Validity of criticism of Cochrane review on closed-system drug-transfer devices

Recently there have been several criticisms,[1-3] including those in an *American Journal of Health-System Pharmacy* commentary by McDiarmid et al.,[1] about the Cochrane Review on closed-system drug-transfer devices (CSTDs).[4] In response, the Cochrane Central editorial team, led by editor in chief of the Cochrane Library Dr. David Tovey, conducted a thorough investigation of the review and confirmed that it and the editorial processes conform to all Cochrane standards. However, the team suggested revision of the review's conclusions, to make it easier for people without methodological expertise to understand them. Based on this recommendation, we have revised the conclusions to read as follows:

> Currently, no firm conclusions can be drawn on the effect of CSTD combined with safe handling versus safe handling alone due to very low certainty evidence available for the main outcomes. Multicentre randomised controlled trials may be feasible depending upon the proportion of people with exposure. The next best study design is interrupted time-series. Future studies should evaluate exposure to a relevant selection of hazardous drugs used in the hospital, and they should measure direct short-term health outcomes.[4]

This is not substantially different from our previous conclusions, which suggested that

> There is currently no evidence to support or refute the routine use of closed-system drug transfer devices in addition to safe handling of infusional hazardous drugs, as there is no evidence of differences in exposure or financial benefits between CSTD plus safe handling versus safe handling alone (very low-quality evidence). None of the studies report health benefits…[4]

We address here the major criticisms voiced and the reasons why our conclusions remain fundamentally the same despite carefully checking the whole review and implementing judicious corrections where necessary.

Criticism 1: The review method was erroneous in examining an intervention that is not used in patients to evaluate its effects on staff. The Cochrane Review methodology is applicable for evaluating the effectiveness of all interventions in healthcare. This includes interventions affecting people with illnesses and those aimed at preventing illnesses. It is rather disconcerting to us that McDiarmid et al.[1] imply that one ought to use different methods to evaluate interventions directed at healthcare professionals, as if those professionals do not deserve the highest quality evidence to guide workplace decisions that affect their own health. The Cochrane Work Group has several reviews that use the Cochrane methodology evaluating interventions aimed at healthcare professionals.[5]

Criticism 2: There was a violation of the key Cochrane principle of demonstrating the homogeneity of the data to be synthesized. The main tool for avoiding the comparison of apples and oranges in all Cochrane Reviews is the careful a priori formulation of a PICO (patient or problem/intervention/comparison/outcome) question that is operationalized as a set of sufficiently exhaustive inclusion and exclusion criteria.[6] Once we were sure that studies were sufficiently similar to synthesize their results, we dealt with residual heterogeneity by performing a subgroup analysis of the data relevant to the Phaseal device. In fact, we had already highlighted that the evidence was mainly related to Phaseal in the main text; now, we explain this in the abstract of the review as well.

Criticism 3: The selection of studies for inclusion was faulty. Here, McDiarmid et al. say the review included too few studies and excluded too many. We reviewed the studies and identified that we had excluded 1 small study errone-

The Letters column is a forum for rapid exchange of ideas among readers of AJHP. Liberal criteria are applied in the review of submissions to encourage contributions to this column.

The Letters column includes the following types of contributions: (1) comments, addenda, and minor updates on previously published work, (2) alerts on potential problems in practice, (3) observations or comments on trends in drug use, (4) opinions on apparent trends or controversies in drug therapy or clinical research, (5) opinions on public health issues of interest to pharmacists in health systems, (6) comments on ASHP activities, and (7) human interest items about life as a pharmacist. Reports of adverse drug reactions must present a reasonably clear description of causality.

Short papers on practice innovations and other original work are included in the Notes section rather than in Letters. Letters commenting on an AJHP article must be received within 3 months of the article's publication.

Letters should be submitted electronically through http://ajhp.msubmit.net. The following conditions must be adhered to: (1) the body of the letter must be no longer than 2 typewritten pages, (2) the use of references and tables should be minimized, and (3) the entire letter (including references, tables, and authors' names) must be typed double-spaced. After acceptance of a letter, the authors are required to sign an exclusive publication statement and a copyright transferal form. All letters are subject to revision by the editors.

ously. We have now updated the review with this particular study included. As expected, the data provided by that study did not alter the conclusions. We excluded studies that used simulation because we were looking at the effect of CSTD when used under real work conditions; our goal was not to prove or disprove their efficacy under laboratory conditions.

Criticism 4: There were variations in control groups. McDiarmid et al. state that "the review's authors reported that the descriptions of the control group practices also varied among the 23 observational cluster studies…this further threatened the desired homogeneity of the comparisons made."

Our review is a synthesis of the evidence on how CSTDs work in addition to safe handling practices in real-life, not ideal, conditions. Therefore, a certain amount of heterogeneity can be expected in the control groups, as in real life. However, it is important to note that the CSTDs did not reduce exposure, as measured by urine tests, regardless of the safe handling practices used.

Criticism 5: The choice of outcomes was faulty. The justification for the choice of outcome measures is strong. They were chosen as the most relevant indicators of intervention effects in agreement with the review's funders (the United Kingdom Oncology Nursing Society) and the set of methodology and topic experts consulted during peer review by the review's publisher, Cochrane Work.

