Cancer Care Ontario

Systemic Treatment Computerized Prescriber Order Entry (ST CPOE): Best Practice Guideline for Intravenous and Oral Chemotherapy

February 2016

CAPCA

Ontario
Cancer Care Ontario

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Statement of Collaboration

The production of the Systemic Treatment Computerized Prescriber Order Entry (ST CPOE): Best Practice Guideline for Intravenous and Oral Chemotherapy was a collaborative effort between many key stakeholders. Joint leadership between the Canadian Association of Provincial Cancer Agencies and Cancer Care Ontario was critical to producing robust and relevant information.

The Canadian Association of Provincial Cancer Agencies is an association of provincially designated cancer programs that have agreed to work together to address common challenges and opportunities to enhance and strengthen the delivery of cancer care in Canada. It provides a forum for the leaders of Canada's cancer delivery system to discuss, compare, learn from and collaboratively address system-wide issues including sustainability, operational efficiency, quality and safety. In this instance, CAPCA initiated and sustained pan-Canadian engagement of clinical, IT and administrative leaders from provincially designated cancer programs.

Cancer Care Ontario is the provincial government's advisor on the cancer and renal systems, as well as on access to care for key health services. The Systemic Treatment Program within Cancer Care Ontario aims to improve equitable access to high-quality cancer care for all patients in Ontario through setting standards and guidelines for all systemic cancer treatments. The Systemic Treatment team provided clinical content expertise and methodological rigor for this guideline.

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Introduction

Patient safety is of utmost importance within healthcare and a particular concern for chemotherapeutic medications. Errors in chemotherapy have a high risk of patient harm because of the narrow therapeutic margin of antineoplastic agents. Gandhi *et al.* (2005) revealed that compared with non-chemotherapy medication errors, chemotherapy errors were 48% more likely to be serious in nature (1). Initial guidelines from the American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) intended to improve safety for intravenous (IV) chemotherapy highlighted standards for prescribing, preparing and administering such drugs which have become readily adopted over time (2). Unique and significant challenges to safe delivery of care are introduced as the use of oral chemotherapy continues to rise. ASCO/ONS and the Canadian Association of Provincial Cancer Agencies (CAPCA) have acknowledged this added complexity to care and potential for medication errors and have provided recommendations to mitigate these risks (2;3).

Over time, there has been an increase in the use of oral take-home chemotherapies, and an increasing number of oral chemotherapy agents have been approved (4). The number of new oral chemotherapeutic agents in development is also increasing; a recent survey of oncology manufacturers estimated that 44% of new therapies under development were oral cancer medications (4). It has been reported that patients prefer oral agents because they are more convenient, allow greater autonomy, and avoid venipuncture and the associated risks of indwelling venous catheters (4).

However, oral chemotherapy also poses growing challenges to patient safety, such as poor adherence and a greater risk of drug-drug and drug-food interactions. Despite the challenges, a survey conducted by Weingart *et al.* (2007) found that fewer safety standards for oral chemotherapy agents have been adopted compared with infusion chemotherapy (5). The same study revealed that the safety standards or recommendations often assume chemotherapy agents will be administered in a monitored clinical environment and overlook that oral anticancer agents are often dispensed outside a healthcare centre (5).

Computerized Prescriber Order Entry (CPOE) systems reduce such medication errors and improve safe delivery of treatment and care (6). CPOE allows prescribers to enter all the details of a patient's treatment into a computer system. Subspecialty systemic treatment CPOE (ST CPOE) systems have arisen over the past decade from home-grown to commercially developed systems. These systems provide unique features and functionality as well as clinical decision support (CDS) required for clinicians during the safe prescribing, dispensing and administration of chemotherapy. ST CPOE systems have been well evaluated for IV chemotherapy; however, their use in an oral chemotherapy setting has not been well studied.

The Systemic Treatment Program at Cancer Care Ontario has a vision to be leaders in the provision of high-quality systemic treatment through innovation, integration and partnership. Patient safety is one of Cancer Care Ontario's top priorities as noted in the Ontario Cancer Plan IV (7), and as identified in many of the strategic priorities within the Systemic Treatment Provincial Plan: *Quality Person-Centred Systemic*

Treatment in Ontario 2014-2019 (8). Cancer treatment is increasing in both complexity and need with an estimated 191,300 new cases of cancer (excluding about 76,100 non-melanoma skin cancers) and 76,600 deaths in Canada in 2014 (9). In Ontario, there are an estimated 73,400 new cancer cases in 2014, compared to 66,710 in 2010 (10). With more complicated regimens and changing models of care, the chances of errors and safety issues also increase.

Using ST CPOE can improve the safety of oral chemotherapy prescribing. However, a recent national survey conducted by CAPCA revealed that only 14.9% of participants had reported routinely using CPOE systems to prescribe oral chemotherapy, while the remaining majority of 65.4% used hand written prescriptions (11). Some provinces reported that 100% of oral cancer drug therapy prescriptions were written by hand.

In February 2014, the second Systemic Treatment Safety Symposium was held in Toronto with a focus on oral chemotherapy safety. Subsequently, a provincial goal of zero handwritten or verbal oral chemotherapy orders by June 30, 2015 (12) was established for Ontario. This goal was in alignment with CAPCA's impending Oral Cancer Drug Therapy Safe Use and Safe Handling Guideline (11), the forthcoming Oral Cancer Drug Therapy Safe Use and Safe Handling Guideline, and the Systemic Treatment Provincial Plan. Given the high use of ST CPOE systems for IV chemotherapy in Ontario at 93% of visits, the use of ST CPOE systems to prescribe oral chemotherapy is being encouraged and system features and functionalities to safely and effectively prescribe oral chemotherapy will need to be carefully evaluated. Several other challenges are still reported such as a lack of education for healthcare providers about oral chemotherapy; poor communication, particularly between hospitals and community pharmacies, and the limited ability to monitor adherence in the community. Both CAPCA and ASCO/ONS advocate for measures such as the use of standardized, regimen-level, pre-printed or electronic forms and having a second healthcare provider independently verify chemotherapy orders prior to preparation (2;3). There is a great need to identify improvements for ST CPOE systems that will support prescription safety for oral anticancer agents in Ontario and across Canada. There is also a need to focus on implementation and change management from both a practical and a research perspective as it relates to ST CPOE systems and these guidelines.

Purpose

The original ST CPOE best practice guidelines, published in 2012, provided evidence-based recommendations to guide the design, selection, implementation and/or evaluation of ST CPOE systems, and to determine the system features and functionalities to support the safe delivery of chemotherapy (6). However, these guidelines focused on IV chemotherapy and did not specifically evaluate issues related to oral chemotherapy. Furthermore, the Oral Cancer Drug Therapy Safe Use and Safe Handling Guideline (11) recommends that the existing ST CPOE Guidelines "should be revised to incorporate oral cancer drug therapy prescribing requirements and should be adopted and followed nationally". This 2016 addendum accomplishes CAPCA's recommendation through a focus on the features and functionality to support the

safe and effective use of ST CPOE systems in oral chemotherapy and includes an update to the 2012 guidelines, highlighting the growing literature for CPOE systems.

Objectives

This review has two objectives, each with corresponding research questions:

Objective 1: To identify the features and functionalities of ST CPOE systems that can be used to support the safe and effective delivery of oral chemotherapy[1].

> *Research question:* What are the functionalities of ST CPOE systems for safe and effective delivery of oral chemotherapy?

Objective 2: To provide evidence for updating existing ST CPOE guidelines.

> *Research questions:* What is the impact of ST CPOE on medication errors? What are the types of clinical decision supports and how can they be effective or ineffective?

Methods

Structured searches of Ovid Medline, EMBASE, CINAHL, Compendex and Cochrane were conducted on February 18, 2015.

For objective 1, the search strategy used a combination of keywords and free-text terms related to two categories: 1) "oral chemotherapy" and "CPOE", and 2) "oral chemotherapy" and "prescribing" (see **Appendix A** for a full list of search strategies). Searches were conducted from 1996 to present for Ovid Medline and EMBASE, and 1982 to present for CINAHL. Compendex was searched for the dates of 1969 to present. Cochrane library was searched without limiting the dates (inception of the database to present). Searches were limited to English language.

For objective 2, Ovid Medline, EMBASE, CINAHL, and COMPENDEX were searched to scan recent literature on CPOE systems for chemotherapy. The same search terms and strategies from the original guidelines were used (6). Searches were limited to the studies published in the last four years (2011 onwards) (**Appendix A**).

Results were uploaded to a Reference Manager database, which was used to screen and manage findings.

[1] For the purpose of this review, oral chemotherapy is defined as all antineoplastic agents used to treat cancer given by mouth. Hormonal agents are included in the definition.

In order to conduct a more comprehensive search, broad web-based search within the United Kingdom (.uk), Australia (.au), New Zealand (.nz), the United States (.gov), Europe (.eu), France (.fr) and Canada (.ca) was performed. Websites of key organizations were also searched, including the Institute of Safe Medication Practices (ISMP) Canada, Canadian Patient Safety Institute, Canada Health Infoway, Ontario MD, Canadian Association of Pharmacy in Oncology (CAPhO), Canadian Agency for Drugs and Technology in Health (CADTH), Certification Commission for Healthcare Information Technology (CCHIT), KLAS, Leapfrog Group, Food and Drug Administration (FDA), Health Canada, Agency for Healthcare Research and Quality (AHRQ), National Cancer Institute, Canadian Partnership Against Cancer (CPAC), Institute for Healthcare Improvement (IHI), Commonwealth Fund, Robert Wood Johnson Foundation, Healthcare Information and Management Systems Society (HIMSS), and the American Society of Clinical Oncology (ASCO).

Using Google Advanced Search, the first five pages of results were visually scanned, and potentially relevant information was organized into an excel-sheet for later review.

Additionally, National Institute for Health and Care Excellence (NICE), OpenGrey, and Health Systems Evidence (McMaster University) were also searched for evidence. Backward reference searching of the included studies was conducted for data extraction.

Those studies that did not meet the inclusion criteria were excluded based on title and abstract when available. When it was not clear in the title and abstract if an article met the inclusion criteria, inclusion was determined by screening the full-text.

