

## **Fluorouracil Incident Root Cause Analysis**

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*Institute for Safe Medication  
Practices Canada®  
Institut pour l'utilisation sécuritaire  
des médicaments du Canada®*

**The Institute for Safe Medication Practices Canada (ISMP Canada)** is an independent national not-for-profit agency committed to the advancement of medication safety in all health care settings. ISMP Canada works collaboratively with the health care community, regulatory agencies and policy makers, provincial, national, and international patient safety organizations, the pharmaceutical industry, and the public to promote safe medication practices.

ISMP Canada's mandate includes collecting, reviewing, and analyzing medication incident and near-miss reports, identifying contributing factors and causes, and making recommendations for the prevention of harmful medication incidents.

ISMP Canada is a key partner in the Canadian Medication Incident Reporting and Prevention System (CMIRPS). Providing assistance with this root cause analysis is consistent with one of ISMP Canada's defined roles in CMIRPS, (i.e. to assist with root cause analysis for selected medication incidents). For information on ISMP Canada's additional roles in the CMIRPS, see the ISMP Canada Web site, <http://www.ismp-canada.org/cmirps.htm> .

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## **Acknowledgements**

ISMP Canada offers sincere condolences to the family of the patient whose tragic death led to this analysis. It is our sincere hope that our findings will result in system improvements that will reduce the likelihood of other patients and families experiencing a similar harmful event.

The analysis team would like to thank the many staff members from the XXXX Cancer Institute, the XXXX Cancer Board and XXXX [residence], who participated in interviews and helped to provide a full understanding of the event.

ISMP Canada is grateful to all individuals working in the Canadian health care community who share learning from medication incidents to inform development of safe medication practices.

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## Executive Summary

On August 22<sup>nd</sup>, 2006, a 43 year old woman died after a medication incident that occurred while she was receiving outpatient care at the XXXX Cancer Institute in XXXX. The cause of death as determined by the coroner was “sequelae of fluorouracil toxicity”. On July 31, the woman had inadvertently received an infusion of fluorouracil over 4 hours that was intended to be administered over 4 days. She was being treated for advanced nasopharyngeal carcinoma, according to a standard protocol that included high-dose fluorouracil and cisplatin in the ambulatory setting. The medication incident was recognized within 1 hour after the infusion was completed. The patient was admitted to hospital 4 days after the incident occurred. Profound mucositis and pancytopenia developed, and the patient experienced hemodynamic collapse and multi-organ failure before her death.

Upon learning of the incident and reviewing the circumstances, the XXXX Cancer Institute leadership immediately implemented a policy requiring patients receiving intravenous therapy with portable electronic pumps to stay at the clinic for one hour after initiation of the infusion, at which time a third independent check of the medication order and pump settings would be completed by a clinic nurse. In addition, the pharmacy label format was reviewed and revised to eliminate the mL/24h information, and a brightly coloured auxiliary label containing information required to program the pump was added. In addition to these immediate actions, the senior leadership of the XXXX Cancer Institute and the XXXX Cancer Board recognized that an in-depth analysis of the medication incident was needed to ensure that the underlying causes of the incident were thoroughly analyzed and would help to reassure the community that appropriate actions to reduce the risk of recurrence would be taken. The Institute for Safe Medication Practices Canada (ISMP Canada) was invited to provide external expertise and, as an agent of the XXXX Cancer Institute’s Medical Quality Assurance Committee, undertake a root cause analysis of this incident.

Root cause analysis is a structured process for reviewing an event, with the goals of determining what happened, why it happened and what can be done to reduce the likelihood of recurrence. ISMP Canada assembled an analysis team that included expertise in medication safety, oncology and human factors engineering to conduct a site visit and subsequent analysis of the findings. The analysis team consulted a number of additional experts in oncology, toxicology, human factors and medication safety, who assisted in the development and review of the recommendations.

The XXXX Cancer Board is recognized as a leader in the field of oncology and has been at the forefront of many improvements in cancer treatments and patient care. The organization’s transparency in its response to the incident and its goal to widely share learning related to the incident analysis demonstrates exceptional leadership. The caring and compassionate staff at the hospital have been shaken by the realization that such an event could occur in their workplace and are determined to do what they can to prevent recurrence.

The same or similar incident could happen in other health care organizations. The system failures that were identified in this event exist in other cancer treatment centres. In fact, similar events have happened before, although causal information and learning from the previous events are either difficult to find or unavailable. ISMP Canada’s research identified 7 similar cases, all of which were fatal (summary available in Appendix 1). Of interest, there is one additional report of a patient receiving a similar overdose of fluorouracil, but by chance this patient did not receive the complete dose of cisplatin, and survived.

Regimens for the treatment of nasopharyngeal cancer use high doses of fluorouracil (and of cisplatin). As a result, medication incidents pose additional risk for toxic effects beyond those associated with the use of lower-dose protocols. The absence of both an antidote for fluorouracil overdose and a defined protocol to treat such an overdose increases the possibility that significant overdoses, such as the one that occurred in this case, will result in death.

A combination of actions and conditions, none of which alone was causal, led to the patient's death in this case. Using a cause-and-effect diagramming process, the ISMP Canada analysis team identified 16 causal factors that contributed to the incorrect administration of fluorouracil or the inability to mitigate the harm from the overdose. These include, among others, issues with the design of the medication order, medication label and information system, devices and work processes. Five additional important associated findings were associated with the patient's care, although a definite causal link to the incident or to the patient's death could not be established. The analysis also uncovered a number of incidental findings that are relevant to the general safety and quality of patient care at the tertiary cancer treatment centre, although they did not directly affect the outcome in this case.

