

Review of economic data on closed system transfer drug for preparation and administration of hazardous drugs

Annaelle Soubieux,¹ Cynthia Tanguay ,¹ Jean Lachaine,² Jean-François Bussières^{1,2}

¹Pharmacy practice research unit, CHU Sainte-Justine, Montreal, Canada
²Faculté de pharmacie, Université de Montréal, Montreal, Canada

Correspondence to

Jean-François Bussières, Unité de Recherche en Pratique Pharmaceutique, Département de pharmacie, Centre Hospitalier Universitaire Sainte-Justine, Montréal, QC H3T 1C5, Canada; jf.bussieres@sss.gouv.qc.ca

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ABSTRACT

Objectives The objectives of this study were to review economic data on the use of closed system drug transfer devices (CSTDs) for preparing and administering hazardous drugs, and to evaluate the quality of data reporting as defined by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).

Methods All references from a recent Cochrane review about CSTDs were evaluated for inclusion. A literature review was also conducted. Articles containing economic data about the use of CSTDs were retained for analysis. Two researchers independently graded the articles according to the 24-item CHEERS checklist.

Results Of the 138 articles identified initially, 12 were retained for analysis. Nine of these studies did not report acquisition costs or did not detail acquisition costs. Six studies reported economic benefits associated with the use of CSTDs, all related to extending the beyond-use date. The mean number of CHEERS criteria fulfilled by the included articles was 9.2 (SD 2.4).

Conclusions CSTDs are costly to acquire. However, few studies have examined the economic impact of these devices, and the existing studies are incomplete. As a result, hospitals planning to implement these devices will be unable to make a sound economic evaluation. Robust economic evaluation of CSTDs is needed.

INTRODUCTION

Hazardous drugs are compounds that are carcinogenic or teratogenic, or that present reproductive, organ or genetic toxicity.¹ Healthcare workers, especially nurses and pharmacy personnel, experience occupational exposure to these hazardous drugs. Various strategies are used to limit surface contamination and workers' exposure, such as using biological safety cabinets, priming intravenous tubing in the pharmacy, using personnel protective devices, and providing training.¹

Closed system drug transfer devices (CSTDs) can be used for preparing and administering hazardous drugs, in conjunction with other safe handling techniques. These devices create a 'closed' environment that prevents aerosols from escaping.¹ Although CSTDs provide additional protection, they must be used inside a safety cabinet for the preparation of hazardous drugs.²

A recent Cochrane review concluded that there is no high-quality evidence to support (or refute) the routine use of these devices in addition to safe handling.³ Even though some studies have shown a reduction in contamination with use of CSTDs,^{4,5} others have reported lower surface contamination

without their use.⁶ Some of these CSTD studies had observation biases and lacked an adequate control group. Many groups have shown a reduction in surface contamination over time, without using CSTDs.^{7,8} Certain technical flaws have also been reported (eg, spills, trouble handling the devices).^{9–11}

A key impediment to use of CSTDs is their high cost.¹² One hospital estimated a yearly cost of US\$1.5 million to implement CSTDs.¹² Another centre stopped its participation in a study because of the high acquisition costs.¹³ Yet another centre reported spending 75% more in implementation costs than what had been estimated by the vendor.¹⁴ To make an informed decision about CSTDs, healthcare organisations must be able to adequately evaluate the costs involved, especially considering the uncertainty regarding the health benefits for workers.

To date, economic evaluations on the use of CSTDs appear to be incomplete.³ The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) can be used to design and evaluate economic data in healthcare settings to ensure adequate reporting of all key variables.¹⁵

The objectives of this study were to review economic data on the use of CSTDs for preparing and administering hazardous drugs and to evaluate the quality of data reporting as defined by the CHEERS criteria.¹⁵

METHODS

Study selection

All references from the Cochrane study were considered³ for inclusion. In addition, a literature review was conducted on 12 March 2018 using the PubMed, CINAHL, HAL, ERUDIT and these.fr databases, a cost-effectiveness analysis registry¹⁶ and the Economic Evaluation Database of the National Health Service (UK).¹⁷ The following search terms were used: 'closed system transfer device' OR 'CSTD'. A manual search was also conducted.

For articles selected on the basis of initial screening of titles, the full text was read to identify articles relevant for this review. All studies that presented economic data on the use of CSTDs were included, even if economic evaluation was not their main goal. A spreadsheet with the following elements was created: author, year and country of each study, the CSTD evaluated; costs and cost savings; and study limitations.



