Canada, France, Hungary, Italy, Japan, Malaysia, Turkey, and the USA took part. Most hospitals were from Canada and the USA. There was also an overlap between hospitals included in the different studies, although there was minimal or no overlap in the period when the samples were collected (i.e. the samples were included only once in the analysis).

In 21 studies, the people who used the intervention (CSTD plus safe handling) and control (safe handling alone) were pharmacists or pharmacy technicians (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Forges 2011; Guillemette 2014; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Miyake 2013; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Yoshida 2009; Yoshida 2011); in two studies, the people who used the intervention and control were nurses in addition to pharmacists or pharmacy technicians (Mullot 2008; Wick 2003).

The CSTDs used in the studies were PhaSeal (13 studies: Chan 2016; Edwards 2013; Guillemette 2014; Hama 2012; Harrison 2006; Miyake 2013; Ozyaman 2016; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Wick 2003; Yoshida 2009), Tevadaptor (1 study: Juhasz 2016), SpikeSwan (1 study: Forges 2011), PhaSeal and Tevadaptor (1 study: Mullot 2008), varied (5 studies: Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017), and not stated (2 studies: Yoshida 2011; Sottani 2012). The descriptions of the control groups varied; although we

provide the details reported in [Characteristics of included studies](#), additional safety measures are likely to have been in place.

The outcomes reported in the studies are exposure (4 studies: Miyake 2013; Sottani 2012; Wick 2003; Yoshida 2009), surface contamination (16 studies: Berruyer 2015; Chauchat 2017; Forges 2011; Guillemette 2014; Harrison 2006; Janes 2015; Miyake 2013; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Wick 2003; Yoshida 2009), and potential cost savings (5 studies: Chan 2016; Edwards 2013; Juhasz 2016; Mullot 2008; Ozyaman 2016). None of the studies that report exposure reported the intraclass correlation coefficient. The remaining two studies did not report the outcomes in a format that could be tabulated or pooled with meta-analysis, as key information was missing and we were unable to obtain it from study authors (Hama 2012; Yoshida 2011).

The duration of exposure of people to CSTD and control measures is relevant only for studies that reported the presence of hazardous drugs in urine (Miyake 2013; Sottani 2012; Wick 2003; Yoshida 2009). This was seven months in Miyake 2013; not reported in Sottani 2012; six months to CSTD without any information on the duration of exposure in the control group in Wick 2003; and two weeks in Yoshida 2009.

With regard to funding, eight studies received no special funding (Berruyer 2015; Chauchat 2017; Edwards 2013; Guillemette 2014; Janes 2015; Juhasz 2016; Poupeau 2016; Roland 2017), six studies received funding from manufacturers of the device being evaluated (Harrison 2006; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Wick 2003), and the remaining nine studies did not report funding (Chan 2016; Forges 2011; Hama 2012; Miyake 2013; Mullot 2008; Ozyaman 2016; Sottani 2012; Yoshida 2009; Yoshida 2011).

Excluded studies

We excluded 56 studies after full-text assessment ([Characteristics of excluded studies](#)). The main reasons for exclusion are as follows.

- Not a primary research study: eight studies (Hospital Infection Control 2005; Kunneva 2016; Laws 2016; Lennan 2017; Meade 2015; Oncology Nurse Advisor 2017; Talsmar 2015).
- Not a study comparing CSTD plus standard care versus standard care: 16 studies (Clark 2013; Connor 2010; Contractor 2015; Cox 2017; Enciso-Zarate 2016; Gilles 2009; Hong 2017; Idell 2009; Kopp 2013; Kurihara 2017; Nygren 2005; Nyman 2007; Odraska 2013; Sessink 1999; Tyler 2017; Yoshida 2013). This reason encompasses studies that introduced other safety measures such as biosafety cabinets or change in the layout of the pharmacy in addition to CSTD as well as studies that cleaned the surfaces for only the CSTD group prior to exposure to

hazardous drugs, which clearly does not estimate the benefits or harms of CSTD plus safe handling versus safe handling alone.

- Simulation study: 29 studies (Blazawski 2013; Chantry 2015; De Aussen 2013; De Prijck 2008; DeFreitas 2012; Favier 2012; Fernandez 2013; Garrigue 2016; Gebel 2015; Gomez-Alvarez 2016; Gonzalez-Haba Pena 2016; Hama 2011; Ikeno 2014; Jorgenson 2008; Le Garlantezec 2011; Lin 2017; McMichael 2011; Nishigaki 2010; Nygren 2008; Perlo 2015; Queruau Lamerie 2012; Rupp 2017; Sanchez-Rubio Ferrandez 2012; Sanchez-Rubio Ferrandez 2012; Sato 2010; Simon 2010;

Smith 2014; Thomas Carey 2011; Vyas 2016).

- Comparison of different CSTDs: two studies (Amos 2012; Ledford 2010).

- Intermittent use of CSTD (not possible to determine whether the outcomes were for CSTD or standard care): one study (McDiarmid 2010).

Risk of bias in included studies

The risk of bias in the included studies is summarised in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green +: Low risk of bias. Yellow ?: Moderate risk of bias or 'No information'. Red -: Serious or critical risk of bias.

	Confounding bias	Selection bias	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Berruyer 2015	?	?	+	?	?	-	-
Chan 2016	?	+	+	?	+	-	-
Chauchat 2017	?	?	+	?	+	-	-
Edwards 2013	?	+	+	?	+	-	-
Forges 2011	?	+	+	-	?	-	+
Guillemette 2014	?	-	+	-	+	-	-
Hama 2012	?	+	+	?	?	-	-
Harrison 2006	?	+	+	?	?	-	-
Janes 2015	?	?	+	?	?	-	-
Juhasz 2016	?	+	+	?	+	-	-
Miyake 2013	?	+	+	-	+	-	+
Mulot 2008	?	+	+	-	+	-	-
Ozyaman 2016	?	+	+	?	+	-	-
Poupeau 2016	?	?	+	?	?	-	-
Roland 2017	?	?	+	?	+	-	-
Sessink 2011	?	?	+	?	+	-	-
Sessink 2013	?	?	+	?	+	-	-
Siderov 2010	?	+	+	?	+	-	+
Simon 2016	?	+	+	-	+	-	-
Sottani 2012	?	?	+	?	+	-	+
Wick 2003	?	+	+	-	+	-	+
Yoshida 2009	?	+	+	-	+	-	+
Yoshida 2011	?	?	+	?	+	-	-

Confounding bias

There is insufficient information to assess the risk of confounding bias in all the studies (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Forges 2011; Guillemette 2014; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Wick 2003; Yoshida 2009; Yoshida 2011). This is because none of the studies reported whether there were any baseline differences in any of the confounding factors.

Selection bias

Thirteen studies are at low risk of selection bias (Chan 2016; Edwards 2013; Forges 2011; Hama 2012; Harrison 2006; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Siderov 2010; Simon 2016; Wick 2003; Yoshida 2009). Nine studies are at moderate risk of selection bias, as the participating centres were probably selected or returned the questionnaire about CSTD use based on their safe handling practices (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Sottani 2012; Yoshida 2011). One study is at serious risk of bias as the sites of sampling differed between CSTD and control groups (Guillemette 2014). None of the studies are at critical risk of bias.

Bias in classification of interventions

All the studies are at low risk of bias since the classification of CSTD versus control was made clearly (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Forges 2011; Guillemette 2014; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Wick 2003; Yoshida 2009; Yoshida 2011).

Bias due to deviations from intended interventions

There is insufficient information to assess the risk of bias due to deviations from intended interventions in 16 studies (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Sottani 2012; Yoshida 2011), as they did not report whether the training periods and other co-interventions were similar in both groups. The remaining seven studies are at serious risk of bias, since it is clear that only CSTD groups received additional training while the control group did not receive an equivalent period of training in safe handling (Forges 2011; Guillemette 2014;

Miyake 2013; Mullot 2008; Simon 2016; Wick 2003; Yoshida 2009).

Bias due to missing data

Seventeen studies are at low risk of bias due to missing data (Chan 2016; Chauchat 2017; Edwards 2013; Guillemette 2014; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Wick 2003; Yoshida 2009; Yoshida 2011). There is insufficient information to assess the risk of bias in the remaining six studies (Berruyer 2015; Forges 2011; Hama 2012; Harrison 2006; Janes 2015; Poupeau 2016), as there is either missing information, the impact of which on the effect estimates is not clear, or it is not clear whether there is missing information in the studies.

Bias in measurement of outcomes

All 23 studies are at serious risk of bias in measurement of outcomes as it appears that none of the studies used blinded assessment of outcomes (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Forges 2011; Guillemette 2014; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Wick 2003; Yoshida 2009; Yoshida 2011).

Bias in selection of the reported result

Six studies are at low risk of bias in selection of the reported result (Forges 2011; Miyake 2013; Siderov 2010; Sottani 2012; Wick 2003; Yoshida 2009). The remaining 17 studies are at serious risk of bias in selection of the reported result: they report results partially (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Guillemette 2014; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Mullot 2008; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Simon 2016; Yoshida 2011).

Overall risk of bias

All the studies are at serious risk of bias (Berruyer 2015; Chan 2016; Chauchat 2017; Edwards 2013; Forges 2011; Guillemette 2014; Hama 2012; Harrison 2006; Janes 2015; Juhasz 2016; Miyake 2013; Mullot 2008; Ozyaman 2016; Poupeau 2016; Roland 2017; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Sottani 2012; Wick 2003; Yoshida 2009; Yoshida 2011).

Effects of interventions

See: [Summary of findings for the main comparison Closed-system transfer device plus safe handling versus safe handling alone for reducing healthcare staff exposure to infusion hazardous drugs: exposure and surface contamination](#); [Summary of findings 2 Closed-system transfer device plus safe handling versus safe handling alone for reducing healthcare staff exposure to infusion hazardous drugs: clinical outcomes](#)

The raw data used for analysis are available in [Appendix 9](#) and [Appendix 10](#).

Primary outcomes

Exposure

Presence of hazardous drugs in urine

Four studies (seven hospitals; 70 participants) report the proportion of people with positive urine tests for exposure ([Miyake 2013](#); [Sottani 2012](#); [Wick 2003](#); [Yoshida 2009](#)). One study is a cross-sectional study involving four hospitals ([Sottani 2012](#)). The other studies are uncontrolled before-after studies, each involving a single hospital ([Miyake 2013](#); [Wick 2003](#); [Yoshida 2009](#)). The drugs measured in these trials are cyclophosphamide alone in two studies ([Miyake 2013](#); [Yoshida 2009](#)), cyclophosphamide or ifosfamide in one study ([Wick 2003](#)), and cyclophosphamide, ifosfamide, or gemcitabine in one study ([Sottani 2012](#)). There is no evidence of differences in the proportion of people with positive urine tests for exposure between the CSTD and control groups for cyclophosphamide alone (RR 0.83, 95% CI 0.46 to 1.52; $I^2 = 0\%$; 2 studies; 2 hospitals; 20 participants); cyclophosphamide or ifosfamide (RR 0.09, 95% CI 0.00 to 2.79; 1 study; 1 hospital; 14 participants); and cyclophosphamide, ifosfamide, or gemcitabine (RR not estimable; 1 study; 4 hospitals; 36 participants) ([Analysis 1.1](#)). There is no alteration in the interpretation of results using the fixed-effect or the random-effects model.

Quality of evidence: the quality of evidence is very low because of the serious risk of bias in the studies (downgraded by one level), imprecision (small sample size (downgraded by one level) and wide confidence intervals (downgraded by one level)).

Subgroup analysis: since there is only one cross-sectional study and this is the only study examining cyclophosphamide, ifosfamide, or gemcitabine, we did not perform a subgroup analysis of uncontrolled before-after studies versus cross-sectional studies. PhaSeal was used in three studies ([Miyake 2013](#); [Wick 2003](#); [Yoshida 2009](#)). The authors of the fourth study did not report which device they used ([Sottani 2012](#)). There is no evidence of differences in the proportion of people with positive urine tests for exposure between the PhaSeal and control groups ([Analysis 2.1](#)).

