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

UKONS Position Statement

Based on currently available evidence (which is of very low quality), there is currently no evidence to support or refute a recommendation the routine use of closed-system drug transfer devices (CSTD) in addition to safe handling of infusional hazardous drugs when compared to safe handling alone. High quality research is needed to provide sufficient and unambiguous information on the potential benefits and costs of CSTD.

UKONS Position

Hazardous drugs include those used for cancer chemotherapy, antiviral drugs, hormones, some bioengineered drugs, and other drugs that have the potential to cause one or more of the following: carcinogenicity (induce cancer), teratogenicity (cause birth defects), developmental toxicity (have an adverse impact on development), reproductive toxicity (interfere with normal reproduction), organ toxicity at low doses (damage organs), or genotoxicity (cause mutations, i.e. alterations in the genetic structure). New drugs that have a structure and toxicity profile that mimic existing hazardous drugs as per above criteria are also considered hazardous. Occupational exposure of healthcare staff to hazardous drugs can decrease fertility and can result in miscarriages, stillbirths, and cancers. Several practices are recommended to reduce this occupational exposure. These include safe handling practices such as the use of protective clothing, gloves, and biological safety cabinets. There is significant uncertainty as to whether the use of closed-system drug-transfer devices (CSTD) in addition to current safe handling practices decreases the exposure and risk of staff contamination to infusional hazardous drugs compared to safe handling alone.

UKONS commissioned a Cochrane systematic review to independently assess the effectiveness of closed-system drug-transfer of infusional hazardous drugs in addition to safe handling versus safe handling alone for reducing the exposure and risk of staff contamination to infusional hazardous drugs. UKONS put out a grant call for conducting the systematic review and awarded the grant to the lead review author, a methodological expert in Cochrane reviews with a medical background. The lead review author selected additional systematic reviewers from UK and content experts (experts in the field: chemotherapy nurse from UK, occupational hygienist from Finland, and pharmacists from Canada).

The review authors 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 until October 2017. They included comparative studies of any study design (irrespective of language, blinding, or publication status) which compared CSTD plus

safe handling versus safe handling alone for infusional hazardous drugs. Two review authors independently identified trials and extracted data. They calculated the risk ratio (RR) and mean difference (MD) with 95% confidence intervals (CI) using both fixed-effect and random-effects models. They assessed risk of bias according to the risk of bias in non-randomised studies of interventions (ROBINS-I) tool, used an intra-cluster correlation of 0.10, and assessed the quality of the evidence using GRADE.

The review included 23 observational cluster studies (conducted in 358 hospitals). The review did not find any randomised controlled trials or formal economic evaluations. In 21 studies, the people who used the intervention (CSTD + 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 most common drugs tested in these studies were cyclophosphamide, ifosfamide, and methotrexate.

Funding: Eight studies received no special funding; six studies received funding from manufacturers of the device being evaluated; the remaining nine studies did not report about funding.

The CSTD used in the studies were Phaseal™ (13 studies), Tevadaptor® (one study), SpikeSwan® (one study), Phaseal™ and Tevadaptor® (one study), variable (five studies), and not stated (two studies). The control group was variably described. All the studies were at serious risk of bias. The quality of evidence was very low for all the outcomes.

The findings are summarised in Table 1. There was no evidence of difference in proportion of surface samples which were contaminated in the pharmacy areas or in patient-care areas between the CSTD and control groups except for 5-fluorouracil, which was lower in the CSTD group than in the control. The amount of cyclophosphamide was lower (by about 50 pg/cm^2) in pharmacy areas between CSTD group and the control group. There was no evidence of difference in the amount of ifosfamide, and methotrexate in pharmacy areas between CSTD group and the control group. There was also no evidence of difference in the amount of cyclophosphamide, ifosfamide, methotrexate, 5-fluorouracil, cytarabine, gemcitabine, and irinotecan in the patient-care areas or pharmacy areas between CSTD group and the control group. None of the studies reported on atmospheric contamination, blood tests, or other measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and micronuclei induction. None of the studies reported short-term health benefits, such as reduction in skin rashes, long-term reproductive health benefits such as infertility and miscarriage, development of any type of cancer, or adverse events.

Five studies (six hospitals) reported 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 meta-analysed. There was significant variability between the studies in terms of whether the use of CSTD resulted in cost-savings (the point estimates of the average potential cost savings ranged between -642,656 (2017) USD and +221,818 (2017) USD).

Subgroup analysis of the devices used and the study design did not reveal any alterations in the results. The remaining subgroup analyses were not performed because of the nature of the data in the systematic review.

Based on the above findings, the authors concluded that there was currently no evidence to support or refute that closed-system drug transfer devices in addition to safe handling of infusional hazardous drugs offers any health or financial benefits compared to safe handling alone. This was based on very low quality (but the best available) evidence on the topic. Given the above conclusions, UKONS can neither recommend nor advise against routinely using closed-system drug transfer devices in addition to safe handling of infusional hazardous drugs compared to safe handling alone.

The authors also recommended that future studies should be designed in such a way as to decrease the risk of bias. They consider that it is feasible to conduct randomised controlled trials depending upon the proportion of people with exposure (urinary contamination with hazardous drugs). If surrogate outcome measures such as surface contamination are used, the samples should be taken by independent persons from pharmacy areas and patient-care areas and 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. Consideration should be also given to testing background environmental surface contamination as a negative control. UKONS agrees with the above and recommends that future research should be high-quality research that provides sufficient and unambiguous information on the potential benefits and costs of CSTD.

Evidence Supporting the Statement

Background

Hazardous drugs include those used for cancer chemotherapy, antiviral drugs, hormones, some bioengineered drugs, and other drugs[1]. 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 (induce cancer), teratogenicity (cause birth defects), developmental toxicity (have an adverse impact on development), reproductive toxicity (interfere with normal reproduction), organ toxicity at low doses (damage organs), or genotoxicity (cause mutations, i.e. alterations in the genetic structure)[1]. New drugs that have a structure and toxicity profile that mimics existing drugs considered hazardous as per above criteria are also considered hazardous[1]. There is a subtle difference between cytotoxic drugs and hazardous drugs. Cytotoxic drugs are medicines that are toxic to human cells[2], 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)[3]. 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[3].

Cytotoxic drugs have anticancer activity and immunosuppressive properties[4]. 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)[3-15].

Hazardous drugs can be administered orally, intravenously by infusions, or intrathecally[3]. 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 the drugs, may come into contact with the drugs. The hazardous drug aerosol formed due to the spillage of drugs during preparation, transport, or administration can be inhaled or absorbed through the skin[16-26]. It has to be noted that other staff (e.g. pharmacists, respiratory therapists, physicians, support staff) working in the hospital that administers hazardous drugs (and not just those who handle the hazardous drugs) can also be exposed to the contamination[17, 19].

Occupational exposure to hazardous drugs increases mutations, which predispose the exposed staff to the development of cancer[1, 27-32]. Maternal occupational exposure to hazardous drugs during pregnancy can cause congenital abnormalities, miscarriages, stillbirths, and low birth weight[1, 27, 33]. Occupational exposure of women to hazardous drugs can also decrease fertility[1, 27, 33]. Other adverse effects include skin rash, hair loss, light-headedness, abnormal blood counts, liver damage, abdominal pain, and vomiting[1, 27].

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[20-22, 25, 34]. There are several guidelines for safe handling of hazardous drugs including those issued by 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 (ASSTSAS)[1, 27, 35-40]. Broadly, these guidelines recommend the identification of the risk, use of biological safety cabinets, use of closed-system drug-transfer devices where reasonably practicable, 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)[1, 27, 35-40].

Closed-system drug-transfer device

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[1]. 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[41-45]. Some devices used in compounding hazardous drugs may not be 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[46] or chemotherapy transfer/reconstitution spikes[47]. However, this position statement covers such devices too and is applicable for all fully closed-system drug-transfer devices as subgroup analysis based on devices was performed by the systematic review authors.

