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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 (Protocol)

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[Intervention Protocol]

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

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To 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.

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 (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) (NIOSH 2004). New drugs that have a structure and toxicity profile that mimics existing drugs considered hazardous as per 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 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 (Chu 2012; Hon 2014; Poupeau 2016; Ramphal 2014; Schierl 2016; Sessink 2011; Sessink 2015; Sugiura 2011; Viegas 2014; Yoshida 2011; Yoshida 2013). 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 (Hon 2014; Ramphal 2014).

Occupational exposure to hazardous drugs increases mutations which 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 of women to hazardous drugs can also decrease fertility (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 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 (AASTSAS) (AASTSAS 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, 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) (AASTSAS 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 (B Braun 2017b) or chemotherapy transfer/reconstitution spikes (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 spillages (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). This may allow reuse of vials and decrease 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 that it 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 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 (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 systematic review will provide the best available evidence regarding this issue.

OBJECTIVES

To 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.

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 less feasible, which is one of the major reasons for the inclusion of non-randomised studies in Cochrane Reviews (Ijaz 2014). Therefore, we will include also other study designs beyond the RCT. We will include comparative studies that are commonly performed in this field, that is, historically controlled studies and cohort studies. We will also include interrupted time-series, controlled-before-and-after (CBA), 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 will include case-control studies because the outcomes following exposure are rare.

Types of participants

We will include 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 will also consider healthcare organisations in which healthcare staff are exposed to infusional hazardous drugs as participants with regards to outcomes such as surface contamination and aerosol contamination.

Types of interventions

We will include trials that have evaluated the effectiveness of closed-system drug-transfer of infusional hazardous drugs (e.g. PhaSeal system and ChemoClave system), with safe handling of infusional hazardous drugs (e.g. including Class II biological safety cabinet, isolator, and personal protective equipment) versus safe handling alone. We will accept any device described as a closed-system drug-transfer device by the manufacturer. We will include trials with any cointerventions provided they are not part of the randomised treatment or have been applied equally in both arms in non-randomised studies.

Types of outcome measures

Primary outcomes

- Exposure defined as either:
  - Environmental exposure measured with: surface samples, splashes, leakage tests, or atmospheric contamination, or
  - 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.

We will accept 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. These outcomes were identified as the most important outcomes for the target population by the Board of the UK Oncology Nursing Society 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 will consider the follow-up times for primary and secondary outcome measurement as: short term defined as up to one year, medium term defined as one to five years, and long term defined as longer than five years.

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

Search methods for identification of studies

Electronic searches

We will conduct a systematic literature search to identify all published and unpublished trials that can be considered eligible for inclusion in this review. We will adapt the search strategy we developed for MEDLINE (see Appendix 1) for use in the other electronic databases. We will impose no restrictions on language of publication. We will translate the key sections of potentially eligible non-English language papers to assess them fully for potential inclusion in the review as necessary.

We will search the following electronic databases from inception to present for identifying potential studies:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library);
- MEDLINE (OvidSP) (Appendix 1);
- Embase (OvidSP);
- NIOSHTIC (OSH-UPDATE);
- NIOSHTIC-2 (OSH-UPDATE);
- HSELINE (OSH-UPDATE);
- CISDOC (OSH-UPDATE);
- CINAHL (EBSCO);
- Science Citation Index Expanded (including Conference Proceedings);
- NHS Economic Evaluation Database (NHS EED);
- European Network of Health Economic Evaluation Databases (EURONHEED);
- Cost-Effectiveness Analysis Registry (CEA) at Tufts University.

We will also conduct a search for unpublished trials in ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/).

Searching other resources

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

Data collection and analysis

Selection of studies

We will conduct the selection of eligible studies in two stages. First, two review authors (KG and LB) will independently screen titles and abstracts of all potentially relevant studies found with our systematic search to exclude studies that clearly do not fulfil the criteria for inclusion. The same review authors will code them as 'include' (eligible or potentially eligible/unclear) or 'exclude'. At this stage, we will exclude all references that clearly do not fulfil our inclusion criteria or that fulfil our exclusion criteria. Second, we will retrieve the full-text study reports/publications and two review authors (KG and LB) will independently assess the full-text and identify studies for inclusion. At this stage, we will include all references that fulfil our inclusion criteria. We will record reasons for exclusion of the ineligible studies assessed as full-texts and report these in a 'Characteristics of excluded studies' table. We will resolve any disagreements through discussion. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA study flow diagram.