Sensitivity analysis: There is also no alteration in the interpretation of results using different intracluster correlation coefficients (ICC) ([Analysis 3.1](#); [Analysis 3.2](#); [Analysis 3.3](#)).

Other measures of exposure

None of the studies reported on blood tests or other measures of exposure to infusion hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, or micronuclei induction.

Environmental contamination

Proportion of surfaces contaminated in pharmacy areas

Fourteen studies (342 hospitals, 3096 surface samples) report the proportion of surface samples that were contaminated with various drugs in the pharmacy areas ([Berruyer 2015](#); [Chauchat 2017](#); [Guillemette 2014](#); [Janes 2015](#); [Miyake 2013](#); [Poupeau 2016](#); [Roland 2017](#); [Sessink 2011](#); [Sessink 2013](#); [Siderov 2010](#); [Simon 2016](#); [Sottani 2012](#); [Wick 2003](#); [Yoshida 2009](#)). Seven are cross-sectional studies involving 284 hospitals ([Berruyer 2015](#); [Chauchat 2017](#); [Janes 2015](#); [Poupeau 2016](#); [Roland 2017](#); [Simon 2016](#); [Sottani 2012](#)), and seven are uncontrolled before-after studies involving 58 hospitals ([Guillemette 2014](#); [Miyake 2013](#); [Sessink 2011](#); [Sessink 2013](#); [Siderov 2010](#); [Wick 2003](#); [Yoshida 2009](#)). There is no evidence of difference in proportion of surface samples that were contaminated between the CSTD and the control groups for any of the drugs in the pharmacy areas ([Analysis 1.2](#)).

- Cyclophosphamide: RR 0.89, 95% CI 0.78 to 1.01; $I^2 = 35\%$ (13 studies: 7 uncontrolled before-after studies ([Guillemette 2014](#); [Miyake 2013](#); [Sessink 2011](#); [Sessink 2013](#); [Siderov 2010](#); [Wick 2003](#); [Yoshida 2009](#)); 6 cross-sectional studies ([Berruyer 2015](#); [Chauchat 2017](#); [Janes 2015](#); [Poupeau 2016](#); [Roland 2017](#); [Simon 2016](#)); 338 hospitals, 2937 surface samples).

- Ifosfamide: RR 0.94, 95% CI 0.74 to 1.19; $I^2 = 8\%$ (9 studies: 3 uncontrolled before-after studies ([Guillemette 2014](#); [Sessink 2011](#); [Wick 2003](#)); 6 cross-sectional studies ([Berruyer 2015](#); [Chauchat 2017](#); [Janes 2015](#); [Poupeau 2016](#); [Roland 2017](#); [Simon 2016](#)); 304 hospitals, 2332 surface samples).

- Methotrexate: RR 0.84, 95% CI 0.58 to 1.22; $I^2 = 0\%$ (6 studies: 1 uncontrolled before-after study ([Guillemette 2014](#)); 5 cross-sectional studies ([Berruyer 2015](#); [Chauchat 2017](#); [Janes 2015](#); [Poupeau 2016](#); [Roland 2017](#)); 280 hospitals, 1781 surface samples).

- 5-fluorouracil: RR 0.65, 95% CI 0.43 to 0.97; $I^2 = 0\%$ (3 studies: 1 uncontrolled before-after study ([Sessink 2011](#)); 2 cross-sectional studies ([Chauchat 2017](#); [Simon 2016](#)); 106 hospitals, 1008 surface samples).

- Cytarabine: RR 0.72, 95% CI 0.18 to 2.86; $I^2 = 43\%$ (2 studies: all cross-sectional studies (Chauchat 2017; Simon 2016); 84 hospitals, 780 surface samples).
- Gemcitabine: RR 0.96, 95% CI 0.60 to 1.54; $I^2 = 0\%$ (2 cross-sectional studies (Chauchat 2017; Simon 2016); 84 hospitals, 780 surface samples).
- Irinotecan: RR 0.36, 95% CI 0.10 to 1.33 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 493 surface samples).
- Docetaxel: not estimable (1 cross-sectional study (Chauchat 2017); 83 hospitals, 493 surface samples).
- Paclitaxel: RR 0.57, 95% CI 0.04 to 9.06 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 493 surface samples).
- Vinorelbine: RR 1.72, 95% CI 0.16 to 18.73 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 493 surface samples).
- Ganciclovir: RR 0.01, 95% CI 0.00 to 27.11 (1 cross-sectional study (Simon 2016); 1 hospital, 287 surface samples).
- Multiple drugs (data on each drug were not available): RR 0.87, 95% CI 0.43 to 1.77 (1 cross-sectional study (Sottani 2012); 4 hospitals, 109 surface samples).

There is no alteration in the interpretation of results using the fixed-effect or the random-effects model.

Quality of evidence: the quality of evidence is very low because of the serious risk of bias in all the studies (downgraded by one level); indirectness of the outcome, as all the outcomes reported are surrogate outcomes (downgraded by one level); and imprecision because of wide confidence intervals (downgraded by one level) or lack of evidence that the observed difference led to decreased exposure or tangible health benefits (downgraded by one level).

Subgroup analysis: there is no evidence of subgroup differences in the analyses that could be stratified by study design (uncontrolled before-after versus cross-sectional studies) (Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5). The device used in eight studies was PhaSeal (Guillemette 2014; Miyake 2013; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Wick 2003; Yoshida 2009). The devices used in five studies were variable (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017). The last study did not report the device used in the study (Sottani 2012). There is no evidence of difference in proportion of surface samples that were contaminated between the PhaSeal and the control groups for any of the drugs other than cyclophosphamide (RR 0.88, 95% CI 0.78 to 0.99; 8 studies; 59 hospitals, 1278 surface samples; Analysis 2.6).

Sensitivity analysis: there is also no alteration in the interpretation of results using different ICCs except for cyclophosphamide and 5-fluorouracil for intracluster coefficients of 0.05, 0.01, and 0.00, and for ganciclovir for ICCs of 0.01 and 0.00 (Analysis 3.4; Analysis 3.5; Analysis 3.6).

Proportion of surfaces contaminated in patient-care areas

Six studies (283 hospitals, 1568 surface samples) reported the proportion of surface samples that were contaminated with various drugs in the patient-care areas (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017; Sottani 2012). There was no evidence of difference in the proportion of surface samples that were contaminated with various drugs in the patient-care areas between the CSTD and control groups in the patient-care areas (Analysis 1.2).

- Cyclophosphamide: RR 1.01, 95% CI 0.86 to 1.18; $I^2 = 0\%$ (5 cross-sectional studies (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017); 279 hospitals, 1535 surface samples).
- Ifosfamide: RR 1.44, 95% CI 0.91 to 2.28; $I^2 = 20\%$ (5 cross-sectional studies (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017); 279 hospitals, 1535 surface samples).
- Methotrexate: RR 1.00, 95% CI 0.55 to 1.85; $I^2 = 0\%$ (5 cross-sectional studies (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017); 279 hospitals, 1535 surface samples).
- 5-fluorouracil: RR 1.09, 95% CI 0.53 to 2.23 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Cytarabine: RR 0.59, 95% CI 0.01 to 24.53 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Gemcitabine: RR 1.13, 95% CI 0.55 to 2.33 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Irinotecan: RR 0.44, 95% CI 0.03 to 6.15 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Docetaxel: RR 0.59, 95% CI 0.01 to 24.53 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Paclitaxel: RR 0.59, 95% CI 0.01 to 24.53 (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Vinorelbine: RR not estimable (1 cross-sectional study (Chauchat 2017); 83 hospitals, 460 surface samples).
- Multiple drugs (data on each drug were not available): RR 2.38, 95% CI 0.69 to 8.23 (1 cross-sectional study (Sottani 2012); 4 hospitals, 33 surface samples).

Quality of evidence: the quality of evidence is very low because of the serious risk of bias in all the studies (downgraded by one level); indirectness, as all the reported outcomes are surrogate outcomes (downgraded by one level); and imprecision, as the confidence intervals are wide (downgraded by one level).

Subgroup analysis: all the analyses stratified by the drug measured in the samples included either uncontrolled before-after studies or cross-sectional studies. Therefore, a subgroup analysis based on study design is not possible. The devices used in five studies varied (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau

2016; Roland 2017), while one study did not report it (Sottani 2012).

Sensitivity analysis: there is also no alteration in the interpretation of results using ICCs of 0.05, 0.01, or 0.00 (Analysis 3.4; Analysis 3.4; Analysis 3.5).

Quantity of contamination in surface samples from pharmacy areas

Seven studies (282 hospitals, 1793 surface samples) report the quantity of contamination with cyclophosphamide from surface samples in pharmacy areas (Berruyer 2015; Chauchat 2017; Guillemette 2014; Janes 2015; Poupeau 2016; Roland 2017; Siderov 2010). Five are cross-sectional studies involving 279 hospitals using various types of CSTD (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017), and two are uncontrolled before-after studies involving three hospitals using PhaSeal (Guillemette 2014; Siderov 2010). The amount of cyclophosphamide was lower in pharmacy areas between the CSTD group and the control group (MD -49.34 pg/cm², 95% CI -84.11 to -14.56 , $I^2 = 0\%$; Analysis 1.3). There is no alteration in the interpretation of results using the fixed-effect or the random-effects model.

In addition, one interrupted time-series study (3 hospitals; 342 samples) provides data on the quantity of contamination with cyclophosphamide from surface samples in pharmacy areas during three, three-week phases: initial phase of no CSTD, followed by CSTD, and then by no CSTD (Harrison 2006). Investigators took biweekly measurements in all three phases. Between the first two phases, the change in the slope between pre-CSTD and CSTD was 3.9439 pg/cm² (95% CI 1.2303 to 6.6576 ; $P = 0.01$). Between the second and third phases, the slope and level were expected to rise again, but the change in the slope between CSTD and post-CSTD withdrawal was -1.9331 pg/cm² (95% CI -5.126 to 1.2598 ; $P = 0.200$), and the level was 14.1670 pg/cm² (SD = 10.6190).

Six studies (280 hospitals, 1749 surface samples) report the quantity of contamination with ifosfamide and methotrexate from surface samples in pharmacy areas (Berruyer 2015; Chauchat 2017; Guillemette 2014; Janes 2015; Poupeau 2016; Roland 2017). Five studies are cross-sectional studies involving 279 hospitals using various types of CSTD (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017), and one study is an uncontrolled before-after study involving one hospital using PhaSeal (Guillemette 2014). There is no evidence of difference in the amount of ifosfamide and methotrexate in pharmacy areas between the CSTD group and the control group (MD -0.32 pg/cm², 95% CI -6.58 to 5.94 , $I^2 = 11\%$ and MD -3.09 pg/cm², 95% CI -13.80 to 7.61 , $I^2 = 0\%$, respectively; Analysis 1.3). There is no alteration in the interpretation of results using the fixed-effect or the random-effects model.

Two studies (84 hospitals, 542 surface samples) report the quantity of contamination with 5-fluorouracil (Chauchat 2017; Forges

2011). Both are cross-sectional studies. One study used variable CSTD (Chauchat 2017), and another used Spike Swan (Forges 2011). There is no evidence of difference in the amount of 5-fluorouracil in pharmacy areas between the CSTD group and the control group (MD 257.87 pg/cm², 95% CI -459.65 to 975.38). One study (83 hospitals, 493 surface samples) reports the quantity of contamination with 5-fluorouracil, cytarabine, gemcitabine, and irinotecan from surface samples in pharmacy areas (Chauchat 2017). This is a cross-sectional study involving 83 hospitals using various types of CSTD (Chauchat 2017). There is no evidence of difference in the amount of 5-fluorouracil, cytarabine, gemcitabine, and irinotecan in pharmacy areas between the CSTD group and the control group (5-fluorouracil: MD 256.00 pg/cm², 95% CI -461.56 to 973.56 ; cytarabine: MD -0.60 pg/cm², 95% CI -15.67 to 14.47 ; gemcitabine: MD -32.70 pg/cm², 95% CI -102.43 to 37.03 ; and irinotecan: MD -18.27 pg/cm², 95% CI -56.89 to 20.35 ; Analysis 1.3).