Closed-system drug-transfer devices work by attempting to provide a leak-proof connection that prevents leaks and spillages[41-45]. 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[42, 44, 45]. This may allow reuse of vials and decrease the costs.

Necessity for the position statement

There is significant variation in the way hazardous drugs are handled by staff. Legislation requires organisations to protect workers' health and safety[27]. 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. 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. It is important, therefore, 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[21, 48]. 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 that it increased the risk of drug absorption through the skin and by inhalation[34]. 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 be actually 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[49-54], 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[49-54], although there are exceptions to this[55]. 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[49, 55].

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[1, 40]. Furthermore, the staff handling hazardous drugs may be anxious about the serious consequences and want to know how well these devices protect them. Therefore, a position statement from UKONS is necessary to address the issue of whether closed-system drug-transfer devices should be used routinely in addition to conventional safe handling for reducing the risk of staff contamination to infusional hazardous drugs.

Methods

UKONS commissioned a Cochrane systematic review to independently assess the effectiveness of closed-system drug-transfer of infusional hazardous drugs in addition to safe handling versus safe handling alone for reducing the exposure and risk of staff contamination to infusional hazardous drugs. UKONS put out a grant call for conducting the systematic review and awarded the grant to the lead review author, a methodological expert in Cochrane reviews with a medical background. The lead review author selected additional systematic reviewers from UK and content experts (experts in the field: chemotherapy nurse from UK, occupational hygienist from Finland, and pharmacists from Canada).

The detailed methodology of the systematic review is available at the Cochrane website[56]. Briefly, the Cochrane review authors 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 until October 2017. They included comparative studies of any study design (irrespective of language, blinding, or publication status) which compared CSTD (any type of CSTD as defined by the study authors) plus safe handling versus safe handling alone for infusional hazardous drugs. They sought the following outcome data: (environmental exposure measured with: surface samples, splashes, leakage tests, or atmospheric contamination; internal exposure measured with urine or blood tests, or with surrogate measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and micronuclei induction; health outcomes such as: skin rashes, reproductive health effects such as infertility or miscarriage, or development of any type of cancer; adverse events (e.g. personal injury due to the use of spikes or needles resulting in infections); and potential cost savings due to reuse of multi-dose vials.

Two review authors independently identified trials and extracted data. They calculated the risk ratio (RR) and mean difference (MD) with 95% confidence intervals (CI) using both fixed-effect and random-effects models. They assessed risk of bias according to the risk of bias in non-

randomised studies of interventions (ROBINS-I) tool[57], used an intra-cluster correlation of 0.10, and assessed the quality of the evidence using GRADE methodology[58].

They also carried out subgroup analyses of different types of closed-system drug-transfer devices whenever possible.

Results

The systematic review authors identified a total of 23 studies after identifying 9033 records from searching the databases. All the 23 studies were cluster studies, i.e. the comparison was between hospitals that used CSTD versus those that did not use CSTD (cross-sectional studies) or between the phase in which CSTD was used versus the phase in which CSTD was not used (interrupted time series or historically controlled studies). Of the 23 included studies, one study (three hospitals) was an interrupted time series[48], 13 studies (65 hospitals) were historically controlled studies[21, 34, 59-69], and nine studies (290 hospitals) were cross-sectional studies[18, 26, 70-76]. In one cross-sectional study, the same isolators in a hospital were used to prepare drugs using CSTD and no CSTD during the same period[72]. In one cross-sectional study, two different isolators from the same hospital were used to prepare drugs: CSTD was used in one isolator and no CSTD was used in the other isolator during the same period[75]. In the remaining seven cross-sectional studies, 91 hospitals used CSTD and 197 hospitals did not used CSTD[18, 26, 70, 71, 73, 74, 76]. The review authors did not find any randomised controlled trials or formal economic evaluations. Overall, 358 hospitals in Australia, Canada, France, Hungary, Italy, Japan, Malaysia, Turkey, USA, were included. Most hospitals were from Canada and USA. However, it should be noted that there is an overlap between hospitals included in the different studies, although there is minimal or no overlap in the period during which 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 + safe handling) and control (safe handling alone) were pharmacists or pharmacy technicians[18, 21, 26, 34, 48, 59-63, 65-67, 69-76]; in two studies, the people who used the intervention and control were nurses in addition to pharmacists or pharmacy technicians[64, 68].

The CSTD used in the studies were Phaseal™ (13 studies[21, 34, 48, 59-61, 63, 65-69, 75]), Tevadaptor® (one study[62]), SpikeSwan® (one study[72]), Phaseal™ and Tevadaptor® (one study[64]), variable (five studies[18, 70, 71, 73, 74]), and not stated (two studies[26, 76]). The control group was variably described.

The outcomes reported in the studies were exposure (4 studies[26, 63, 68, 76]), surface contamination (16 studies[18, 21, 34, 48, 63, 66-76]) and potential cost savings (five studies[59, 60, 62, 64, 65]). In the studies that reported exposure or surface contamination, the intra-cluster correlation coefficient was not reported in any of the studies. The outcomes were not reported in a format that could be tabulated or meta-analysed in the remaining two studies as key information was missing[26, 61].

The most common drugs tested in these studies were cyclophosphamide, ifosfamide, and methotrexate. For a full list of drugs tested in each study, please refer to the ‘Characteristics of Included Studies’ in the Cochrane review[56].

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[63, 68, 69, 76]. This varied between two weeks and seven months in the three studies that provided this information[63, 68, 69].

Funding: Eight studies received no special funding[18, 34, 60, 62, 70, 71, 73, 74]; six studies received funding from manufacturers of the device being evaluated[21, 48, 66-68, 75]; the remaining nine studies did not report about funding[26, 59, 61, 63-65, 69, 72, 76].

A total of 56 studies were excluded (Characteristics of excluded studies). The main reasons for exclusion were that the studies were not primary research study, did not compare CSTD + standard care versus standard care (for example, introduction of other safety measures such as biosafety cabinets or change in the lay-out of the pharmacy in addition to the introduction of CSTD, cleaning only the CSTD group prior to exposure of the surfaces to hazardous drugs, which clearly do not estimate the benefits or harms of CSTD + safe handling versus safe handling alone), simulation studies, comparison of different CSTDs, and intermittent use of CSTD (not possible to determine whether the outcomes were for CSTD or standard care).

Risk of bias in included studies and quality of evidence

The risk of bias in the included studies is summarised in Figure 1. All the studies were at serious risk of bias in one or more domains. For detailed assessment of risk of bias and quality of evidence, please see Cochrane review[56].

Figure 1: Risk of bias in the studies

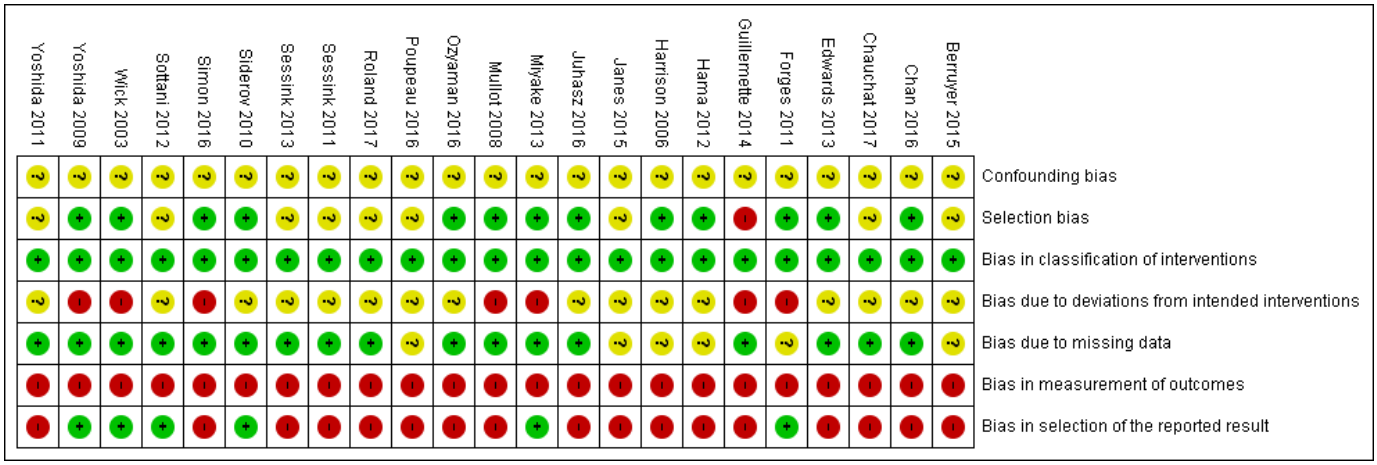

Figure 1 shows that all the studies were at high risk of bias in one or more domains (aspects of study design). The red circles indicate that the study was at high risk of bias for the domain; the yellow circle indicates that the risk of bias in the study was not clear for the domain, and green circle indicates that the risk of bias was low for the domain.