Data extraction and management

We will use an Excel-based data collection form for study characteristics and outcome data that has been piloted on at least one study in the review. Two review authors (KG and LB) will extract 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, gender, inclusion criteria, and exclusion criteria.
- Interventions: description of intervention, comparison (elements included in safe handling in the control group), and cointerventions.
- 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) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus. One review author (KG) will transfer data into Review Manager 5 (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A third review author (CT) will spot-check study characteristics and data for accuracy against the trial report. Should we decide to include studies published in one or more languages in which our author team is not proficient, we will arrange for a native speaker or someone sufficiently qualified in each foreign language to fill in a data extraction form for us.

Assessment of risk of bias in included studies

For each RCT, two review authors (KG and LB) will independently assess risk of bias using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion. We will 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 will grade each potential risk of bias as high, low, or unclear, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for a sample obtained and analysed by an automated machine may be very different than for an outcome such as time for preparation of the drug). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

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

- 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.
- 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 group).
- Changes or differences in drug residue on the drug vials because of different batches or different manufacturers of the drug.

We will 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 (Evers 2005) or the Philips 2004 checklist.

We will consider all domains other than blinding of healthcare providers to be key domains. We will judge a study to have a high risk of bias overall when we judge one or more key domains to have a high risk of bias. Conversely, we will judge a study to have a low risk of bias when we judge low risk of bias for all key domains. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will enter the outcome data for each study into the data tables in Review Manager 5 to calculate the treatment effects (RevMan 2014). We will use odds ratio if we include case-control studies or risk ratio if we do not identify any case-control studies for dichotomous outcomes (this is because risk ratios are much easier to interpret; however, risk ratios cannot be calculated in case-controlled trials without the use of risk from another study), and mean differences for continuous outcomes. If only effect estimates and their 95% confidence intervals or standard errors are reported in studies, we will enter these data into Review Manager 5 using the generic inverse variance method (RevMan 2014). We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader, and report where the directions were reversed if this was necessary. When the results cannot be entered in either way, we will describe them in the 'Characteristics of included studies' table, or enter the data into additional tables.

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

Unit of analysis issues

For studies that employ a cluster-randomised design and that report sufficient data to be included in the meta-analysis but do not make an allowance for the design effect, we will calculate the design effect based on a fairly large assumed intra-cluster correlation of 0.10. We base this assumption of 0.10 being a realistic estimate by analogy on studies about implementation research (Campbell 2001). We will follow the methods stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) for the calculations.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data are missing, such as standard deviations or correlation coefficients, and they cannot be obtained from the authors, we will 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 will assess the clinical homogeneity of the results of included studies based on similarity of population, intervention, outcome, and follow-up. We will consider populations as similar when they are staff who are exposed to infusional hazardous drugs, for example, oncology nurses or pharmacists who handle infusional hazardous drugs. We will consider interventions as similar when it is clear that the system is a closed-system drug transfer device. We will combine results data produced by each of the measures of contamination separately (e.g. urine tests, surface contamination, atmospheric contamination, and surface contamination) and we will combine cancer- and fertility-related outcome data separately. We will regard follow-up times of up to one year, between one to five years, and longer than five years as different.

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (above 50% as per *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)), we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

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

Data synthesis

We will pool data from studies we judge to be clinically homogeneous using Review Manager 5 software (RevMan 2014). If two or more studies provide usable data in any single comparison, we will perform meta-analysis. However, we will not pool data from different study designs (i.e. RCT and non-randomised studies). For costs, we will use an international exchange rate based on purchasing power parities (PPPs) to convert cost estimates to UK pound sterling (GBP), and we will use the gross domestic product (GDP) deflators (or implicit price deflators for GDP) to convert cost estimates to 2017 GBP 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 will use both a fixed-effect model and a random-effects model to perform the meta-analyses and will report the more conservative model. When the I^2 statistic is higher than 75%, we will not pool results of studies in meta-analysis.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. device A versus safe handling and device B versus safe handling) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

'Summary of findings' table

We will create a 'Summary of findings' table using all outcomes (i.e. immediate to short-term contamination, short-term health benefits, long-term reproductive health benefits, development of any type of cancers, adverse events, and potential cost savings). We will use 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 relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use 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. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes.