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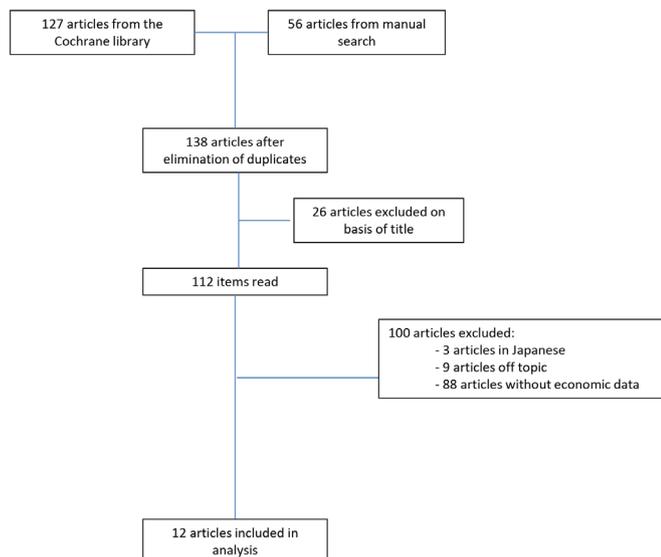


Figure 1 Selection of studies for inclusion in review.

Quality of reporting

For all included studies, the CHEERS checklist was applied ($n=24$ criteria). For each study, every criterion was reviewed (and categorised as yes, no or not applicable) independently by two members of the research team (AS, CT). Differences were resolved by consensus.

RESULTS

Economic data on the use of CSTDs

A total of 12 studies were included (figure 1)^{10 11 18–27}: 10 original articles, one thesis and one poster presentation. Studies were conducted in six countries: USA ($n=4$), Spain ($n=3$), France ($n=2$), Malaysia ($n=1$), Hungary ($n=1$) and Turkey ($n=1$). All but one of the studies took place in a hospital setting; the single exception was conducted in a veterinary setting.²³ The PhaSeal device (Becton Dickinson) was the CSTD most frequently evaluated (in nine of the 12 studies).

Six of the studies presented economic data about preparing and administering hazardous drugs, four examined the costs of preparation only, and two did not provide details of the economic evaluation.

Two studies presented actual costs (table 1), six showed estimated costs (table 2), and four used a combination of actual and estimated costs (table 3). Five studies concluded that there were cost savings associated with using CSTDs, whereas

seven showed that costs increased. Among the five studies that reported cost savings, two did not calculate the acquisition costs. Notably, acquisition cost was the direct cost that was most frequently evaluated ($n=10$). However, seven of these studies did not provide detailed itemisation of costs. Other direct costs included workers' time ($n=2$) and drug costs ($n=5$). One study evaluated the additional waste generated by the CSTDs,¹⁰ and another evaluated the cost of drugs lost in the 'dead space' of these devices.¹⁸ Of the eight studies evaluating the costs, four did not detail costs per dose prepared (CSTDs or conventional system). Six studies evaluated cost savings in terms of being able to extend the beyond-use date beyond that specified by US Pharmacopoeia standards (from 6 hours to 7 days), hypothesising that the CSTD could prolong sterility up to 7 days.

Quality of reporting

Two studies were excluded from the CHEERS analysis: the poster presentation, which lacked detailed results,¹⁹ and one study that contained only a brief mention of costs and no formal economic evaluation.²⁰ Among the remaining 10 studies, the mean number of CHEERS criteria fulfilled was 9.2 (SD 2.4) out of 24. The maximum number of criteria observed in a single study was 12. In most studies, key elements were lacking, notably an abstract with structured economic data, a control group (or details about selection of controls), the study perspective, the choice of outcome measures and their efficacy, an uncertainty analysis, and sources of funding (figure 2). None of the studies included a sensitivity analysis. In only four studies did the authors declare no conflicts of interest; five others declared conflicts of interests related to the manufacturers, and three studies failed to mention potential conflicts.

DISCUSSION

CSTD costs

Only 12 studies that presented results on costs associated with the use of CSTDs were found, and all were of low quality. This dearth of data is unfortunate, considering the high costs of these devices. In addition, no study presented a thorough economic evaluation that met most or all of the CHEERS criteria, and key results were lacking from all of the studies.