Effects of interventions

The results are summarised in Table 1. There was no evidence of difference in proportion of surface samples which were contaminated in the pharmacy areas or in patient-care areas between the CSTD and control groups except for 5-fluouracil in pharmacy areas. The amount of cyclophosphamide was lower (by about 50 pg/cm^2) in pharmacy areas between CSTD group and

the control group. There was no evidence of difference in the amount of ifosfamide and methotrexate in pharmacy areas between CSTD group and the control group. There was also no evidence of difference in the amount of cyclophosphamide, ifosfamide, methotrexate, 5-fluorouracil, cytarabine, gemcitabine, and irinotecan in the patient-care areas or pharmacy areas between CSTD group and the control group. None of the studies reported on atmospheric contamination, blood tests, or other measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and micronuclei induction. None of the studies reported short-term health benefits, such as reduction in skin rashes, long-term reproductive health benefits such as infertility and miscarriage, development of any type of cancer, or adverse events.

Table 1: Summary of findings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of hospitals (samples; studies)	Quality of the evidence (GRADE)
	Assumed risk Safe handling alone	Corresponding risk Closed-system transfer device plus safe handling			
Exposure (urine tests for exposure) (Figure 1)					
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)[63, 69]	⊕⊖⊖⊖ **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)[68]	⊕⊖⊖⊖ **very low**[a,b,c]
Cyclophosphamide, ifosfamide, or gemcitabine	There were no participants with exposure in either group.			4 hospitals (36 participants; 1 study)[76]	⊕⊖⊖⊖ **very low**[a,b,c]
Other measures of exposure	None of the studies reported on blood tests, or other measures of exposure to infusional hazardous drugs such as urine mutagenicity, chromosomal aberrations, sister chromatid exchanges, and micronuclei induction.				
Surface contamination (proportion of surfaces contaminated)					
Pharmacy areas					
Cyclophosphamide	**507 per 1000**	**451 per 1000** (395 to 512)	**RR 0.89** (0.78 to 1.01)	338 hospitals (2937 samples; 13 studies)[18, 21, 34, 63, 66-71, 73-75]	⊕⊖⊖⊖ **very low**[a,b,d,e]
Ifosfamide	**267 per 1000**	**251 per 1000** (197 to 317)	**RR 0.94** (0.74 to 1.19)	304 hospitals (2332 samples; 9 studies)[18, 21, 34, 68, 70, 71, 73-75]	⊕⊖⊖⊖ **very low**[a,b,d]
Methotrexate	**102 per 1000**	**85 per 1000**	**RR 0.84**	280 hospitals	⊕⊖⊖⊖

		(59 to 124)	(0.58 to 1.22)	(1781 samples; 6 studies)[18, 34, 70, 71, 73, 74]	**very low**[a,b,d]
5-fluorouracil	**139 per 1000**	**90 per 1000** (60 to 135)	**RR 0.65** (0.43 to 0.97)	106 hospitals (1008 samples; 3 studies)[21, 71, 75]	⊕⊖⊖⊖ **very low**[a,d,f]
Cytarabine	**267 per 1000**	**192 per 1000** (48 to 762)	**RR 0.72** (0.18 to 2.86)	84 hospitals (780 samples; 2 studies)[71, 75]	⊕⊖⊖⊖ **very low**[a,b,d]
Gemcitabine	**322 per 1000**	**309 per 1000** (193 to 496)	**RR 0.96** (0.60 to 1.54)	84 hospitals (780 samples; 2 studies)[71, 75]	⊕⊖⊖⊖ **very low**[a,b,d]
Irinotecan*, *docetaxel*, *paclitaxel*, *vinorelbine*, *ganciclovir*, *multiple drugs[†]	There was 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 and safe handling alone			Irinotecan, docetaxel, paclitaxel, vinorelbine: 83 hospitals (493 samples; 1 study)[71] Ganciclovir: 1 hospital (287 samples; 1 study)[71] Multiple drugs: 4 hospitals (109 samples; 1 study)[76]	⊕⊖⊖⊖ **very low**[a,b,d]
Patient-care areas					
Cyclophosphamide	**440 per 1000**	**444 per 1000** (378 to 519)	**RR 1.01** (0.86 to 1.18)	279 hospitals (1535 samples; 5 studies)[18, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d]
Ifosfamide	**71 per 1000**	**102 per 1000** (64 to 161)	**RR 1.44** (0.91 to 2.28)	279 hospitals (1535 samples; 5 studies)[18, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d]
Methotrexate	**25 per 1000**	**25 per 1000** (14 to 46)	**RR 1.00** (0.55 to 1.85)	279 hospitals (1535 samples; 5	⊕⊖⊖⊖ **very low**[a,b,d]

				studies) [18, 70, 71, 73, 74]	
***5-fluorouracil*, *cytarabine*, *gemcitabine*, *irinotecan*, *docetaxel*, *paclitaxel*, *vinorelbine*, *multiple drugs*[†]**	There was 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			5-fluorouracil, cytarabine, gemcitabine, irinotecan, docetaxel, paclitaxel, vinorelbine: 83 hospitals (493 samples; 1 study)[71] Multiple drugs: 4 hospitals (33 samples; 1 study)[76]	⊕⊖⊖⊖ **very low**[a,b,d]
Surface contamination (quantity of surface contamination (pg/cm²))					
Pharmacy areas					
Cyclophosphamide[¤]	The mean cyclophosphamide in the control group was **124.30** pg/cm²	The mean cyclophosphamide in the intervention group was **49.34 lower** (84.11 lower to 14.56 lower)	**MD -49.34** (-84.11 to -14.56)	282 hospitals (1793 samples; 7 studies)[18, 34, 67, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,f]
Ifosfamide	The mean ifosfamide in the control group was **10.8** pg/cm²	The mean ifosfamide in the intervention group was **0.32 lower** (6.58 lower to 5.94 higher)	**MD -0.32** (-6.58 to 5.94)	280 hospitals (1749 samples; 6 studies)[18, 34, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d]
Methotrexate	The mean methotrexate in the control groups was **18.23** pg/cm²	The mean methotrexate in the intervention group was **3.09 lower** (13.80 lower to 7.61 higher)	**MD -3.09** (-13.80 to 7.61)	280 hospitals (1749 samples; 6 studies)[18, 34, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d]
5-fluorouracil	The mean 5-fluorouracil in the control groups was **8720.5** pg/cm²	The mean 5-fluorouracil in the intervention group was **257.87 higher** (459.65 lower to 975.38 higher)	**MD 257.87** (-459.65 to 975.38)	84 hospitals (542 samples; 2 studies)[71, 72]	⊕⊖⊖⊖ **very low**[a,b,d]
***Cytarabine*,**	There was no evidence of difference in the			83 hospitals	⊕⊖⊖⊖