Quality of evidence: the quality of evidence is very low because of the serious risk of bias in all the studies (downgraded by one level); indirectness, as all the reported outcomes are surrogate outcomes (downgraded by one level); and imprecision, as the confidence intervals are wide (downgraded by one level) or there is no evidence that the observed difference led to decreased exposure or tangible health benefits (downgraded by one level).

Subgroup analysis: there is no evidence of subgroup differences based on study design for the drugs for which we could perform subgroup analyses (Analysis 2.7; Analysis 2.8; Analysis 2.9). Two studies used PhaSeal (Guillemette 2014; Siderov 2010), while one study used Spike Swan (Forges 2011). We could not perform tests for subgroup differences as there is no comparison using two different types of CSTD. Only one study reports the use of a single type of CSTD (PhaSeal) before measuring ifosfamide and methotrexate in pharmacy areas. There is no evidence of difference in the amount of ifosfamide and methotrexate between PhaSeal and control groups (ifosfamide: MD -2.59 pg/cm², 95% CI -26.75 to 21.57 ; and methotrexate: MD 10.34 pg/cm², 95% CI -34.01 to 54.69 ; Guillemette 2014; Analysis 2.10). All the studies that measured the quantity of contamination in patient-care areas used varied CSTDs, so we could not perform a subgroup analysis based on device.

Sensitivity analysis: there is also no alteration in the interpretation of results using ICCs of 0.05, 0.01, and 0.00 (Analysis 3.7; Analysis 3.8; Analysis 3.9).

Quantity of contamination in surface samples from patient-care areas

Five studies (279 hospitals, 1535 surface samples) report the quantity of contamination from surface samples in different drugs (cyclophosphamide, ifosfamide, and methotrexate) in patient-care areas (Berruyer 2015; Chauchat 2017; Janes 2015; Poupeau 2016; Roland 2017). All studies have a cross-sectional design and used

various types of CSTD. There is no evidence of difference in the amount of cyclophosphamide, ifosfamide, and methotrexate in patient-care areas between CSTD group and the control group (cyclophosphamide: MD -13.34 pg/cm², 95% CI -36.01 to 9.32 , $I^2 = 0\%$; ifosfamide: MD 3.59 pg/cm², 95% CI -3.45 to 10.63 , $I^2 = 0\%$; and methotrexate: MD 0.10 pg/cm², 95% CI -0.57 to 0.78 , $I^2 = 0\%$) (Analysis 1.3).

One cross-sectional study (83 hospitals, 460 surface samples) using various types of CSTD reports the quantity of contamination with 5-fluorouracil, cytarabine, gemcitabine, and irinotecan from surface samples in patient-care areas (Chauchat 2017). There is no evidence of difference in the amount of 5-fluorouracil, cytarabine, gemcitabine, and irinotecan in patient-care areas between CSTD group and the control group (5-fluorouracil: MD -43.90 pg/cm², 95% CI -141.51 to 53.71 ; cytarabine: MD -0.20 pg/cm², 95% CI -0.79 to 0.39 ; gemcitabine: MD 0.47 pg/cm², 95% CI -1.77 to 2.71 ; and irinotecan: MD -0.05 pg/cm², 95% CI -0.15 to 0.05 ; Analysis 1.3).

Quality of evidence: the quality of evidence is very low because of the serious risk of bias in all the studies (downgraded by one level); indirectness, as all the outcomes reported are surrogate outcomes (downgraded by one level); and imprecision, as the confidence intervals are wide (downgraded by one level). In addition, there is evidence of publication bias for the quantity of cyclophosphamide in patient areas (downgraded by one level).

Subgroup analysis: all studies used various types of CSTD.

Sensitivity analysis: there is also no alteration in the interpretation of results using ICCs of 0.05, 0.01, and 0.00 (Analysis 3.7; Analysis 3.8; Analysis 3.9).

Atmospheric contamination

None of the studies report atmospheric contamination.

Short-term health outcomes

None of the studies report short-term health outcomes such as skin rashes.

Medium-term health outcomes

None of the studies report medium-term health outcomes such as reproductive health effects (infertility or miscarriage).

Long-term health outcomes

None of the studies report long-term health outcomes such as development of any type of cancer.

Secondary outcomes

Adverse events

None of the studies report adverse events.

Potential cost savings due to reuse of multi-dose vials

Five studies report on cost savings for drugs or the devices used for administration or both (Chan 2016; Edwards 2013; Juhasz 2016; Mullot 2008; Ozyaman 2016). None of the studies included personnel costs (i.e. the time spent by healthcare professionals on preparation or administration) while calculating the overall costs. Four studies are uncontrolled before-after studies conducted in a single hospital (Chan 2016; Edwards 2013; Mullot 2008; Ozyaman 2016), and one is an uncontrolled before-after study conducted in two hospitals (Juhasz 2016). Only three studies included the costs of CSTD in the calculation of cost differences (Chan 2016; Edwards 2013; Mullot 2008). The remaining two studies did not (Juhasz 2016; Ozyaman 2016). The cost savings due to CSTD are based on the potential of CSTD to maintain drug sterility for a longer period of time. However, only one study included the costs based on actual drug consumption (Mullot 2008); since this study also included the costs of CSTD, these cost savings are actual cost savings. Two studies calculated the actual drugs costs in CSTD group but calculated the potential cost savings based on the number of drug vials that would have been used if CSTD were not used (Chan 2016; Edwards 2013). The remaining two studies simulated cost savings based on the drug remaining in the vials (Juhasz 2016; Ozyaman 2016). Sufficient data for meta-analysis were available for only one study (Chan 2016). For these two reasons (variability in the calculation of costs and the lack of sufficient data to perform the meta-analysis), we have tabulated the data in Table 1, where we report the annual cost savings both as originally reported and after conversion to 2017 USD using the PPP conversion rates and GDP deflators reported in the October 2017 version of the World Economic Outlook Database.

As noted in Table 1, there is significant variability between the studies in terms of whether the use of CSTD results in cost savings (the point estimates of the average potential cost savings range between (2017) USD $-642,656$ and (2017) USD $+221,818$). Therefore, we cannot reach any conclusion on whether the use of CSTD in general or a particular type of CSTD results in cost savings. However, the study that reported actual cost savings reported higher costs in the CSTD group than the control group (Mullot 2008). The quality of evidence is very low for this outcome because of the serious risk of bias in all the studies (downgraded by one level) and the significant variability of the results between the studies both in magnitude and direction (downgraded by two levels).

Subgroup analysis

We will perform the following subgroup analyses given sufficient data in future updates of this review; the reasons for not performing these in this review are stated below.

- Study design (CBA studies versus other non-randomised study designs): there are no CBA studies.
- Study design (individual versus cluster unit of analysis): all studies are cluster studies.
- Professional role (pharmacy technician versus chemotherapy nurse versus other healthcare staff): no separate data were reported for different professional roles in the two studies that included nurses.
- Duration of possible exposure: the range of exposure to

hazardous drugs is from two weeks to seven months in the studies that reported the presence of hazardous drugs in urine and the duration of exposure. Thus, all the studies included participants who had short-term exposure to hazardous drugs and short-term follow-up.

- Control (safe handling following UK HSE standards): none of the studies took place in the UK, and none of the studies report whether they followed UK HSE standards.

Reporting bias

There was is evidence of reporting bias or small study effects for the following outcomes measured in at least five studies either by visualisation or by Egger's test ([Figure 3](#); [Figure 4](#)).

Figure 3. Funnel plot of comparison: I Closed-system transfer device plus safe handling versus safe handling alone, outcome: I.2 Proportion of surfaces contaminated.

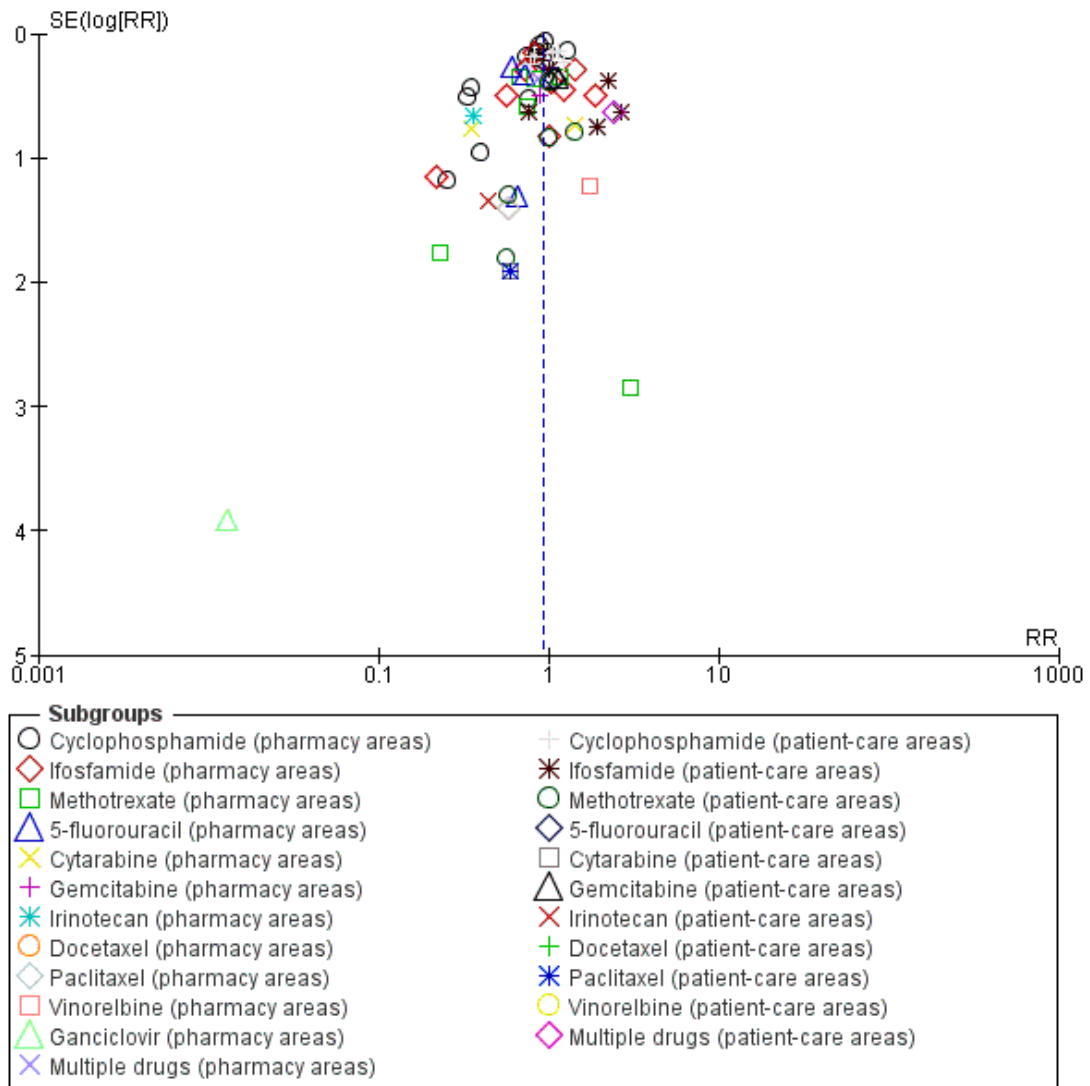
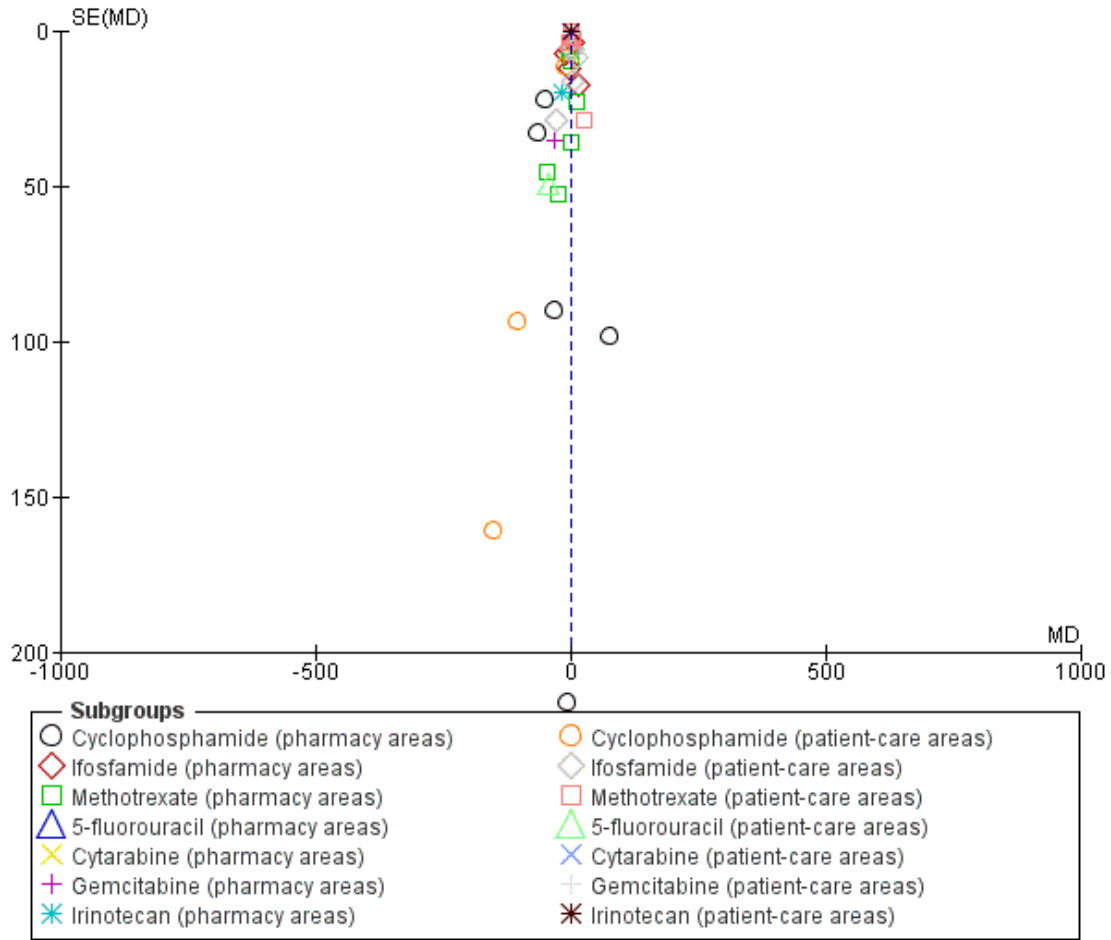