This report identifies opportunities for implementation of system safeguards and safety enhancements. Certain of the specific findings are applicable to all health service organizations and the recommendations are directed to several components and levels of health care systems, both nationally and internationally.

It is hoped that the findings and recommendations provided in this report will be of assistance to the administration and staff of the XXXX Cancer Board in their efforts to continually enhance patient safety.

## Objectives

The objectives of the root cause analysis were to:

1. Develop an understanding of the circumstances surrounding the fluorouracil event through a review of relevant documents, interviews with staff, examination of the physical environment where the incident occurred, and observation of related work processes.
2. Use the Canadian Root Cause Analysis Framework, co-developed by the Canadian Patient Safety Institute, ISMP Canada and Saskatchewan Health, to determine the contributing factors and root causes underlying the event circumstances.
3. Recommend actions to reduce the likelihood of this and similar events in health care institutions.

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## Introduction and Context

On July 31, 2006, a 43-year-old woman with nasopharyngeal cancer received over 4 hours an infusion of fluorouracil (5250 mg) that was intended to be administered over 4 days. On the same day, prior to the fluorouracil administration, she received 100 mg of cisplatin as per the cancer treatment protocol. The patient's cancer was advanced, but the prescribed treatment was being given with the expectation of effectiveness. However, she died on August 22 from the sequelae of fluorouracil toxicity which was cumulative with cisplatin toxicity. The XXXX Cancer Board invited ISMP Canada to provide external expertise, as an agent of the XXXX Cancer Institute Medical Quality Assurance Committee, to undertake a root cause analysis of this event. Root cause analysis is a structured process for reviewing an event with the goals of determining what happened, why it happened, and what can be done to reduce the likelihood of a recurrence.

Analysis of medication incidents identifies hazards, issues, contributing factors, and underlying causes. The resulting information can be used to develop safeguards to prevent similar adverse events, or to mitigate harm to patients if incidents do occur again. The underlying causes of a medication incident are typically beyond the control of an individual. Practices that rely on an expectation of perfect performance by human beings are doomed to fail, for the simple reason that everyone errs, and does so frequently. To succeed in reducing harm, we must therefore transform the thinking of health care personnel about why incidents occur. This transformation is the fundamental principle that drives our approach to medication incident analysis.

Substantive improvements in the safety of medication use can only be achieved if we understand latent failures or underlying weaknesses in the medication use system and then take high-leverage actions to enhance the system design. Leadership in many health service organizations will be critical to successfully applying the learning from this event analysis.

## Root Cause Analysis – Overview

Root cause analysis is defined in the Canadian Root Cause Analysis Framework<sup>1</sup> as “an analytic tool that can be used to perform a comprehensive, system-based review of critical incidents. It includes the identification of the root and contributory factors, determination of risk reduction strategies, and development of action plans along with measurement strategies to evaluate the effectiveness of the plans.”

Root cause analysis in healthcare is best conducted by a multidisciplinary team, involving individuals knowledgeable about medication safety, as well as knowledgeable in the clinical area of focus. Information is gathered through interviews with staff members who were directly and indirectly involved, as well as family members when possible. In addition, the team reviews the location where the incident occurred, examines the drugs, devices, environment and work processes involved, and reviews relevant documentation and literature.

The analysis team proceeds through a series of probing questions focused on answering “why” and “caused by” questions to delineate the various factors that contributed to the event and which, if left unmitigated, could contribute to another event. The focus is on systems and processes and their interaction with individuals, with the understanding that the individuals involved did not intentionally act to cause harm, and given the same set of circumstances, the outcome would be the same for any individuals involved. The root cause analysis process encourages high-leverage system changes that, if implemented, will have lasting effects on safety.

Recommended changes incorporate strategies such as forcing functions, standardization, simplification, and automation. Staff education and policy changes may be required, but on their own these measures are not sufficient to ensure sustained change. Relevant literature and practice standards are considered in formulating recommendations and actions. To give a specific example; one of the recommendations from this event is to re-design ambulatory medication infusion pumps to have built-in programming safeguards which would prevent input of an excessive rate of infusion. To help understand the significance of such a system enhancement we provide an analogous example from the automotive industry: as a result of learning from fatal accidents, cars were re-designed with a forcing function so that it would not be possible to place a car in “drive” or in “reverse” without first having a foot on the brake.

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<sup>1</sup> Canadian Patient Safety Institute, Institute for Safe Medication Practices Canada, Saskatchewan Health. Canadian Root Cause Analysis Framework, Canadian Patient Safety Institute, Edmonton: March, 2006.

## Methods

ISMP Canada assembled an analysis team of five health care professionals: three pharmacists with expertise in medication safety, an oncology nurse, and a physician who is also a human factors engineer. One ambulatory care manager from the XXXX Cancer Institute and the XXXX Cancer Board Patient Safety Officer participated as members of the analysis team, but did not participate in interviews with the staff directly involved in the event. Additional consultants to the analysis team included oncology nurses, pharmacists, physicians, toxicology, human factors and medication safety experts. Local assistance and logistics support for the site visit was provided by XXXX patient safety staff.

The review was undertaken in three parts:

**a) Off-site preparation and information gathering**

Relevant documents were provided for review by the ISMP Canada team before the site visit.

**b) On-site information gathering**

The on-site portion of the review took place on October 30 and 31 and November 1, 2006.

Interviews were conducted with:

- XXXX corporate executive team
- XXXX senior leadership
- Internal critical incident review team
- Nursing and medical staff directly and indirectly involved in the event, as well as staff knowledgeable about usual care processes
- Pharmacy administrators and front-line staff
- Biomedical engineering manager
- Medical staff from the Intensive Care Unit at the University of XXXX Hospital
- Staff from XXXX House (a local residence for patients undergoing cancer treatment)
- Representative from the Health Quality Council of XXXX (also conducting an external review of the event)

The consultant team examined the physical environment where the event occurred and observed usual work processes in the Medical Clinic, Day Care Unit, and Pharmacy.