The following were determined to be out of scope: linked modules, impact of closed-loop medication systems vs. non-integrated systems and barcoding. Linked modules, such as nursing administration and pharmacy verification/dispensing modules are often thought to be part of ST CPOE systems; however, they are sufficiently complex that they were excluded as a more detailed analysis would be required. The impact of CPOE systems on multi-modality therapy as it relates to clinical inter-operability and transmissions standards were out of scope.

Screening

Multiple reviewers conducted title and abstract screening (VK, NL, AC, JK).

For both objectives 1 and 2, the same inclusion criteria from the original ST CPOE guidelines were applied:

- Published English-language reports of CPOE in the oncology setting or in the non-oncology adult outpatient setting;
- Phase II or III randomized controlled trials (RCTs), other comparative studies, single-arm studies, practice guidelines and systematic reviews, with or without meta-analyses;
- The most recent paper that evaluated a given data set.

In addition, for objective 1, studies and reports were included if they described any features and/or functionalities of ST CPOE systems that can be used for effective delivery of oral chemotherapy; or

recommendations for CPOE systems that can be applied for delivery of oral chemotherapy; or recommendations for the prescribing of oral chemotherapy that can be applied to CPOE systems.

For objective 2, studies and reports were included if they described ST CPOE features and functionalities in the oncology setting, or in the non-oncology adult outpatient setting leading to safe and effective medication prescribing.

Studies related to e-prescribing (the framework that allows clinicians to send prescriptions to a pharmacy electronically), clinical processes of e-prescribing, and pharmacy dispensing were excluded. It is important to note that the literature often uses the term "electronic prescribing" to imply prescribing through a computerized prescriber ordering system and these articles were included.

Studies specific to the pediatrics setting do not meet the inclusion criteria for objective 1, but articles from pediatric oncology settings were included as examples to address general features and functionalities of ST CPOE for objective 2.

The full texts of articles that met the inclusion criteria in the title and abstract screening were obtained. Full text screening was undertaken by an independent reviewer (JK) for objective 1, and was carried out by multiple reviewers (VK, NL, AC) for objective 2.

Data Extraction

One reviewer (JK) performed data extraction. The process was guided by a template (see **Appendix B**), developed for this review and approved by all authors. Data related to the purpose of the study, study design, sample, CPOE system features and functionalities, and implications/recommendations were abstracted.

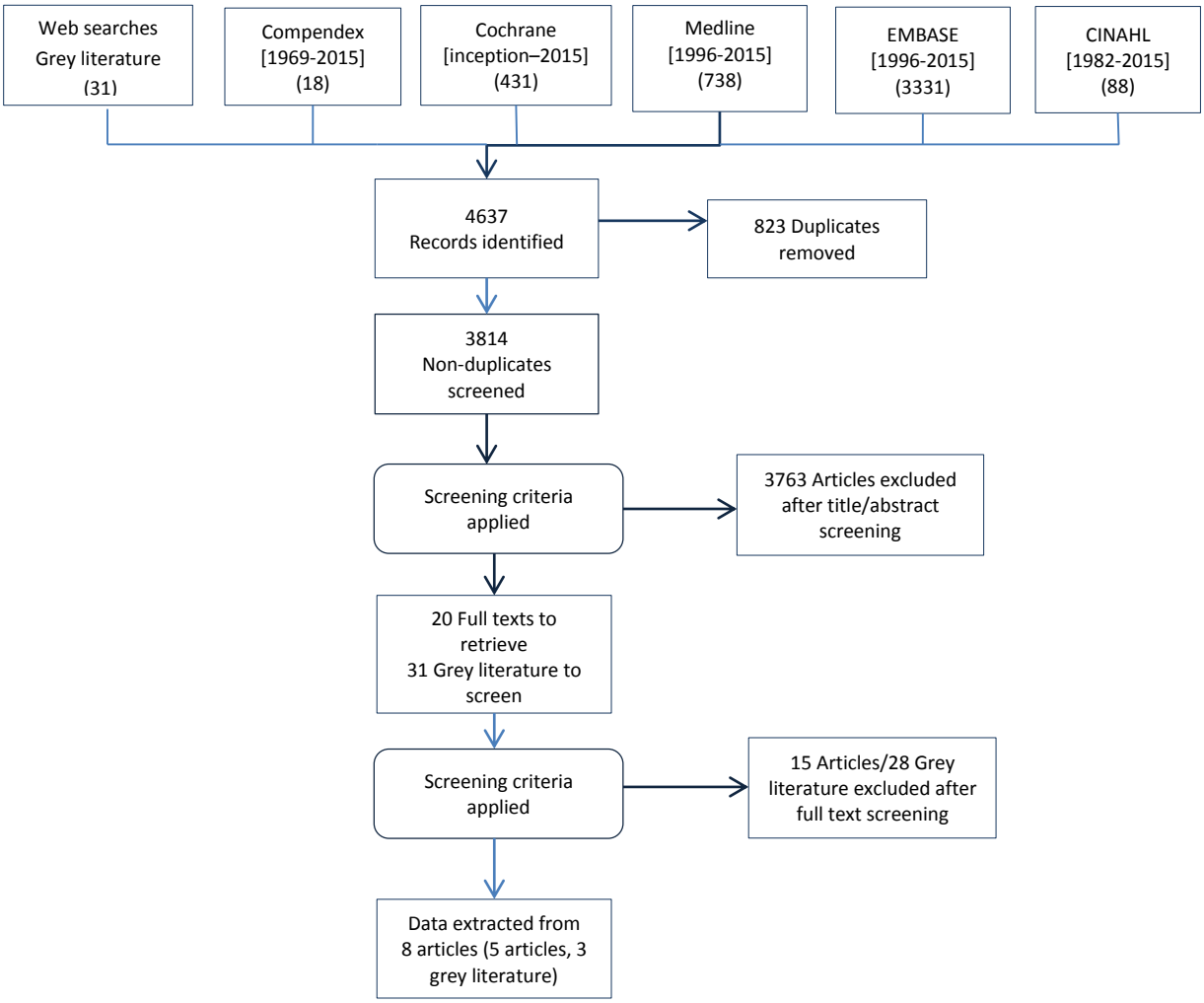
From a methodological perspective, due to the heterogeneity in study designs of the identified references and the lack of published randomized controlled trials, a quality appraisal was not conducted in this review.

Results

Objective 1: ST CPOE in oral chemotherapy

A total of 4637 unique articles (**Figure 1**) were identified through the search strategies, of which 823 duplicates were removed. Screening criteria were applied for the titles and abstracts of 3814 articles. After title and abstract screening, a total of 20 potentially relevant published articles were identified. Comprehensive web searches yielded 31 results. After full text screening, 42 articles were excluded. Data were extracted from 8 articles.

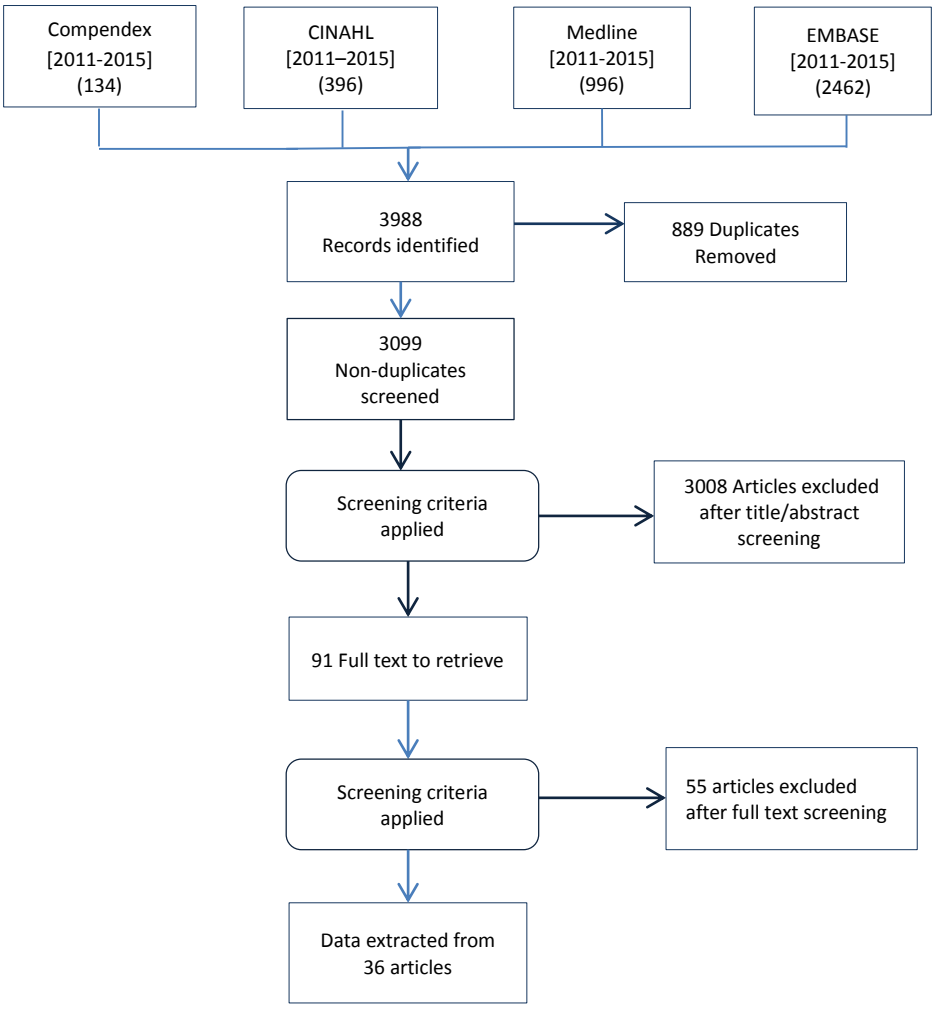
Figure 1: PRISMA flow diagram for objective 1



Objective 2: Evidence update for the original guidelines

A total of 3988 unique articles (**Figure 2**) were identified through the search strategies, of which 889 duplicates were removed. Screening criteria were applied for the titles and abstracts of 3099 articles. After title and abstract screening, a total of 91 potentially relevant articles were identified. All of these references were assessed for eligibility in full texts. Data were extracted from 36 articles.

Figure 2. PRISMA flow diagram for objective 2



Characteristics of the included studies

The 2012 ST CPOE guidelines included 48 studies, with the publication years ranging from 1996 to 2011. This addendum is evidenced by 44 published studies[2], published between 2007 and 2014. Most studies were published in the last 4 years (2011 onward), except for two studies that were published in 2007 (13) and 2010 (14), respectively. This shows that ST CPOE has been an active area of growing research.