Figure 4. Funnel plot of comparison: I Closed-system transfer device plus safe handling versus safe handling alone, outcome: I.3 Quantity of surface contamination (pg/cm²).



- Proportion of surfaces contaminated
 - Ifosfamide (pharmacy areas): P = 0.929
 - Methotrexate (pharmacy areas): P = 0.768
 - Cyclophosphamide (patient-care areas): P = 0.454
 - Ifosfamide (patient-care areas): P = 0.582
 - Methotrexate (patient-care areas): P = 0.438
- Quantity of surface contamination
 - Cyclophosphamide (pharmacy areas): P = 0.662
 - Ifosfamide (pharmacy areas): P = 0.509
 - Methotrexate (pharmacy areas): P = 0.479

- Ifosfamide (patient-care areas): P = 0.391
- Methotrexate (patient-care areas): P = 0.956

The only exceptions for this are for differences in the proportion of surfaces contaminated with cyclophosphamide and quantity of cyclophosphamide in patient-care areas, which are statistically significant (P = 0.026 and P = 0.002). This is because the point estimate of the difference between CSTD and control group is less in the studies with the least standard error (i.e. the studies that contributed more to the analysis) compared to the other studies

(which contributed less to the meta-analysis), indicating potential small-study effects.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Closed-system transfer device safe handling versus safe handling alone for reducing healthcare staff exposure to infusional hazardous drugs: clinical outcomes					
Patient or population: healthcare staff who handle infusional hazardous drugs Settings: hospitals Intervention: closed-system transfer device plus safe handling Control: safe handling alone					
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of hospitals (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Safe handling alone	Closed-system transfer device plus safe handling			
Health outcomes	None of the studies report health outcomes such as skin rashes, reproductive health effects (infertility or miscarriage), or development of any type of cancer				
Adverse events	None of the studies report this outcome.				
Potential cost savings	The studies used different methods of calculating the costs and reported results in formats that could not be pooled via meta-analysis. There is significant variability between the studies in terms of whether the use of CSTD results in cost savings (the point estimates of the average potential cost savings ranged between (2017) US D−642,656 and (2017) USD +221,818*		6 hospitals (5 studies)	⊕○○○ Very low ^{a,b}	

*Negative sign indicates cost savings and positive sign indicate increased costs due to the use of closed-system transfer device

CI: confidence interval; **CSTD**: closed-system transfer device.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aThe studies are at serious risk of bias (downgraded one level for risk of bias).

^bThere is very serious inconsistency in magnitude and direction of effect (downgraded two levels for inconsistency).

DISCUSSION

Summary of main results

In this systematic review, we included 23 observational studies comparing CSTD plus safe handling versus safe handling alone. There are no randomised controlled trials on this topic. Twenty-one studies report one or more outcomes for this review. However, the only outcomes reported in these 21 studies are exposure, surface contamination, and potential cost savings. None of the studies report important health outcomes relevant for healthcare staff exposed to infusional hazard drugs such as reduction in skin rashes, infertility, miscarriage, or the development of any type of cancer.

In terms of exposure, there is no evidence of differences between CSTD plus safe handling versus safe handling alone. Decreased exposure, as defined by the presence of one or more hazardous drugs within the body (established via e.g. urine testing) or in the immediate vicinity (established via surface sampling), can result in health benefits as exposure to hazardous drugs is associated with development of cancer, decreased fertility, congenital abnormalities, miscarriages, stillbirths, and low birthweight (Connor 2014; HSE 2017; NIOSH 2004).

There is evidence of a reduction in the proportion of samples that were contaminated with 5-fluorouracil and in the quantity of cyclophosphamide contamination in the CSTD plus safe handling group versus safe handling alone in pharmacy areas. There is no evidence of differences for any of the other drugs in proportion of surfaces contaminated or quantity of surface contamination in pharmacy areas. Nor is there evidence of differences in the proportion of surfaces contaminated or the quantity of surface contamination in patient areas.

With regards to cyclophosphamide, the surface contamination in pharmacy areas is about 50 pg/cm² less in the intervention group than in the control. There are multiple issues with this small difference. Firstly, the reduction compared to the baseline levels reported in the studies is very small. Secondly, the difference in quantity of contamination was found only for one drug in the pharmacy area (and did not extend to patient-care areas or other drugs), that is, the healthcare staff are still exposed to cyclophosphamide in other areas and other hazardous drugs in pharmacy and patient-care areas. Moreover, by design, CSTDs do not protect healthcare staff from hazardous orally administered drugs. Therefore, the healthcare staff may be exposed to hazardous oral drugs, which can lead to the same ill effects of infusional hazardous drugs. However, hazardous oral drugs were not typically reported in the studies comparing CSTD plus safe handling versus safe handling alone, making it difficult to assess the potential effect of reducing some specific infusional hazardous drugs. Because of the many hazardous drugs to which healthcare professionals are exposed, any assessment of surface contamination and exposure by measuring a limited number of hazardous drugs can only be an estimation of the overall exposure (Connor 2006). A correlation between two outcomes does

not make one outcome a good surrogate of another (Bucher 1999; Fleming 1996; Kim 2015; Prentice 1989; Rupp 2017a; Yudkin 2011). A reduction in the surface contamination by CSTD should result in decreased exposure or increased health benefits for it to be called a good surrogate outcome. To summarise, the importance of this small reduction in cyclophosphamide in terms of reducing overall exposure and improving health benefits is not known.

With regards to 5-fluorouracil, there is no evidence of reduction in quantity of 5-fluorouracil despite a reduction in the proportion of surfaces contaminated with 5-fluorouracil. There are several possible explanations for this. One possibility is that there was insufficient power to detect a reduction in quantity of 5-fluorouracil. Even if this were the case (and there was an actual reduction in 5-fluorouracil), the same issues arise that did for a reduction in cyclophosphamide: does this reduction decrease overall exposure or does it lead to health benefits. A second possibility is that despite a reduction in the surfaces contaminated with 5-fluorouracil, the overall quantity of contamination with 5-fluorouracil is the same. A third possibility is that the differences may be due to different studies included under the outcome, which may reflect selective outcome reporting, which may in turn indicate that there is actually no reduction in the quantity of 5-fluorouracil. In the second and third possibilities, it is unknown whether reducing the proportion of surfaces contaminated with 5-fluorouracil without reducing its overall quantity leads to a decrease in overall exposure or to an improvement in health.

All things considered, there is substantial uncertainty in whether the addition of CSTD to safe handling practices decreases exposure or has any reduction in exposure or provides health benefits in healthcare staff using infusional hazardous drugs.

There is significant variability in the potential cost savings. The way that the cost savings were calculated varied significantly between the studies. A meta-analysis is not possible because of the variability in the methods used in calculating potential cost savings and the lack of sufficient information to perform the meta-analysis. Only one study includes the costs based on actual drug consumption and costs of CSTD (Mullor 2008). This study reports higher costs. The other studies simulated cost savings, which is likely to overestimate them. None of the studies include personnel costs (costs involved in preparing the drugs and administration of the drugs) when evaluating the cost savings. Overall, there is great uncertainty in whether CSTD saves any money. Future studies should include the total actual drug costs (based on actual drug consumption rather than potential drug consumption), CSTD costs, and personnel costs (costs involved in preparing the drugs and administration of the drugs).

Based on the above observations, there is currently no evidence to recommend the routine use of CSTD in addition to safe handling of infusional hazardous drugs, either to attain decreased exposure, health benefits, or financial benefits.

Overall completeness and applicability of evidence

Although we did not restrict the inclusion of studies based on the hospital size, all the studies that provide information on the size of the hospitals included only hospitals with at least 50 beds. Therefore, the evidence is applicable only to such hospitals. Most of the information for this review comes from pharmacy areas; therefore the evidence is applicable only for these areas. However, patient-care areas are equally important, as healthcare staff are also exposed to residual hazardous drugs in these settings. Again, if studies use surrogate measures such as surface contamination to estimate the potential health benefit of CSTD, they should measure surface contamination in patient-care areas in order to provide a reasonable estimate of the health benefits of using CSTD. The healthcare professionals in the studies that provide data were mostly pharmacists or pharmacy technicians. Therefore, the evidence is mainly applicable for pharmacists and pharmacy technicians. Most of the studies that provide information for this review evaluated the use of PhaSeal; therefore the findings are mostly applicable to PhaSeal.

Quality of the evidence

The overall quality of evidence is very low. The major reasons for this are as follows.