**c) Off-site analysis and research**

- The analysis process was conducted over a period of several weeks from the ISMP Canada head office, with the involvement of off-site team members through conference calls.
- A pump usability test was conducted by a human factors engineer with assistance from a pharmacist and is available in Appendix 2.
- A search was conducted for information about other similar incidents. Sources of information included national and international medication and device incident reporting programs, as well as case reports in the medical literature and internet.
- Preliminary analysis findings were shared with XXXX senior management on February 22<sup>nd</sup> and with the Health Quality Council of XXXX on February 27th, 2007.

## Understanding the Event

An important component of root cause analysis is a thorough understanding of “what happened”. The team begins by reviewing an “initial understanding” of the event and identifying unanswered questions and information gaps. The information-gathering process includes interviews with staff who were directly and indirectly involved, hospital administrators, and representatives of other relevant departments, review of pertinent documents (e.g., patient’s health record, organization policies and procedures), examination of the physical environment where the event and other relevant processes took place, and observation of usual work processes. This information is synthesized into a “final understanding”, which is then used by the team to begin the “why” portion of the analysis.

### Initial Understanding

“A woman in her 40s died last week after she was mistakenly given a lethal overdose of a standard chemotherapy drug while undergoing treatment at the XXXX Cancer Institute. Instead of receiving the intravenous drug continuously over four days, the woman received the dose over four hours on July 31 from a pump that had been programmed in error. She died Aug. 22 at the University of XXXX Hospital from complex causes, including a failure of multiple organs, as well as widespread internal bleeding.”

*From: XXXX. We cannot eliminate human error. XXXX Journal, Thursday, August 31, 2006.*

### Final Understanding

The final understanding developed by the analysis team is presented in diagrammatic form following this text description, and in tabular form in Appendix 3.

A 43-year-old woman was seen in the Head and Neck Clinic of the XXXX Cancer Institute on Friday, July 28, and electronic chemotherapy orders were completed for Monday, July 31. The order stated “5-Fluorouracil 5250 mg (at 4,000 mg/m<sup>2</sup>) Intravenous once continuous over 4 days”, with administration instructions “Continuous infusion via ambulatory infusion pump (Baseline regimen dose = 1000 mg/m<sup>2</sup>/day = 4000 mg/m<sup>2</sup>/4days)”. (A copy of the order is available in Appendix 4.)

The patient had previously been treated with chemotherapy and radiation from May 10 to June 22 and was to start three cycles of adjuvant chemotherapy with cisplatin and fluorouracil. At this clinic visit, the clinic nurse reviewed the orders, the results of lab work (WBC 4.8, platelets 363), and the patient’s height and weight to ensure all was in order for chemotherapy administration on Monday, July 31. The “bay” pharmacist also reviewed the order and completed the calculations required for pharmacy staff to enter the drug order into the pharmacy information system and prepare the dose. The chemotherapy order was delivered to the pharmacy and

entered into the pharmacy information system by a pharmacy technician. The cisplatin and fluorouracil solutions were then prepared, with additional checks by a pharmacist.

The patient presented to the Medical Day Care Unit at 9:45 am on Monday, July 31 and received pre-hydration, pre-medications (ondansetron, dexamethasone, and lorazepam), cisplatin, and post-hydration per usual procedure and protocol. At approximately 2:30 pm, the nurse (RN #1) prepared to administer the fluorouracil and programmed the infusion pump (Abbott AIM Plus, model 13967), using the calculator on the computer to calculate the infusion rate. The calculated rate (28.8 mL/h) was observed to match a number on the pharmacy label. RN #1 requested a “chemo check”, and RN #2 came to do the check while on the way to perform another task. RN #2 could not find a calculator, so did the calculation mentally and on paper, and confirmed the programming, finishing by locking the pump. Both nurses signed the blue handwritten medication administration record documenting the total dose of fluorouracil to be infused (5250 mg). RN #1 also electronically signed for the total dose in the computer. At approximately 2:30 pm, RN #1 initiated the infusion and reviewed the pump functionality with the patient. Instructions were given to the patient to return for pump disconnection after 4 days. The patient was discharged home from the clinic to XXXX House, where she was residing for the duration of her treatment regimen.

Between 6:30 and 7 pm, the patient noticed that the pump was beeping and, upon investigation, discovered that the fluorouracil bag was empty. A XXXX House volunteer drove the patient and a friend back to the XXXX immediately. The patient was seen by the evening Nursing Supervisor, who disconnected the pump and flushed the line. The Nursing Supervisor contacted the physician on call, who advised that nothing could be done – there was no antidote – and that the patient should be advised to call the next morning. The Nursing Supervisor counselled the patient, explaining that she had received a large amount of drug over a short time and could become very ill, emphasizing the risk of nausea and vomiting and need for maintenance of hydration. The Nursing Supervisor completed a paper incident report and placed it with the pump in the Day Care Clinic for follow up the next day by the Unit Manager. The Nursing Supervisor also contacted the Unit Manager by telephone to advise of the incident.