Among the studies included, 15 studies described one or more features and/or functionalities of ST CPOE systems that may support safe and effective delivery of oral chemotherapy, and five studies included strategies and/or recommendations for oral chemotherapy. Twenty-one studies discussed the types of CDS and their effectiveness, and 11 studies reported impacts of ST CPOE systems on medication errors. A total of eight studies provided evidence unique to the oncology setting. Four studies were unique to oral chemotherapy, while one study related to IV chemotherapy only. Three studies contained evidence and implications for both oral and IV chemotherapy.

Table 1. Number of studies by research question/topic (not mutually exclusive)

Research Question/ Topic	Number of documents	Reference numbers
Features and/or functionalities of ST CPOE systems	15	13-27
Strategies and/or recommendations for the safe delivery of oral chemotherapy	5	14, 16, 17, 21, 22
Clinical decision support (CDS) functions	21	15, 17, 23, 31, 33-49
Impact of ST CPOE on medication errors	11	14, 15, 18, 19, 24, 25, 27, 31, 37-39

Table 2. Studies related to oncology setting

Area	Number of documents	Reference numbers
Oral chemotherapy	4	14, 16, 17, 21
Intravenous (IV) chemotherapy	1	19
Oral and IV chemotherapy	3	14, 15, 23

[2] Four articles met the inclusion criteria of both objectives 1 and 2.

Features and functionalities of ST CPOE systems in oral chemotherapy

The evidence search identified 15 studies that described the features and functionalities of CPOE systems for safe delivery of oral chemotherapy (13–27). For the purpose of this review, features and functionalities were categorized as follows: functionality, usability, system integration, information standards, and security. Recommendations on the features and functionalities of ST CPOE systems for oral chemotherapy are summarized in **Table 3**.

Functionality

Thirteen studies were identified that described the functionalities of CPOE systems for the safe delivery of oral chemotherapy (13–25). The following features were identified in terms of functionality: dosing calculation tools, regimen build/templates, information display and alerts, and order reviews.

Dosing calculation tool

Dosing calculation tools can be used to reduce the risk of dosing errors. For example, the Chemotherapy Assistance Program (CAP), which is a comprehensive CPOE system, provides automatic selection for oral cancer drugs available in different dosage strengths (15). To illustrate, for two dosages (150mg, 500mg) available for oral capecitabine, CAP identifies the optimal combination of available dosages once the dose of capecitabine is determined for a patient (15).

Other examples of dosing calculation tools identified rely on weight, height, or body surface area (BSA) calculations (14,17). For example, the Longitudinal Medical Records (LMR) module reported in Weingart *et al.* (2012) uses a weight-based, height-based, or body surface area (BSA)-based dosing calculation function (17). For orders with weight or BSA-based dosing, the module uses the most recent weight recorded in the medical record (if < 30 days) and the most recent height (if < 1 year) to calculate the BSA, which is used to determine the final dose (17).

Sklarin *et al.* (2011) described safety enhancements in electronic chemotherapy order entry at a cancer center, which includes built-in calculators in the order entry form (18). These calculators automatically calculate the treatment dose with default base doses when an order form is opened. For example, dosing formulas include dose per m^2, per kg, flat dose, and area under the curve (AUC). Data modifiers include ideal body weight and adjusted/ideal body weight. Dosing can be capped for individual drugs in specified regimens, and dose rounding is automated per pre-defined rules. Likewise, Chen and Lehmann (2011) (19), and Crossno *et al.* (2007) (13) described a tool that checks the weight and height of a patient, and automatically calculates BSA, BMI and ideal body weight and adjusts treatment doses. For example, the system alerts the prescriber if the calculated values are outside the normal range (19).

Regimen build/templates

Regimen building functions promote best practices by allowing prescribers to easily choose among clinically appropriate options and convey the correct quantity information regardless of dosage form (20).

Regimen building support functions may vary between CPOE systems, and require enhancing the system interface and drug selection tools.

Collins and Elsaid (2011) described a regimen template with drug-specific defaults in the order form (16). These included standardized minimum dosing, frequency and duration, and entry fields for cycle number and days in cycle. Similar functions were reported in the LMR module that includes a feature for medication choice lists with default doses and frequencies (17). Dosing calculation tools and drug-interaction alerts would support this function as well.

Information display and alerts

Programmed alerts

Programmed alerts are widely reported CDS functions of CPOE systems. The use of daily and weekly dose-limit warnings and drug-specific maximum dose warnings were reported in five studies (13,14,16–18).

Alerts can also be generated for new prescriptions (17), prescription renewals (17), geriatric dose warnings (17), renal dose warnings (17), drug interactions and allergies (16–18,23), and inappropriate prescribing of pill splitting (22).

Galanter *et al.* (2013, 2014) described an indication alert function (24,25). With integration into the Electronic Medical Record (EMR), this alert function prompts prescribers to update the medical record for patients whose electronic problem list (coded indications) does not contain an indication specific to the ordered medicine (24,25). If a clinician selects an incorrect medication due to a pick-list or memory error, an alert interrupts the ordering process and the clinician is forced to review the selected drug's indication against the patient and his or her problem list (25). While it is not clear how the alerts intercepted errors in this study, the authors suggested that the appearance of an alert forces the prescriber to reflect on the order process allowing errors to be self-identified and corrected (25).

Data management

The organization and display of information in a CPOE system can also support clinical decision-making and reduce errors. For example, the LMR module described by Weingart *et al.* (2012) (17), displayed the patient's primary cancer diagnosis; if the patient had received infusion chemotherapy, the diagnosis was pulled into the oral chemotherapy prescription automatically. The prescriber could also add or modify the diagnosis, adding the cycle number and clinical trial number, if desired (17).

Sklarin *et al.* (2011) also described a CPOE system that utilized efficient data management and display of information, where applicable recent lab results were displayed on the order form along with predefined treatment parameters (18). Physicians could copy and reorder an entire chemotherapy order set for a subsequent cycle of therapy, thereby reducing dose transcription errors (18).

Order reviews

CPOE systems can improve the safety of oral chemotherapy orders by labelling the drug as a chemotherapy agent, by providing drug-specific guidance on appropriate laboratory monitoring, by displaying critical laboratory values, by displaying drug interactions and dosing regimens (16). CPOE systems can support order review by linking drug therapy guidelines to order sets and allowing access to the pharmacy system to view prior dispensed doses (18). Order verification ensures that prescribed doses, treatment intervals and administration details are appropriate for the patient and their specific conditions (21).

Security

Security of CPOE systems can be ensured by using user authorization features (13,16,18). For example, Collins and Elsaid (2011) described how order entry is restricted to attending physicians within their scope of practice (16). Another study described a system that can identify the type of healthcare provider and allow them to enter orders in accordance with their credentials. Chemotherapy agents were coded such that only credentialed providers were allowed to access and order those drugs (13). In addition to this body of evidence on security of the CPOE systems, other best practices and evidence guidelines on privacy and security measures of relevant electronic health and pharmacy systems[3] offer broader guidance on ensuring the integrity of health-related data.

System Integration

Although a number of studies described examples of CPOE systems that were integrated with electronic health records (EHR) or electronic medical records (EMR) systems, these examples may not be applicable to the Ontario context due to our current lack of standardized and centralized patient records. The CPOE system described in Sklarin *et al.* (2007) allowed providers access to the pharmacy system to view prior dispensed doses (18). Weingart *et al.* (2012, 2014) described functionalities of integrated systems. A system is integrated into the Longitudinal Medical Records (LMR), a multi-feature electronic medical record shared among clinicians across the affiliated healthcare institutions (17,23). The LMR prescription module allows the prescribers to identify and manage different classes of drugs, and offers standard electronic features such as medication choice lists (17). The system also has the capacity to check new prescription orders against the LMR medication list. This integrated system allows prescribers to identify

[3] These guidance documents include:

- COACH Guidelines for the Protection of Health Information: http://www.coachorg.com/en/practices/Privacy_Security_Guidelines_Series.asp
- Canada Health Infoway Electronic Health Record (HER) Privacy and Security Requirements: https://www.infoway-inforoute.ca/en/component/edocman/resources/technical-documents/389-ehr-privacy-and-security-requirements
- COACH's 2013 eSafety Guidelines: http://www.coachorg.com/en/practices/2013-eSafety-Guidelines.asp
- NAPRA Pharmacy Practice Management Systems (PPMS): Requirements to Support NAPRA's "Model of Standards of Practice for Canadian Pharmacists": http://napra.ca/pages/Practice_Resources/ppms.aspx
- The Canadian CPOE Toolkit https://www.cpoe-toolkit.ca/

potential interactions between a patient's regular outpatient medications recorded in the LMR and any new chemotherapy orders entered into the system. It also automatically displays cancer diagnosis and dosing calculation based on a patient's weight and height.

Usability

Involving key stakeholders and end users in system design can ensure system usability. The majority of studies included in this review reported that clinical teams were broadly involved in developing CPOE systems. For example, Collins and Elsaid (2011) reported that a clinical pharmacy team participated in developing the oral chemotherapy CPOE for formulary oral agents (16). Additionally, safety-oriented enhancements of the LMR prescription module, including the ability to order oral chemotherapy based on automatic dose calculation (for details, please see *Functionality – Dosing calculation tool* for details), and cancer diagnosis display (for details, please see *Functionality – Data management*) were developed with guidance from physicians, nurses, pharmacy, and information technology colleagues (17). The use of needs assessments has also been reported as a means to improve usability (19). Chen and Lehmann (2011) reported that a needs assessment of care providers in pediatric oncology became the basis of the system design (19). Programming the right CDS rules such as designing and implementing non-interruptive alert functions (for details, please see *Clinical Decision Support functions of CPOE systems – Alert functions*) can also improve usability.

Information Standards

Information standards can reduce errors such as mis-selection of products that have similar-looking or similar-sounding names or similar-looking packages. Technological solutions integrated into dispensing systems can support information standards. These solutions involve manipulation of written text to highlight the distinguishing syllable(s) or characters between similar drug names, as in TALLman lettering (26). Although TALLman lettering can enhance dispensing accuracy, it may increase error rates if it interferes with the reading of a medicine name or prolongs reading time. To prevent overuse or misuse of TALLman lettering, its use is recommended for a small percentage of confusable medicines (e.g. based on ISMP recommendations), and at the point of dispensing when medicines are selected from lists (26).