Risk of bias: all the studies are at serious risk of bias. The main reasons for this are the use of co-interventions (for example, additional training of staff in CSTD without the control group receiving the same amount of training in safe handling) and lack of blinded measurement of outcomes. None of the studies report using an independent person (blinded to the groups) for obtaining surface samples. In addition, we assigned a 'no information' label for confounding bias on all the studies due to inadequate information regarding details such as the surfaces being clean prior to the start of the exposure. This is a particularly important problem with uncontrolled before-after studies since standard cleaning techniques may not be sufficient to get rid of the surface contamination, which might mean that the surfaces might have had several years of exposure to contamination in the 'safe handling alone' group, while those in the 'CSTD group plus safe handling' group are exposed to only a short period of exposure to contamination (a few months typically) because of thorough cleaning prior to start of CSTD. Even when the exposure outcome was measured objectively, such as with a urine test where the levels can be measured using automated equipment, we found the risk of bias to be serious.

Future studies should try to address these issues by using appropriate study designs that ensure that the only difference between CSTD and control is the use of CSTD, and that an independent person (blinded to the groups) obtains surface samples. Another major issue is selective reporting bias, as in many instances study authors did not report their results fully. While we acknowledge

that it is not mandatory to register observational studies, future studies should publish a protocol prior to conducting the study and report all the results so that it is clear that results are not reported based on the observations.

Inconsistency: there is no evidence of inconsistency in the results for exposure; however, there is major inconsistency in the methodology and results of potential cost savings by CSTD. In particular, we noted major differences in the results between studies that used actual cost savings and simulated cost savings. Future studies should report the actual cost savings rather than simulated cost savings.

Indirectness of evidence: because of the many hazardous drugs to which healthcare professionals are exposed, any assessment of exposure by measuring a limited number of hazardous drugs can only be an estimation of the overall exposure (Connor 2006). In addition, surface contamination can be considered a surrogate for exposure since there is an association between the two variables (Connor 2006).

Imprecision: as shown in the sample size calculations below, the sample size included in this review is too small to detect a difference in urinary exposure. In the absence of information on how much difference in proportion of samples contaminated or in quantity of contamination is clinically beneficial, it was not easy to assess whether the overall sample size was sufficient to detect differences between CSTD and control for surface contamination.

Publication bias: visualisation of funnel plots and Egger's test did not reveal any publication bias for most of the outcomes in which at least five studies were included. Registration of studies prior to conducting them allows better assessment of both selective reporting and publication bias.

Potential biases in the review process

We followed the protocol we formulated before we started conducting this Cochrane systematic review (Gurusamy 2017). The only major deviation is the sensitivity analysis using different intracluster correlation coefficients (ICCs). However, we performed this only to assess the reason for the differences in the conclusions reached by us and a number the study authors; in particular, we did not use these post hoc sensitivity analyses to make any inferences about the effect of CSTD.

While we have minimised the errors in study selection and data extraction by independent, duplicate performance of these processes, we may have missed studies that do not mention CSTD in the title or abstract. It is impractical to review the full text of all references (we identified 7321 unique references using our search strategy). In this regard, we followed our protocol of screening the title and abstract and obtaining full texts for references considered relevant based on the full text. Besides, these studies (which do not mention CSTD in the title or abstract) are likely to show no evidence of benefit of CSTD (the probable reason for not men-

tioning CSTD in the title or abstract); therefore, our conclusions are unlikely to change.

None of the studies reported an ICC. Therefore, we used the value of 0.10 decided a priori based on studies about implementation research (Campbell 2001). The results were robust in a sensitivity analysis using 0.05 for the ICC (i.e. half the correlation noted in similar studies) for most analyses; therefore, our conclusions would probably not change even if the studies had reported the intracluster correlation. However, we recommend that study authors report intracluster correlations in the future to enable accurate estimation of their results.

Agreements and disagreements with other studies or reviews

This is the first systematic review on the topic. We disagree with the study authors who concluded that routine CSTD use is beneficial (Edwards 2013; Hama 2012; Juhasz 2016; Miyake 2013; Ozyaman 2016; Sessink 2011; Sessink 2013; Siderov 2010; Simon 2016; Wick 2003; Yoshida 2011). Ignoring the design effect by not adjusting the effect estimates for intracluster correlation can lead to an underestimation of random errors (Killip 2004); consequently this could lead to erroneous conclusions. Ignoring the design effect by the study authors, the risk of bias in the studies, and the excessive importance given to unvalidated surrogate outcomes by the study authors are the major differences in the conclusions between this systematic review and the primary research studies. We also disagree with any guidelines or recommendations that CSTD should be used routinely whenever possible (HSE 2017; NIOSH 2004; USP 2017), for the same reasons we disagree with the study authors who concluded that routine CSTD use is beneficial.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence to support or refute the routine use of closed-system drug-transfer devices in addition to safe handling of infusional hazardous drugs, as there is currently no evidence of differences in exposure or financial benefits between CSTD plus safe handling versus safe handling alone (very low-quality evidence). None of the studies report health benefits.

Implications for research

Future studies should be designed in such a way as to decrease the risk of bias.

Study design

Well-designed multicentre randomised controlled trials may be feasible if the exposure, as measured by urine samples, is high (please see sample size calculations below). The next best study design is interrupted time-series, which is likely to provide a better estimate than uncontrolled before-after studies or cross-sectional studies. In all types of study designs, investigators should take steps to ensure that there are no other differences between CSTD and control groups, so that they can obtain a reasonable estimate of decrease in exposure and the health benefits of using CSTD. This includes measures such as proper cleaning of the surfaces prior to exposure of both the intervention and control groups (i.e. all surfaces should be cleaned and samples taken to ensure that they are clean, followed by exposure to an equivalent period of time in the safe handling alone group as in the CSTD plus safe handling group), so that there is no residual contamination. Likewise, staff in both groups should receive an equal period of training for CSTD plus safe handling and safe handling alone of infusional hazardous drugs. This will ensure that the effect observed is the true effect due to CSTD. Other information of interest includes the annual drug use within the centre, description of the tasks performed by the staff, and the safe handling practices used, so that it is possible to estimate the effect of CSTD in different situations. Studies should register their protocol prospectively, for example in journal publications, ClinicalTrials.gov, or scientific repositories such as zenodo.org.

Population

Staff exposed to infusional hazardous drugs.

Study arms

Intervention: CSTD plus safe handling.

Control: safe handling alone or other measures such as central priming of intravenous tubes, cleaning of vials, cleaning of surfaces, management of patient excreta and storage in addition to safe handling (multi-arm randomised controlled trials or factorial trial design).

Outcomes

Primary outcome: exposure to an appropriate selection of hazardous drugs used in the hospitals.

Secondary outcomes: health benefits and cost-effectiveness.

In the future, studies using exposure as an outcome should measure exposure to a relevant selection of hazardous drugs in order to provide a reasonable estimate of the health benefits of using CSTD. Surface contamination should be considered less important than exposure. This is because the staff are exposed to other unmeasured hazardous drugs and contamination in patient-care areas. Using surface contamination as the primary outcome has the potential to lead to complacency in handling drugs.

Sample size calculations

The baseline risk of cancers in people exposed to hazardous drugs is 0.3% (Ratner 2010). Using an alpha error of 5%, power of 80%, and a relative risk reduction of 20%, the unadjusted sample size required is 234,830. Using an ICC of 0.10 and the median cluster size of 13 observed in the studies that report on exposure, the sample size adjusted for clustering is 516,626.

The baseline risk of congenital anomalies in women who were exposed to hazardous drugs is 0.1% to 6.0% (Connor 2014). Using the median baseline risk of congenital anomalies and the same parameters as for the previous sample size calculation, the unadjusted sample size required is 30,078 and the adjusted sample size is 66,172.

The risk of stillbirths, miscarriages, and tubal pregnancies in women exposed to hazardous drugs is 0.1% to 25.9%, depending on the methods used to calculate the risk (Connor 2014). This results in an unadjusted sample size of 31,474 and an adjusted sample size of 69,243 using the median baseline risk of 2.2% and the same parameters of above.

The true incidence of acute ill health effects due to exposure to infusion hazardous drugs is not known. Using an estimate of 5% of people using safe handling practices with the remaining parameters remaining the same as above, an unadjusted sample size of 13,492 and adjusted sample size of 29,682 is required.

None of these outcomes can be explored in randomised controlled settings because these sample sizes are impractical, even if the ICC were much smaller than 0.10. About 77% of people using safe

handling alone had hazardous drugs in their urine, based on the median baseline risk in the studies included in this systematic review. Using a relative risk reduction of 44% (median risk reduction in the three studies in which one or more people in the safe handling group had hazardous drugs in the urine), an alpha error of 5%, power of 80%, an ICC of 0.10, and a cluster size of 13, the unadjusted sample size required is 66 and the adjusted sample size is 145. This can be achieved, but requires multicentre studies. However, other studies have indicated that none of the healthcare staff had positive urine samples (Poupeau 2017; Sottani 2012), which may reflect high quality safety handling practices or differences in methodology used to collect urine (spot urine sample versus 24-hour urine sample). If the rates of urinary exposure are low, then it will be difficult to conduct a randomised controlled trial, and interrupted time-series may be a good alternative.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Berruyer 2015

Methods	Cross-sectional study; cluster study	
Participants	Country: Canada Number of clusters: 36 Number excluded: 1 (2.8%) Reason for exclusion: one hospital did not provide reply to the CSTD status Number included: 35 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and methotrexate Professional role: pharmacy technician/pharmacist Size of the hospitals/wards: at least 50 beds	
Interventions	Group 1: CSTD + standard care (variable) (N = 7) Group 2: standard care (variable including removal of outer packaging and cleaned vials after receipt in some hospitals) (N = 28)	
Outcomes	Outcomes reported: surface contamination	
Notes	Authors provided additional information.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres may have done so based on their pharmacological practices
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Unclear risk	Risk of bias: no information Comment: insufficient information to judge whether there was bias due to missing data (i.e. the

Berruyer 2015 (Continued)

		hospital which did not reply about CSTD status may have done so because of the intervention or the outcome)
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported

Chan 2016

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: Malaysia Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: not measured Professional role: pharmacists or pharmacy technicians Size of the hospitals/wards: 852 beds
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: Standard care (not stated) (N = 1)
Outcomes	Outcomes reported: potential cost savings
Notes	Authors provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined

Chan 2016 (Continued)

Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were probably included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: actual savings based on the reuse of the drug were not reported despite being probably collected

Chauchat 2017

Methods	Cross-sectional study; cluster study	
Participants	Country: Canada Number of clusters: 83 Number excluded: 0 (0%) Number included: 83 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, methotrexate, 5-fluorouracil, cytarabine, gemcitabine, irinotecan, and other drugs Professional role: pharmacy technician/pharmacist Size of the hospitals/wards: > 50 beds	
Interventions	Group 1: CSTD + standard care (variable) (N = 31) Group 2: standard care (not stated) (N = 52)	
Outcomes	Outcomes reported: surface contamination	
Notes	Unpublished data	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups

Chauchat 2017 (Continued)

Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres may have done so based on their pharmacological practices
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: results were not reported fully

Edwards 2013

Methods	Uncontrolled before-after cohort study; cluster study	
Participants	Country: USA Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: not measured Professional role: pharmacy (not clear whether pharmacist or pharmacy technician) Size of the hospitals/wards: 335 beds	
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (not stated) (N = 1)	
Outcomes	Outcomes reported: potential cost savings	
Notes	Authors provided additional information.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Edwards 2013 (Continued)

Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were probably included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: actual savings based on the reuse of the drug were not reported despite being probably collected

Forges 2011

Methods	Cross-sectional study; cluster study
Participants	Country: France Number of clusters: 2 Number excluded: not stated Number included: 2 Chemotherapy agents tested for contamination: 5-fluorouracil Professional role: pharmacy technician Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (Spike Swan) (N = 1) Group 2: standard care (isolators, gloves, and daily washing) (N = 1)
Outcomes	Outcomes reported: surface contamination

Forges 2011 (Continued)

Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the isolators were all in the same centre and some preparations were made with CSTD while others were not made with CSTD
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: only the intervention group received additional training and supervision
Bias due to missing data	Unclear risk	Risk of bias: no information Comment: insufficient information to judge whether there was bias due to missing data
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	Low risk	Risk of bias: low Comment: the authors appear to have reported all the results

Guillemette 2014

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: Canada Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and methotrexate Professional role: pharmacy technician Size of the hospitals/wards: > 500 beds

Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (biological safety cabinets) (N = 1)	
Outcomes	Outcomes reported: surface contamination	
Notes	Authors provided additional information	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	High risk	Risk of bias: serious Comment: although the research was performed in the same centre, different sites were chosen for sampling from the intervention and control
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: the technicians received additional training prior to the intervention
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported

Hama 2012

Methods	Uncontrolled before-after cohort study; cluster study	
Participants	Country: Japan Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: cyclophosphamide Professional role: pharmacists Size of the hospitals/wards: > 150 patients per day	
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (personal protective equipment) (N = 1)	
Outcomes	None of the outcomes of interest were reported.	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Unclear risk	Risk of bias: no information Comment: insufficient information to judge whether there was bias due to missing data
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups

Hama 2012 (Continued)

Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported, but even these were not reported in a format from which inferences could be made
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Harrison 2006

Methods	interrupted time-series; cluster study
Participants	Country: USA Number of clusters: 6 Number excluded: 0 (0%) Number included: 6 Chemotherapy agents tested for contamination: cyclophosphamide, fluorouracil Professional role: pharmacists Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 3) Group 2: standard care (biological safety cabinets, latex rubber chemoprotective gloves, disposable gowns, and aseptic and negative-pressure mixing techniques) (N = 3)
Outcomes	Outcomes reported: surface contamination
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups

Harrison 2006 (Continued)

Bias due to missing data	Unclear risk	Risk of bias: no information Comment: insufficient information to judge whether there was bias due to missing data
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: the authors have not reported the results fully and this seems to be dependent upon the results

Janes 2015

Methods	Cross-sectional study; cluster study
Participants	Country: Canada Number of clusters: 51 Number excluded: 2 (3.9%) Reason for exclusion: 2 hospitals did not provide reply to the CSTD status Number included: 49 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and methotrexate Professional role: pharmacy technician/pharmacist Size of the hospitals/wards: at least 50 beds
Interventions	Group 1: CSTD + standard care (variable) (N = 12) Group 2: standard care (variable including removal of outer packaging and cleaned vials after receipt in some hospitals) (N = 37)
Outcomes	Outcomes reported: surface contamination
Notes	Authors provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres may have done so based on their pharmacological practices

Janes 2015 (Continued)

Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Unclear risk	Risk of bias: no information Comment: insufficient information to judge whether there was bias due to missing data (i.e. the hospitals which did not reply about CSTD status may have done so because of the intervention or the outcome)
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported

Juhasz 2016

Methods	Uncontrolled before-after cohort study; cluster study	
Participants	Country: Hungary Number of clusters: 4 Number excluded: 0 (0%) Number included: 4 Chemotherapy agents tested for contamination: not measured Professional role: pharmacy (not clear whether pharmacist or pharmacy technician) Size of the hospitals/wards: 335 beds	
Interventions	Group 1: CSTD + standard care (Tevadaptor) (N = 2) Group 2: standard care (not stated) (N = 2)	
Outcomes	Outcomes reported: potential cost savings	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge

Juhasz 2016 (Continued)

		whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centres
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were probably included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: actual savings based on the reuse of the drug were not reported despite being probably collected

Miyake 2013

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: Japan Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: cyclophosphamide Professional role: pharmacist Size of the hospitals/wards: 655 beds
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (not stated) (N = 1)
Outcomes	Outcomes reported: exposure and surface contamination
Notes	-

Miyake 2013 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: the pharmacists received training prior to use of CSTD. No such training was provided in the control group
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	Low risk	Risk of bias: low Comment: all results seem to be reported

Mullot 2008

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: France Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: not measured Professional role: pharmacist, pharmacy technician, nurse Size of the hospitals/wards: not stated, but about 150 preparations per day
Interventions	Group 1: CSTD + standard care (PhaSeal/Tevadaptor) (N = 1) Group 2: standard care (hood with laminar flow, isolators, neoprene gloves, air intake with standard needles (no spike use)) (N = 1)

Mullot 2008 (Continued)

Outcomes	Outcomes reported: potential cost savings	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: the personnel received training prior to use of CSTD. No such training was provided in the control group
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were probably included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: results were not reported in a format that could be meta-analysed

Ozyaman 2016

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: Turkey Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: not measured

	Professional role: pharmacy (not clear whether pharmacist or pharmacy technician) Size of the hospitals/wards: not stated	
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (not stated) (N = 1)	
Outcomes	Outcomes reported: potential cost savings	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were probably included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: actual savings based on the reuse of the drug were not reported despite being probably collected

Poupeau 2016

Methods	Cross-sectional study; cluster study	
Participants	Country: Canada Number of clusters: 48 Number excluded: 2 (4.2%) Reason for exclusion: Two hospitals did not provide reply to the CSTD status Number included: 46 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and methotrexate Professional role: pharmacy technician/pharmacist Size of the hospitals/wards: at least 50 beds	
Interventions	Group 1: CSTD + standard care (variable) (N = 12) Group 2: standard care (variable including removal of outer packaging and cleaned vials after receipt in some hospitals) (N = 34)	
Outcomes	Outcomes reported: surface contamination	
Notes	Authors provided additional information	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres may have done so based on their pharmacological practices
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Unclear risk	Risk of bias: no information Comment: insufficient information to judge whether there was bias due to missing data (i.e. the hospitals which did not reply about CSTD status may have done so because of the intervention or the outcome)

Poupeau 2016 (Continued)

Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported

Roland 2017

Methods	Cross-sectional study; cluster study
Participants	Country: Canada Number of clusters: 66 Number excluded: 0 (0%) Number included: 66 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and methotrexate Professional role: pharmacy technician/pharmacist Size of the hospitals/wards: at least 50 beds
Interventions	Group 1: CSTD + standard care (variable) (N = 23) Group 2: standard care (variable including removal of outer packaging and cleaned vials after receipt in some hospitals) (N = 43)
Outcomes	Outcomes reported: surface contamination
Notes	Authors provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres may have done so based on their pharmacological practices
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups

Roland 2017 (Continued)

Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported

Sessink 2011

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: USA Number of clusters: 44 Number excluded: 0 (0%) Number included: 44 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and 5-fluorouracil Professional role: pharmacist Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 22) Group 2: standard care (class II BSCs, protective gloves, disposable gowns, and aseptic and negative-pressure mixing techniques using needle syringes) (N = 22)
Outcomes	Outcomes reported: surface contamination
Notes	Authors provided additional information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres were probably selected based on their pharmacological practices

Sessink 2011 (Continued)

Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported and none could be used for the systematic review

Sessink 2013

Methods	Uncontrolled before-after cohort study; cluster study	
Participants	Country: USA Number of clusters: 60 Number excluded: 0 (0%) Number included: 60 Chemotherapy agents tested for contamination: cyclophosphamide Professional role: pharmacist Size of the hospitals/wards: not stated	
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 30) Group 2: standard care (not stated) (N = 30)	
Outcomes	Outcomes reported: surface contamination	
Notes	Authors provided additional information.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge

Sessink 2013 (Continued)

		whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres were probably selected based on their pharmacological practices
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported and none could be used for the systematic review

Siderov 2010

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: Australia Number of clusters: 4 Number excluded: 0 (0%) Number included: 4 Chemotherapy agents tested for contamination: cyclophosphamide Professional role: pharmacist Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 2) Group 2: standard care (not stated) (N = 2)
Outcomes	Outcomes reported: surface contamination
Notes	-

Siderov 2010 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	Low risk	Risk of bias: low Comment: all results seem to be reported

Simon 2016

Methods	Cross-sectional study; cluster study
Participants	Country: France Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: cyclophosphamide; cytarabine; cytarabine; dacarbazine; doxorubicin; fluorouracil; ganciclovir; gemcitabine; ifosfamide; irinotecan Professional role: pharmacist Size of the hospitals/wards: not stated

Simon 2016 (Continued)

Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (isolators and personal protective equipment (gloves, sterile drapes, compresses)) (N = 1)	
Outcomes	Outcomes reported: surface contamination	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in 2 isolators in the same centre: in 1 isolator, CSTD was used; in the other it was not
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: the pharmacists received received training prior to use of CSTD. No such training was provided in the control group
Bias due to missing data	Low risk	Risk of bias: low Comment: almost all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: only selected results were reported and none could be used for the systematic review

Sottani 2012

Methods	Cross-sectional study; cluster study	
Participants	Country: Italy Number of clusters: 4 Number excluded: 0 (0%) Number included: 4 Chemotherapy agents tested for contamination: cyclophosphamide, ifosfamide, and gemcitabine Professional role: pharmacy technician Size of the hospitals/wards: not stated	
Interventions	Group 1: CSTD + standard care (not stated) (N = 3) Group 2: standard care (not stated) (N = 1)	
Outcomes	Outcomes reported: exposure and surface contamination	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres were probably selected based on their pharmacological practices
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups

Sottani 2012 (Continued)

Bias in selection of the reported result	Low risk	Risk of bias: low Comment: all results seem to be reported
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Wick 2003

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: USA Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: cyclophosphamide and ifosfamide Professional role: pharmacist, pharmacy technician, nurse Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (not stated) (N = 1)
Outcomes	Outcomes reported: exposure and surface contamination
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: the pharmacists/technicians/nurses received received training prior to use of CSTD. No such training was probably provided in the control group
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis

Wick 2003 (Continued)

Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	Low risk	Risk of bias: low Comment: all results seem to be reported

Yoshida 2009

Methods	Uncontrolled before-after cohort study; cluster study
Participants	Country: Japan Number of clusters: 2 Number excluded: 0 (0%) Number included: 2 Chemotherapy agents tested for contamination: cyclophosphamide Professional role: pharmacist Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (PhaSeal) (N = 1) Group 2: standard care (Biological safety cabinet and personal protection equipment) (N = 1)
Outcomes	Outcomes reported: exposure and surface contamination
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Low risk	Risk of bias: low Comment: the research was performed in the same centre
Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	High risk	Risk of bias: serious Comment: the pharmacists received received training prior to use of CSTD. No

Yoshida 2009 (Continued)

		such training was probably provided in the control group
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	Low risk	Risk of bias: low Comment: all results seem to be reported

Yoshida 2011

Methods	Cross-sectional study; cluster study
Participants	Country: Japan Number of clusters: 5 Number excluded: not stated Number included: 5 Chemotherapy agents tested for contamination: cyclophosphamide; 5-fluorouracil, gemcitabine, and platinum-containing drugs Professional role: pharmacist Size of the hospitals/wards: not stated
Interventions	Group 1: CSTD + standard care (not stated) (N = 3) Group 2: standard care (variable) (N = 2)
Outcomes	None of the outcomes of interest were reported.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding bias	Unclear risk	Risk of bias: no information Comment: no information to judge whether the confounding factors were balanced across groups
Selection bias	Unclear risk	Risk of bias: moderate Comment: the participating centres were probably selected based on their pharmacological practices

Yoshida 2011 (Continued)

Bias in classification of interventions	Low risk	Risk of bias: low Comment: the intervention and control were well defined
Bias due to deviations from intended interventions	Unclear risk	Risk of bias: no information Comment: no information to judge whether the co-interventions were similar across the groups
Bias due to missing data	Low risk	Risk of bias: low Comment: all samples were included in the analysis
Bias in measurement of outcomes	High risk	Risk of bias: serious Comment: the outcome assessors do not seem to be blinded to the groups
Bias in selection of the reported result	High risk	Risk of bias: serious Comment: the authors have not reported the results in a format from which inferences could be made