gemcitabine, and irinotecan	amount of cytarabine, gemcitabine, and irinotecan in pharmacy areas between closed-system transfer device plus safe handling and safe handling alone			(493 samples; 1 study)[71]	**very low**[a,b,d]
Patient-care areas					
Cyclophosphamide	The mean cyclophosphamide in the control groups was **168**	The mean cyclophosphamide in the intervention group was **13.34 lower** (36.01 lower to 9.32 higher)	**MD -13.34** (-36.01 to 9.32)	279 hospitals (1535 samples; 5 studies)[18, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d,e]
Ifosfamide	The mean ifosfamide in the control group was **4.59**	The mean ifosfamide in the intervention group was **3.59 higher** (3.45 lower to 10.63 higher)	**MD 3.59** (-3.45 to 10.63)	279 hospitals (1535 samples; 5 studies)[18, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d]
Methotrexate	The mean methotrexate in the control groups was **1.42**	The mean methotrexate in the intervention group was **0.10 higher** (0.57 lower to 0.78 higher)	**MD 0.10** (-0.57 to 0.78)	279 hospitals (1535 samples; 5 studies)[18, 70, 71, 73, 74]	⊕⊖⊖⊖ **very low**[a,b,d]
5-fluorouracil, cytarabine, gemcitabine, and irinotecan	There was 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)[71]	⊕⊖⊖⊖ **very low**[a,b,d]
Other measures of contamination	None of the studies reported on atmospheric contamination.				

*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).
CI: Confidence interval; MD: Mean difference; RR: Risk ratio

† 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[48]. Biweekly measurements were made in all three phases[48]. Between the first two phases, the change in the slope between pre-CSTD and CSTD was 3.9439 pg/cm^2, 95% CI 1.2303 to 6.6576 (P = 0.010). 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/cm^2, 95% CI -5.126 to 1.2598 (P = 0.200) and the level was 14.167 pg/cm^2 (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.

[a]The study/studies was/were at serious risk of bias (downgraded one level for risk of bias).
[b]The confidence intervals were wide (downgraded one level for imprecision).
[c]The sample size was small (downgraded one level for imprecision).
[d]This is a surrogate measure of health benefit (downgraded one level for indirectness).
[e]There was possible evidence of publication bias (Egger's test P-value < 0.05) (downgraded one level for publication bias).
[f]There is no evidence that this small difference in levels of cyclophosphamide leads to decreased exposure or tangible health benefits (downgraded one level for imprecision).

Figure 2: Urine tests for contamination

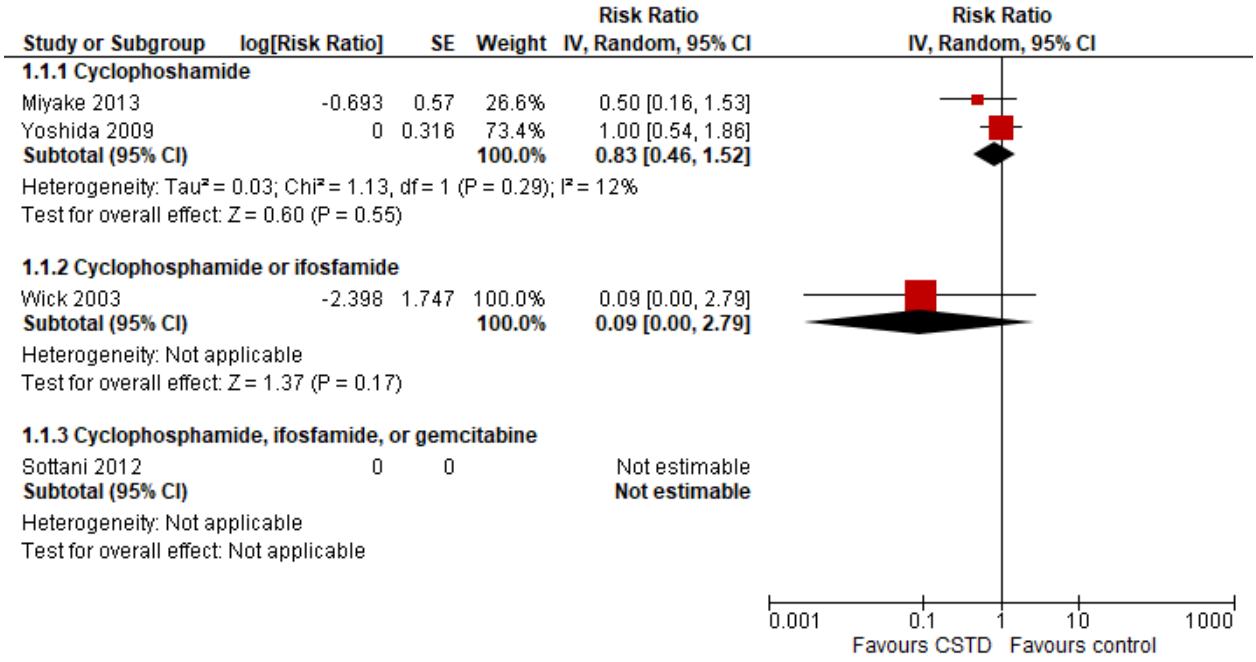

Figure 2 shows that there was no evidence of difference in urinary contamination with infusional hazardous drugs.