On the morning of Tuesday, August 1, the Unit Manager and RN #1 checked the pump data history and verified that the pump had been programmed with an incorrect rate. The Unit Manager contacted the patient by telephone and advised that there could be serious side effects and that she should come to the clinic for monitoring. The patient felt well and preferred not to come to hospital. When informed that RN #1 wanted to speak with her to apologize, the patient stated “Tell [ ] not to worry about it”. The Unit Manager later saw the attending physician in the clinic and asked if the physician had heard about the incident; and learned that this person had not yet been informed. The Unit Manager and the physician looked at the pump and reviewed the programming. The Unit Manager told the physician that the patient had been contacted that morning and was feeling well and preferred not to come to hospital. The Unit Manager gave the patient’s phone number to the physician, who indicated a plan to follow up with the patient. The physician began a literature search to determine what could be done, checking about the possibility of hemodialysis and looking for predictors of what could happen. After speaking with the physician, the Unit Manager called the patient back to remind her to call if any sign of mouth sores.

On Wednesday August 2, the physician spoke with a XXXX medical oncologist/pharmacologist: this person confirmed that dialysis would not be helpful. They discussed investigational agents that might be helpful but decided it would be difficult to obtain such agents through Health Canada’s Special Access Program and these drugs would be of questionable value in any case.

The physician contacted the patient and although she was feeling well, she agreed to come in the next day.

On Thursday, August 3, the patient was seen at the clinic. The patient was experiencing nausea and vomiting and mentioned discomfort in her throat. She was given IV hydration and antiemetics. Blood tests were done (WBC 10.6, platelets 388) and admission was planned for the following day, as there were no beds available at the time.

On Friday, August 4, the patient was treated in the ambulatory care clinic with IV fluids, ondansetron, dexamethasone, and metoclopramide while waiting for a bed to become available. Blood tests were repeated. The patient was admitted to the inpatient medical oncology unit after 6:00 pm that day. On admission, patient rated pain in her mouth as 5/10 and described vague nausea but refused analgesia and antiemetics. Lab results August 4: WBC 9.4, platelets 259.

On Saturday, August 5, the covering physician contacted the patient's husband and advised him personally of the pump programming error.

From Friday, August 4, to Friday, August 11, the patient was an inpatient on the medical oncology unit, receiving supportive care in the form of IV fluids, antiemetics, antidiarrheals, specially compounded mouthwash, dexamethasone and morphine. From Friday, August 4 to Monday, August 7, the patient experienced similar levels of pain in her mouth, nausea with occasional emesis, and diarrhea approximately twice per day. The patient was afebrile for the duration of her admission.

Lab results, Sunday, August 6: WBC 6.2, platelets 204.

On Tuesday, August 8, the frequency of diarrhea increased to 5 loose bowel movements; no complaints of nausea were noted.

On Wednesday, August 9 in the evening, the patient experienced four episodes of severe diarrhea and vomited twice. Lab results Wednesday, August 9: WBC 0.2; platelets 83.

On Thursday, August 10 at 4:47 am, the patient was seen by the resident on call. The patient was tachycardic (pulse ~140) and had bright green emesis with occasional bright red blood. The resident considered the possibility of a small-bowel obstruction or cholecystitis. A stat electrocardiogram was done and appeared normal. Radiograph and bloodwork were ordered to be completed on an urgent basis in the morning. Radiography report identified "a striking paucity of bowel gas within the abdomen....such that the bowel is presumably fluid filled, although it could be either dilated or collapsed". Lab results, August 10: WBC 0.1, platelets 38. The patient had two additional episodes of vomiting dark green bile during the day on Thursday, August 10; no diarrhea.

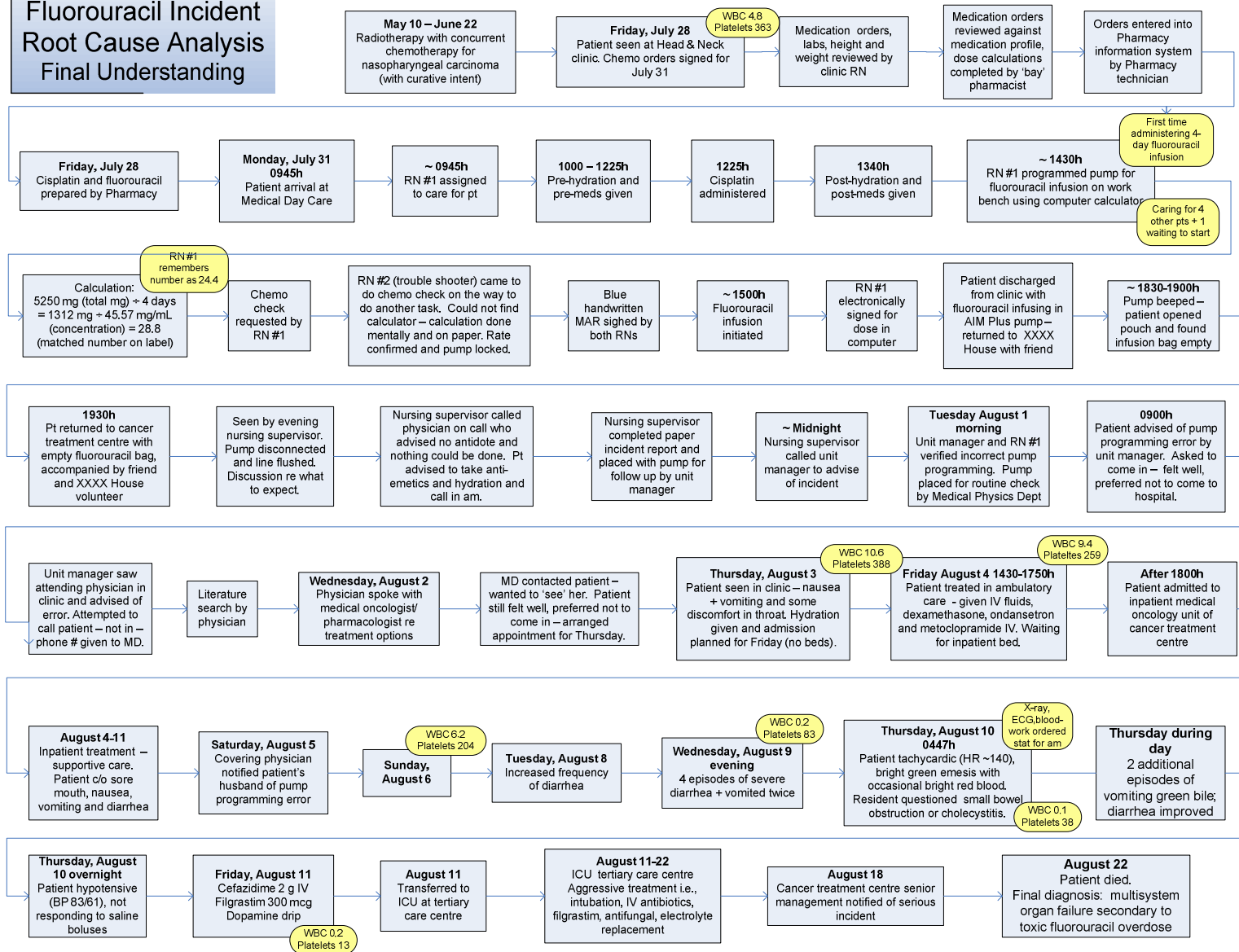
Overnight between Thursday, August 10, and Friday, August 11, the patient complained of bilateral numbness in the hands and feet. She was found to be hypotensive (blood pressure 83/61 mm Hg), tachycardic (pulse 130). Saline boluses were ordered but were not effective. At 6:35 am, her blood pressure decreased to approximately 72/50 mm Hg.