Avoiding inappropriate abbreviations is also recommended (27). Although there is a "Do Not Use" list for abbreviations established by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and ISMP, system providers are not required to upgrade the list. In order to ensure updating the list of inappropriate abbreviations, upgrading the system is highly recommended (27).

Table 3. Recommendations for ST CPOE system features and functionalities for oral chemotherapy

Priority Level
E = Essential; must be included in ST CPOE application
D = Desirable; not as critical for initial implementation, but inclusion could improve quality

Recommendation
[Oral] – Signifies recommendations relating to oral chemotherapy only
[IV] – Signifies recommendations relating to IV only

System feature, functionality	Recommendation	Priority level
Functionality	System checks ordered dose against a knowledge base (e.g. local guidelines of best practice or other references) of relevant dose and frequency ranges (13,14,16,17,18) • For single dose, can set up minimum or maximum dose allowed, per dose, per day or per course for each available route of the drug • Checking against frequency and duration that are pre-set for the regimen System incorporates logic for determining cycle scheduling and treatment duration (days between cycles and total number of cycles) (16) • Cycle number information should be available, including start day • Day of cycle should be clearly defined for each drug System has appropriate alerts for dose checking	E
	System has dose calculation built into electronic ordering system using units consistent with jurisdictional standards (e.g. height in meters and weight in kilograms) (13–15,17,18) • Automatically calculates dosing and modifications, based on dosing algorithms using, for example, patient weight, height, CL_{cr}, target AUC, sex, age	E
	System has customizable alerts for new prescription versus renewals (17) [Oral]	E
	System has the ability to have customizable safety guardrails for modifying orders (17) • E.g. Starter set of rules for medications requiring consideration of renal or hepatic status in dosing	E

System feature, functionality	Recommendation	Priority level
	System has appropriate alerts for (16–18,23): • Allergies (e.g. acknowledgement/override of alert) • Drug-drug interactions	E
	System has appropriate alerts for (22): • Inappropriate pill splitting, where applicable	E
	System presents diagnosis and option to customize printing and formatting of chemotherapy orders and take-home prescriptions to meet best practice recommendations (e.g. including diagnosis, no repeats on oral chemotherapy [Oral]) (17)	E
	System displays relevant laboratory values during order entry and review (18) System allows proceed criteria to be documented on the regimen template (18)	E
	Ordering subsequent cycles (18) • Changes made in chemotherapy dosing to be carried into subsequent cycles	E
	System displays relevant laboratory values, drug interactions, allergy status and dosing regimen during order entry and review (16)	E
	System provides access to chemotherapy drug mixing instructions, solubility information, stability information, monitoring and storage expiration information (16,18) System automatically calculates dose modifications based on laboratory parameters (e.g. renal or hepatic function) (16,18)	E
	System has the ability to link to protocol from the order (16,18) • Link regimen template or order to references or treatment guidelines • Direct link from order to clinical trial protocols	E
	System has alerts with clear and concise messaging, indicating interacting drugs, actions for clinical management and a statement indicating the consequences of over-riding the alert (28)	E
	System includes context-specific patient laboratory data into drug-drug interaction alerts (e.g. display serum potassium lab results for an interaction that may cause hyperkalemia) (29,30)	D
	System has the ability to integrate with appropriate clinical decision support systems (CDSS) when not available within the ST CPOE system (e.g. knowledge bases that support dosing information support, provincial drug repository, etc.) (31)	E

System feature, functionality	Recommendation	Priority level
	System must support the development and use of regimen templates including the ability to link to a specific diagnosis group or clinical trial (16)	E
Security	System has the ability to label relevant drugs such as chemotherapy agents, so only credentialed providers can prescribe or administer these medications (13,16,18)	E
Usability	Involve key stakeholders and end users in system design (e.g. prescribers, pharmacists, nurses, information technology professionals, decision support, clinical informatics, quality representative, patients) (16,17,19)	E
	Alerts are non-interruptive to order entry workflow by considering human factors principles in their design (e.g. personalization of alert display) (28,32–35) System categorizes alerts into groups and assigns action to the alert based on severity and risk. Clinically insignificant alerts are minimized (28,32–35)	E
Information Standard	The information display should be clear and organized to prevent the clinician from making errors with look-alike, sound-alike drugs or juxtaposition errors (e.g. use of TALLman lettering) (26)	E
	System must follow the Joint Commission and ISMP's standards regarding abbreviations, symbols and dose designations (26)	E

Evidence Update:

The search of studies published in the last four years found new evidence from 21 studies on CDU functions of CPOE systems and their effectiveness. Eleven studies were identified to provide evidence on impact of CPOE on medication errors. These studies provide evidence unique to the oncology setting (including both oral and IV chemotherapy), but also include evidence from non-oncology setting. A summary of updated evidence on the ST CPOE features and functionalities is shown in **Appendix C**.

1. The impact of CPOE on medication errors

The positive impact of CPOE systems on medication errors was widely reported in studies from both oncology and non-oncology settings (**Table 4**).

Oncology setting

Oral chemotherapy setting

Jatoi *et al.* (2010) reported near-miss rates of prescription errors for capecitabine and temozolomide, four months after a new safety mechanism was implemented (14). The new safety mechanism was a double check for electronic capecitabine and temozolomide prescriptions by an oncology pharmacist within 24 hours of patient's receipt. This review detected 12 prescriptions with a 10% or greater discrepancy from the intended dose, and yielded monthly near-miss rates of 3.7%, 4%, 1.7%, and 0.8% for the four month period.

Other oncology setting

Chen and Lehmann (2011) reported on CPOE implementation in a pediatric oncology setting. The study showed that the number of medication-related patient safety events decreased by 39%, and chemotherapy related events declined by 48% in the first year after implementation (19). Additionally, Cho *et al.* (2013) conducted an assessment of the efficiency and safety of the comprehensive CAP for ordering oncology medications and found that for CAP orders, incorrect dose and agent errors were reduced by 43.9% and 31.6%, respectively (15).

Non-Oncology setting

Similar to the findings above, 4 additional studies reported a decrease in medication errors as a result of using CPOE systems in non-oncology settings. Abramson *et al.* (2011) compared medication error rates between 2432 paper prescriptions at baseline and 1543 paper prescriptions and 536 electronic prescriptions at follow up (36). Among electronic prescribing system adopters, 20.5% of prescriptions contained at least one error, and among non-adopters, 29.8% of prescriptions contained at least one error. It was also reported that as a result of the electronic chemotherapy order system, the number of incomplete orders dropped from 197 to 77 within one year after implementation (18). Further, Galanter *et al.* (2013; 2014) reported how indication-based alerts (for details, please see *Functionality- Regimen build* section) in a CPOE system can prevent patient medication errors and drug name confusion errors. Study outcomes showed that an interception rate for wrong-patient errors was 0.25 per 1000 alerts (25). Another study by the same authors reported that indication alerts intercepted 1.4 drug name confusion errors per 1000 alerts (24).

New error types

The evidence update discovered additional error types that were not reported in the original ST CPOE guidelines such as wrong-patient medication errors (i.e. when a patient is accidentally prescribed another patient's medication) (25), and drug name confusion errors (i.e. the mis-selection of products that have similar-looking or similar-sounding names or similar-looking packages) (24).

Indication-based alerts during data entry reduced wrong-patient medication errors. Evidence also suggests that these errors may be reduced by other means, including having the prescriber make a single-click confirmation that they had verified patient identity before entering an electronic order (25), and

having the prescriber re-key a patient's initials, gender and age before entering an electronic order or displaying a picture of the patient at the time of final order (25).

Strategies to reduce drug name confusion errors include eliminating one of the two confusing products from the formulary, adding labels to shelves where products are stored, adding warnings to computer order entry systems, and using mixed-case (TALLman lettering; see *Information Standards* for details) (24).

While CPOE systems may reduce errors, it is important to acknowledge that in some cases these systems may introduce other errors. For example, Nanji *et al.* (2011) reported new errors generated after implementing CPOE and showed that 11.7% of prescriptions completed by electronic system contained errors (37). The most common error identified in this study was omitted information (60.7% of all errors) (37). The study found that the severity of prescribing errors varied significantly depending on which computerized prescribing system was used, suggesting differences in either the system designs or implementation (37).

Table 4. Error rates before and after CPOE system implementation

Study	Setting	Method	N Prescriptions/ sample	Overall errors (including near-miss) (%)	Errors by type Pre-CPOE vs. Post-CPOE
Jatoi *et al.* (2010) (14)	Oncology - Oral chemo	Pilot project implementation (only post data presented)	NR	12 prescriptions with a 10% of greater discrepancy from the intended dose Near-miss rate at 1 month 3.7%/ 2 months 4% / 3 months 1.7% / 4 months 0.8%	• Treatment duration • Frequency of dosing • Incorrect data for calculation
Chen and Lehmann (2011) (19)	Pediatric oncology	Retrospective data analysis	NR	Before implementation 132 medication related events 1 year after implementation N = 80 (39% decrease)	• Chemotherapy related events: declined by 48% • Prescribing: decreased by 67% • Transcription: eliminated • Dispensing events: decreased by 42% • Administration: decreased by 33%
Abramson *et al.* (2011) (36)	Non-oncology	Pre/post implementation	2432 paper prescriptions (Baseline); 1543 paper prescriptions 536 electronic prescriptions	Electronic prescribing system adopters, 20.5% of prescriptions contained at least one error Non- adopters, 29.8%	• Prescribing errors: 26% vs. 16% • Rule violations: 49.8% vs. 5.8% • Near misses: 2% vs. 1.8% • Alert advanced (preventable by advanced CDSS): 2.6 vs. 21.7 • Alert basic (preventable by basic CDSS): 13.1 vs. 10.4
Cho *et al.* (2013) (15)	Oncology	Retrospective data analysis	54,561 chemotherapy prescription orders	N/A	For CAP orders, incorrect dose and agent errors were reduced by 43.9% and 31.6% respectively

