Automated compounding technology and workflow solutions for the preparation of chemotherapy: a systematic review

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ABSTRACT

Objectives The current systematic review (SR) was undertaken to summarise the published literature reporting the clinical and economic value of automation for chemotherapy preparation management to include compounding workflow software and robotic compounding systems.

Methods Literature searches were conducted in MEDLINE, Embase and the Cochrane Library on 16 November 2017 to identify publications investigating chemotherapy compounding workflow software solutions used in a hospital pharmacy for the preparation of chemotherapy.

Results 5175 publications were screened by title and abstract and 18 of 72 full publications screened were included. Grey literature searching identified an additional seven publications. The SR identified 25 publications relating to commercial technologies for compounding (Robotic compounding systems: APOTEC Achemo (n=12), CytoCare (n=5) and RIVA (n=1); Workflow software: Cato (n=6) and Diana (n=1)). The studies demonstrate that compounding technologies improved accuracy in dose preparations and reduced dose errors compared with manual compounding. Comparable levels of contamination were reported for technologies compared with manual compounding. The compounding technologies were associated with reductions in annual costs compared with manual compounding, but the impact on compounding times was not consistent and was dependent on the type of compounding technology.

Conclusions The published evidence suggests that the implementation of chemotherapy compounding automation solutions may reduce compounding errors and reduce costs; however, this is highly variable depending on the form of automation. In addition, the available evidence is heterogeneous, sparse and inconsistently reported. A key finding from the current SR is a 'call to action' to encourage pharmacists to publish data following implementation of chemotherapy compounding technologies in their hospital, which would allow for evidence-based recommendations on the benefits of chemotherapy compounding technologies.

INTRODUCTION

There are potentially serious risks associated with the prescribing, dispensing, administration, and monitoring of chemotherapy.¹ Chemotherapy compounding is a high-risk medical practice due to the toxicity of antineoplastics and the risk of contamination during the manufacturing process.

The primary risk for patients includes errors in product identification, dose calculation, dose measurement, and drug preparation labelling.^{2,3} Medical staff are also exposed to the risk of accidental exposure to antineoplastics during drug preparation or administration due to accidental inhalation, ingestion, injection and percutaneous absorption.^{4,5} Traces of antineoplastics have been detected in healthcare workers' urine samples, despite the use of safety cabinets for manual chemotherapy compounding.⁶

Chemotherapy-related medication-error prevention is a high priority within pharmacies and hospitals. There are international clinical guidelines that report strategies for preventing medication errors.^{7–11} Recent guidelines from the American Society of Health-System Pharmacists acknowledge that technologies to automate the preparation of chemotherapy are emerging¹⁰ and these include chemotherapy compounding workflow technology solutions consisting of chemotherapy workflow software and robotic compounding systems. Such systems have the potential to minimise and prevent chemotherapy medication errors (eg, due to the miscalculation of concentrations, inaccurate preparations and incorrect use of diluent), reduce environmental contamination and reduce the exposure of healthcare workers to chemotherapeutics. In addition, these technologies may also allow for more cost-effective chemotherapy preparation compared with manual compounding. Compounding workflow software systems enable verification of chemotherapy preparations and improve the documentation of preparations using computer software, barcode technology and cameras.¹⁰ In comparison, robotic compounding workflow systems enclose and automate the chemotherapy compounding production process. Workflow software technologies are the most common of the technologies¹⁰; robotic technologies cost substantially more than workflow software technologies, both in terms of initial capital costs and costs associated with installation and implementation. Compounding workflow systems can introduce significant quality, safety, and manpower benefits into an existing work process without substantial capital expenditure.

Following the development of such automated technologies, it is critical to evaluate their implementation in a real-world hospital setting to ensure that the proposed benefits are apparent in daily use.