At 7:45 am on Friday, August 11, a decision was made to transfer the patient to the intensive care unit at the nearby tertiary *acute care* facility. Ceftazidime 2 g IV and filgrastim 300 mcg were administered, and a dopamine drip was started before transfer. Lab results prior to transfer: WBC 0.2, platelets 13.

From Friday, August 11, to Tuesday, August 22, the patient was treated aggressively with IV antibiotics, filgrastim, antifungals, and electrolyte replacement; she required intubation. The patient's condition gradually worsened, multi-organ system failure developed, and life support was removed on August 22. The coroner's report listed the cause of death as "sequelae of fluorouracil toxicity".

The senior administration team was notified of the event on August 18.

# Fluorouracil Incident Root Cause Analysis Final Understanding





## Cause-and-Effect Analysis

Following development of the final understanding of the event, the ISMP Canada team produced a series of “cause-and-effect” diagrams. Cause-and-effect diagramming is a problem-solving technique used to methodically determine the system-based causes of an event under review. The diagrams form the basis for identification of root causes and contributing factors, as well as important associated and incidental findings (factors that are identified as important for patient safety but for which a definite causal or contributory link cannot be established).

For appropriate analysis, it is critical to correctly identify the defined event, which is the starting point for the cause-and-effect diagramming. Once the event has been defined, the root causes and contributing factors are determined by asking a series of “why” or “caused by” questions to work back from the “sharp end” of the event (the care provided by individuals) toward the “blunt end” (underlying system deficiencies). Some of the “whys” are actions performed by an individual, whereas others may be underlying conditions or circumstances. This questioning process generates elemental causal sets, which are then expanded to create causal chains to provide a better understanding of the event.

This event was not the result of a single “root cause”. Rather, a combination of actions and conditions, which on their own would not have caused the death, occurred simultaneously and together were causal. This section of the report describes the team’s findings related to the root causes and contributing factors.

A detailed description and diagrammatic representation of the multiple contributing factors and root causes that led to the event, follows.

### Description of Causes and Effects

The defined event for this analysis was the death of a patient due to the sequelae of fluorouracil toxicity, cumulative with cisplatin toxicity.

Three primary causal chains leading to the patient’s death were identified:

#### **Fluorouracil overdose**

The patient received fluorouracil at a rate 24 times greater than the intended rate of infusion. This resulted in an overdose of fluorouracil, i.e., the full 4 days of a high-dose protocol (5250 mg) was administered over a period of 4 hours.

Seven causal chains led to an infusion rate entered as 28.8 mL/h instead of 1.2 mL/h: miscalculation; opportunity for false confirmation on label; information required to program pump not part of medication administration record; double check process failed; complex workload and multitasking; no feedback from pump; and low knowledge of hazard.

#### **Design of the chemotherapy protocol**

The amount of fluorouracil contained in the infusion bag, as per the high-dose fluorouracil protocol for nasopharyngeal carcinoma, was to be administered as an infusion over 4 days.

Inadvertent administration in 4 hours resulted in an overdose. Cisplatin was administered as a single dose of 100 mg as per protocol.

### **Inability to mitigate harm from fluorouracil and cisplatin**

The maximum tolerated dose or lethal dose is not clearly defined in the literature. The absence of a pharmacologic antidote or defined treatment protocol for fluorouracil overdose increased the likelihood that a significant overdose would cause harm. (See also Appendix 5: Mitigation of Harm from Fluorouracil.) The absence of a defined treatment protocol to reverse cisplatin toxicity increased the potential for cumulative toxicity with fluorouracil

Two causal chains led to an inability to mitigate harm from fluorouracil and cisplatin: no pharmacologic antidote or defined protocol to treat overdose and no defined protocol to reverse cisplatin toxicity

Each of the causal chains was further expanded to provide a detailed understanding of the underlying causes of the patient's death.