Only one study took into account actual acquisition costs. Actual acquisition costs ranged between \$15.73 and \$24.09 per dose. However, costs were not detailed, and acquisition costs were often the only costs used. In four of the eight studies evaluating the costs, the costs per dose were not detailed. The number of preparations varied from one hospital to another, so cost per dose is probably the most relevant outcome for readers to position themselves on

Table 1 Economic data on closed system drug transfer devices from studies that reported actual costs

Reference	CSTD	Costs		Cost savings		CHEERS criteria	Limitations
		Type	Values	Type	Values		
Ozyaman (2016) Turkey ¹⁹	PhaSeal (compared with conventional system)	Not evaluated	Not evaluated	Extension of BUD	€36 137/3 months	NA	Acquisition costs not evaluated. Partial data reported (as a poster).
Kicenuik <i>et al</i> (2017) USA ²³	Equashield PhaSeal (compared with conventional system)	Acquisition costs, administration time	Equashield: US\$15.73/dose 24 s/dose PhaSeal: US\$24.09/dose 29.1 s/dose Conventional: 26.9 s/dose	Not evaluated	Not evaluated	12/24	Phaseal sold by the unit and Equashield sold in bulk. Simulated administrations. Acquisition costs not evaluated for conventional system. Conflicts of interest: CSTDs provided free of charge by the manufacturers.

BUD, beyond-use date; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CSTD, closed system transfer device; NA, not applicable.

Table 2 Economic data on closed system drug transfer devices from studies that reported cost estimates

Reference	CSTD	Costs		Costs saving		CHEERS criteria	Limitations
		Type	Values	Type	Values		
		Estimated costs	US\$16/dose	Not evaluated	Not evaluated		
Massoomi <i>et al</i> (2008) USA ²⁰	PhaSeal	Estimated costs	US\$16/dose	Not evaluated	Not evaluated	NA	Costs not detailed. No control group. Conflicts of interest not specified.
Mullot <i>et al</i> (2008) France ¹⁰	Tevadaptor Phaseal	Estimated costs: acquisition costs, sterilisation costs, volume of waste, preparation time	Phaseal: €3000/week €156 000/year (for ~24 400 preparations) Tevadaptor: €3180/week €160 000/year (for 24 400 preparations)	Not evaluated	Not evaluated	8/24	Costs and costs per dose not detailed. No control group without CSTD.
Rowe <i>et al</i> (2012) USA ²¹	PhaSeal	Not evaluated	Not evaluated	Extension of BUD	US\$385 444/6 months	10/24	Costs not detailed. Theoretical reported savings. No control group. Conflict of interest: Carmel Pharma
Juhász (2016) Hungary ²²	Tevadaptor (compared with conventional system)	Not evaluated	Not evaluated	Estimated savings by extension of BUD	Centre 1: €13 529/3 months Centre 2: €4199.82/3 months	13/24	Acquisition costs not evaluated.
Forte Pérez-Minayo <i>et al</i> (2016) Spain ¹¹	SmartSite Vented Phial Access Device SmartSite VialShield Closed Access Device	Estimated costs	€105 600/year (if CSTD used for all preparations, ~24 000 preparations) €42 560/year (if CSTD used for selected preparations, 4300 preparations)	Not evaluated	Not evaluated	6/24	Costs and costs per dose not detailed. Use of a single component of the CSTD (awl)*. No comparison with a conventional system.
Calzado-Gómez <i>et al</i> (2017) Spain ¹⁸	Phaseal, SmartSite, Carefusion VM04, Hospira Clave CH70, Hospira Clave CH74, Fresenius Extrasprike, Chemo V Minisprike, ChemoAide	Estimated acquisition costs, drug loss	Between €5.57 (Carefusion) and €8.44/ preparation (Hospira) Between €255 668/year (Phaseal) and €544 808/year (Chemo V Minisprike) Up to 0.78 mL lost/phial	Not evaluated	Not evaluated	12/24	No control group without CSTD. Conflicts of interest not specified.

* Awl: perforator

BUD, beyond-use date; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CSTD, closed system transfer device; NA, not applicable.

Table 3 Economic data on closed system drug transfer devices from studies that reported both actual and estimated costs