CSTD: closed-system transfer device.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amos 2012	Comparison of different CSTDs
Blazawski 2013	Simulation study
Chantry 2015	Simulation study
Clark 2013	Not a study comparing CSTD versus standard care
Connor 2010	Not a study comparing CSTD versus standard care
Contractor 2015	Not a study comparing CSTD versus standard care
Cox 2017	Not a study comparing CSTD versus standard care
De Ausen 2013	Simulation study

(Continued)

De Prijck 2008	Simulation study
DeFreitas 2012	Simulation study
Enciso-Zarate 2016	Not a study comparing CSTD versus standard care
Favier 2012	Simulation study
Fernandez 2013	Simulation study
Garrigue 2016	Simulation study
Gebel 2015	Simulation study
Gilles 2009	Not a study comparing CSTD versus standard care
Gomez-Alvarez 2016	Simulation study
Gonzalez-Haba Pena 2016	Simulation study
Hama 2011	Simulation study
Hong 2017	Not a study comparing CSTD versus standard care
Hospital Employee Health 2005	Not a primary research study
Hospital Infection Control 2005	Not a primary research study
Idell 2009	Not a study comparing CSTD versus standard care
Ikeno 2014	Simulation study
Jorgenson 2008	Simulation study
Kopp 2013	Not a study comparing CSTD versus standard care
Kunneva 2016	Not a primary research study
Kurihara 2017	Not a study comparing CSTD versus standard care
Laws 2016	Not a primary research study
Le Garlantezec 2011	Simulation study
Ledford 2010	Comparison of different CSTDs

(Continued)

Lennan 2017	Not a primary research study
Lin 2017	Simulation study
McDiarmid 2010	Intermittent use of CSTD (not possible to determine whether the outcomes are for CSTD or standard care)
McMichael 2011	Simulation study
Meade 2015	Not a primary research study
Nishigaki 2010	Simulation study
Nygren 2005	Not a study comparing CSTD versus standard care
Nygren 2008	Simulation study
Nyman 2007	Not a study comparing CSTD versus standard care
Odraska 2013	Not a study comparing CSTD versus standard care
Oncology Nurse Advisor 2017	Not a primary research study
Perlo 2015	Simulation study
Querua Lamerie 2012	Simulation study
Rupp 2017	Simulation study
Sanchez-Rubio Ferrandez 2012	Simulation study
Sanchez-Rubio Ferrandez 2012a	Simulation study
Sato 2010	Simulation study
Sessink 1999	Not a study comparing CSTD versus standard care
Simon 2010	Simulation study
Smith 2014	Simulation study
Talsmar 2015	Not a primary research study
Thomas Carey 2011	Simulation study
Tyler 2017	Not a study comparing CSTD versus standard care

(Continued)

Vyas 2016	Simulation study
Yoshida 2013	Not a study comparing CSTD versus standard care

CSTD: closed-system transfer device.

DATA AND ANALYSES

Comparison 1. Closed-system transfer device plus safe handling versus safe handling alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urine tests for exposure	4		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Cyclophosphamide	2		Risk Ratio (Random, 95% CI)	0.83 [0.46, 1.52]
1.2 Cyclophosphamide or ifosfamide	1		Risk Ratio (Random, 95% CI)	0.09 [0.00, 2.79]
1.3 Cyclophosphamide, ifosfamide, or gemcitabine	1		Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2 Proportion of surfaces contaminated	14		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 Cyclophosphamide (pharmacy areas)	13		Risk Ratio (Random, 95% CI)	0.89 [0.78, 1.01]
2.2 Ifosfamide (pharmacy areas)	9		Risk Ratio (Random, 95% CI)	0.94 [0.74, 1.19]
2.3 Methotrexate (pharmacy areas)	6		Risk Ratio (Random, 95% CI)	0.84 [0.58, 1.22]
2.4 5-fluorouracil (pharmacy areas)	3		Risk Ratio (Random, 95% CI)	0.65 [0.43, 0.97]
2.5 Cytarabine (pharmacy areas)	2		Risk Ratio (Random, 95% CI)	0.72 [0.18, 2.86]
2.6 Gemcitabine (pharmacy areas)	2		Risk Ratio (Random, 95% CI)	0.96 [0.60, 1.54]
2.7 Irinotecan (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	0.36 [0.10, 1.33]
2.8 Docetaxel (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2.9 Paclitaxel (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	0.57 [0.04, 9.06]
2.10 Vinorelbine (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	1.72 [0.16, 18.73]
2.11 Ganciclovir (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	0.01 [0.00, 27.11]
2.12 Multiple drugs (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	0.87 [0.43, 1.77]
2.13 Cyclophosphamide (patient-care areas)	5		Risk Ratio (Random, 95% CI)	1.01 [0.86, 1.18]
2.14 Ifosfamide (patient-care areas)	5		Risk Ratio (Random, 95% CI)	1.44 [0.91, 2.28]
2.15 Methotrexate (patient-care areas)	5		Risk Ratio (Random, 95% CI)	1.00 [0.55, 1.85]
2.16 5-fluorouracil (patient-care areas)	1		Risk Ratio (Random, 95% CI)	1.09 [0.53, 2.23]
2.17 Cytarabine (patient-care areas)	1		Risk Ratio (Random, 95% CI)	0.59 [0.01, 24.53]

2.18 Gemcitabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.13 [0.55, 2.33]
2.19 Irinotecan (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.44 [0.03, 6.15]
2.20 Docetaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.01, 24.53]
2.21 Paclitaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.01, 24.53]
2.22 Vinorelbine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2.23 Multiple drugs (patient-care areas)	1	Risk Ratio (Random, 95% CI)	2.38 [0.69, 8.23]
3 Quantity of surface contamination (pg/cm²)	8	Mean Difference (Random, 95% CI)	Subtotals only
3.1 Cyclophosphamide (pharmacy areas)	7	Mean Difference (Random, 95% CI)	-49.34 [-84.11, -14.56]
3.2 Ifosfamide (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-0.32 [-6.58, 5.94]
3.3 Methotrexate (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-3.09 [-13.80, 7.61]
3.4 5-fluorouracil (pharmacy areas)	2	Mean Difference (Random, 95% CI)	257.87 [-459.65, 975.38]
3.5 Cytarabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-0.6 [-15.67, 14.47]
3.6 Gemcitabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-32.7 [-102.43, 37.03]
3.7 Irinotecan (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-18.27 [-56.89, 20.35]
3.8 Cyclophosphamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	-13.34 [-36.01, 9.32]
3.9 Ifosfamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	3.59 [-3.45, 10.63]
3.10 Methotrexate (patient-care areas)	5	Mean Difference (Random, 95% CI)	0.10 [-0.57, 0.78]
3.11 5-fluorouracil (patient-care areas)	1	Mean Difference (Random, 95% CI)	-43.9 [-141.51, 53.71]
3.12 Cytarabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.20 [-0.79, 0.39]
3.13 Gemcitabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	0.47 [-1.77, 2.71]
3.14 Irinotecan (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.05 [-0.15, 0.05]

Comparison 2. Subgroup analysis (based on study design and device)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urine tests for exposure (PhaSeal only)	3		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Cyclophosphamide	2		Risk Ratio (Random, 95% CI)	0.83 [0.46, 1.52]
1.2 Cyclophosphamide or ifosfamide	1		Risk Ratio (Random, 95% CI)	0.09 [0.00, 2.79]
2 Proportion of surfaces contaminated with cyclophosphamide in pharmacy areas: stratified by study design	13		Risk Ratio (Random, 95% CI)	0.89 [0.78, 1.01]
2.1 Uncontrolled before-after studies	7		Risk Ratio (Random, 95% CI)	0.87 [0.76, 0.99]
2.2 Cross-sectional studies	6		Risk Ratio (Random, 95% CI)	0.92 [0.72, 1.19]
3 Proportion of surfaces contaminated with ifosfamide in pharmacy areas: stratified by study design	9		Risk Ratio (Random, 95% CI)	0.94 [0.74, 1.19]
3.1 Uncontrolled before-after studies	3		Risk Ratio (Random, 95% CI)	0.85 [0.64, 1.14]
3.2 Cross-sectional studies	6		Risk Ratio (Random, 95% CI)	1.00 [0.65, 1.53]
4 Proportion of surfaces contaminated with methotrexate in pharmacy areas: stratified by study design	6		Risk Ratio (Random, 95% CI)	0.84 [0.58, 1.22]
4.1 Uncontrolled before-after studies	1		Risk Ratio (Random, 95% CI)	3.00 [0.01, 777.04]
4.2 Cross-sectional studies	5		Risk Ratio (Random, 95% CI)	0.83 [0.57, 1.22]
5 Proportion of surfaces contaminated with 5-fluorouracil in pharmacy areas: stratified by study design	3		Risk Ratio (Random, 95% CI)	0.65 [0.43, 0.97]
5.1 Uncontrolled before-after studies	1		Risk Ratio (Random, 95% CI)	0.61 [0.36, 1.03]
5.2 Cross-sectional studies	2		Risk Ratio (Random, 95% CI)	0.71 [0.38, 1.34]
6 Proportion of surfaces contaminated (PhaSeal only)	8		Risk Ratio (Random, 95% CI)	Subtotals only
6.1 Cyclophosphamide (pharmacy areas)	8		Risk Ratio (Random, 95% CI)	0.88 [0.78, 0.99]
6.2 Ifosfamide (pharmacy areas)	4		Risk Ratio (Random, 95% CI)	0.84 [0.63, 1.11]
6.3 Methotrexate (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	3.00 [0.01, 777.04]
6.4 5-fluorouracil (pharmacy areas)	2		Risk Ratio (Random, 95% CI)	0.61 [0.36, 1.02]
6.5 Cytarabine (pharmacy areas)	1		Risk Ratio (Random, 95% CI)	0.35 [0.08, 1.58]

6.6 Gemcitabine (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.88 [0.33, 2.33]
6.7 Ganciclovir (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.01 [0.00, 27.11]
7 Quantity of surface contamination with cyclophosphamide in pharmacy areas (pg/cm ²): stratified by study design	7	Mean Difference (Random, 95% CI)	-49.34 [-84.11, -14.56]
7.1 Uncontrolled before-after studies	2	Mean Difference (Random, 95% CI)	-255.35 [-1144.66, 633.96]
7.2 Cross-sectional studies	5	Mean Difference (Random, 95% CI)	-49.02 [-83.82, -14.22]
8 Quantity of surface contamination with ifosfamide in pharmacy areas (pg/cm ²): stratified by study design	6	Mean Difference (Random, 95% CI)	-0.32 [-6.58, 5.94]
8.1 Uncontrolled before-after studies	1	Mean Difference (Random, 95% CI)	-2.59 [-26.75, 21.57]
8.2 Cross-sectional studies	5	Mean Difference (Random, 95% CI)	-0.78 [-8.58, 7.03]
9 Quantity of surface contamination with methotrexate in pharmacy areas (pg/cm ²): stratified by study design	6	Mean Difference (Random, 95% CI)	-3.09 [-13.80, 7.61]
9.1 Uncontrolled before-after studies	1	Mean Difference (Random, 95% CI)	10.34 [-34.01, 54.69]
9.2 Cross-sectional studies	5	Mean Difference (Random, 95% CI)	-3.92 [-14.96, 7.11]
10 Quantity of surface contamination (pg/cm ²): stratified by devices	3	Mean Difference (Random, 95% CI)	Subtotals only
10.1 Cyclophosphamide (pharmacy areas; PhaSeal)	2	Mean Difference (Random, 95% CI)	-255.35 [-1144.66, 633.96]
10.2 Ifosfamide (pharmacy areas; PhaSeal)	1	Mean Difference (Random, 95% CI)	-2.59 [-26.75, 21.57]
10.3 Methotrexate (pharmacy areas; PhaSeal)	1	Mean Difference (Random, 95% CI)	10.34 [-34.01, 54.69]
10.4 5-fluorouracil (pharmacy areas; SpikeSwan)	1	Mean Difference (Random, 95% CI)	14300.0 [-47951.46, 76551.46]