Figure 3: Forest plot of proportion of surfaces contaminated

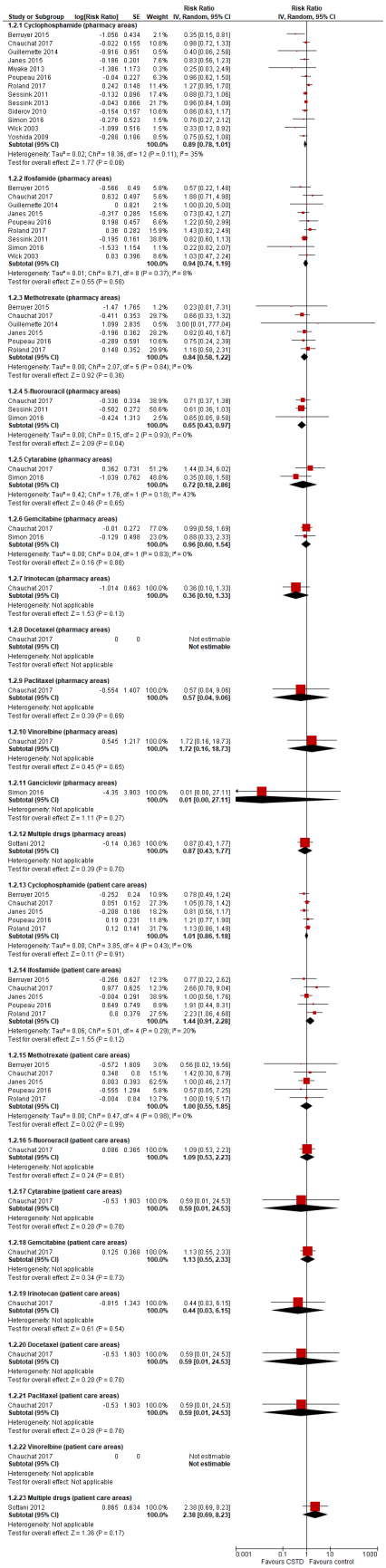
Risk Ratio
Risk Ratio
Study or Subgroup log[Risk Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
1.2.1 Cyclophosphamide (pharmacy areas)
Berruyer 2015 -1.056 0.434 2.1% 0.35 [0.15, 0.81]
Chauchat 2017 -0.022 0.155 10.8% 0.98 [0.72, 1.33]
Guillemette 2014 -0.916 0.951 0.5% 0.40 [0.06, 2.58]
Janes 2015 -0.186 0.201 7.6% 0.83 [0.56, 1.23]
Miyake 2013 -1.386 1.173 0.3% 0.25 [0.03, 2.49]
Poupeau 2016 -0.04 0.227 6.3% 0.96 [0.62, 1.50]
Roland 2017 0.242 0.148 11.4% 1.27 [0.95, 1.70]
Sessink 2011 -0.132 0.096 17.4% 0.88 [0.73, 1.06]
Sessink 2013 -0.043 0.066 21.7% 0.96 [0.84, 1.09]
Siderov 2010 -0.154 0.157 10.6% 0.86 [0.63, 1.17]
Simon 2016 -0.276 0.523 1.5% 0.76 [0.27, 2.12]
Wick 2003 -1.099 0.516 1.5% 0.33 [0.12, 0.92]
Yoshida 2009 -0.288 0.186 9.5% 0.75 [0.52, 1.08]
Subtotal (95% CI) 100.0% 0.89 [0.78, 1.01]
Heterogeneity: Tau² = 0.02; Chi² = 18.36, df = 12 (P = 0.11); I² = 35%
Test for overall effect: Z = 1.77 (P = 0.08)
1.2.2 Ifosfamide (pharmacy areas)
Berruyer 2015 -0.566 0.49 5.8% 0.57 [0.22, 1.48]
Chauchat 2017 0.632 0.497 5.6% 1.88 [0.71, 4.98]
Guillemette 2014 0 0.821 2.1% 1.00 [0.20, 5.00]
Janes 2015 -0.317 0.285 15.6% 0.73 [0.42, 1.27]
Poupeau 2016 0.198 0.457 6.6% 1.22 [0.50, 2.99]
Roland 2017 0.36 0.282 15.9% 1.43 [0.82, 2.49]
Sessink 2011 -0.195 0.161 38.8% 0.82 [0.60, 1.13]
Simon 2016 -1.533 1.154 1.1% 0.22 [0.02, 2.07]
Wick 2003 0.03 0.396 8.6% 1.03 [0.47, 2.24]
Subtotal (95% CI) 100.0% 0.94 [0.74, 1.19]
Heterogeneity: Tau² = 0.01; Chi² = 8.71, df = 8 (P = 0.37); I² = 8%
Test for overall effect: Z = 0.55 (P = 0.58)
1.2.3 Methotrexate (pharmacy areas)
Berruyer 2015 -1.47 1.765 1.2% 0.23 [0.01, 7.31]
Chauchat 2017 -0.411 0.353 29.7% 0.66 [0.33, 1.32]
Guillemette 2014 1.099 2.835 0.5% 3.00 [0.01, 777.04]
Janes 2015 -0.196 0.362 28.2% 0.82 [0.40, 1.67]
Poupeau 2016 -0.289 0.591 10.6% 0.75 [0.24, 2.39]
Roland 2017 0.148 0.352 29.9% 1.16 [0.58, 2.31]
Subtotal (95% CI) 100.0% 0.84 [0.58, 1.22]
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 5 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.92 (P = 0.36)
1.2.4 5-fluorouracil (pharmacy areas)
Chauchat 2017 -0.336 0.334 38.9% 0.71 [0.37, 1.38]
Sessink 2011 -0.502 0.272 59.6% 0.61 [0.36, 1.03]
Simon 2016 -0.424 1.313 2.5% 0.65 [0.05, 8.58]
Subtotal (95% CI) 100.0% 0.65 [0.43, 0.97]
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)
1.2.5 Cytarabine (pharmacy areas)
Chauchat 2017 0.362 0.731 51.2% 1.44 [0.34, 6.02]
Simon 2016 -1.039 0.762 48.8% 0.35 [0.08, 1.58]
Subtotal (95% CI) 100.0% 0.72 [0.18, 2.86]
Heterogeneity: Tau² = 0.42; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 0.46 (P = 0.65)
1.2.6 Gemcitabine (pharmacy areas)
Chauchat 2017 -0.01 0.272 77.0% 0.99 [0.58, 1.69]
Simon 2016 -0.129 0.498 23.0% 0.88 [0.33, 2.33]
Subtotal (95% CI) 100.0% 0.96 [0.60, 1.54]
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.88)
1.2.7 Irinotecan (pharmacy areas)
Chauchat 2017 -1.014 0.863 100.0% 0.36 [0.10, 1.33]
Subtotal (95% CI) 100.0% 0.36 [0.10, 1.33]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
1.2.8 Docetaxel (pharmacy areas)
Chauchat 2017 0 0 Not estimable
Subtotal (95% CI) Not estimable
Heterogeneity: Not applicable
Test for overall effect: Not applicable
1.2.9 Paclitaxel (pharmacy areas)
Chauchat 2017 -0.554 1.407 100.0% 0.57 [0.04, 9.06]
Subtotal (95% CI) 100.0% 0.57 [0.04, 9.06]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)
1.2.10 Vinorelbine (pharmacy areas)
Chauchat 2017 0.545 1.217 100.0% 1.72 [0.16, 18.73]
Subtotal (95% CI) 100.0% 1.72 [0.16, 18.73]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
1.2.11 Ganciclovir (pharmacy areas)
Simon 2016 -4.35 3.903 100.0% 0.01 [0.00, 27.11]
Subtotal (95% CI) 100.0% 0.01 [0.00, 27.11]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
1.2.12 Multiple drugs (pharmacy areas)
Sottani 2012 -0.14 0.363 100.0% 0.87 [0.43, 1.77]
Subtotal (95% CI) 100.0% 0.87 [0.43, 1.77]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
1.2.13 Cyclophosphamide (patient care areas)
Berruyer 2015 -0.252 0.24 10.9% 0.78 [0.49, 1.24]
Chauchat 2017 0.051 0.152 27.3% 1.05 [0.78, 1.42]
Janes 2015 -0.208 0.186 18.2% 0.81 [0.56, 1.17]
Poupeau 2016 0.19 0.231 11.8% 1.21 [0.77, 1.90]
Roland 2017 0.12 0.141 31.7% 1.13 [0.86, 1.49]
Subtotal (95% CI) 100.0% 1.01 [0.86, 1.18]
Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
1.2.14 Ifosfamide (patient care areas)
Berruyer 2015 -0.266 0.627 12.3% 0.77 [0.22, 2.62]
Chauchat 2017 0.977 0.625 12.3% 2.66 [0.78, 9.04]
Janes 2015 -0.004 0.291 38.9% 1.00 [0.56, 1.78]
Poupeau 2016 0.649 0.749 8.9% 1.91 [0.44, 8.31]
Roland 2017 0.8 0.379 27.5% 2.23 [1.06, 4.68]
Subtotal (95% CI) 100.0% 1.44 [0.91, 2.28]
Heterogeneity: Tau² = 0.06; Chi² = 5.01, df = 4 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.55 (P = 0.12)
1.2.15 Methotrexate (patient care areas)
Berruyer 2015 -0.572 1.809 3.0% 0.56 [0.02, 19.56]
Chauchat 2017 0.348 0.8 15.1% 1.42 [0.30, 6.79]
Janes 2015 0.003 0.393 62.5% 1.00 [0.46, 2.17]
Poupeau 2016 -0.555 1.294 5.8% 0.57 [0.05, 7.25]
Roland 2017 -0.004 0.84 13.7% 1.00 [0.19, 5.17]
Subtotal (95% CI) 100.0% 1.00 [0.55, 1.85]
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 4 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)
1.2.16 5-fluorouracil (patient care areas)
Chauchat 2017 0.086 0.365 100.0% 1.09 [0.53, 2.23]
Subtotal (95% CI) 100.0% 1.09 [0.53, 2.23]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
1.2.17 Cytarabine (patient care areas)
Chauchat 2017 -0.53 1.903 100.0% 0.59 [0.01, 24.53]
Subtotal (95% CI) 100.0% 0.59 [0.01, 24.53]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
1.2.18 Gemcitabine (patient care areas)
Chauchat 2017 0.125 0.368 100.0% 1.13 [0.55, 2.33]
Subtotal (95% CI) 100.0% 1.13 [0.55, 2.33]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
1.2.19 Irinotecan (patient care areas)
Chauchat 2017 -0.815 1.343 100.0% 0.44 [0.03, 6.15]
Subtotal (95% CI) 100.0% 0.44 [0.03, 6.15]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
1.2.20 Docetaxel (patient care areas)
Chauchat 2017 -0.53 1.903 100.0% 0.59 [0.01, 24.53]
Subtotal (95% CI) 100.0% 0.59 [0.01, 24.53]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
1.2.21 Paclitaxel (patient care areas)
Chauchat 2017 -0.53 1.903 100.0% 0.59 [0.01, 24.53]
Subtotal (95% CI) 100.0% 0.59 [0.01, 24.53]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
1.2.22 Vinorelbine (patient care areas)
Chauchat 2017 0 0 Not estimable
Subtotal (95% CI) Not estimable
Heterogeneity: Not applicable
Test for overall effect: Not applicable
1.2.23 Multiple drugs (patient care areas)
Sottani 2012 0.865 0.634 100.0% 2.38 [0.69, 8.23]
Subtotal (95% CI) 100.0% 2.38 [0.69, 8.23]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)
0.001 0.1 1 10 1000
Favours CSTD Favours control

Figure 3: There was no evidence of difference in the proportion of surfaces contaminated in the pharmacy areas or patient care areas except for 5-fluouracil in pharmacy areas.