Study	Setting	Method	N Prescriptions/ sample	Overall errors (including near-miss) (%)	Errors by type Pre-CPOE vs. Post-CPOE
Galanter *et al.* (2013) (25)	Non-oncology	Retrospective data analysis	127,320 alerts generated by the system	N/A	An interception rate for wrong-patient errors was 0.25 per 1000 alerts
Galanter *et al.* (2014) (24)	Non-oncology	Retrospective data analysis	127,458 indication alerts generated by the system	N/A	Indication alerts intercepted 1.4 drug name confusion errors per 1000 alerts
Nanji *et al.* (2011) (37)	Non-oncology	Retrospective data analysis	3850 computer generated prescriptions	N/A	• Errors associated with electronic prescription: 11.7% contained errors • The most common error was omitted information (60.7% of all errors)
Sklarin *et al.* (2011) (18)	Oncology	Retrospective data analysis	N/A	Incomplete orders dropped from 197 to 77 in a year after implementing an online prescribing system	N/A
Leung (2012) (38)	Non-oncology	Pre/post implementation	2000 charts	34% reduction in preventable ADEs, 29.5% increase in potential ADEs after implementation	• Overall rate of ADEs: 14.6% vs. 18.7% • Preventable ADEs : 10.6% vs. 7% • Non-preventable ADEs : 44.4% vs. 57.5%
Kazemi *et al.* (2011) (31)	Non-oncology	Pre/post implementation	248 patients	Significant error reduction (34%) after decision support was added to the CPOE	Dose errors more intercepted than frequency errors

Joy *et al.* (2012)
 	
(39)
	Non-oncology	Pre/post implementation	48,840 orders	41% reduction in the rate of errors 3 months following CPOE implementation	• Pre-implementation error types:
					  ○ missed entry, wrong dose
					  ○ incomplete orders
					• Post-implementation error types:
					  ○ duplicate therapy
					  ○ wrong dose
					  ○ wrong formulation
					  ○ wrong frequency

2. Types of Clinical Decision Support functions of CPOE systems

Types of CDS functions were categorized into general features, alert functions, treatment guidelines concordance, and data management/ontology. The following information may be used to help guide the selection of ST CPOE systems or add-ons to systems by providing an overview of features and functions, which have been developed to support the management of patients on chemotherapy, and/or have been shown to improve the management of patients on chemotherapy. In general, features include dosing calculation support (31,40,41), drug interaction alerts (40,41,32,42), allergy checking (40,41), access to drug information (40), display of laboratory results (40), clinical guideline support (29,41), and adverse drug event monitoring (41).

General Features

Ahmed *et al.* (2013) described the current use of CPOE prescribing in acute NHS hospital trusts in the UK, and the use of multiple CPOE systems within the same hospital (40). Authors conducted a survey on the prevalence of system use, the number of different systems in each hospital, and stages of the patient pathway in which a CPOE system was used. Sixty-nine percent of respondent hospitals used at least one form of CPOE at the time of the survey, with 56% of those having more than one system.

The key patient safety related decision support functionalities identified were checking proper dosage (i.e. maximum/minimum dose warning), dose calculation, drug interaction alerts, access to drug information, allergy checking, and display of lab results. The results of the study indicated that decision support functionality varied widely, and only 13% of respondents used an inpatient CPOE system. The study concluded that a wide variation in systems may create challenges for staff training and patient safety, because clinicians may make errors in using different systems with different decision support features.

Cornu *et al.* (2014) reported physicians' perceived usefulness of different types of CDSS (41). This study conducted a survey among physicians questioning their experiences with drug prescribing and the perceived usefulness and desired features of future CDSSs. The results of the study showed that drug-drug interaction checking, drug-allergy checking, and dosing information support (dosage support based on maximal dosage per prescription) were considered as most useful. Automated clinical guidelines and adverse drug event monitoring were evaluated as least useful (e.g. alert promoting guideline concordance and flagging monitoring for certain toxicity).

Kazemi *et al.* (2011) described CDSS functions in the neonatal ward. These included a renal function evaluator, and patient specific knowledge inquirer for dosing (31). CDSS has a knowledge base, which contains relevant dose and frequency ranges. At the time of order entry, the system examines the dose and frequency of each prescribed medication from a dosing knowledge base. The clinical inference unit calculates the patient specific appropriate dose and frequency based on available patient information, (e.g. calculated glomerular filtration rate) and compares the results with the prescribed dose and frequency. If the prescribed dose or frequency is not within the normal range, the system informs the

prescriber by a warning message and asks for correction. If the prescriber accepts the correction, the order is automatically updated based on the system recommendation (31). If the prescriber ignored a warning, the next warning appears when one of the decision criteria was changed in the renewed order or a new erroneous dose and/or frequency was set for that medication. Benefits of these CDSS functions on reducing medication errors and prescribers' workflow efficiency were widely discussed in the literature. Kazemi *et al.* (2011) indicated that errors were significantly reduced after the decision support functions were added to the CPOE system (31). Kruer *et al.* (2012) described the benefit of warnings and alerts for safe prescribing and prescribers' workflow (43). By giving the prescribers alerts on drug interactions, impaired renal clearance and standard dosing in real-time, CPOE systems can reduce the frequency of inappropriate orders, and reduce the number of phone calls that prescribers may make for clarification.

Two studies provided descriptions of dose checking functions and their impact on practice. Boussadi *et al.* (2013) assessed the advanced CDSS for renally-cleared drug dosing control (44). They established 962 clinical decision rules to fire "exceeds max daily dose" alerts and "under-dose" alerts and implemented these rules as an alert system integrated to the CPOE system. The outcome showed the alert system fired more appropriate alerts than pharmacists, and made fewer errors than pharmacists in analyzing drug dose prescriptions (44).

Boussadi *et al.* (2011) described an expert dose checking system called DoseChecker that was developed for pharmacists (45). The primary purpose of this system is to calculate CrCl (creatinine clearance) and verify that the dosages are appropriately adjusted for renal dysfunction. The system uses patient data, automatically calculates CrCl, and checks the patient's current dose and dosage interval against the user-defined rules that contain allowable dosages for all ranges of renal function. If a patient's dosage is outside the range, an alert and a recommendation for the proper dosage is printed in the pharmacy (46). Pharmacists contacted physicians for about 41% of DoseChecker system alerts and physicians accepted 75% of the pharmacists' recommendations, indicating that DoseChecker helped identify inappropriate dosages and improved patient safety.

Alert Functions

Studies described the drug related decision support alert as a critical CDSS function for reducing potential adverse drug events and improving patient safety. Despite the benefit, clinicians often ignore alerts. Alert fatigue is a widely reported issue in literature (17,23,47,48,33,34). One study reported that physicians ignored 96% of dose-limit warnings for oral chemotherapy, because of the mismatch between dosing recommendations and the warnings (17). Another study that evaluated the frequency of computerized alerts concluded one third of the alerts triggered were technically preventable (47).

Studies attempted to identify the reasons for high override rates and they found that the interactions for which the alerts are generated often lacked clinical significance (32). A number of studies identified strategies and recommendations to design alert functions to achieve their full potential for improving patient safety.

Phansalkar *et al.* (2013) highlighted design and implementation of alert functions that should not interrupt clinician workflow (32,35). They reported criteria for assessing drug-drug interactions (DDI) in the generation of alerts (32). Authors suggest that assessing alerts on the basis of severity is one of the most important measures to reduce alert overriding because the severity of an interaction is related to the risk/benefit of using the drug pair concomitantly. Clinical information such as the inherent danger of the drug combination and the extent to which the presence of risk factors predisposes the patient to the interaction is also important to assess the severity of the interaction. Probability of interaction is another important criterion. The third criterion, clinical implications signify the management burden of the interaction, the monitoring planned and prescriber awareness of the interaction. Management burden is defined as the course of action a clinician may have to take for each potential drug interaction. Patient characteristics such as age, gender, concurrent disease, alcohol and/or drug use, and other active medications are also important because they may alter the characteristics of the drug in consideration, resulting in possible DDIs. Evidence supporting the interaction is another criterion for assessing the biological plausibility of a DDI. Consideration of these criteria may help clinicians identify critical DDIs for use in electronic health records, and reduce disruptive alerts in design and implementation of a CPOE system.

Smithburger (2011) described similar improvement strategies for DDI alert functions (42):

- System uses tier alerts based on severity;
- System provides evidence-based alerts;
- Utilization of expert panels and clinical experience to improve alert severity congruence;
- Utilizing more than one commercially available system for CDSS system development;
- Decrease interruptions to prescribers by removing insignificant alerts;
- Regularly re-evaluate and update knowledge bases used to generate DDI alerts.

Many studies highlighted the importance of designing alerts that are not interruptive for prescribers' workflow. To evaluate whether alerts are interruptive to workflow, Phansalkar (2014) evaluated DDI alerts for compliance with human factors principles (28). The most common weakness found in the alerts pertained to the absence of characteristics such as alert prioritization, clear and concise alert messages indicating interacting drugs, actions for clinical management, and a statement indicating the consequences of over-riding the alert. For further discussions on human factors principles, please refer to the discussion section of the 2012 CPOE guidelines (6).

To support physicians' workflow better, the concept of 'asynchronous alerting' was suggested by Perna (2012) (33). This is a highly elaborate tab that includes information on the patient's vitals, medications, care providers' names, and other information. This tab appears as highlighted in red without interrupting the workflow of clinicians. For the same purpose, Coleman *et al.* (2013) suggested alert personalization (34). This study suggests that allowing individual users to personalize the interface design of alerts such as alter icon management, font size, or background color can improve usability and receptivity of system alerts. Personalization can also be done automatically based on a user's familiarity with certain risk situations, training and expertise.

Another study investigated factors of CDSS that influence prescriber-alert interactions and identified strategies to enhance alert design (49). It reports strategies including: system design transparency, external cross checks of alert system logic, ensuring prescriber awareness, standardizing alert interface designs across systems, and keeping alert system reliability.

Studies also reported context-enhanced alerting as an advanced function to prevent alert fatigue. Duke *et al.* (2011, 2013) described the integration of context-specific patient laboratory data into the standard DDI alerts (29,30). Context-enhanced alerting is an alert function that assigns to each DDI a set of concepts specifying the patient data elements to be displayed (e.g. electrolyte levels) when the alert is triggered (29,30). The outcome of this study showed that availability of patient-specific data significantly affected DDI evaluation and management (30). Physicians agreed strongly that context-specific DDI alerts support clinical decision making, increase their confidence in management of drug interactions, and saves time (30). However, conflicting results were reported in terms of clinicians' actual adherence to alerts (29,30), suggesting further research is required to improve the effectiveness of context-enhanced alerting and to determine strategies for redesigning and implementing the function.

