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ORIGINAL RESEARCH ARTICLE

Responding to drug shortages and rising costs: IV chemotherapy drug use optimization achieved by closed safety devices in hospital pharmacies

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Abstract

Aim The aim of this article was to assess whether the use of closed system drug transfer devices (CSTDs) can successfully extend the shelf-life of intravenous (IV) cytotoxic drugs and thus contribute to financial savings to the pharmacy budget.

Methodology In two study centres, two 6-month studies of the same design were conducted simultaneously. Three months of withdrawal of IV cytotoxic drugs from vials using conventional needle/syringe methods was compared with 3 months of using a CSTD (Tevadaptor®). During the study, the maximal withdrawable drug quantity from vials and loss due to discarding residuals, mostly in connection with sterility concerns, were measured according to the applied techniques. As the applied CSTD system eliminates microbiological risks, drug shelf-life was extended with CSTD use in the second period. The costs of drugs using conventional dispensing versus CSTD use were also compared.

Results The amount of drug remaining in vials did not significantly differ between needle/syringe and CSTD use. Amount of drugs saved by CSTD use (through the extension of their shelf-life) was significant in all comparisons. For a set of 9 and 20 generic IV chemotherapy drugs, annual drug cost savings of €54,117 (Centre 1) and €16,901 (Centre 2) may be achieved, representing 3.9 and 3.4 % of the pharmacy budgets of the respective centres. When expensive IV biological drugs are considered, budget savings of up to 18.6 % may be achieved with CSTD use.

Conclusion Microbiological stability is the largest obstacle in efficient IV drug utilization. It usually means a 24-h expiry after preparation, although the physicochemical stability of the drug exceeds this period. The use of a CSTD, combined with a standard aseptic environment, provides sterility for the admixture during the preparation process. Taking advantage of the extended drug shelf-lives of drugs provided by the use of a CSTD (Tevadaptor® in this study), a significant amount of drug can be saved, resulting in financial benefits for the pharmacy budget.

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Introduction

The problem of drug costs

With new and more promising cancer therapies on the rise, the cost of cancer treatment poses a significant challenge to many health systems. Pharmacists in several countries are being confronted with ensuring adequate drug supplies to an increasing number of patients while maintaining the financial balance of pharmacy budgets. However, rising costs of oncology drugs make the pharmacy's mission difficult to achieve. As Kantarjian et al. noted "The average cancer drug price for approximately 1 year of therapy or total treatment duration in the United States was less than $US10,000 before 2000, and had increased to $US30,000–50,000 by 2005. In 2012, 12 of the 13 new drugs approved for cancer indications were priced above $US100,000 per year of therapy" [1]. That is, when the co-insurance on a drug is set around 30 %, patients may decide to opt out from the entire treatment when drug costs total $US12,000–40,000 annually [2]. However, the

problem of drug costs is not restricted to the US market; Danzon and Furukawa showed that prices and availability of biologicals can be very similar in several developed countries including the US [3]. Authors also suggested that the rise in the cost of oncology treatment may be attributed to greater spending on high-price molecular formulations, including biologicals. However, biologicals are developed to be efficacious only in a subgroup of a patient population; therefore, they are costly to develop and target a much smaller number of potential users [4, 5]. For example, for trastuzumab to become accessible for patients in Latin America, the price of trastuzumab should be decreased by 69.6–94.9 % relative to international reference prices. For a hospital pharmacist to achieve such an astronomical discount through regular price negotiations is not an option. What then can hospital pharmacists do to contribute to pharmacy cost containment and to respond positively to the increasing number of cancer patients looking for ever-more innovative therapies? One potential solution hospital pharmacists may consider is the use of closed system drug transfer devices that can help save intravenous (IV) drugs by utilizing any drug residuals for subsequent patient care.