### **Pump programmed in accord with miscalculation**

The nurse programming the pump (RN #1) omitted a step in the calculation sequence (i.e.  $total\ dose\ in\ mg \div 4\ days \div 24\ hours \div concentration\ in\ mg/mL = rate\ in\ mL/h$ ) and calculated the rate to be 28.8 mL/h instead of 1.2 mL/h. Factors contributing to this miscalculation included the following:

- The separation of some patient care responsibilities among the disciplines made it less likely that physicians and pharmacists would be aware of (i) the complexity of calculations required by nursing staff to administer medications and (ii) a need to “map” and prominently display important information among the order, MAR, label and pump.
- RN #1 had a low index of suspicion regarding the high volume rate calculated because of lack of familiarity with the protocol. RN #1 was new to the Day Care Unit, and this was the first time RN #1 had to administer a 4-day fluorouracil infusion. The calculated rate of 28.8 mL/h was not unusual for other IV infusions used in the clinic.
- The calculation was not validated with a mental approximation (i.e., if total volume is 130 mL and hourly rate is approximately 30 mL/h, infusion will last approximately 4 hours, not 96 hours as intended). A recognized human factors phenomenon occurs when our senses are bombarded with information. Our attention becomes focused on information that requires our concentration (e.g., complex calculation) and other information (e.g., high volume rate) is not noticed.<sup>2</sup>

### **Opportunity for false confirmation on label**

The design of the pharmacy-generated label was not in accord with the information needed by nurses:

- The label included unnecessary information (e.g., the 24 hour administration rate), which was presented in a position of prominence on the label (the correct hourly rate was listed in parentheses after the 24 hour rate).
- The label format did not reflect pump programming requirements. Pharmacy staff were not familiar with the pump's functionality and were not involved in evaluating the pump.

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<sup>2</sup> Green Marc. “Inattentional Blindness” and Conspicuity. Visual Expert Human Factors. Available at: <http://www.visualexpert.com/Resources/inattentionalblindness.html>.

- The information on the label was based on an interpretation of legal requirements and professional guidelines. There was no process in place to periodically review label content and format.
- Human factors engineering principles such as: prominence of critical information and optimal sequence of information display; optimal font size and style, appropriate use of white space, high-contrast printing (rather than low-contrast dot matrix printing), appropriate number of significant digits in numeric values (i.e., *not* presenting concentration to 2 decimal places) were not applied to label design.
- Limited standardization of procedures between the two tertiary cancer treatment centres in the provincial cancer board inhibited optimization of the CPOE and pharmacy information systems and prevented optimal medication order and pharmacy label design. Standardization with the assistance of automation can be a high-leverage strategy for guiding safe medication practices.

### **Information required to program pump not part of medication administration record and not included in physician order**

Critical information was not clearly “mapped” among the medication order, the medication administration record (MAR), the pharmacy label, and the infusion pump:

- The medication order was written as total dose over 4 days.
- Nurses transcribed the total dose onto a handwritten MAR, which was used to document the double check process, and maintained as an ongoing record of care over time. (Total dose administered was also electronically signed in the computer system)
- Information needed to program the pump (i.e. total volume and rate of infusion) was not included on the MAR because it was not part of the medication order.
- Nursing staff were required to complete a complicated mathematical calculation to convert total dose in mg over 4 days to a rate in mL per hour.
- The information needed to program the pump, although provided by the pharmacy-generated label, was not displayed in an optimal way.

Together, these factors increased the complexity of the pump programming process.

Chemotherapy processes are not fully standardized within the provincial cancer board, despite shared use of the computerized prescriber order entry (CPOE) and pharmacy information systems. Variations in practice, including the use of different brands of infusion pump, made it difficult to build common sets of medication orders for chemotherapy protocols, including the high-dose fluorouracil protocol.

### **Double-check processes failed**

The calculation check as completed on this occasion did not detect the miscalculation. There was no calculator readily available on the workbench, so the checking RN (RN #2) performed the calculation mentally and on a scrap of paper.

- The double-check process was not embedded into a checklist, and there was no requirement to document the calculation. The calculation check was not validated with mental approximation, as described above.
- Checking functions in nursing practice are not structured and incorporated into work flow routines. It is typical for nurses to be “pulled away” from other tasks to complete checking functions, in contrast to processes for other disciplines (e.g. pharmacy). In the

case under review, the nurse completing the check was on the way to perform another task at the time.

- Distractions arising from the busy environment of the unit might have played a role in the miscalculation and the failed double check.
- The double-check process was not truly independent.<sup>3</sup>

### **Complex workload and multitasking**

Nursing staff in the Day Care Unit are required to complete many tasks virtually simultaneously. As the final health care professional in the medication use process for administration of cancer chemotherapy, the nurse is responsible for checking the results of laboratory tests and the patient's condition to ensure appropriateness of medication administration; reviewing the medication order, label and calculations; programming the pump; and providing education to patients about the medications they are receiving and about potential complications that may arise with the infusion pump. (RN #1 described teaching the patient about the pump while attending to her IV access site dressing.)

- Work processes require multitasking; the various tasks are not laid out in a step-wise fashion and checklists are not used;
- Multiple human factors design flaws with the infusion pump increased the cognitive load associated with programming the infusion pump. (A usability test completed on the infusion pump is described in Appendix 3). The pump programming options are not intuitive. For example:
  - Must scroll to find “continuous” option
  - Programming choices are listed as “mg/mL”, “μ/mL” or “mL” (actually mL/h)
  - “Container size” = volume to be infused

### **No feedback from pump**

This particular brand of infusion pump does not include programming safeguards that would prevent nursing staff from programming a dose that exceeds the dose contained in the pump library. (Pump safeguards can include preset dose ranges with the ability to prevent programming doses outside the range, or preset rates that prevent programming a rate outside the range.) In addition, the infusion pump review program is designed to show pump data entry fields only; in other words, the pump does not integrate the information to provide feedback about the programmed duration of infusion.