We will compile an additional GRADE table showing all our decisions about the quality of evidence and their justifications.

Subgroup analysis and investigation of heterogeneity

We will carry out the following subgroup analyses.

- Study design: CBA studies versus other non-randomised study designs; unit of analysis is individual versus unit of analysis is cluster.
- 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 will 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 will use the Chi^2 test to test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

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

Reaching conclusions

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

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REFERENCES

Additional references

AASTSAS 2008

AASTSAS. Prevention Guide Safe Handling of Hazardous Drugs, 2008. asstsas.qc.ca/sites/default/files/publications/documents/Guides_Broch_Depl/GP65A_hazardous_drugs.pdf (accessed 27 June 2017).

ASHP 2006

American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *American Journal of Health-System Pharmacy* 2006;**63**(12):1172–91.

Awad 2009

Awad A, Stuve O. Cyclophosphamide in multiple sclerosis: scientific rationale, history and novel treatment paradigms. *Therapeutic Advances in Neurological Disorders* 2009;**2**(6): 50–61.

B Braun 2017a

B Braun. Onguard® closed system transfer device (CSTD), 2017. www.bbraunusa.com/products.html?prid=PRID00006969 (accessed 7 June 2017).

B Braun 2017b

B Braun. 0.2 micron air venting filter, hydrophobic, 2017. us.bbraunoem.com/cps/rde/xchg/oem-bbraunoem-en-us/hs.xsl/products.html?prid=S4001002 (accessed 23 June 2017).

Bateman 2015

Bateman R, Santillo M, Hardy L, Lennan E (NHS Pharmaceutical Quality Assurance Committee). Guidance on the safe handling of monoclonal antibody (mAb) products, 5th edition, 2015. ukons.org/downloads/Proposed_national_requirements_for_overlabelling_of_foreign_%28non-English_language%29_imported_medicines.pdf (accessed 27 June 2017).

BD 2017a

Becton Dickinson. BD Phaseal™ system for hazardous drug handling. System components, 2017. www.bd.com/pharmacy/phaseal/components.asp (accessed 7 June 2017).

BD 2017b

Becton Dickinson. Chemo safety system, 2017. www.carefusion.com/our-products/infusion/iv-therapy/chemo-safety-system (accessed 7 June 2017).

BNF 2017

British National Formulary. Cytotoxic drugs, 2017. bnf.nice.org.uk/treatment-summary/cytotoxic-drugs.html (accessed 7 June 2017).

Brogan 2000

Brogan PA, Dillon MJ. The use of immunosuppressive and cytotoxic drugs in non-malignant disease. *Archives of Disease in Childhood* 2000;**83**(3):259–64.

Campbell 2001

Campbell MK, Mollison J, Grimshaw JM. Cluster trials in implementation research: estimation of intracluster correlation coefficients and sample size. *Statistics in Medicine* 2001;**20**(3):391–9.

Cassidy 2011

Cassidy J, Saltz L, Twelves C, Van Cutsem E, Hoff P, Kang Y, et al. Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients. *Annals of Oncology* 2011;**22**(12): 2604–9.

Chu 2012

Chu WC, Hon CY, Danyluk Q, Chua PP, Astrakianakis G. Pilot assessment of the antineoplastic drug contamination levels in British Columbian hospitals pre- and post-cleaning. *Journal of Oncology Pharmacy Practice* 2012;**18**(1):46–51.

Connor 2005

Connor TH, Sessink PJ, Harrison BR, Pretty JR, Peters BG, Alfaro RM, et al. Surface contamination of chemotherapy drug vials and evaluation of new vial-cleaning techniques: results of three studies. *American Journal of Health-System Pharmacy* 2005;**62**(5):475–84.

Connor 2014

Connor TH, Lawson CC, Polovich M, McDiarmid MA. Reproductive health risks associated with occupational exposures to antineoplastic drugs in health care settings: a review of the evidence. *Journal of Occupational and Environmental Medicine* 2014;**56**(9):901–10.