Economic savings and drug transfer devices

Closed system drug transfer devices (CSTDs) were originally developed for the protection of healthcare staff from exposure of hazardous IV drugs. Over time, drug manufacturers have published results that support the sterility and stability of IV drugs when kept in a CSTD under appropriate conditions [6]. However, the literature is not very extensive regarding the use of CSTDs to save unused drug volumes. Extending drug shelf-life or beyond-use dating, as these techniques are called, may hold promise for saving unused volumes of IV drugs and making these costly drugs available for an increased number of patients. Vandenbroucke and Robays showed that different methods of IV cytotoxic drug preparation can save drug volumes and costs for the pharmacy [7]. In their three scenarios of preparing IV cytotoxics, they (1) discarded the residual fraction of the drug, (2) set aside residuals and used them until the end of the day, or (3) utilized drug residuals until the physical/chemical expiry date. After 3086 preparations, an average cost reduction of €17–38 per preparation was recorded in 2006, with total financial savings of 7–15 %. Walker et al. reported that, by extending the shelf-life of doxorubicin, epirubicin and mitoxantrone in several Ontario-based cancer centres, drug waste was reduced to <1 % for epirubicin, <15 % for doxorubicin and <35 % for mitoxantrone [8]. However, savings in these studies were not the outcome of using a CSTD. Another study evaluated the potential cost savings of using a CSTD by extending the shelf-life of cytotoxic drugs up to 7 days beyond their expiry date [9]. Throughout the experiment, they saved a mean drug residual of 29 % for all vials. Their extrapolated annual financial savings by not discarding residual drug volumes totaled $US703,047. Savings of this magnitude may provide increased opportunities for the pharmacy through multi-dosing of drug vials and by making budget funds available to treat more patients with cancer.

For hospital pharmacists to make a decision on multi-dosing from the same drug vial over an extended period of time, the most pressing concern is to maintain drug sterility and physicochemical stability. There are several scientific papers published on the topics of extended drug sterility and stability, which provide evidence for pharmacy practice. De Prijck et al. demonstrated the microbiological safety of drugs coupled with protective medical devices and concluded that appropriate operator training and adequate disinfection of the vial before connecting the device should ensure that systems remain sterile [10]. The medical device industry has also demonstrated sterility up to 7 [11] and 28 days [6]. As for physical and chemical stability, as early as 1991, Northcott et al. showed that, under appropriate storage conditions, the stability of carboplatin, 5-fluorouracil and mitoxantrone had been maintained for up to 14 days [12]. Zhang and Trissel demonstrated that pemetrexed was chemically stable for 2 days at room temperature and for 31 days when refrigerated in dextrose 5 % and NaCl 0.9 % injections [13]. Zhang et al. also showed ifosfamide and mesna being physicochemically stable over 14 days in 0.9 % sodium chloride infusions [14]. As a condition of temperature, infusion solution, infusion bag type and concentration levels, paclitaxel has been shown to remain stable for 3–20 days when diluted [15]. The above are only a few examples of the vast literature that can be accessed by pharmacists to arrive at an informed decision concerning whether the shelf-life of a drug can be safely extended, and if so, for how long. However, there is a paucity of data for outcomes relating to IV drug loss with CSTD use versus conventional IV drug dispensing via needle/syringe, the actual benefits in terms of drug volumes (mL/mg) pharmacists may realize by using a CSTD, and the potential budgetary savings achieved by extending the shelf-life of IV drugs using a CSTD. This study will address these issues.

Study aims

The primary aim of this study is to help understand the extent to which closed systems can save drug residuals left in vials to be reused in subsequent therapies. The secondary goal is to translate these IV drug volume savings to cost savings of the pharmacy budget; that is, to understand the magnitude of financial benefits provided by extending the

shelf-life of IV drugs and to identify the individual contribution of drugs to such financial savings. Therefore, authors of this research conducted two sets of clinical studies using the Tevadaptor® CTSD to study drug and cost savings in two hospital pharmacies, and the impact of extending the shelf-life of drugs on potential drug supplies and pharmacy budgets.

Methodology

The study was conducted in two hospital pharmacies in the following regional oncology centres: the National Institute of Oncology in Budapest, a comprehensive cancer centre whose infusion preparation laboratory supplies 240 beds (Study 1); and the Zala County Hospital, whose chemotherapy laboratory supplies a 38-bed oncology ward (Study 2).