Treatment Guideline Concordance

The CAP allows only standardized pre-defined regimens to be used, which are pre-registered following departmental review by the cancer clinics, the pharmacy and the insurance audit team (15). The purpose of this system is to ensure that treatment protocols comply with existing guidelines.

Data Management/Ontology

The CAP, an advanced ordering system customized for prescribing chemotherapy medications, uses a structured data management scheme that includes chemotherapy-related data, such as cancer stage, treatment line, chemotherapy cycle, toxicity and response evaluation (15). In addition, the CAP system integrates with medical records, previous treatment history, and treatment outcomes for each patient. Patient medical records for every inpatient or outpatient visit are represented by digital images, which help the prescribers visualize future treatment plans and keep all clinical staff up-to-date. Compared to an existing standard CPOE system, the advanced features of CAP resulted in significant improvements for all types of near-miss errors (15).

Discussion

Both CAPCA and ASCO/ONS recognize that the increasing use of oral chemotherapy poses new safety challenges given the relative lack of standards for prescribing, dispensing and administration compared to IV chemotherapy. To improve the safety of prescribing oral chemotherapy, both organizations recommend CPOE or pre-printed orders where CPOE is not available. Cognitive verification of the prescription by a trained clinician is recommended for all forms of anticancer drugs. Although cognitive verification was not identified as a CPOE feature in the literature, it is important to include from a clinical perspective.

Based on these recommendations and this literature update, the following features and functions support best practices for safe and effective prescribing of oral chemotherapy in CPOE.

The system:

- Integrates laboratory and up-to-date medication reconciliation systems to facilitate order review before the prescription leaves the hospital / cancer centre;
- Includes regimen-building features with minimal manual customization, such as regimen-specific default dosing, commonly suggested dose modifications, antiemetics and other supportive medications;
- Includes a CDSS that is capable of identifying clinically significant drug interactions and allergies, since many oral chemotherapy agents have multiple drug interactions;
- Displays recommended information parameters at the point of order entry and verification in the cancer clinic, and/or by the community pharmacist (e.g. diagnosis, cycle number, start date, height, weight, BSA, others);
- Allows for customized printing of generated orders on the take-home chemotherapy prescription (e-prescribing modules to transmit these relevant parameters, where available);
- Include a feature to allow for cognitive verification by a clinician with oncology experience (desirable);
- Uses appropriate drug nomenclature, including the use of TALLman lettering where recommended by the ISMP, use of USP standard abbreviations for dosage units and standard units for weight and measures, etc.;
- Avoids use of abbreviations, symbols and dose designations from ISMP Canada's "Do not use: Dangerous abbreviations, symbols and dose designations" list;
- Identifies correct dosage form and strength(s) of medications available;
- Includes automatic rounding for each dose, based on dosage strengths available;
- Allows for automatic calculation of dosage strength per dose and the total quantity of each dosage strength to be dispensed (if multiple strengths required);
- Automatically generates clear instructions for medication administration, including the combination of tablets/capsules to be taken, if applicable;

- Clearly displays the percentage of dose modification and its rationale.

Since the 2012 ST CPOE guidelines, an increasing body of evidence suggests that CPOE reduces medication errors in the oncology setting, including prescribing errors associated with oral chemotherapy (10,11). This evidence update also found that CPOE created new errors, for example, wrong patient medication errors and drug name confusion errors (20,21). New errors emphasize the need to develop CPOE systems with features and functionalities to improve safety.

Recommended general features highlighted in this update include:

- Feature to confirm patient identity (e.g. single-click confirmation);
- Use of information standards (e.g. TALLman lettering to prevent drug name confusion errors);
- Pre-defined regimens with dose and frequency ranges (ability to link regimens to treatment guidelines is an essential feature);
- Context-enhanced, non-interruptive alerts generated by CDSS (e.g. clinically significant drug interaction alerts)

Despite the potential safety benefits of CDSS generated alerts, these are still not widely used, as alert fatigue continues to be reported (43–46). Clinicians may override alerts that lack clinical significance and/or interrupt workflow. To overcome these problems, alerts should be evidence-based and tiered based on severity. For example, more than one commercially available knowledge database should be used for CDSS development and updated regularly. Clinically insignificant alerts should be minimized. Context-enhanced alerting, where patient-specific data (i.e. laboratory values) is presented alongside relevant alerts, is desirable. Finally, alerts should be non-interruptive to order entry workflow by considering human factors principles in their design (e.g. personalization of alerts).

There are several limitations of this review, which though they are discussed in more detail under future directions, are itemized here:

1) A possible lack of application to the design of electronic prescriptions, as electronic prescriptions are both considered out of scope and not the current standard of practice in Canada, although they would facilitate communication from the prescriber to the community pharmacist;

2) In addition to electronic prescribing, other features that are not yet widely available, including system to system integration and advanced features of the CAP System;

3) Standards, regardless of level or jurisdiction.

The scope of this review was specific and as a result narrow, so some best practices, standards, guidelines and approaches to address privacy related issues may not have been identified, including for example the COACH privacy guidelines, Canada Health Infoway certification requirements for privacy, security and interoperability. Standards from other jurisdictions that are relevant and may increase relevance and usability of these guidelines, such as the Office of the National Coordinator for Health Information Technology Certification of EHR Technology, should also be considered during implementation.

Future Directions

There is a growing body of evidence and guidance to support the development, use and adoption of CPOE and ST CPOE systems, but there is a relative lack of information to support implementation. Further, studies that demonstrate significant variation in the type of prescribing errors made regardless of system used, suggest differences either in the system design, in implementation strategies, or both (37). Better clinician training and change management strategies during implementation, as well as monitoring and modification of system features and functionality, will likely support safer prescribing. For example, features designed to prevent errors of omission, incomplete drug names, and inappropriate abbreviations are necessary. For oral chemotherapy, there is a need for cognitive verification of prescriptions and development of CDS with appropriate features. Cognitive verification could be prototyped similar to nursing independent double checking within nursing administration systems. Finally, opportunities to seamlessly link clinical interoperability and transmission standards between ST CPOE systems and linked modules (e.g. nursing administration, electronic prescribing, and pharmacy dispensing and verification) need to be explored.

Within health care, although there is a movement towards full medication management systems for mitigating many integration issues related to medication safety, current systems are not ideal. These systems often lack integration and/or clinical inter-operability among pharmacy inventory, pharmacy clinical management, clinician prescribing, nursing administration and dispensing modules. Integration of these processes is vital. For example, information flow of key patient contextual data, such as laboratory values, and maintaining or viewing documentation related to treatment, are both important when prescribing chemotherapy. Integration of safety features such as barcoding for positive patient identification and identity-dependent medication administration is also necessary. Possible interoperability between ST CPOE and adverse event reporting systems should be explored given the increased focus on adverse event reporting at the point of care. Finally, medication management systems often have electronic prescribing modules that require both clinical and transmission standards between prescribing systems and receiving dispensing systems in pharmacies. These standards have yet to be developed for electronic prescribing of oral chemotherapy. They will need to include authentication and documentation of cognitive verification of prescriptions by pharmacists or other trained clinicians at prescribing centres.

Several other areas for future research of ST CPOE systems exist. For example, variation in individual and drug regimen naming was addressed as a significant area for improvement. The use of abbreviated drug regimen naming systems may not be similar from jurisdiction to jurisdiction. For example, the regimen nomenclature FOLFOX (**Fol**inic Acid, **F**luorouracil, and **Ox**aliplatin) may not mean the same dosing or administration protocol for the individual drugs within the regimen. Moreover, recent attempts to differentiate look-alike sound-alike drugs pointed out the importance of modernizing the World Health Organization's International Non-Proprietary Naming System. An improvement in this would help address

development and implementation of information technology, including CPOE systems. It will also assist with data management and allow for better comparisons across systems and within large geographical areas. For example, standardized nomenclature may assist with comparison of quality measures such as treatment guideline concordance or issues of drug funding. Moreover, standard regimen sets that could be used at the pre-implementation phase of any vendor system would be of value. In addition, studies evaluating post-implementation maintenance and evaluation of such systems are lacking. Areas for improvement include standards for regimen review and modification, alert triggering evaluation and modification, and ensuring optimal use of CDS and alerts. Additional research would help ensure that we use ST CPOE systems to their maximal benefit to achieve the goal of safe, high-quality care.

Appendix A: Search Strategies (Objective 1)

Ovid MedLine

No.	Term	Hits
1	exp Medical Order Entry Systems/	1511
2	exp Drug Therapy, Computer-Assisted/	1108
3	computerized physician order entry.mp.	511
4	computerized prescriber order entry.mp.	76
5	computerized provider order entry.mp.	251
6	cpoe.mp.	749
7	exp Electronic Prescribing/	552
8	moe.mp	623
9	OR/ 1-8	3938
10	Chemo*.mp.	362076
11	Antineoplastic?.mp	278082
12	exp Antineoplastic Protocols/	78372
13	exp Antineoplastic Agents	498915
14	exp Chemotherapy, Adjuvant/	26932
15	OR/10-14	499582
16	Oral*.mp.	317537
17	exp Administration, Oral/	69423
18	exp Self Administration/	6198
19	“take home”.mp.	1760
20	OR/16-19	727691
21	15 AND 20	25443
22	exp Drug Prescriptions/	17454
23	*Prescriptions/	18221
24	Prescri*.mp.	105423
25	OR/7, 22-24	107379
27	9 AND 21	18
28	21 AND 25	828
29	limit 27 to (english language and yr="1996 -Current")	17
30	Limit 28 to (english language and yr="1996 -Current")	731
31	29 or 30	738

Ovid EMBASE

No	Terms	Results
1	exp Computerized Provider Order Entry/	2316
2	Computerized physician order entry.mp.	877
3	Computerized prescriber order entry.mp.	128
4	cpoe.mp.	1165