Easty 2015

Easty AC, Coakley N, Cheng R, Cividino M, Savage P, Tozer R, et al. Safe handling of cytotoxics: guideline recommendations. *Current Oncology* 2015;**22**(1):e27–37.

Egger 1997

Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315** (7109):629–34.

Equashield 2017

Equashield LLC. Equashield®, 2017. www.equashield.com/ (accessed 7 June 2017).

Evers 2005

Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. *International Journal of Technology Assessment in Health Care* 2005;**21**(2):240–5.

Favier 2003

Favier B, Gilles L, Ardiet C, Latour JF. External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. *Journal of Oncology Pharmacy Practice* 2003;**9**(1):15–20.

Fernandes Moca Trevisani 2013

Fernandes Moca Trevisani V, Castro AA, Ferreira Neves Neto J, Atallah AN. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/14651858.CD002265.pub3

Fleury-Souverain 2014
Fleury-Souverain S, Nussbaumer S, Mattiuzzo M, Bonnabry P. Determination of the external contamination and cross-contamination by cytotoxic drugs on the surfaces of vials available on the Swiss market. *Journal of Oncology Pharmacy Practice* 2014;**20**(2):100–1.

Ge 2015
Ge Y, Peng Q, Zhang S, Zhou H, Lu X, Wang G. Cyclophosphamide treatment for idiopathic inflammatory myopathies and related interstitial lung disease: a systematic review. *Clinical Rheumatology* 2015;**34**(1):99–105.

Guillemette 2014
Guillemette A, Langlois H, Voisine M, Merger D, Therrien R, Mercier G, et al. Impact and appreciation of two methods aiming at reducing hazardous drug environmental contamination: the centralization of the priming of IV tubing in the pharmacy and use of a closed-system transfer device. *Journal of Oncology Pharmacy Practice* 2014;**20**(6): 426–32.

Harrison 2006
Harrison BR, Peters BG, Bing MR. Comparison of surface contamination with cyclophosphamide and fluorouracil using a closed-system drug transfer device versus standard preparation techniques. *American Journal of Health-system Pharmacy* 2006;**63**(18):1736–44.

Hartman 2001
Hartman AR, Fleming GF, Dillon JJ. Meta-analysis of adjuvant cyclophosphamide/methotrexate/5-fluorouracil chemotherapy in postmenopausal women with estrogen receptor-positive, node-positive breast cancer. *Clinical Breast Cancer* 2001;**2**(2):138–43.

Hazlewood 2016
Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. *Cochrane Database of Systematic Reviews* 2016, Issue 8. [DOI: 10.1002/14651858.CD010227.pub2

Healthmark 2017
Healthmark. Chemo spikes: chemotherapy reconstitution spikes, 2017. www.healthmark.ca/2-36-10-Chemo-Spikes_en.html?ProduitID=21 (accessed 23 June 2017).

Hedmer 2005
Hedmer M, Georgiadi A, Bremberg ER, Jonsson BA, Eksborg S. Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden. *Annals of Occupational Hygiene* 2005;**49**(7):629–37.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 (updated March 2011) The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hon 2014
Hon CY, Teschke K, Demers PA, Venners S. Antineoplastic drug contamination on the hands of employees working throughout the hospital medication system. *Annals of Occupational Hygiene* 2014;**58**(6):761–70.

HSE 2017
Health and Safety Executive. Safe handling of cytotoxic drugs in the workplace, 2017. www.hse.gov.uk/healthservices/safe-use-cytotoxic-drugs.htm (accessed 7 June 2017).

ICUMED 2017
ICU Medical Inc. Chemoclave® needlefree closed systems and closed system transfer devices (CSTDs), 2017. www.icumed.com/products/oncology/hazardous-drug-closed-systems-and-cstds/chemoclave.aspx (accessed 7 June 2016).

Ijaz 2014
Ijaz S, Verbeek JH, Mischke C, Ruotsalainen J. Inclusion of nonrandomized studies in Cochrane systematic reviews was found to be in need of improvement. *Journal of Clinical Epidemiology* 2014;**67**(6):645–53.