Two parallel studies were implemented between May and October of 2014 in these hospital pharmacies. The study design consisted of a 6-month observation period, divided into two 3-month phases. In the first phase, IV cytotoxic drugs selected for monitoring in the studies were withdrawn from vials using the conventional needles/syringe method. In the second phase, a CSTD (Tevadaptor®) was used to withdraw the monitored drugs. The goal of the studies was to assess differences between these two methods of IV drug preparation with regard to drug loss and financial outcomes. Before these studies were conducted, a 1-month preliminary investigation of Tevadaptor® use had been conducted to acquire the proper use of the closed device and to assess whether using Tevadaptor® over a needle/syringe method indeed resulted in better outcomes in terms of the amount of drug (mg) saved.

To collect final data, the studies used the CATO system, a software-aided pharmacy and oncology patient management system supporting individualized drug preparation. CATO also records drug residuals left in the vials, prompts pharmacists to reuse the drug as long as there is drug left and/or drug expiration allows reuse, and records the discarded quantities and unused surpluses. Data on discarded residuals and recovery losses left in vials were downloaded from CATO for needle/syringe and Tevadaptor® aided preparation over each respective 3-month phase. Predictions on potential annual drug savings and calculated financial benefits were extrapolated from 3-month data. The CATO system provides data for the precise amount (mg) of drug loss, which can be transferred easily by the mg unit prices into accurate money loss. Net purchase prices, current in 2014, were taken into consideration, extrapolated to €/mg for each drug. Calculations were based on net prices offered by the suppliers according to valid institutional and country medicine tenders in the examined 6-month period in 2014.

Standard pharmacy practice for the needle/syringe method was that study drugs opened at the beginning of the working day were discarded at the end of the day, regardless of their recommended use-by date. To extend the shelf-life of the study drugs, Tevadaptor® was used. Teva has published evidence that Tevadaptor® maintains microbiological sterility and chemical stability of selected oncology drugs, manufactured by Teva, for up to 28 days [9]. The manufacturers' summaries of product characteristics were used to guide the shelf-life of the selected study drugs. However, based on the published literature [10, 12, 17], a final decision was made to extend the shelf-life of drugs monitored in our study by 4–14 days, following evidence-based recommendations. Study 1 extended the shelf-life of drugs up to a maximum of 14 days following literature evidence [16, 17], whereas study 2 extended drug usability based on manufacturers' recommendations ranging from 24 to 72 h.

Because of non-normal data distribution, where appropriate, nonparametric statistics (Mann–Whitney, independent samples U tests) were used to analyze outcomes. Level of significance was set at 5 %. Analyses were performed by SPSS Windows 20.0 version.

Results

One of the main purposes of the trial was to assess whether conventional needle/syringe drug preparation would lead to the same or different outcomes in drug recovery as Tevadaptor®-aided preparation (i.e. comparison of 'dead volumes' of selected drugs using the two preparation techniques). Table 1 shows results of maximally achievable drug withdrawal by needle/syringe or Tevadaptor®. In the majority of cases, using Tevadaptor® to withdraw drugs resulted in less loss of drugs (measured in mL) relative to conventional needle/syringe techniques. However, statistical comparisons found no significant difference between the two methods in terms of the drug residuals left in the vials ($Z = -0.264$; $p = 0.809$). Despite the fact that Tevadaptor® uses a much more complex withdrawal system to provide absolute integrity during the process compared with simple needles, it has no negative effect on drug-withdrawing potency.

In study 1, there was a mean of 8.47 % drug loss when drugs had been withdrawn by traditional needle/syringe techniques (Table 2). Compared with needle/syringe, withdrawing drugs with Tevadaptor® decreased the loss to 1.22 % (Table 2). With regard to the total amount of drugs saved over the 3-month study period, 35,769 mg of drugs were recovered using Tevadaptor® rather than needle/

Table 1 Efficacy of needle/syringe and Tevadaptor® with regard to drug withdrawal from vial

Drug (mg in vial)	Maximum amount (mg) withdrawn	
	Needle/syringe	Tevadaptor®
Carboplatin (450)	460.2	465.0
Epirubicin (50)	51.7	52.53
Epirubicin (100)	102.8	102.56
Etoposide (200)	204.47	202.72
Ifosfamid (1000)	984.62	1002.5
Ifosfamid (2000)	1987.57	1992.44
Liposomal doxorubicin (50)	50.92	50.61
Mitomycin (20)	19.59	20.02
Mitoxantrone (10)	10.25	10.07
Mitoxantrone (20)	20.4	19.89
Panitumumab (100)	105.6	101.98
Pegylated liposomal doxorubicin (20)	20.48	20.32
Pemetrexed (100)	106.87	103.82
Pemetrexed (500)	506.07	499.62
Vinorelbine (10)	9.86	9.74
Vinorelbine (50)	51.39	49.7