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Objectives

This systematic review (SR) was undertaken to review the published literature on the clinical and economic value of chemotherapy compounding workflow technology solutions compared with manual compounding, across all brands. The primary focus was the benefit of technology solutions in terms of efficiency/productivity, patient safety, contamination and costs. The SR was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹²

METHODS

Search strategy

Searches of MEDLINE In-Process, MEDLINE, Embase and the Cochrane Library were performed via Ovid on 16th November 2017. The search strategy used to interrogate the Embase database is provided in the online supplementary file, table 1. Supplementary searches of conference proceedings for the Clinical Pharmacy Congress, World Congress on Clinical Pharmacy and Pharmacy Practice, Medication Safety Conference, European Association of Hospital Pharmacists, American Pharmacists Association Congress, International Society for Pharmacoeconomics and Outcomes Research, American Society of Clinical Oncology, European Society for Medical Oncology, Clinical Oncology Society of Australia and British Oncology Pharmacy Association were conducted from 2014 to 2017. Additional searches of pharmacist societies including the Institute for Safe Medication Practices, Royal Pharmaceutical Society and European Association of Hospital Pharmacists were also conducted.

Inclusion and exclusion criteria

Search results were screened for studies of any design reporting at least one outcome measure of interest (ie, clinical or economic) related to patients receiving chemotherapy or healthcare professionals responsible for the prescription, compounding, and dispensing of antineoplastics with robotic/automated compounding device/computer software used in a hospital pharmacy. English language publications and publications with an abstract in English published post-2000 were included. Full details of the eligibility criteria are provided in table 1.

Study selection and data extraction

Citations of interest were identified by a member of the team (authors SB or SAM) and verified by an independent reviewer (authors SB or SAM), based on title and abstract. Full publications were obtained for all citations of interest and were assessed by one reviewer and verified by a second reviewer. Any uncertainties were resolved through discussion. Data were extracted into an Excel spreadsheet by one reviewer and checked against the original publication by a second reviewer.

Quality assessment

Included primary studies were assessed using the quality assessment tool for quantitative studies of the Effective Public Health Practice Project (EPHPP).¹³ The EPHPP tool is considered suitable for use in SR publications including studies of different designs.

Table 1 Eligibility criteria for study inclusion in the SR

Criteria	Inclusion	Exclusion
Population	Subjects with cancer receiving chemotherapy Pharmacists and other healthcare professionals responsible for the prescription, compounding, and dispensing of antineoplastics	–
Intervention	Any robotic/automated compounding device/computer software used in a hospital pharmacy Both gravimetric and volumetric compounding were of interest*	► External compounding services
Outcomes	Clinical: ► Dose accuracy and precision ► Prescribing, preparation, dispensing, and administration errors (eg, % discrepancy between compounded and prescribed drug quantity) ► Contamination of the work area, for example, surface wipe sampling ► Number of robot-compounded chemotherapy doses rejected (and those associated with software) ► ADEs/potential ADEs ► Mortality Economic: ► Total compounding time ► Total reconstitution time of lyophilised drugs into intravenous syringes/bags/bottles ► Number of doses prepared/failed preparations ► Robot % operational time ► Medication wastage/recycled, and vials reused ► Staff-associated costs, for example, training, FTEs employed/redeployed	► Healthcare workers' perception
Study design	Included: ► Randomised controlled trials ► Prospective/retrospective observational studies (including single-centre studies) ► Audits ► Ethnographic studies ► Budget impact analyses ► Cost studies	► News articles ► Letters ► Editorials ► Reviews ► Bulletins ► Guidelines
Date of publication/territory of interest	Restricted to publications published from 2000 No restriction on territory of interest	Articles published prior to 2000
Language of publication	English language publications or foreign language publications with an English abstract	–

*Gravimetric analysis uses a known specific gravity to quantitatively determine the amount of a substance based on measured weight versus volumetric analysis which employs the markings on a syringe to visually measure the amount of liquid being added or removed during the compounding process.

ADE, adverse drug events; FTE, full-time equivalent; SR, systematic review.

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Due to the inconsistent reporting of outcomes across the primary studies, a formal quantitative evidence synthesis of the results was not feasible. Rather, a qualitative summary of the results was reported. In general, studies were well reported and all studies were rated as having a moderate global rating with the exception of Yaniv 2017 which was rated as weak due to the study design.¹⁴

RESULTS

A total of 5797 unique citations were identified in the electronic searches and after removal of 622 duplicates, 5175 articles were screened by title and abstract. In total, 5103 articles were excluded, and 72 articles were potentially relevant and following full publications review, 18 publications were included.^{14–31} Hand searching yielded an additional seven publications for inclusion.^{32–38} Therefore, a total of 25 publications met the inclusion criteria (figure 1).^{14–38} All studies were published from 2009 onwards. A summary of study design and results is provided in the online supplementary file, table 2. The results of the quality assessment are provided in the online supplementary file, table 3.