ISOPP 2007
International Society of Oncology Pharmacy Practitioners Standards Committee. ISOPP standards of practice. Safe handling of cytotoxics. *Journal of Oncology Pharmacy Practice* 2007;**13 Suppl**:1–81.

Mahmoodi 2017
Mahmoodi M, Soleyman-Jahi S, Zendehdel K, Mozdarani H, Azimi C, Farzanfar F, et al. Chromosomal aberrations, sister chromatid exchanges, and micronuclei in lymphocytes of oncology department personnel handling anti-neoplastic drugs. *Drug and Chemical Toxicology* 2017;**40**(2):235–40.

Mason 2003
Mason HJ, Morton J, Garfitt SJ, Iqbal S, Jones K. Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy. *Annals of Occupational Hygiene* 2003;**47** (8):681–5.

McDiarmid 2010
McDiarmid MA, Oliver MS, Roth TS, Rogers B, Escalante C. Chromosome 5 and 7 abnormalities in oncology personnel handling anticancer drugs. *Journal of Occupational and Environmental Medicine* 2010;**52**(10): 1028–34.

McDiarmid 2014
McDiarmid MA, Rogers B, Oliver MS. Chromosomal effects of non-alkylating drug exposure in oncology personnel. *Environmental and Molecular Mutagenesis* 2014; **55**(4):369–74.

Moretti 2015
Moretti M, Grollino MG, Pavanello S, Bonfiglioli R, Villarini M, Appolloni M, et al. Micronuclei and chromosome aberrations in subjects occupationally exposed to antineoplastic drugs: a multicentric approach. *International Archives of Occupational and Environmental Health* 2015;**88**(6):683–95.

Mulder 2015
Mulder RL, Paulides M, Langer T, Kremer LC, van Dalen EC. Cyclophosphamide versus ifosfamide for paediatric and young adult bone and soft tissue sarcoma patients. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD006300.pub2

Naito 2012
Naito T, Osawa T, Suzuki N, Goto T, Takada A, Nakamichi H, et al. Comparison of contamination levels on the exterior surfaces of vials containing platinum anticancer drugs in Japan. *Biological & Pharmaceutical Bulletin* 2012; **35**(11):2043–9.

NCBI 1978
National Center for Biotechnology Information. Cytotoxins, 1978. www.ncbi.nlm.nih.gov/mesh/68003603 (accessed 7 June 2017).

NIOSH 2004
National Institute for Occupational Safety and Health. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings, 2004. www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf (accessed 7 June 2017).

Nunes 2015
Nunes AA, da Silva AS, Souza KM, Koury Cde N, de Mello LM. Rituximab, fludarabine, and cyclophosphamide versus fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia: a systematic review with meta-analysis. *Critical Reviews in Oncology/hematology* 2015;**94** (3):261–9.

Philips 2004
Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment* 2004;**8**(36): 1–158.

Poormoghim 2012
Poormoghim H, Moradi Lakeh M, Mohammadipour M, Sodagari F, Toofaninjed N. Cyclophosphamide for scleroderma lung disease: a systematic review and meta-analysis. *Rheumatology International* 2012;**32**(8):2431–44.

Poupeau 2016
Poupeau C, Tanguay C, Caron NJ, Bussieres JF. Multicenter study of environmental contamination with cyclophosphamide, ifosfamide, and methotrexate in 48 Canadian hospitals. *Journal of Oncology Pharmacy Practice* 2016 Oct 31;**Epub ahead of print**. [DOI: 10.1177/1078155216676632

Power 2014
Power LA, Sessink PJ, Gesy K, Charbonneau F. Hazardous drug residue on exterior vial surfaces: evaluation of a commercial manufacturing process. *Hospital Pharmacy* 2014;**49**(4):355–62.

Ramphal 2014
Ramphal R, Bains T, Vaillancourt R, Osmond MH, Barrowman N. Occupational exposure to cyclophosphamide in nurses at a single center. *Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine* 2014;**56**(3):304–12.