syringe (Table 2). That is, a total of 143,078 mg of generic drugs may be saved over the course of 1 year should standard pharmacy practice include the use of a CSTD. Reusing drugs for additional patients saved a total of €13,529 from the pharmacy budget (Table 2). Projecting the 3-month outcomes over a year, using Tevadaptor® to extend IV drug shelf-life may contribute to €54,117 of savings to the pharmacy budget, provided that drug prices stayed constant over the year.

In study 2, over the 3-month period, the total amount of the drug recovered was 104,482 mg using Tevadaptor® rather than needle/syringe, which translated to a total savings of €4200 (Table 2). Converting these outcomes to annual savings, there may be a potential 417,928 mg of drugs recovered if open vials are not discarded, but used in line with manufacturers' recommendations. Such savings should benefit the pharmacy budget by €16,901 annually. Because we studied off-patent oncology drugs, acquisition costs of these drugs explain why a large amount of drug recovered resulted in a relatively small saving for the pharmacy budget. However, note that a mean of 83.6 % of drug loss was saved.

The differences in results between the two studies are explained by the size of the two hospitals where the studies were conducted. Study 2 was carried out in an oncology unit of a regional hospital, which had a significantly smaller patient turnover than observed in the national centre where Study 1 was conducted. Therefore, drug waste is much greater in smaller care units where often fewer patients may share a dose of the same drug.

Table 3 provides the results for special classes of drugs commonly viewed as very promising for positive patient outcomes and usually highly expensive for most health systems. Therefore, saving both on drug residuals and costs can significantly impact patient drug supply and pharmacy budgets. We studied these drugs separately to show the magnitude of savings that may be achieved. In a smaller oncology unit where fewer patients are scheduled for treatment every day, drug waste may be much higher than in more patient-dense oncology hospital units.

Relative to the loss with conventional syringe/needle use, CSTD use recovered a mean of almost 100 % of the four monitored biological drugs, and 60 % of the two advanced small-molecular chemotherapy drugs. A total of 7772 mg of drugs was recovered by using Tevadaptor® to save residuals left in open vials. This amount may provide a full treatment cycle for a number of new patients attending treatment on the following days. Because of the high cost of these drugs, savings on the four selected biologicals and the two small molecular drugs in this study may result in financial savings equal to €32,035 over 3 months. Extending the shelf-life of only six selected high-efficiency drugs may provide full treatment for a number of new patients, as well as end up saving €128,140 in the annual pharmacy budget. Both outcomes represent huge potential for managing drug supplies/shortages and contribute to maintaining costs of otherwise seriously constrained health systems.

When we combined results of both studies and compared those outcomes achieved by Tevadaptor® to extend drug shelf-life, Tevadaptor® saved significantly greater drug volumes than the traditional needle/syringe technique ($Z = -3.184$; $p < 0.001$ and $Z = -3.675$; $p < 0.001$). The use of Tevadaptor® to extend drug shelf-life resulted in economic savings for the pharmacy budget. The greatest and by far the most significant difference ($Z = -4.532$; $p < 0.001$) between using a CSTD and the standard needle/syringe method emerged for expensive biological drugs, where the use of Tevadaptor® resulted in large residual drug savings (per mg). Therefore, when the cost of the medical device was also factored in, using Tevadaptor® to extend shelf-life of drugs brought financial benefits for the pharmacy budget.