Figure 4: Quantity of surface contamination (pg/cm²)

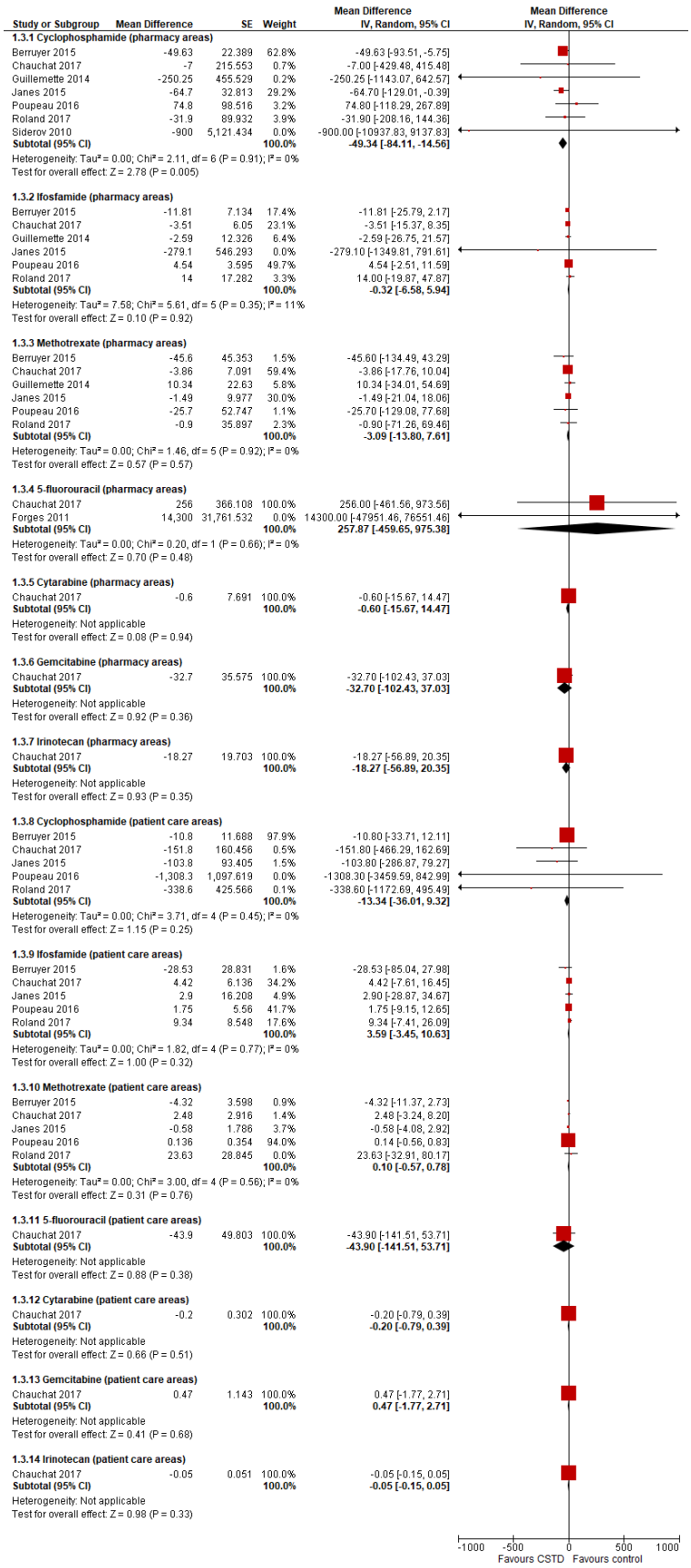
Mean Difference
Mean Difference
Study or Subgroup Mean Difference SE Weight IV, Random, 95% CI
IV, Random, 95% CI
1.3.1 Cyclophosphamide (pharmacy areas)
Berruyer 2015 -49.63 22.389 62.8% -49.63 [-93.51, -5.75]
Chauchat 2017 -7 215.553 0.7% -7.00 [-429.48, 415.48]
Guillemette 2014 -250.25 455.529 0.2% -250.25 [-1143.07, 642.57]
Janes 2015 -64.7 32.813 29.2% -64.70 [-129.01, -0.39]
Poupeau 2016 74.8 98.516 3.2% 74.80 [-118.29, 267.89]
Roland 2017 -31.9 89.932 3.9% -31.90 [-208.16, 144.36]
Siderov 2010 -900 5,121.434 0.0% -900.00 [-10937.83, 9137.83]
Subtotal (95% CI) 100.0% -49.34 [-84.11, -14.56]
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 6 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
1.3.2 Ifosfamide (pharmacy areas)
Berruyer 2015 -11.81 7.134 17.4% -11.81 [-25.79, 2.17]
Chauchat 2017 -3.51 6.05 23.1% -3.51 [-15.37, 8.35]
Guillemette 2014 -2.59 12.326 6.4% -2.59 [-26.75, 21.57]
Janes 2015 -279.1 546.293 0.0% -279.10 [-1349.81, 791.61]
Poupeau 2016 4.54 3.595 49.7% 4.54 [-2.51, 11.59]
Roland 2017 14 17.282 3.3% 14.00 [-19.87, 47.87]
Subtotal (95% CI) 100.0% -0.32 [-6.58, 5.94]
Heterogeneity: Tau² = 7.58; Chi² = 5.61, df = 5 (P = 0.35); I² = 11%
Test for overall effect: Z = 0.10 (P = 0.92)
1.3.3 Methotrexate (pharmacy areas)
Berruyer 2015 -45.6 45.353 1.5% -45.60 [-134.49, 43.29]
Chauchat 2017 -3.86 7.091 59.4% -3.86 [-17.76, 10.04]
Guillemette 2014 10.34 22.63 5.8% 10.34 [-34.01, 54.69]
Janes 2015 -1.49 9.977 30.0% -1.49 [-21.04, 18.06]
Poupeau 2016 -25.7 52.747 1.1% -25.70 [-129.08, 77.68]
Roland 2017 -0.9 35.897 2.3% -0.90 [-71.26, 69.46]
Subtotal (95% CI) 100.0% -3.09 [-13.80, 7.61]
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 5 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)
1.3.4 5-fluorouracil (pharmacy areas)
Chauchat 2017 256 366.108 100.0% 256.00 [-461.56, 973.56]
Forges 2011 14,300 31,761.532 0.0% 14300.00 [-47951.46, 76551.46]
Subtotal (95% CI) 100.0% 257.87 [-459.65, 975.38]
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)
1.3.5 Cytarabine (pharmacy areas)
Chauchat 2017 -0.6 7.691 100.0% -0.60 [-15.67, 14.47]
Subtotal (95% CI) 100.0% -0.60 [-15.67, 14.47]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)
1.3.6 Gemcitabine (pharmacy areas)
Chauchat 2017 -32.7 35.575 100.0% -32.70 [-102.43, 37.03]
Subtotal (95% CI) 100.0% -32.70 [-102.43, 37.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
1.3.7 Irinotecan (pharmacy areas)
Chauchat 2017 -18.27 19.703 100.0% -18.27 [-56.89, 20.35]
Subtotal (95% CI) 100.0% -18.27 [-56.89, 20.35]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)
1.3.8 Cyclophosphamide (patient care areas)
Berruyer 2015 -10.8 11.688 97.9% -10.80 [-33.71, 12.11]
Chauchat 2017 -151.8 160.456 0.5% -151.80 [-466.29, 162.69]
Janes 2015 -103.8 93.405 1.5% -103.80 [-286.87, 79.27]
Poupeau 2016 -1,308.3 1,097.619 0.0% -1308.30 [-3459.59, 842.99]
Roland 2017 -338.6 425.566 0.1% -338.60 [-1172.69, 495.49]
Subtotal (95% CI) 100.0% -13.34 [-36.01, 9.32]
Heterogeneity: Tau² = 0.00; Chi² = 3.71, df = 4 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)
1.3.9 Ifosfamide (patient care areas)
Berruyer 2015 -28.53 28.831 1.6% -28.53 [-85.04, 27.98]
Chauchat 2017 4.42 6.136 34.2% 4.42 [-7.61, 16.45]
Janes 2015 2.9 16.208 4.9% 2.90 [-28.87, 34.67]
Poupeau 2016 1.75 5.56 41.7% 1.75 [-9.15, 12.65]
Roland 2017 9.34 8.548 17.6% 9.34 [-7.41, 26.09]
Subtotal (95% CI) 100.0% 3.59 [-3.45, 10.63]
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
1.3.10 Methotrexate (patient care areas)
Berruyer 2015 -4.32 3.598 0.9% -4.32 [-11.37, 2.73]
Chauchat 2017 2.48 2.916 1.4% 2.48 [-3.24, 8.20]
Janes 2015 -0.58 1.786 3.7% -0.58 [-4.08, 2.92]
Poupeau 2016 0.136 0.354 94.0% 0.14 [-0.56, 0.83]
Roland 2017 23.63 28.845 0.0% 23.63 [-32.91, 80.17]
Subtotal (95% CI) 100.0% 0.10 [-0.57, 0.78]
Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 4 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
1.3.11 5-fluorouracil (patient care areas)
Chauchat 2017 -43.9 49.803 100.0% -43.90 [-141.51, 53.71]
Subtotal (95% CI) 100.0% -43.90 [-141.51, 53.71]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
1.3.12 Cytarabine (patient care areas)
Chauchat 2017 -0.2 0.302 100.0% -0.20 [-0.79, 0.39]
Subtotal (95% CI) 100.0% -0.20 [-0.79, 0.39]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
1.3.13 Gemcitabine (patient care areas)
Chauchat 2017 0.47 1.143 100.0% 0.47 [-1.77, 2.71]
Subtotal (95% CI) 100.0% 0.47 [-1.77, 2.71]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
1.3.14 Irinotecan (patient care areas)
Chauchat 2017 -0.05 0.051 100.0% -0.05 [-0.15, 0.05]
Subtotal (95% CI) 100.0% -0.05 [-0.15, 0.05]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
-1000 -500 0 500 1000
Favours CSTD Favours control