Ramsay 2003
Ramsay CR, Matowe L, Grilli R, Grimshaw JM, Thomas RE. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):613–23.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rodriguez-Peralvarez 2017
Rodriguez-Peralvarez M, Guerrero-Misas M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2017, Issue 3. [DOI: 10.1002/14651858.CD011639.pub2

Schierl 2016
Schierl R, Masini C, Groeneveld S, Fischer E, Bohlandt A, Rosini V, et al. Environmental contamination by cyclophosphamide preparation: comparison of conventional manual production in biological safety cabinet and robot-assisted production by APOTECAchemo. *Journal of Oncology Pharmacy Practice* 2016;**22**(1):37–45.

Sessink 2011
Sessink PJ, Connor TH, Jorgenson JA, Tyler TG. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *Journal of Oncology Pharmacy Practice* 2011;**17**(1):39–48.

Sessink 2015
Sessink PJ, Leclercq GM, Wouters DM, Halbardier L, Hammad C, Kassoul N. Environmental contamination, product contamination and workers exposure using a robotic system for antineoplastic drug preparation. *Journal of Oncology Pharmacy Practice* 2015;**21**(2):118–27.

Skov 1992
Skov T, Maarup B, Olsen J, Rorth M, Winthereik H, Lynge E. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. *British Journal of Industrial Medicine* 1992;**49**(12):855–61.

Sterne 2016
Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Sugiura 2011
Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T. Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological

monitoring of occupational exposure to cyclophosphamide. *Journal of Oncology Pharmacy Practice* 2011;**17**(1):14–9.

USP 2017
US Pharmacopeial Convention (USP). General chapter <800> Hazardous drugs - handling in healthcare settings, 2017. http://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare (accessed 14 October 2017).

Viegas 2014
Viegas S, Padua M, Veiga AC, Carolino E, Gomes M. Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals. *Environmental Monitoring and Assessment* 2014;**186**(11):7807–18.

Yoshida 2011
Yoshida J, Koda S, Nishida S, Yoshida T, Miyajima K, Kumagai S. Association between occupational exposure levels of antineoplastic drugs and work environment in five hospitals in Japan. *Journal of Oncology Pharmacy Practice* 2011;**17**(1):29–38.

Yoshida 2013
Yoshida J, Koda S, Nishida S, Nakano H, Tei G, Kumagai S. Association between occupational exposure and control measures for antineoplastic drugs in a pharmacy of a hospital. *Annals of Occupational Hygiene* 2013;**57**(2): 251–60.

Zhu 2017
Zhu LB, Liu LL, Yao L, Wang LN. Efficacy and safety of tacrolimus versus cyclophosphamide for primary membranous nephropathy: a meta-analysis. *Drugs* 2017;**77** (2):187–99.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. (closed-system transfer device* or closed system transfer device* or CSTD or closed-system drug transfer device* or closed system drug transfer device* or closed-system drug-transfer device* or closed system drug-transfer device* or CSDTD).tw.
2. (Phaseal or Spikes or Equashield or Texium or SmartSite or Alaris or VialShield or LifeShield or ChemoClave or Tevadaptor or OnGuard or HDClean).tw.
3. (effect* or control or controls* or controla* or controle* or controli* or controll* or evaluation* or program*).tw.
4. (work or works* or work'* or worka* or worke* or workg* or worki* or workl* or workp* or occupation* or prevention* or protect*).tw.
5. 2 and 3 and 4
6. 1 or 5

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: KG.

Designing the protocol: KG.

Co-ordinating the protocol: KG.

Designing search strategies: KG.

Writing the protocol: KG.

Providing general advice on the protocol: LB, CT, EL, MK, and JFB.

Securing funding for the protocol: KG.

DECLARATIONS OF INTEREST

Kurinchi Gurusamy and Lawrence Best: We received a grant for GBP 12,000 from the UK Oncology Nursing Society to conduct this Cochrane Review.

Cynthia Tanguay: I am a member of the Working Committee on the Safe Handling of Hazardous Drugs established by the Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS).

Elaine Lennan: None known.

Mika Korva: None known.

Jean-François Bussières: I am a member of the Working Committee on the Safe Handling of Hazardous Drugs established by the Association paritaire pour la santé et la sécurité du travail du secteur affaires sociales (ASSTSAS).

The outcomes were chosen by the funders of this review, the board of the UK Oncology Nursing Society who represent the target population of the interventions evaluated. However, the peer referees also considered these outcomes to be the most important.

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