5	Medical order entry.mp.	68
6	exp Computer assisted drug therapy/	792
7	exp Electronic prescribing/	1344
8	OR/1-7	4105
9	Chemo*.mp	900423
10	exp Cancer chemotherapy/ or exp Adjuvant chemotherapy/ or exp Chemotherapy/	434804
11	exp Antineoplastic agent/	1573691
12	OR/ 9-11	2062084
13	Oral*.mp.	1017536
14	exp Oral drug administration/	391255
15	exp Drug self administration/	8101
16	“take home”.mp.	2698
17	OR/13-16	1027394
18	12 AND 17 (oral chemo)	162362
19	8 AND 18 (oral chemo AND cpoe)	32
20	*prescription/	26861
21	Prescri*.mp.	262925
22	OR/7, 20-21 (prescribing)	262925
23	18 AND 22 (oral chemo AND prescribing)	4406
24	19 OR 23	4428
25	Limit 24 to (English language and yr=”1996 – Current”)	3331

Cochrane Library

No	Terms	Results
1	MeSH descriptor: [Admistration, Oral] explode all trees	20250
2	MeSH descriptor: [Self Administration] explode all trees	653
3	Oral*	115151
4	“take home”	283
5	OR/1-4	116493
6	MeSH descriptor: [Antineoplastic Agents] explode all trees	10377
7	MeSH descriptor: [Antineoplastic Protocols] explode all trees	11130
8	MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees	3379
9	Antineoplastic?	13
10	Chemo*	45518
11	OR/6-10	49785
12	5 AND 11	8323
13	MeSH descriptor: [Drug Prescriptions] explode all trees	631
14	MeSH descriptor: [Prescriptions] explode all trees	91
15	MeSH descriptor: [Electronic Prescribing] explode all trees	25
16	Prescri*	16150
17	MeSH descriptor: [Medical Order Entry Systems] explode all trees	67
18	MeSH descriptor: [Drug Therapy, Computer-Assisted] explode all trees	150

19	Computerized physician order entry	224
20	Computerized prescriber order entry	13
21	Computerized provider order entry	126
22	CPOE	32
23	OR/15-22	450
24	OR/13-16	16300
25	12 AND 23	29
26	12 AND 24	425
27	25 OR 26	434
28	27 – Cochrane Groups	431

CINAHL

No.	Terms	Results
1	(MH "Electronic Order Entry")	1564
2	(MH "Drug Therapy, Computer Assisted")	253
3	"cpoe"	366
4	"computerized physician order entry"	230
5	"computerized prescriber order entry"	68
6	"computerized provider order entry"	134
7	(MH "chemotherapy, Cancer") OR (MH "Chemotherapy, Adjuvant")	12990
8	"chemo*"	32200
9	(MH "Antineoplastic Agents")	15799
10	OR/7-9	42524
11	"oral*"	57835
12	(MH "Administration, Oral") OR (MH "Medication Administration: Oral (Iowa NIC)")	7510
13	"take home"	631
14	(MH "Self Administration")	1835
15	OR/ 11-14	60171
16	OR/1-7	1874
17	(MH "Prescriptions, Drug")	4162
18	(MH "Medication Prescribing (Iowa NIC)")	1
19	"prescri*"	45987
20	OR/17-19	45987
21	10 AND 15	2678
22	16 AND 21	0
23	20 AND 21	89
24	22 OR 23	88

Search Strategies (Objective 2)

Ovid MedLine

No.	Term	Hits
1	exp Medical Order Entry Systems/	1511
2	exp Drug Therapy, Computer-Assisted/	1108
3	computerized physician order entry.mp.	511
4	computerized prescriber order entry.mp.	76
5	computerized provider order entry.mp.	251
6	cpoe.mp.	749
7	exp Electronic Prescribing/	552
8	OR/ 1-7	3324
9	limit 8 to (english language and yr="2011 -Current")	996

Ovid EMBASE

No	Terms	Results
1	exp Computerized Provider Order Entry/	2297
2	Computerized physician order entry.mp.	874
3	Computerized prescriber order entry.mp.	126
4	cpoe.mp.	1159
5	MOE.mp	1090
6	Medication order entry.mp.	47
7	exp Computer assisted drug therapy/	792
8	OR/1-8	5177
9	limit 8 to (english language and yr="2011 -Current")	2462

CINAHL

Terms	Search Options	Results
TX computerized physician order entry **OR TX** computerized prescriber order entry **OR TX** computerized provider order entry **OR TX** medication order entry **OR** **TX** cpoe **OR** **TX** computer assisted drug therapy	**Limiters** - Published date: 20110101 – 20150218; English language	396

COMPENDEX

Terms	Search Options	Results
computerized physician order entry **OR** computerized prescriber order entry **OR** computerized provider order entry **OR** medication order entry **OR** cpoe	**Limiters** - Published date: 20110101 – 20150218; English language	134

Appendix B: Data Extraction template

Below is a sample abstraction table used to extra data from the included literatures.

Source	Purpose of the study	Study Method	Facility, Location	Features/functionalities (usability, functionality, system integration)	Outcomes/impacts/ Recommendations
Collins (2011) Using an enhanced oral chemotherapy computerized provider order entry system to reduce prescribing errors and improve safety	To assess the severity and probability of failures in the inpatient oral chemotherapy order, review and administration process in a large medical center	Prospective cohort study	Rhode Island Hospital (RIH), USA	**Functionality** 1) System access and permissions: Order entry is restricted to attending physicians within scope of practice. Residents are restricted from accessing ordering screen 2) Information display and alerts: - Programmed drug-specific maximum dose alerts and frequency options - Displays alert that the selected drug is a chemotherapeutic agent - Specific alerts regarding critical laboratory values and dosing regimens appear during order review 3) Regimen templates: - Instituting drug-specific defaults to standardized minimum dosing, frequency and duration, drug-specific maximum dose alerts and entry fields for cycle number and day in cycle 4) Monitoring: - Prompting orders for appropriate laboratory indicators for review - Labeling the drug as chemotherapy agents, specific critical laboratory values, drug interactions and dosing regimen appear during review - Drug therapy guidelines directly linked to the order set and provide clinical guidelines regarding dosing as well as recommended monitoring	**Main outcome measured**: pharmacist-intercepted oral chemotherapy prescribing errors over a 24 month period (before) and over a 6 month period (after) were analyzed according to the error type (e.g. errors in clinical decision making, errors in transcription or errors related to prescribing policy) **Results**: Approximately 69% reduction in the risk of prescribing errors as a result of CPOE ($p = 0.023$)(OR = 0.31; 95%CI=[0.11-0.86])

Appendix C: Summary of evidence for ST CPOE system features and functionalities

The following tables 1-5 summarize (a) updated evidence and evidence sources on the features and functionalities included in the original guidelines and (b) new evidence and sources on the system features and functionalities that apply to oral chemotherapy. The features and functionalities in these tables are categorized in the same way as the original Appendix A tables from the 2012 guidelines (p. 88-95).

Legend:
[Oral] – Signifies recommendations relating to oral chemotherapy only
[IV] – Signifies recommendations relating to IV only

Table 1: Features that reduce the potential for medication errors through integrated safety alerts and reminders

Features that reduce the potential for medication errors through integrated safety alerts and reminders	Source
System has alerts with clear and concise messaging, indicating interacting drugs, actions for clinical management and a statement indicating the consequences of over-riding the alert System includes context-specific patient laboratory data into drug-drug interaction alerts (e.g. display serum potassium lab results for an interaction that may cause hyperkalemia)	28, 29, 30
System has the ability to customize rules for decision support tools, specific warnings System has the ability to customize safety guardrails for modifying orders, for example: • Starter set of rules for medications requiring consideration of renal or hepatic status in dosing • Warning based on patient diagnosis System has customizable alerts for: • Treatment duplication • Allergies (e.g. acknowledgement/override of alert)	2012 Guideline, 16-18, 22, 23

Features that reduce the potential for medication errors through integrated safety alerts and reminders	Source
• Drug-drug interactions • New prescription versus renewals • Inappropriate pill splitting, where applicable [Oral] • Dose /dosing frequency checking (e.g. alert is generated when dose order is outside of the preset maximum or minimum dose range) • Cycle start date too early System has the ability to alert for early and late reorders with appropriate customization [Oral] When an alert is triggered, the user can take the actions suggested directly from the alert dialog box to modify or discontinue treatment; rationale for the modification are indicated on the order	
System has the ability to alert at drug prescribing, verification and administration when patient values are outside of laboratory parameters Following an alert, system allows proceed criteria to be documented (i.e. allows pre-set treatment parameters, for verifying patient's actual lab work against these)	2012 Guideline, 16, 18
System has the ability for users to view pending tasks to ensure the safety delivery of chemotherapy (e.g. critical lab values) System has the ability for users to view pending tasks to manage workflow efficiency (e.g. expiring orders)	2012 Guideline
System allows documentation and provider authentication of medication dispensing: • Lot number • Expiry date • Manufacturer	2012 Guideline
System has improved dosing logic and allows for complex instructions: • Doses requiring multiple dosage strengths	2012 Guideline

Features that reduce the potential for medication errors through integrated safety alerts and reminders	Source
• Alternate day dosing (e.g. 100-125-100-125mg) • Dose tapering (e.g. steroids) • Dose titrations • Treatment interruptions (e.g. hold on weekends or due to toxicity) • Total daily dose calculations and displays on order • Predefined template with absolute dose (e.g. drugs where standard dose is not dependent on BSA) • Dosing capping in a specific regimen at a pre-set dosage ▪ If dose is capped, system alerts user that value has been capped • Predefined AUC dosing in regimen template [IV] • System automatically calculates dose modifications based on laboratory parameters (e.g. renal or hepatic function	
System has dose calculation built into electronic ordering system using units consistent with jurisdictional standards (e.g., height in meters and weight in kilograms) • Automatically calculates dosing and modifications, based on dosing algorithms using, for example, patient weight, height, CrCl, target AUC, sex, age • Expresses dose as weight based or BSA-based, as target AUC [IV] or “flat dose”, depending on the drug in ordering, dispensing and administering • Calculates and display BSA based on the most recent height and weight values recorded in the system • Option to select various equations available for BSA and CrCl calculations (e.g., Cockcroft Gault, Jelliffe, Mosteller, etc.) • Alerts the prescriber to absolute and percentage changes in height, weight, or creatinine when reordering an active regimen; the prescriber can then choose whether to use the old or new values to calculate doses for the current treatment • Ability to calculate and display CrCl values in mL/min, and ensure serum creatinine that is used for dose calculations does not fall outside of a pre-set acceptable range; the serum creatinine value used to calculate the dose should be recorded for reference	2012 Guideline, 13-15, 17, 18