Figure 4 shows that the amount of cyclophosphamide was lower (by about 50 pg/cm^2) in pharmacy areas between CSTD group and the control group. It also shows that there is no evidence of difference in the amount of ifosfamide and methotrexate in pharmacy areas between CSTD group and the control group. There was also no evidence of difference in the amount of cyclophosphamide, ifosfamide, methotrexate, 5-fluorouracil, cytarabine, gemcitabine, and irinotecan in the patient-care areas or pharmacy areas between CSTD group and the control group.

Table 2 Potential cost savings

Study name	Country	Number of hospitals	Device used	Method of calculation	Cost-difference in original currency*	Cost-difference in USD 2017 equivalent*
Chan 2016[59]	Malaysia	1	Not stated	Actual costs of drugs and CSTD used during the period	+148,632 (2015) MYR	+221,818 (2017) USD
Edwards 2013[60]	USA	1	Phaseal	Actual costs for CSTD, actual costs for drug use in CSTD group and hypothetical calculation of drugs necessary if CSTD was not used	-596,491 (2012) USD	-642,656 (2017) USD
Juhasz 2016[62]	Hungary	2	Tevadoptor	Simulation costs based on potential drug left behind in the vial; costs of CSTD were not included	-70,913 (2014) Euros	-61,202 (2017) USD
Mullot 2008[64]	France	1	Phaseal/Tevadoptor	Actual costs of drugs and CSTD used during the period	+160,680 (2006) Euros	+155,144 (2017) USD
Ozyaman 2016[65]	Turkey	1	Phaseal	Simulation costs based on potential drug left behind in the vial; costs of CSTD were not included	-22,064 (2014) Euros	-23,370 (2017) USD

Footnotes

* Negative sign indicates cost savings and positive sign indicates increased costs.

Abbreviations: MYR = Malaysian Ringets; USD = US dollar

Table 2 shows that the five studies (six hospitals) that reported the potential cost savings through the use of CSTD used different methods of calculating the costs and the results were not reported in a format that could be meta-analysed. There was significant variability between the studies in terms of whether the use of CSTD resulted in cost-savings (the point estimates of the average potential cost savings ranged between -642,656 (2017) USD and +221,818 (2017) USD).

Subgroup analysis

Subgroup analysis of the devices used did not reveal any alterations in the results. A subgroup analysis based on study design did not reveal any differences in the results reported by uncontrolled before-after studies and cross-sectional studies. There remaining subgroup analyses were not performed because of the nature of the data in the systematic review.

Sensitivity analysis

The results of proportion of surfaces contaminated with some drugs in the pharmacy areas were sensitive to the intracluster correlation coefficients used: at very low intracluster correlation coefficients (of 0.01 or 0.00), the proportion of surfaces contaminated with cyclophosphamide, 5-fluorouracil, and ganciclovir were lower with CSTD group than in standard group; the proportion of surfaces contaminated with cyclophosphamide and 5-fluorouracil were lower with CSTD group than in standard group with an intracluster correlation coefficient of 0.05 as well. The remaining analyses were not sensitive to the correlation coefficients used.

Reporting bias

There was no evidence of reporting bias/small study effects for the any of the outcomes with at least five studies either by visualisation or by Egger's test. The only exceptions for this were for the proportion of surfaces contaminated with cyclophosphamide and quantity of cyclophosphamide in patient-care areas which were statistically significant (P = 0.026 and P = 0.002). This was because the point estimate of the difference between CSTD and control group was less in the studies with 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 effect.

Discussion

Overall, the systematic review authors included a total 23 observational studies comparing CSTD plus safe handling versus safe handling alone in the systematic review. There were no randomised controlled trials on this topic. Twenty one studies reported one or more outcomes for the systematic review. However, the only outcomes reported in these 21 studies were exposure, surface contamination or potential cost savings. None of the studies reported 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 was no evidence of differences between CSTD plus safe handling versus safe handling alone. Decreased exposure as defined by presence of one or more

drugs can result in improved health benefits such as decreased cancers, miscarriages, or infertility (as exposure to hazardous drugs is associated with development of cancer, decreased fertility, congenital abnormalities, miscarriages, stillbirths, and low birth weight [1, 27, 33].

There was evidence of a reduction in the proportion of samples which were contaminated with 5-fluorouracil and the quantity of cyclophosphamide in CSTD plus safe handling versus safe handling in pharmacy areas. There was no evidence of differences for any of the other drugs in proportion of surfaces contaminated or quantity of surface contamination in pharmacy areas. There was also no evidence of differences in proportion of surfaces contaminated or quantity of surface contamination in patient areas.