As we mention clearly in the discussion, the sole reliance on surrogate outcomes has its drawbacks. Environmental contamination—measured as surface samples, splashes, leakage tests, or atmospheric contamination—is a surrogate outcome for exposure, as can be measured with urine tests. Overall, out of 24 comparisons in pharmacy areas or patient-care areas, there was a reduction in the proportion of surfaces contaminated in only 1 comparison, and out of 15 comparisons in pharmacy areas or patient-care areas, there was a reduction in the quantity of contamination in only 2 comparisons. Therefore, there is lot of uncertainty as to whether CSTDs reduce even these surrogate outcomes of exposure.

Criticism 6: The tool used to assess for risk of bias was faulty. The critics point out that we used a different risk of bias tool. Currently ROBINS-I is Cochrane's validated tool of choice to be used in assessing the risks of bias (previously referred to as study quality) of nonrandomized intervention studies. As we indicated clearly, the objectives were to evaluate the effectiveness of CSTDs in addition to safe handling versus safe handling alone—in other words, evaluating an intervention rather than an exposure.

Criticism 7: The assessment of outcomes was not adequately blinded. Properly blinded outcome assessment for subjective assessments involves blinding the person who takes the samples as well the laboratory technicians who perform the analysis. The sampling of environmental samples is highly subjective. In the only included study that mentioned blinding,[7] the study authors do not mention how the person who obtained the samples was blinded, which is especially relevant when the compounding units were different in the intervention group and wipe samples were taken before and after the daily cleaning process.

Criticism 8: Results showing that CSTDs decreased surface contamination were omitted. Per the advice of the Cochrane Central editorial team, we have removed the exact numbers of the different drugs in different areas, as there is too much uncertainty. We have retained the precise numbers in the Summary of Findings table, which accompanies the abstract. We have provided all the results in the Summary of Findings table.

Criticism 9: The conclusions do not agree with those of the agencies, some of which support the use of CSTDs. We have collected the evidence systematically and interpreted the evidence based on what we found. Cochrane Reviews do not provide recommendations because readers' decisions depend also on other arguments, such as their values and preferences. We do not know why some agencies support the use of CSTDs, because the reasoning behind their recommendations has not been clearly stated.

We believe that the cited criticism distracts readers from the main message that there is currently insufficient evidence to conclude whether the addition of CSTDs to safe handling practices is beneficial or harmful and that further well-designed studies are necessary to answer this question sufficiently. Moreover, we would like to stress that there are preventive interventions other than CSTDs that should be implemented regardless of the use of CSTDs, such as cleaning and providing sufficient staff.

Our Cochrane Review has now been republished fully amended and is available at https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012860.pub2/. It has been firmly established that it constitutes the best available evidence.

1. McDiarmid MA, Polovich M, Power LA et al. Published review of closed-system drug-transfer devices: limitations and implications. *Am J Health-Syst Pharm.* 2018; 75:1982-5.
2. Power LA, Polovich M, McDiarmid MA. Cochrane review on CSTDs misses the mark (2018). https://www.pharmacypracticenews.com/Clinical/Article/09-18/Cochrane-Review-on-CSTDs-Misses-the-Mark/52639 (accessed 2019 Feb 13).
3. Connor TH. Evidence of CSTD benefits: a rebuttal. *Cleanrooms & Compounding.* 2018. https://www.pppmag.com/article/2304 (accessed 2019 Feb 13).
4. Gurusamy KS, Best LM, Tanguay C et al. Closed-system drug-transfer devices plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional hazardous drugs in healthcare staff. *Cochrane Database Syst Rev.* 2018; 3:CD012860.
5. Cochrane reviews about occupational safety and health. https://work.cochrane.org/cochrane-reviews-about-occupational-safety-and-health (accessed 2019 Feb 13).
6. Gurusamy KS, Best LM, Tanguay C et al. Closed-system drug-transfer devices plus safe handling of hazardous drugs versus safe handling alone for reducing exposure to infusional hazard-

ous drugs in healthcare staff (protocol). *Cochrane Database Syst Rev.* 2017; 11:CD012860.
7. Simon N, Vasseur M, Pinturaud M et al. Effectiveness of a closed-system transfer device in reducing surface contamination in a new antineoplastic drug-compounding unit: a prospective, controlled, parallel study. *PLoS One.* 2016; 11:e0159052.

Kurinchi S. Gurusamy, MBBS, Ph.D.
Division of Surgery and Interventional Science
University College London
London, United Kingdom
k.gurusamy@ucl.ac.uk

Jani Ruotsalainen, M.Sc.
Cochrane Work Group
Kuopio, Finland

Jos Verbeek, M.D., Ph.D.
Cochrane Work Group
Kuopio, Finland

Cynthia Tanguay, M.Sc.
Unité de Recherche en Pratique Pharmaceutique
CHU Sainte-Justine
Montreal, Canada

Lawrence Best, B.Sc.
Division of Surgery and Interventional Science
University College London
London, United Kingdom

Elaine Lennan, Ph.D.
Department of Chemotherapy
University Hospital Southampton
Southampton, United Kingdom

Mika Korva, M.Sc.
Finnish Institute of Occupational Health
Turku, Finland

Jean-Francois Bussieres, Ph.D.
Unité de Recherche en Pratique Pharmaceutique
CHU Sainte-Justine
Montreal, Canada

The authors have declared no potential conflicts of interest.

Keywords: closed-system drug-transfer devices

DOI 10.1093/ajhp/zxz136