Features that reduce the potential for medication errors through integrated safety alerts and reminders	Source
System checks ordered dose against a knowledge base (e.g. local guidelines of best practice or other references) of relevant dose and frequency ranges • Single dose medication dosage checking • Cumulative lifetime medication dosage checking (e.g., doxorubicin) • For single dose, can set up minimum or maximum dose allowed, per dose, per day or per course for each available route of the drug • Designates explicit routes, units, diluents for medications and prohibit selection of other routes/units during the order process (e.g. IV only for vincristine)	2012 Guideline, 13, 14, 16, 17, 18
System has the ability to pre-define dose rounding rules into the regimens and dose calculators • Rounds to a dose that can be reasonably measured based on vial size which is practical to measure and deliver • Calculates dose for oral chemotherapy drugs with multiple dosage strengths (e.g. capecitabine available in 500 and 150 mg strengths). Doses rounded to the nearest available combination as set by the institution/jurisdiction [Oral]	2012 Guideline
System allows institution-defined options for orders and order components. Ability to highlight most appropriate or recommended choice. For example: • Propose alternative in a given order set (e.g. pre-set with certain breakthrough antiemetic medication options) • Ability to build IV/PO route alternatives for the same drug	2012 Guideline
System has the ability to incorporate text instructions or recommendations within order sets • For example: drug funding information related to regimen, hospital formulary status, if certain drugs need to be held on selected treatment days	2012 Guideline
System has logic for displaying, timing and documenting linked orders based on: Sequential links, time offset links, mutually exclusive orders, drugs mixed in same bag and split dose.	2012 Guideline

Features that reduce the potential for medication errors through integrated safety alerts and reminders	Source
• Two or more medications must be given in a specified sequence • Allows regimen builder to set up relative times for chemo administration ○ E.g. mesna is to be given at four and eight hours after cyclophosphamide; system will automatically calculate mesna administration time on the order or the MAR if cyclophosphamide administration time is known • Standing and PRN doses cannot be given at the same time. Incorporate logic for handling PRN dosing, have appropriate frequency logic (multiple doses over multiple days) • Drugs mixed in same bag, e.g. ifosfamide and mesna admixed in the same bag • Split dose, e.g. doxorubicin dose volume required to be given in two separate syringes	
System has order verification function for cognitive review of orders. Order locking occurs when the order is in pharmacy and/or nursing verification. Signing off on order verification is required prior to order processing • Verify orders electronically by pharmacy and/or nursing after prescriber signs • Prevent order changes once the order is in review by pharmacy or nursing • Prohibit order changes that have completed verification unless order is “unlocked” by pharmacy or nursing System alerts for post-verification sign-off of modified order sets	2012 Guideline

Table 2: Features that enhance workflow with pertinent instructions that are easily understood and organized

Features that enhance workflow with pertinent instructions that are easily understood and organized	Source
System has the ability to configure eligibility screening criteria based on data in the system • Screening for treatment eligibility purposes, including funding • Criteria may include gender, cancer diagnosis, stage, performance status, etc. System has the ability to monitor patient entrance/exit processes (e.g. restricted access programs such as clinical trials, restricted drug distribution programs, surgery type/date, etc.)	2012 Guideline
System enables user roles to be defined with access to order set management, and provides the ability to restrict access to individual order sets by user role or department • Order entry and regimen building restricted to individuals within their scope of practice or determined by local medical directives • Requires signed chemotherapy orders to be verified by an authorized user prior to preparation System has the ability to build two-party orders (prescriber writes orders in a pending status until verified through pharmacy and/or nursing; orders made in advance can be kept in "hold" status pending relevant clinical/laboratory parameters)	2012 Guideline
System should facilitate ease and speed of building and changing orders • Use of quick means (e.g. drop-down menu) System is customizable for users to locate and display individual and groups of orders in different ways for safety and efficiency reasons (e.g. prescribers ordering chemotherapy regimens by disease-site) For example: • Easy-to-find order sets (search or filtering; diagnosis and intent based, etc.)	2012 Guideline

Features that enhance workflow with pertinent instructions that are easily understood and organized	Source
• Shortcut to order sets frequently used by prescriber • Captures and displays at least two protocol/clinical trial identifiers associated with a patient's single treatment regimen	
System allows the identification of patients receiving multi-modality therapy (e.g. chemotherapy and radiation)	2012 Guideline
System displays and alerts for allergies and serious adverse events as coded using NCI CTCAE	2012 Guideline
Features of the documentation section follow guidelines from health professional and regulatory organizations. Example: Ability to capture independent checks and nurse co-signature such as date and name stamps from two practitioners	2012 Guideline
System has the ability to label relevant drugs such as chemotherapy agents, so only credentialed providers can prescribe or administer these medications	13, 16, 18
System has medication sequencing within an order: • Medications within the order can be added, removed, copied or re-sequenced easily • Subsequent doses can be placed relative to the date of the first dose (e.g. Day 7)	2012 Guideline
System captures and displays disease-specific pathology information or non-anatomic prognostic indicators as discrete data or in a free text field • For example: anatomic site, histology/pathology, biomarkers, grade, lesion size, chromosomal rearrangements and other characteristics of cancers used to predict response, estimate prognosis and/or direct treatment	2012 Guideline
System allows documentation or update of staging, confirmation of diagnosis and treatment intent prior to ordering chemotherapy	2012 Guideline

Features that enhance workflow with pertinent instructions that are easily understood and organized	Source
System has the ability to view order statuses (from prescribing, dispensing to administration) with automatic real-time updates to manage workflow System traces medication products to an order from their preparation/dispensing to administration Real-time electronic transmission to hospital pharmacy systems occurs [IV] so that order re-entry is not required, to prevent delays and potential transcription errors Real-time electronic transmission to pharmacy dispensing systems (e.g. e-prescribing) occurs so that re-entry is not required, to prevent delays and potential transcription errors [Oral] System must allow users to view current medication orders in real time and be made aware of changes made by any other user	2012 Guideline
System has the option to customize printing and formatting of chemotherapy orders and take-home prescriptions to meet best practice recommendations (e.g. including diagnosis, no repeats on oral chemotherapy [Oral])	17

Table 3: Features that reduce variation and unintentional oversight of orders

Features that reduce variation and unintentional oversight of orders	Source
System must support the development and use of regimen templates including the ability to link to a specific diagnosis group or clinical trial	2012 Guideline, 16
System has the ability to pre-load modifiable local/jurisdictional regimens to assist in the building of a final version	2012 Guideline
System provides adequate space for items in order data fields to allow entering and viewing information without truncating any data	2012 Guideline
System displays relevant laboratory values, drug interactions, allergy status and dosing regimen during order entry and review	16, 18
System presents diagnosis, drug name, dose, route of administration, dosage form, dose units, frequency, duration, diluent nomenclature and other abbreviations • Consistent with nomenclature used by the institution or ISMP standards • Acceptance of generic drug names • Ability to present brand names in upper case lettering System should follow the Joint Commission and ISMP's standards regarding abbreviations, symbols and dose designations. The information display should be clear and organized to prevent the clinician from making errors with look-alike, sound-alike drugs or juxtaposition errors (e.g. use of TALLman lettering)	2012 Guideline, 16, 26
System allows for therapeutic options during regimen builds. For example: • Link protocols for hydration, growth factors, supportive medications or hypersensitivity management, rescue medications, urine alkalinization, etc. to appropriate regimens	2012 Guideline

Features that reduce variation and unintentional oversight of orders	Source
• Antiemetic modules or associations of individual antiemetics with chemotherapy medications specified at regimen build	
System incorporates logic for determining cycle scheduling and treatment duration (days between cycles and total number of cycles) • Preset the frequency of cycles • Cycle number information should be available, including start day. • Day of cycle should be clearly defined for each drug • Cycles can be specified to repeat a number of times	2012 Guideline, 16
System tracks progress and changes in the regimen over time. Reasons for modification are indicated on the order and can be accessed by relevant system users. Options include the following: • Changes made in chemotherapy dosing to be carried into subsequent cycles • Ability to order subsequent cycle based on the regimen template • Ability to hold, delay, omit, delete and resume treatment, proceed notes, verbal orders, interventions by health professionals, with reasons for each intervention • Ability to document that certain treatment day(s) have been omitted, delayed or discontinued, so these do not appear as "not administered" in subsequent cycles (e.g. reason for discontinuing therapy) • Alert if chemotherapy drug is discontinued after the last cycle was ordered • System requests a reason when user changes treatment or dosing to those different from the original protocol, and notifies user that the dosing for this cycle is different from the previous cycle	2012 Guideline, 18
Logic in dose modification displays: • A percentage value • An entered value ("flat dose") • Via preset dose levels	2012 Guideline
System provides date logic in orders	2012 Guideline

Features that reduce variation and unintentional oversight of orders	Source
• Automatic date and time generation, dates fill in automatically for multiday/week therapy • Ability to update the calendar easily and push dates accordingly	
For selected medications, the system displays different dosing indications per intent (e.g. prn, cyclic vs. continuous dosing) to be chosen by the prescriber	2012 Guideline

Table 4: Integrate and coordinate care by communicating best practices among healthcare providers

Features that integrate and coordinate care by communicating best practices among healthcare providers	Sources
System has the ability to select medications and regimens that default to formulary options or have those listed first • Contains all dosage strengths available for drugs; however, institution can pre-set default dosage forms and strengths based on local availability, to avoid "over-specification" (e.g. need to select identical generic products from different manufacturers) • Supports in dosage form selection; takes into account maximum dosage and dosage forms available	2012 Guideline
System enables direct linkage to the MAR	2012 Guideline

Table 5: Features that modify practice through evidence-based care

Features that modify practice through evidence-based care	Sources
System provides access to chemotherapy drug mixing instructions, solubility information, stability information, monitoring and storage expiration information • May reside within system or be provided through links to external sources	2012 Guideline, 16, 18
System has the ability to identify order sets as being concordant with provincial/jurisdictional, institutional or formulary clinical guidelines	
System has the ability to link to protocol from the order • Link regimen template or order to references or treatment guidelines • Link from order to clinical trial protocols	2012 Guideline, 16, 18

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