Seven publications reporting on chemotherapy workflow software were included in the SR: six publications reporting on Cato^{15–17 33 34 38} and one publication reporting on Diana.³⁵ In comparison, 18 publications reporting on robotic compounding systems were included; 12 publications reporting on APOTECachemo^{14 18–27 32}; 5 publications reporting on CytoCare^{28–31 36} and 1 on RIVA.³⁷ The quality of the included primary studies (see online supplementary file, table 3) was generally graded as moderate or weak due to the absence of randomised controlled study designs.³⁹

Robotic compounding systems

APOTECachemo was the most comprehensively studied robot.^{14 18–27 32} A single study reported the progressively robotised preparation of chemotherapy from 2007 (first generation) to 2011 (third generation).^{22 23} All remaining studies did not state the generation of the APOTECachemo robot and the mean dose accuracy for the third-generation robot was reported to be 0.8% (standard deviation (SD) 1.7%).^{22 23}

Results highlighted variability in the dose accuracy of the robot for different classes of chemotherapy (figure 2).^{18 19 22 23 25 26 32} For example, a single study reported the mean relative errors of compounding with APOTECachemo for trastuzumab were –3.7% compared with 2.54% for etoposide.¹⁹ Further, a study reported that the dose accuracy of compounding with

Figure 2 Error rates/dosing accuracy across the studies investigating APOTECachemo. Dark blue relates to APOTECachemo compounded preparations and light blue related to manual compounded preparation. *Outcomes reported as % error rate. †Outcomes reported as % dose accuracy. ‡Outcomes reported as absolute % error responses. §Outcomes reported as mean dose error. ¶Outcomes reported as mean % relative errors. ††Data from the third-generation robot and all other data from Palma 2012/2014 are from the first-generation robot.

Figure 3 Mean preparation times reported across the studies investigating APOTECachemo. Dark blue relates to APOTECachemo compounded preparations and light blue related to manual compounded preparation. *Data reported for the third generation APOTECachemo robot. †Data reported assumed to be for the first-generation APOTECachemo robot (installed September 2007) (data converted from seconds to minutes from figure 1 of publication).

APOTECachemo for paclitaxel oleate was -0.28% compared with -3.3% for a docetaxel combination.²⁵

A single study investigating contamination associated with APOTECachemo reported comparable contamination levels with manual compounding of cyclophosphamide infusion bags over 4 days, reporting that the contamination of infusion bags was lower with the robot.²¹ A cost volume analysis indicated that annual total cost savings with APOTECachemo were reported only after the preparation of 34 000 units per year, primarily due to the fixed costs of the robot (the study evaluated 10 routinely used agents including fluorouracil, cyclophosphamide, gemcitabine, trastuzumab, bevacizumab, oxaliplatin, cisplatin, paclitaxel, irinotecan and etoposide).¹⁹ Use of APOTECachemo was associated with a longer preparation time compared with manual compounding (figure 3),^{18 19 22 23} with the exception of a single study reporting on the compounding of abiraxane.²⁶

Five publications reported on the implementation of CytoCare^{28–31 36}, two of which investigated first-generation robotic compounding systems.^{29 30} A comparative study investigating a range of chemotherapy agents suggested that CytoCare improved dose medication accuracy compared with manual compounding; failed accuracy measurements, 0.9% vs 12.5% respectively.³⁰ A further study investigating environmental contamination during the robotic preparation of cyclophosphamide reported that CytoCare was associated with lower levels of contamination (product and worker exposure) compared with manual preparation.³¹

Only minor savings in labour costs were reported for CytoCare compared with manual compounding across a range of chemotherapy agents (mean labour cost per preparation \$5.22 vs \$5.10 respectively),³⁰ and the implementation of CytoCare was not associated with a subsequent reduction in the number of full-time equivalent (FTE) pharmacists or technicians investigating the compounding of several different agents.²⁸ However, lower skilled staff were able to operate CytoCare and it was both cheaper and simpler to train staff to operate CytoCare versus manual compounding.³⁶ Consistent with findings for APOTECachemo, CytoCare was associated with an increased overall preparation time compared with manual compounding (figure 4).^{28 30}