Discussion and conclusions

This paper aimed to demonstrate that using a CSTD will not affect the drug volumes withdrawn from vials compared with needle and syringe methods. It also set out to show that when extending the shelf-life of drugs, with the

Table 2 Drug and financial savings over a 3-month period for selected cytotoxic drugs

Drug	Loss (%)		Discarded drug loss (mg) during Aug–Oct		Savings with Tevadaptor®		
	Needle/syringe (May–Jul)	Tevadaptor® (Aug–Oct)	Needle/syringe (calculated)	Tevadaptor® (actual)	Drug saved (mg)	% drug saved	Money saved (€)
Study 1							
Carboplatin	1.15	0.72	1648.42	1034.38	614.04	37.25	61.39
Epirubicin	0.70	0.28	248.70	100.49	148.21	59.59	37.79
Etoposide	2.23	2.17	1812.15	1757.04	55.11	3.04	6.05
Iphosphamide	6.19	1.93	40,211.64	12,544.75	27,666.89	68.8	1711.19
Methotrexate	7.38	0.29	6822.73	268.38	6554.35	96.07	245.79
Mitomycin	29.52	2.02	281.19	19.21	261.98	93.17	594.42
Mitoxantrone	18.19	0.55	264.76	8.07	256.69	96.95	5764.14
Pegylated liposomal doxorubicin	7.19	0.26	201.52	7.38	194.14	96.34	5039.29
Vinorelbine	3.71	2.75	69.77	51.58	18.19	26.07	69.25
Mean	8.47	1.22				64.14	
Total					35,769.60		13,529.31
Study 2							
Carboplatin	14.84	0.22	1319.22	2.64	1316.58	99.80	42.48
Cisplatin	12.76	12.76	1972.60	1972.60	0.00	0.00	0.00
Cyclophosphamide	27.06	1.41	16,533.57	16.54	16,517.04	99.90	555.53
Dacarbazine	6.78	0.25	590.03	1.48	588.55	99.75	82.13
Docetaxel	4.03	0.17	162.35	2.85	159.50	98.25	36.53
Doxorubicin	5.74	0.57	1273.18	12.73	1260.45	99.00	264.14
Liposomal doxorubicin	10.36	0.42	60.99	0.61	60.38	99.00	38.35
Epirubicin	4.81	0.73	610.52	4.70	605.83	99.23	199.44
Etoposide	8.65	2.44	5004.91	35.75	4969.17	99.29	296.96
Fluorouracil	33.11	1.63	61,302.78	38.32	61,264.46	99.94	151.21
Gemcitabine	17.19	1.55	11,497.89	7.19	11,490.71	99.94	121.11
Ifosfamide	9.18	0.33	3363.32	1.12	3362.20	99.97	138.79
Irinotecan	3.98	0.48	810.20	3.95	806.25	99.51	86.42
Methotrexate	2.62	2.62	394.62	394.62	0.00	0.00	0.00
Mitomycin	2.10	0.18	22.62	2.26	20.36	90.00	34.22
Mitoxantrone	1.53	0.11	24.22	2.42	21.80	90.00	731.54
Oxaliplatin	17.02	1.66	1058.40	7.06	1051.34	99.33	275.18
Paclitaxel	7.09	0.37	976.32	3.26	973.07	99.67	96.33
Raltitrexedum	0.88	0.03	14.39	0.14	14.25	99.04	1027.62
Topotecan	1.21	1.21	10.18	10.18	0.00	0.00	21.89
Mean	9.54	1.46				83.58	
Total					104,481.91		4199.82

aid of a CSTD, pharmacists should be able to optimize drug loss and recover drug volumes that can be utilized for patient care. And finally, the paper was to address economic benefits that should arise from saving drug residuals otherwise discarded in standard practice.

As for the first aim of our study, we demonstrated no significant statistical difference between needle and syringe and CSTD performance in terms of withdrawing drugs. Both methods resulted in the same amount of volumes (mL) recovered from drug vials. This observation is important for current users of needle and syringe techniques who are thinking about changing to CSTDs. As shown in this paper, using CSTDs to transfer drugs will not negatively affect drug volumes recovered from vials.

Table 3 Drug and financial savings over 3-month study period for expensive, selected biological and small molecular drugs

Drug (studies from which data are derived)	Discarded drug loss (mg)		Cost of drug loss (€)		Drug savings with Tevadaptor®		
	Needle/ syringe	Tevadaptor®	Needle/ syringe	Tevadaptor®	Drug saved (mg)	% drug saved	Money saved
Biological drugs							
Bevacizumab (2)	3454.58	8.63	13,201.43	33.01	3445.94	99.75	13,168.43
Cetuximab (2)	1168.51	1.16	2871.64	2.87	1167.34	99.90	2868.77
Panitumumab (1 and 2)	2013.08	161.21	9321.01	746.44	1851.87	91.99	8574.57
Trastuzumab (2)	630.46	1.05	1992.94	3.32	629.41	99.83	1989.62
Mean						97.87	
Total			27,387.02	785.64	7094.56		26,601.39
Advanced small-molecular chemotherapy drugs							
Liposomal doxorubicin (1)	362.80	54.08	5561.04	828.94	308.72	85.09	4732.10
Pemetrexed (1 and 2)	1039.91	671.22	1086.77	385.30	368.69	35.45	701.47
Mean						60.27	
Total			6647.81	1214.24	677.41		5433.57