With regards to cyclophosphamide, the difference was about 50 pg. There are multiple issues with this small difference. Firstly, the difference in quantity of cyclophosphamide reduced was only a very small reduction compared to the baseline levels reported in the studies. Secondly, the difference in quantity of contamination was found only for one drug in the pharmacy area (and not in patient-care areas and not for other drugs), i.e. the healthcare staff are still exposed to cyclophosphamide in other areas and other hazardous drugs in pharmacy and patient-care areas. It is important to highlight that by design, CSTD do not protect healthcare staff from oral hazardous drugs. Therefore, the healthcare staff may be exposed to oral hazardous drugs, which can lead to the same ill-effects of infusional hazardous drugs. However, oral hazardous 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[77]. Just a correlation between two outcomes does not make one outcome a good surrogate of another[78-83]. 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-fluouracil, there was no evidence of reduction in quantity of 5-fluouracil despite a reduction in the proportion of surfaces contaminated with 5-fluouracil. There are several possible explanations for this. One possibility is that there was insufficient power to detect a reduction in quantity of 5-fluouracil. Even if this was the case (and there was an actual reduction in 5-fluouracil), the same issues that arise for a reduction in cyclophosphamide arise, i.e. does this reduction decrease overall exposure or improve health benefits. A second possibility is that despite a reduction in the surfaces contaminated with 5-fluouracil, 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 and may indicate that there was actually no reduction in quantity of 5-fluorouracil. In the second and third possibilities, whether a reduction in the proportion of surfaces contaminated with 5-fluouracil without a reduction in quantity of 5-fluouracil leads to a decrease in overall exposure or improvement in health benefits is not known.

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

There was significant variability in the potential cost savings. The way that the cost savings were calculated varied significantly between the studies. A meta-analysis was 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 included the costs based on actual drug consumption and costs of CSTD[64]. This study reported higher costs. The other studies simulated cost savings which is likely to overestimate the cost savings. None of the studies included personnel costs (costs involved in preparing the drugs and administration of the drugs) into account while 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 for decreased exposure, health benefits, or financial benefits.

Although the systematic review authors did not restrict the inclusion of studies based on the hospital size, all the studies which provided information on the size of the hospitals included only hospitals with at least 50 beds. Therefore, the evidence is applicable only in 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 exposed to residual hazardous drugs in patient-care areas too. 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-areas in order to provide a reasonable estimate of the health benefits of using CSTD. The healthcare professionals in the studies that provided data were mostly pharmacists or pharmacy technicians. Therefore, the evidence is mainly applicable for pharmacists and pharmacy technicians. Majority of the studies that provided information for this review reported on PhaSeal; therefore, the findings are mostly applicable to PhaSeal.

The overall quality of evidence was very low. The major reasons for this were the risk of bias in the studies, the outcomes reported in the studies, and the differences in methodology between the studies. All the studies were at serious risk of bias. The main reasons for this were the use of co-interventions (for example, additional training of staff in CSTD without the control group not receiving the same amount of training in safe handling) and lack of blinded measurement of outcomes. None of the studies reported the use of an independent person (blinded to the groups) for obtaining surface samples. In addition, all the studies were classified as 'no information' for confounding bias since inadequate information such as the surfaces being clean prior to start of the exposure. This is particularly a major 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 outcome measured was an objective outcome such as urine exposure where the levels can be measured using automated equipment, the risk of bias was serious. Future studies should try to address these issues by appropriate study design which ensures that the only difference between CSTD and control is the use of CSTD and the use of an independent person (blinded to the groups) for obtaining surface samples. Another major issue was the selective reporting bias. Results were not reported fully in many instances suggesting selective reporting bias. While we acknowledge that it is not mandatory to register observational studies, future studies should publish a protocol prior to conduct of the study and report all the results, so that it is clear that the results have not been reported based on the observations.

There was major inconsistency in the methodology and results of potential cost savings by CSTD. In particular, major differences in the results were noted between studies that used actual cost savings and simulated cost savings. Future studies should report the actual cost savings rather than simulate the cost savings.

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[77]. In addition, surface contamination can be considered a surrogate for exposure since there is association between surface contamination and exposure[18].

As shown in the sample size calculations below, the sample size included in this review was too small to detect a difference in urinary exposure. In the absence of information on how much difference in proportion of samples contaminated or 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.

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 conduct to allow better assessment of selective reporting bias will also allow better assessment of publication bias.

The systematic review authors followed the protocol which they formulated before the start of the study. The only major deviation was the sensitivity analysis using different intra-cluster correlation coefficients. However, they performed this only to assess the reason for the differences in the conclusions reached by the systematic review authors and a number the study authors; in particular, they did not use these post hoc sensitivity analyses to make any inferences on the effect of CSTD.

While the systematic review authors had minimised the errors in study selection and data extraction by independent study selection and data extraction, there is a potential that they had missed studies which did not mention about CSTD in the title or abstract. It is impractical to review the full text of all references (the study authors identified 7321 unique references using their search strategy). In this regard, they followed their 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 mentioning about CSTD in the title or abstract); therefore, the systematic review authors' conclusions are unlikely to change.

The intra-cluster correlation coefficient was not reported in any of the studies. Therefore, the systematic review authors used the intra-cluster correlation coefficient of 0.10 decided a priori based on studies about implementation research[84]. The results were robust in a sensitivity analysis of using 0.05 for intra-cluster correlation coefficient (i.e. half the correlation noted in similar studies) for most analyses; therefore, the systematic review authors' conclusions are unlikely to change if the studies had reported the intra-cluster correlation. However, the systematic review authors recommend the study authors to report intra-cluster correlation in future to enable accurate estimation of the results.

This is the first systematic review on the topic. The systematic review authors disagree with the study authors who concluded that routine CSTD use is beneficial[21, 26, 60-63, 65-68, 75]. Ignoring the design effect by not adjusting the effect estimates for intra-cluster correlation can lead to an underestimation of random errors[85]; therefore, 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.

The systematic review authors also disagreed with any guidelines or recommendations that CSTD should be used routinely whenever possible[1, 27, 40]. The possible reasons for our disagreement with those guidelines or recommendations that CSTD should be used routinely are the same as the reasons why we disagree with the study authors who concluded that routine CSTD use is beneficial.

Conclusions

Based on their findings that there was currently no evidence of differences in exposure or financial benefits between CSTD plus safe handling versus safe handling alone (very low quality evidence) and absence of reporting of health benefits by any of the studies, the systematic review authors concluded that 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.

The systematic review authors provided the following recommendations for future research on this issue. Future studies should be designed in such a way as to decrease the risk of bias in them. Well-designed multi-centred randomised controlled trials may be feasible if the exposure as measured by urinary samples is high (please Cochrane review for full details). The next best study design is interrupted time series, which are likely to provide a better estimate than uncontrolled before-after studies or cross-sectional studies. In all types of study designs, 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 decrease in exposure and the health benefits of using CSTD. This includes measures such as proper cleaning of the surfaces prior to exposure of the groups to CSTD plus safe handling or safe handling alone (i.e. all surfaces

should be cleaned and samples taken to ensure that they are clean, followed by exposure to a 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 and equal period of training of staff to perform CST plus safe handling or safe handling alone of infusional hazardous drugs in both groups. This will ensure that the effect observed is the true effect due to CSTD. The studies should also report on 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. Such studies should register the protocol prospectively, for example in journal publications, ClinicalTrials.gov, or scientific repositories such as https://zenodo.org/. Such studies could compare CSTD plus safe handling with 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 and can use multi-arm randomised controlled trials or factorial trial design. The primary outcome in such studies can be exposure to an appropriate selection of hazardous drugs used in the hospitals; the secondary outcomes can be health benefits and cost-effectiveness. In 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. The review authors estimate that it will be impossible to conduct randomised controlled trials powered to measure differences in health benefits. However, they estimate that 145 participants are necessary to estimate differences in exposure if the urinary contamination with hazardous drugs is high, which is feasible. They also highlight that if the urinary contamination with hazardous drugs is 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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