Reference	CSTD	Costs		Costs saving		CHEERS criteria	Limitations
		Type	Values	Type	Values		
Edward <i>et al</i> (2013) USA ²⁴	Phaseal	Acquisition cost	US\$106 557/year	Extension of BUD	US\$96 349 /50 days Estimated annual cost US\$703 047 /year The average waste avoidance per phial was 29%	10/24	Acquisition costs and costs per dose not detailed. Conventional system: drugs discarded immediately after first use (overestimates savings). Conflicts of interest: funding from Celgene, Millennium and Seattle Genetics.
Barny <i>et al</i> 2015 France ²⁵	Phaseal (compared with conventional system)	Acquisition costs, preparation time, ganciclovir costs	Phaseal: €39.04±37.26 /preparation Conventional system: €34.19±11.39/preparation	Estimated savings by extension of BUD	€4.62 (2 days extension) €11.64/ preparation (7 days extension),	10/24	Costs not detailed. Conflict of interest: thanks to Becton Dickinson.
González-Haba <i>et al</i> 2016 Spain ²⁹	ChemoClave (eight combinations tested)	Acquisition costs, preparation time, estimated annual cost	Between €4.46 and €8.52/dose Between 41.0 and 77.0 s/dose €300000/year	Estimated savings if not all parts of the system are used	€1.03/dose €39069/year	6/24	Acquisition costs not detailed. No control group without CSTD. Simulated preparations. Conflicts of interest not specified.
Chan <i>et al</i> 2016 Malaysia ²⁶	Phaseal (compared with conventional system)	Acquisition costs (CSTD +other consumables), drug costs, estimated cost per dose, estimated annual cost Estimated costs for conventional system.	Phaseal: US\$92072/3 months US\$23106/3 months (acquisition costs only) US\$40.92/preparation US\$368289/year Conventional system: US\$83155/3 months US\$6988/3 months (acquisition costs only)	Extension of BUD	10.5% of drug costs	11/24	Costs per dose for conventional system not detailed. Conflict of interest: Becton Dickinson provided information.

BUD, beyond-use date; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CSTD, closed system transfer device.

the economic impact of CSTDs in their hospital. Economic evaluations on the use of CSTDs should also consider storage, elimination of waste,¹⁴ implementation and training time, and the quantity of drugs lost in the devices.

COST SAVINGS

There was marked inconsistency in the conclusions: some studies presented high costs, and others reported important cost savings. The savings were based mainly on extending the beyond-use date. The US Pharmacopoeia requires a preparation to be used within 6 hours. Some authors claim that using a CSTD can preserve the sterility and that preparations can be kept for up to 7 days.^{21 28} Studies supporting this claim have methodological flaws and lack a control group to evaluate the level of contamination when compounding without CSTD. It could be argued that the sterility of most antineoplastic drug preparations would be kept when compounded in a biological safety cabinet by a properly trained technician. For instance, Rowe *et al*²¹ found that 1.86% of samples were contaminated, but attributed this to an outside contamination. No tests were conducted without using a CSTD. In addition, cost savings were mostly theoretical and failed to take into account that the entire volume of a phial would not necessarily be used in the 7 days following its preparation.

Quality of reporting

The majority of the CHEERS criteria were not reported. In the included studies, the reported methods for calculating costs lacked

details, and cost data were incomplete. Future studies should detail all costs (and cost savings) to allow generalisation and reproducibility. Sensitivity analyses should also be conducted. Authors of future studies are encouraged to review the CHEERS checklist to improve the quality of the results reported; the criteria should also be reviewed when designing the study. In addition to comparing several CSTDs, authors should make sure to include the costs of the conventional system for preparing and administering hazardous drugs and determine the quantity of devices needed per dose and overall. None of the included studies involved a formal economic evaluation. Such a study should also be free from any conflict of interest. Ideally, economic studies should also include efficacy criteria. Although the US Pharmacopoeia² recommends use of CSTDs for the administration of hazardous drugs, this organisation also emphasises that there is no guarantee that all CSTDs will perform adequately. A performance protocol for CSTDs is needed, in addition to well conducted studies designed to evaluate if their use can lead to measurable health benefits for workers.

A centre looking to implement CSTDs should critically review the literature to support their choice. It should first include an evaluation of their current working practices to identify other safe handling practices that could be applied. It is recommended that environmental monitoring is performed twice per year to identify the current state of surface contamination; it would be ideal to have at least 1 year of data before implementing a change to avoid confusing the effect of an increase in workers' awareness with the effect of the change implemented. Centres should make sure that