Additionally, in some cases we saw Tevadaptor® outperform traditional techniques; however, on average there was no real difference favouring one technique over the other.

The two study arms demonstrated that using a CSTD both for off-patent, generic oncology drugs as well as for expensive bioengineered medicines resulted in statistically significant drug savings (amount of drug residuals reused for subsequent therapies) over standard pharmacy practice. According to our observations, a total amount of 143,078 and 104,482 mg of drugs may have been recovered annually had CSTDs been applied to the preparation of these drugs. Because Tevadaptor® has the ability to maintain drug sterility and stability, pharmacists are able to extend expiry of residual volumes after each preparation. Such performance of a CSTD can significantly benefit pharmacy drug supplies without the risk of compromising the quality of patient care.

Our additional aim was to assess financial benefits (if any) that may be achieved by using a CSTD. Our results showed financial gains both for generic molecules and more expensive bioengineered drugs. For a set of 9 and 20 generic drugs, €54,117 and €16,935 in annual financial savings were calculated as a result of CSTD use. Considering the annual pharmacy budget of both study hospitals (€1.4 million and €504,210, respectively), these savings on off-patent chemotherapy drugs represented 3.87 and 3.36 % of the pharmacy budget, respectively. While 4 % savings for the pharmacy budget on a hospital basis may not be translated as 'significant', 4 % financial savings on a national scale may provide excess funds for governments that can be redistributed for additional drug supplies to meet patient demands.

When patented, expensive, bioengineered drugs were considered, economic savings increased exponentially. A total amount of 7772 mg of drugs had been recovered over 3 months of use. That is, an annual total of 31,088 mg of expensive biological drugs may have been saved by applying a CSTD. Almost half of this amount (13,168 mg) would have been recovered from bevacizumab. Assuming a 70-kg patient receiving a second-line FOLFOX protocol (10 mg/kg) over six cycles, a total of 4200 mg bevacizumab is required for therapy. Out of the 13,168 mg bevacizumab saved, an additional three patients may have received a full line of therapy that otherwise would have been unavailable due to drug loss. If the therapeutic choice was first-line (5 mg/kg), six additional patients may have been involved in treatment. While these patient numbers may not seem outstanding, keep in mind that our data were associated with a 30-bed oncology unit. Larger units may save significantly greater volumes of drugs, opening up even more treatment opportunities for additional patients. Each additional patient involved in treatment offers a 100 % new treatment opportunity for these individuals.

When economic benefits were considered, selected biological drugs had a massive impact on the total annual budget saved. The combined benefit of using a CSTD to save bioengineered drug residuals was €128,136 per year. Since the annual pharmacy budget was €504,120, savings on these bioengineered drugs represented 25.41 % of the annual budget. Such savings, even in more economically developed countries, are significant and should be exploited. Our findings were in line with Edwards et al. [9], who saved 29 % on drugs by using a CSTD in a large military hospital in the US. They reported over $US700,000 annual savings at 2013 drug prices. Last but not least, applying CSTDs to save on drugs will not only benefit the pharmacy budget and patients at large but will also protect pharmacy staff from exposure to those otherwise hazardous drugs.

Strengths of this paper include the exact measurements and records obtained from the CATO-aided preparation systems used in study pharmacies as well as the extension of drug shelf-life based on scientific evidence from the literature. Limitations include the short study period (3 months), which may not have accounted for seasonal variations in drug demand. Also, the study did not represent all oncology centres on the national scale. We recommend that this study be replicated in other settings and more countries to make sure that reported benefits apply across various health systems.

Compliance with ethical standards

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Conflicts of interest Á. Juhász, G. Batka and A. Szücs declare that they have no conflicts of interest relevant to the content of this manuscript.

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