### **Low knowledge of hazard**

Information about previous fatal events with high-dose fluorouracil is difficult to find or not available. Sharing of information about adverse events is not well developed in health care, and existing information is difficult to access because of a lack of transparency and coordination. (Similar fluorouracil incidents are summarized in Appendix 1.) Exceeding the dose limits for an agent and excessively rapid infusion of chemotherapy are both low frequency events. Experience is unlikely to prepare general clinicians to recognize and manage the optimal response.

Practitioners perceived that the hospital's systems were safe because there were few or no previous sentinel events. This perception was supported by the lack of feedback to staff about incidents reported via the new electronic incident reporting system and the absence of a well-developed near-miss reporting system.

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<sup>3</sup> See Appendix 5: Glossary of Terms, Independent double-check

## Description of Important Associated Findings

The defined event in this analysis was the death of a patient who received an overdose of fluorouracil. Root cause analyses often uncover important associated findings and incidental findings. Associated findings are factors associated with the care of the patient that form the basis for additional recommended actions but for which a definite causal link with the defined event cannot be established. Incidental findings are factors that have little bearing on the outcome of the case but that are relevant to the general quality and safety of patient care. Incidental findings follow this section on associated findings.

### **Lack of information on medical management of previous fluorouracil overdoses**

Information about the medical management of fluorouracil overdose was not readily available.

- Information about previous similar incidents is difficult to find or not available. The medical literature contains only scattered anecdotal reports.
- Sharing of information about adverse events in health care is not well developed. Information in reporting programs for medication and device incidents is not transparent and is not consistently categorized using the same taxonomy, which increases the difficulty of accessing the limited information that is available.
- There is no standard definition for chemotherapy “overdose”. Fixed dose limits by agent cannot be reached because the drugs are dosed on an individual basis and the dosing rules vary by regimen.
- A poison information centre was not contacted for assistance. Immediate notification of a poison information centre might have yielded useful initial guidance and access to toxicology experts.

### **Lack of coordinated team response to event**

The response to the event was not well coordinated.

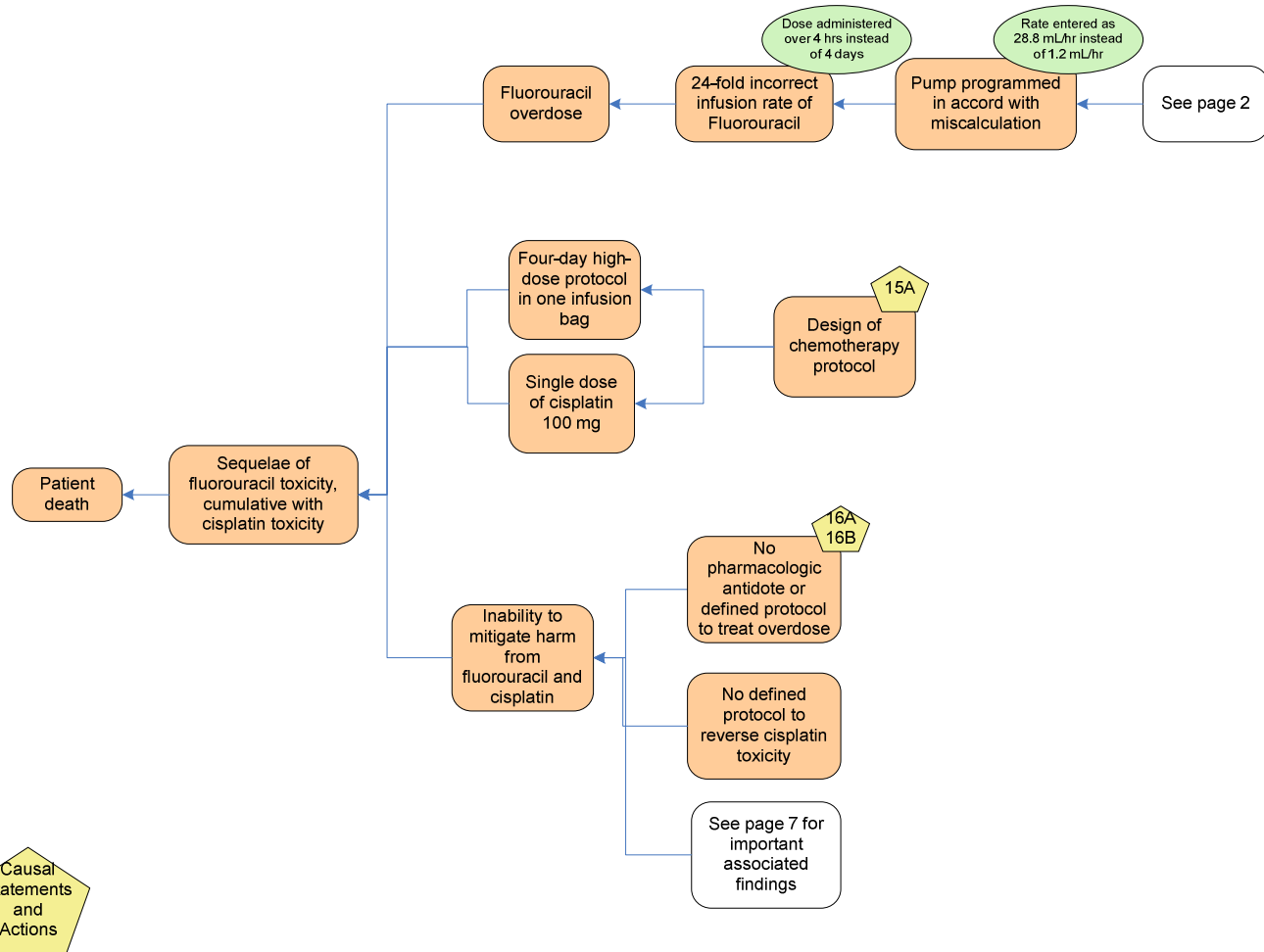
- There was no system in place to triage incidents for potential harm and to identify the need for intervention to prevent patient harm. The electronic medication incident reporting system automatically sends an e-mail alert to designated senior managers for all incidents coded as major or critical. However, this incident report was coded as “moderate”, possibly because of the lack of immediate clinical effect. The senior administration team was not alerted until August 18 (18 days after the event occurred and 7 days after the patient was transferred to the tertiary *acute care* facility).
- There was no protocol in place to manage an unexpected adverse medication event. In the setting of chemotherapy overdose or infusion error, the determination of the need for immediate and short-term mitigation measures requires extensive training in chemotherapy pharmacology. These determinations must be made as soon as possible for best outcome.
- Care providers’ perceptions of the life-threatening nature of the incident appeared to vary. Fluorouracil is commonly used in lower-dose protocols for treatment of other types of cancer, which would have a lower likelihood of harm when involved in a medication incident.
- The lack of documentation of expected outcome and plan of care (including treatment options considered and rejected) may have contributed to the variation in perception.