A single study investigating RIVA reported that chemotherapy preparation waiting times for patients (defined as the time

patients waited in 'Ready for Chemo') were reduced by 36% following implementation of the robot.³⁷

Compounding workflow systems

Six publications investigated Cato (generation of the software not stated).^{15–17 33 34 38} A single study investigating the compounding of 28 common chemotherapy agents reported a mean per cent difference between the prescribed dose and final accuracy dose of -0.62% (range: -5.04% to 4.97%) and highlighted the gravimetric technique to be key to the workflow process, detecting the largest proportion of dose errors.¹⁶ In general, pharmacy compounding time was reduced with Cato compared with manual compounding (figure 5).^{16 34 38}

No data on environmental contamination with Cato were reported. Installation of Cato for compounding 28 common chemotherapy agents resulted in annual labour cost savings of \$158 000 versus preinstallation.¹⁶ A further study reported estimated annual savings of £456 809 following the installation of Cato for the preparation of 40 doses of paclitaxel and bevacizumab extrapolated over 12 months, with the largest proportion of cost savings from campaign compounding and minimum wasted value.³⁸

Figure 4 Preparation times reported across the studies investigating CytoCare. Dark blue relates to CytoCare compounded preparations and light blue relates to manual compounded preparation. Note that some conversions were applied to generate the graph (ie, reported seconds converted to minutes).

Figure 5 Mean preparation times reported across the studies investigating Cato. Dark blue relates to Cato compounded preparations and light blue relates to manual compounded preparations without compounding workflow software.

A single study reporting on the Diana workflow system (unclear territories and locations) reported that the real-world accuracy of preparations for 14 different agents (including carboplatin, cyclophosphamide, fluorouracil and paclitaxel) was improved compared with the published accuracy specifications for Diana (reported as the first SD).³⁵

DISCUSSION

The SR identified 25 publications relating to commercial technologies for chemotherapy compounding.^{14–38} While current guidelines do not discuss the benefits of automated compounding technology in great detail, the use of gravimetric technology is recommended in the preparation of chemotherapy.⁹ Indeed, the benefits of gravimetric versus manual volumetric preparation of hazardous compounded sterile products in terms of faster preparation and improved accuracy and staff perception has been confirmed in a recent US study conducted at a medical centre inpatient pharmacy.⁴⁰

In general, the studies reporting on commercial technologies were inconsistent in terms of their design and the format of reporting of outcomes. The primary comparison of interest for the current review was that of automated compounding technologies with manual compounding approaches. This is because manual compounding is still widely used for the preparation of chemotherapy in all territories of interest.

In summary, the compounding technologies demonstrated improved accuracy in dose preparation and a reduction in dose errors compared with manual compounding.^{14–36} The current SR highlights a lack of data relating to the patient health consequences of chemotherapy accuracy and dose errors in studies investigating compounding technologies. However, research suggests that errors during the treatment of cancer can potentially lead to physical, psychological and social consequences for the patient.⁴¹

Contamination levels were variable with robotic compounding systems and were either comparable or lower than manual compounding processes.^{18 21 31} The compounding technologies were associated with reductions in annual costs compared with manual compounding,^{16 19 30 32 36 38} but the impact on compounding times was not consistent and was dependent on the type of compounding technology under investigation.^{16 18 19 22 23 26 29 30 33 34 37 38} The SR highlights data gaps across

several commercial brands in demonstrating their end-to-end solution from prescription to administration. Two key data gaps include the use of barcode-assisted medication administration (BCMA) and electronic prescribing. Targeted literature searches failed to identify studies relating to BCMA in the oncology setting, but a previous SR investigating the effect of BCMA on the frequency, type, and severity of medication administration errors in the hospital inpatient setting reported BCMA to be associated with a reduction in errors; however, long-term effects on error reduction were often not assessed.⁴² A recent review identified publications reporting on the implementation of electronic prescribing systems for chemotherapy in ambulatory and inpatient care settings.⁴³ Results indicated that electronic prescribing resulted in a statistically significant reduction in prescribing errors, primarily those involving dose calculation or adjustment.⁴³

Due to inherent differences between robotic compounding systems (limited to compounding stage only) and workflow compounding systems (which can impact across the entire workflow), it would not be relevant to directly compare the two technologies, and indeed maximum benefit may be achieved by combining workflow software and robotic compounding systems.