Comparison 3. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urine tests for exposure (ICC = 0.05)	4		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 Cyclophosphamide	2		Risk Ratio (Random, 95% CI)	0.82 [0.44, 1.52]

1.2 Cyclophosphamide or ifosfamide	1	Risk Ratio (Random, 95% CI)	0.09 [0.00, 1.99]
1.3 Cyclophosphamide, ifosfamide, or gemcitabine	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2 Urine tests for exposure (ICC = 0.01)	4	Risk Ratio (Random, 95% CI)	Subtotals only
2.1 Cyclophosphamide	2	Risk Ratio (Random, 95% CI)	0.81 [0.43, 1.51]
2.2 Cyclophosphamide or ifosfamide	1	Risk Ratio (Random, 95% CI)	0.09 [0.01, 1.48]
2.3 Cyclophosphamide, ifosfamide, or gemcitabine	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
3 Urine tests for exposure (ICC = 0.00)	4	Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Cyclophosphamide	2	Risk Ratio (Random, 95% CI)	0.81 [0.43, 1.51]
3.2 Cyclophosphamide or ifosfamide	1	Risk Ratio (Random, 95% CI)	0.09 [0.01, 1.36]
3.3 Cyclophosphamide, ifosfamide, or gemcitabine	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
4 Proportion of surfaces contaminated (ICC = 0.05)	14	Risk Ratio (Random, 95% CI)	Subtotals only
4.1 Cyclophosphamide (pharmacy areas)	13	Risk Ratio (Random, 95% CI)	0.87 [0.76, 0.99]
4.2 Ifosfamide (pharmacy areas)	9	Risk Ratio (Random, 95% CI)	0.94 [0.73, 1.23]
4.3 Methotrexate (pharmacy areas)	6	Risk Ratio (Random, 95% CI)	0.84 [0.60, 1.19]
4.4 5-fluorouracil (pharmacy areas)	3	Risk Ratio (Random, 95% CI)	0.65 [0.45, 0.94]
4.5 Cytarabine (pharmacy areas)	2	Risk Ratio (Random, 95% CI)	0.68 [0.17, 2.67]
4.6 Gemcitabine (pharmacy areas)	2	Risk Ratio (Random, 95% CI)	0.95 [0.64, 1.43]
4.7 Irinotecan (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.36 [0.11, 1.19]
4.8 Docetaxel (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
4.9 Paclitaxel (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.57 [0.05, 7.13]
4.10 Vinorelbine (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	1.72 [0.20, 15.25]
4.11 Ganciclovir (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.01 [0.00, 3.43]
4.12 Multiple drugs (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.87 [0.49, 1.53]
4.13 Cyclophosphamide (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.00 [0.86, 1.17]
4.14 Ifosfamide (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.46 [0.91, 2.34]
4.15 Methotrexate (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.01 [0.57, 1.76]

4.16 5-fluorouracil (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.09 [0.57, 2.10]
4.17 Cytarabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 18.10]
4.18 Gemcitabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.13 [0.58, 2.20]
4.19 Irinotecan (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.44 [0.04, 4.97]
4.20 Docetaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 18.10]
4.21 Paclitaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 18.10]
4.22 Vinorelbine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
4.23 Multiple drugs (patient-care areas)	1	Risk Ratio (Random, 95% CI)	2.38 [0.79, 7.17]
5 Proportion of surfaces contaminated (ICC = 0.01)	14	Risk Ratio (Random, 95% CI)	Subtotals only
5.1 Cyclophosphamide (pharmacy areas)	13	Risk Ratio (Random, 95% CI)	0.83 [0.73, 0.96]
5.2 Ifosfamide (pharmacy areas)	9	Risk Ratio (Random, 95% CI)	0.89 [0.66, 1.21]
5.3 Methotrexate (pharmacy areas)	6	Risk Ratio (Random, 95% CI)	0.85 [0.62, 1.16]
5.4 5-fluorouracil (pharmacy areas)	3	Risk Ratio (Random, 95% CI)	0.65 [0.47, 0.90]
5.5 Cytarabine (pharmacy areas)	2	Risk Ratio (Random, 95% CI)	0.64 [0.17, 2.51]
5.6 Gemcitabine (pharmacy areas)	2	Risk Ratio (Random, 95% CI)	0.93 [0.69, 1.24]
5.7 Irinotecan (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.36 [0.12, 1.08]
5.8 Docetaxel (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
5.9 Paclitaxel (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.57 [0.06, 5.79]
5.10 Vinorelbine (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	1.72 [0.23, 12.73]
5.11 Ganciclovir (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.01 [0.00, 0.27]
5.12 Multiple drugs (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.87 [0.57, 1.32]
5.13 Cyclophosphamide (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.00 [0.85, 1.17]
5.14 Ifosfamide (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.47 [0.91, 2.38]
5.15 Methotrexate (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.01 [0.60, 1.69]
5.16 5-fluorouracil (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.09 [0.59, 2.00]

5.17 Cytarabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 13.92]
5.18 Gemcitabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.13 [0.61, 2.09]
5.19 Irinotecan (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.44 [0.05, 4.13]
5.20 Docetaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 13.92]
5.21 Paclitaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 13.92]
5.22 Vinorelbine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
5.23 Multiple drugs (patient-care areas)	1	Risk Ratio (Random, 95% CI)	2.38 [0.89, 6.33]
6 Proportion of surfaces contaminated (ICC = 0.00)	14	Risk Ratio (Random, 95% CI)	Subtotals only
6.1 Cyclophosphamide (pharmacy areas)	13	Risk Ratio (Random, 95% CI)	0.82 [0.72, 0.94]
6.2 Ifosfamide (pharmacy areas)	9	Risk Ratio (Random, 95% CI)	0.85 [0.59, 1.21]
6.3 Methotrexate (pharmacy areas)	6	Risk Ratio (Random, 95% CI)	0.86 [0.63, 1.16]
6.4 5-fluorouracil (pharmacy areas)	3	Risk Ratio (Random, 95% CI)	0.65 [0.48, 0.88]
6.5 Cytarabine (pharmacy areas)	2	Risk Ratio (Random, 95% CI)	0.64 [0.16, 2.46]
6.6 Gemcitabine (pharmacy areas)	2	Risk Ratio (Random, 95% CI)	0.91 [0.73, 1.13]
6.7 Irinotecan (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.36 [0.13, 1.05]
6.8 Docetaxel (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
6.9 Paclitaxel (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.57 [0.06, 5.48]
6.10 Vinorelbine (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	1.72 [0.24, 12.15]
6.11 Ganciclovir (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.01 [0.00, 0.09]
6.12 Multiple drugs (pharmacy areas)	1	Risk Ratio (Random, 95% CI)	0.87 [0.60, 1.26]
6.13 Cyclophosphamide (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.00 [0.85, 1.17]
6.14 Ifosfamide (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.48 [0.91, 2.38]
6.15 Methotrexate (patient-care areas)	5	Risk Ratio (Random, 95% CI)	1.01 [0.61, 1.67]
6.16 5-fluorouracil (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.09 [0.60, 1.97]
6.17 Cytarabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 14.36]

6.18 Gemcitabine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	1.13 [0.62, 2.06]
6.19 Irinotecan (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.44 [0.05, 3.93]
6.20 Docetaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 14.36]
6.21 Paclitaxel (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.59 [0.02, 14.36]
6.22 Vinorelbine (patient-care areas)	1	Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
6.23 Multiple drugs (patient-care areas)	1	Risk Ratio (Random, 95% CI)	2.38 [0.92, 6.12]
7 Quantity of surface contamination (pg/cm²) (ICC = 0.05)	8	Mean Difference (Random, 95% CI)	Subtotals only
7.1 Cyclophosphamide (pharmacy areas)	7	Mean Difference (Random, 95% CI)	-49.47 [-81.21, -17.73]
7.2 Ifosfamide (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-0.95 [-7.63, 5.72]
7.3 Methotrexate (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-2.78 [-12.45, 6.89]
7.4 5-fluorouracil (pharmacy areas)	2	Mean Difference (Random, 95% CI)	258.40 [-397.11, 913.91]
7.5 Cytarabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-0.6 [-14.37, 13.17]
7.6 Gemcitabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-32.7 [-96.40, 31.00]
7.7 Irinotecan (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-18.27 [-53.55, 17.01]
7.8 Cyclophosphamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	-30.44 [-90.78, 29.90]
7.9 Ifosfamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	3.59 [-2.88, 10.07]
7.10 Methotrexate (patient-care areas)	5	Mean Difference (Random, 95% CI)	0.10 [-0.51, 0.72]
7.11 5-fluorouracil (patient-care areas)	1	Mean Difference (Random, 95% CI)	-43.9 [-133.57, 45.77]
7.12 Cytarabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.20 [-0.74, 0.34]
7.13 Gemcitabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	0.47 [-1.59, 2.53]
7.14 Irinotecan (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.05 [-0.14, 0.04]
8 Quantity of surface contamination (pg/cm²) (ICC = 0.01)	8	Mean Difference (Random, 95% CI)	Subtotals only
8.1 Cyclophosphamide (pharmacy areas)	7	Mean Difference (Random, 95% CI)	-49.85 [-78.93, -20.77]
8.2 Ifosfamide (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-1.29 [-7.89, 5.32]

8.3 Methotrexate (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-1.93 [-10.50, 6.64]
8.4 5-fluorouracil (pharmacy areas)	2	Mean Difference (Random, 95% CI)	259.55 [-341.76, 860.87]
8.5 Cytarabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-0.6 [-13.23, 12.03]
8.6 Gemcitabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-32.7 [-91.14, 25.74]
8.7 Irinotecan (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-18.27 [-50.63, 14.09]
8.8 Cyclophosphamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	-49.62 [-133.49, 34.25]
8.9 Ifosfamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	3.59 [-2.39, 9.58]
8.10 Methotrexate (patient-care areas)	5	Mean Difference (Random, 95% CI)	0.06 [-0.81, 0.94]
8.11 5-fluorouracil (patient-care areas)	1	Mean Difference (Random, 95% CI)	-43.9 [-126.66, 38.86]
8.12 Cytarabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.2 [-0.70, 0.30]
8.13 Gemcitabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	0.47 [-1.43, 2.37]
8.14 Irinotecan (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.05 [-0.13, 0.03]
9 Quantity of surface contamination (pg/cm ²) (ICC = 0.00)	8	Mean Difference (Random, 95% CI)	Subtotals only
9.1 Cyclophosphamide (pharmacy areas)	7	Mean Difference (Random, 95% CI)	-50.15 [-78.51, -21.79]
9.2 Ifosfamide (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-1.36 [-7.81, 5.09]
9.3 Methotrexate (pharmacy areas)	6	Mean Difference (Random, 95% CI)	-1.32 [-9.47, 6.84]
9.4 5-fluorouracil (pharmacy areas)	2	Mean Difference (Random, 95% CI)	260.18 [-326.79, 847.16]
9.5 Cytarabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-0.6 [-12.93, 11.73]
9.6 Gemcitabine (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-32.7 [-89.74, 24.34]
9.7 Irinotecan (pharmacy areas)	1	Mean Difference (Random, 95% CI)	-18.27 [-49.86, 13.32]
9.8 Cyclophosphamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	-53.61 [-141.33, 34.10]
9.9 Ifosfamide (patient-care areas)	5	Mean Difference (Random, 95% CI)	3.60 [-2.27, 9.46]
9.10 Methotrexate (patient-care areas)	5	Mean Difference (Random, 95% CI)	0.03 [-1.02, 1.08]
9.11 5-fluorouracil (patient-care areas)	1	Mean Difference (Random, 95% CI)	-43.9 [-124.84, 37.04]
9.12 Cytarabine (patient-care areas)	1	Mean Difference (Random, 95% CI)	-0.2 [-0.69, 0.29]