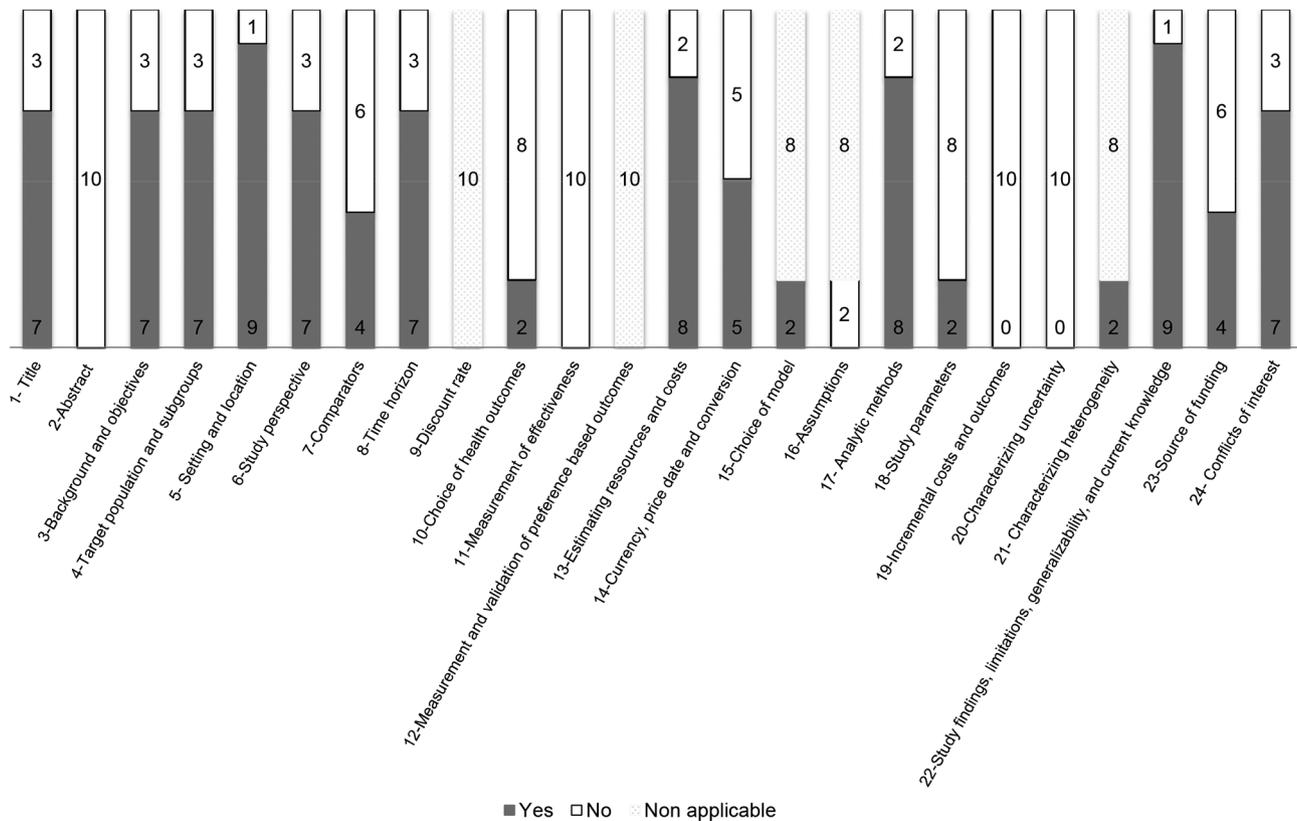


Figure 2 Evaluation of study quality according to CHEERS tool (Consolidated Health Economic Evaluation Reporting Standards), with data presented as number of studies meeting each criterion.

they consider all costs incurred, which in addition to acquisition costs include additional workload, training resources, storage, incineration of material and potential drug loss in the device.

Strengths and limitations

Two authors independently rated the studies according to the CHEERS checklist. Given the general lack of economic data in the literature, we included all studies that presented costs, even though none of the included studies presented a formal economic evaluation. In the CHEERS analysis, we rated a criterion as 'present' if the study fulfilled any aspect (not necessarily all aspects) of the relevant

CHEERS statement (ie, minimal level). Even so, the CHEERS scores were low, and the analysis was conservative.

CONCLUSIONS

This literature review identified a lack of properly conducted economic evaluations of CSTDs, despite their high acquisition costs. As a result, hospitals that are considering implementation of these devices will be unable to make a sound and informed decision.

We advocate for a robust and complete economic evaluation of the use of CSTDs for the preparation and administration of hazardous drugs.

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ORCID iD

Cynthia Tanguay <http://orcid.org/0000-0003-0969-6051>

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What is already known on this subject

- ▶ There is no high-quality evidence to support (or refute) the routine use of closed system drug transfer devices (CSTDs) in addition to safe handling regarding the reduction of surface contamination.
- ▶ In a context of budgetary constraints, economic evaluation of the use of CSTDs appears to be incomplete.
- ▶ CSTDs are an expensive technology.

What this study adds

- ▶ This is the first review of the literature on the economic data of CSTDs and evaluation of the quality of data reporting as defined by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) criteria.
- ▶ This literature review identified a lack of properly conducted economic evaluations of CSTDs, despite their high acquisition costs.

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