Both robotic and workflow compounding systems were associated with reductions in annual costs compared with manual compounding.^{16 19 32 38} and data from recently published studies suggest that these reductions may result from improvements in staff utilisation and supply cost savings with automated versus manual preparation.^{44–46} However, a cost-volume analysis suggests that the higher annual fixed costs of robotic systems results in a high breakeven point in terms of the number of preparations required (34 000 preparations annually) in return for the initial investment.¹⁹ Robotic systems consistently demonstrated increased preparation times compared with manual compounding, a finding which suggests that robotic compounding systems introduce unintended consequences in terms of workflow efficiency.^{18 19 22 23 26 29 30} In contrast, Cato, a chemotherapy workflow software solution demonstrated reduced preparation times in comparison with manual compounding.^{16 33 34 38} Cato is the only intervention included in the SR which manages the entire workflow for oncology therapy management, although it must be noted that no published data relating to workflow stages other than compounding were identified for this system. However, workflow compounding systems must interface with other electronic medical record (EMR) systems and incorporate all types of intravenous medications (ie, antibiotics, parenteral nutrition) and not just chemotherapy to fully realise their closed loop potential. Robotic systems may have a place in the preparation of ‘simple’, standard dose-banded chemotherapy agent orders received in advance which have a long expiry, and which do not need to be dispensed to a named patient (eg, gemcitabine, cyclophosphamide); they are less likely to be routinely used for the compounding of ‘complex’ variable dose agents. Productivity or efficiency of both workflow solutions and robotic systems is influenced by the time between prescription and administration. Larger time spans and longer drug shelf lives enable better utilisation of robot technology. Key potential benefits of automation using robotic compounding systems which have not been considered in the literature related to chemotherapy compounding are the ability of automated solutions to reduce both needlestick and repetitive strain injuries due to the nature of the process and the postures required in the manual preparation of cytotoxic drugs and to reduce the skillset required to operate machinery.

While the automation of chemotherapy compounding has the potential to offer both clinical and economic benefits in the hospital pharmacy setting, the current SR highlights a lack of published evidence reflecting the real-life challenges following the implementation of automation solutions in hospital pharmacies. This may be a consequence of the fact that 10 of the studies were sponsored by the technology manufacturers. For example, issues which are not highlighted by the current published evidence base include the potential requirement for on-site specialists to address issues arising with robotic compounding systems: an FTE staff member may be required to load and unload compounds to the robot which is associated with an incremental cost. Also, robotic compounding systems are limited in the size of vials that can be handled and not always able to manipulate ampoules, intravenous pumps or cassettes, which impacts the processes they are able to undertake. There may also be country-specific differences, with certain countries having embraced the adoption and utilisation of EMR more readily than others (ie, those with a larger number of EMR Adoption Model 6 and 7 hospitals as defined by the Healthcare Information and Management Systems Society). There are also a number of barriers to adoption of automated compounding technologies including the high initial costs of installation/implementation and the perceived lack of robust, high-quality published evidence concerning the economic/clinical benefits (which has been confirmed by the current SR).

Limitations

The results of the current SR must be interpreted in light of several potential limitations. The SR was restricted to English-language publications which may limit the global relevance of the findings. The absence of evidence for many commercial chemotherapy compounding technologies (ie, KIRO Oncology, CHIMIO and Oncofarm) is indicative of a lack of peer-reviewed studies in this field, which may result from publication bias. The overall quality of the evidence base was low. This is primarily due to the observational nature of the included studies, as such studies are associated with well-characterised bias from unknown confounders which can impact outcome measurements.

The studies included in the SR are heterogeneous in several aspects of their study design and outcomes reported both within and between the evidence base for each of the five technology systems. Notable factors contributing to heterogeneity across the evidence base include the generation/version of technology was rarely reported across the studies and difference in the performance of first- and third-generation robotic systems has been observed in practice^{22,23}; it was often challenging to ascertain the time between technology implementation and study initiation (and staff training); the study durations ranged from 4 days²¹ to 3 years²⁹; methods of data collection (technician observations or using data from technology software) and the potential bias which can be associated with observations and the potential Hawthorne effect^{47,48} and the inconsistent reporting of outcomes. These limitations impact our ability to conduct a robust synthesis of the evidence from multiple studies for a particular technology or to generate indirect inferences between technologies.

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