- Certain clinical information was not available or did not appear to have been acted upon. For example, there is no documentation of follow-up of symptoms of gastrointestinal toxic effects and tachycardia occurring early on August 10, the potential for dexamethasone to mask fever and infection appears not to have been recognized, filgrastim and prophylactic antibiotics were not administered until immediately before the patient's transfer to tertiary care, and a daily complete blood count was not ordered.

# Fluorouracil Incident

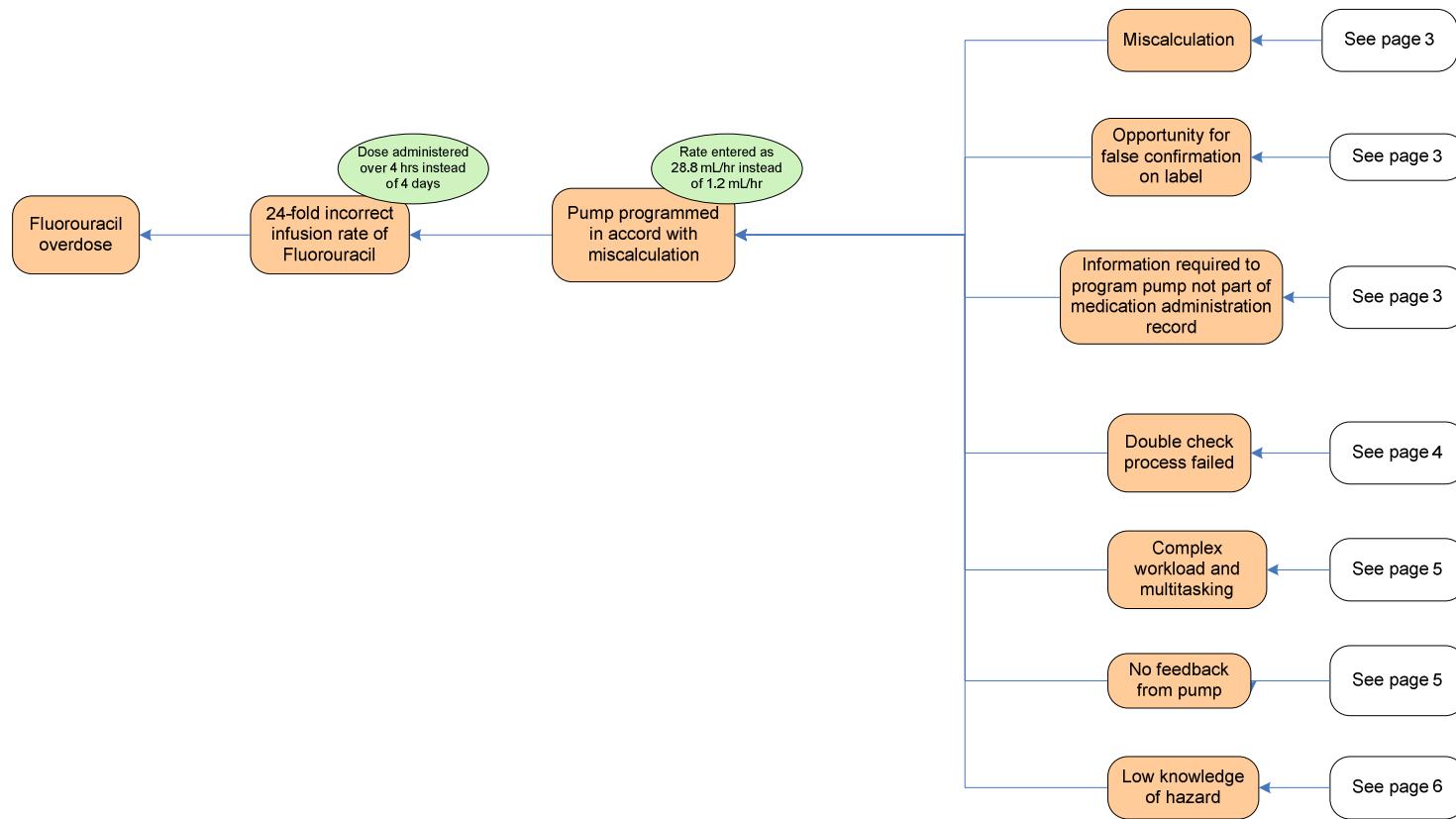
## Root Cause Analysis

### Cause and Effect Diagram



# Fluorouracil Incident

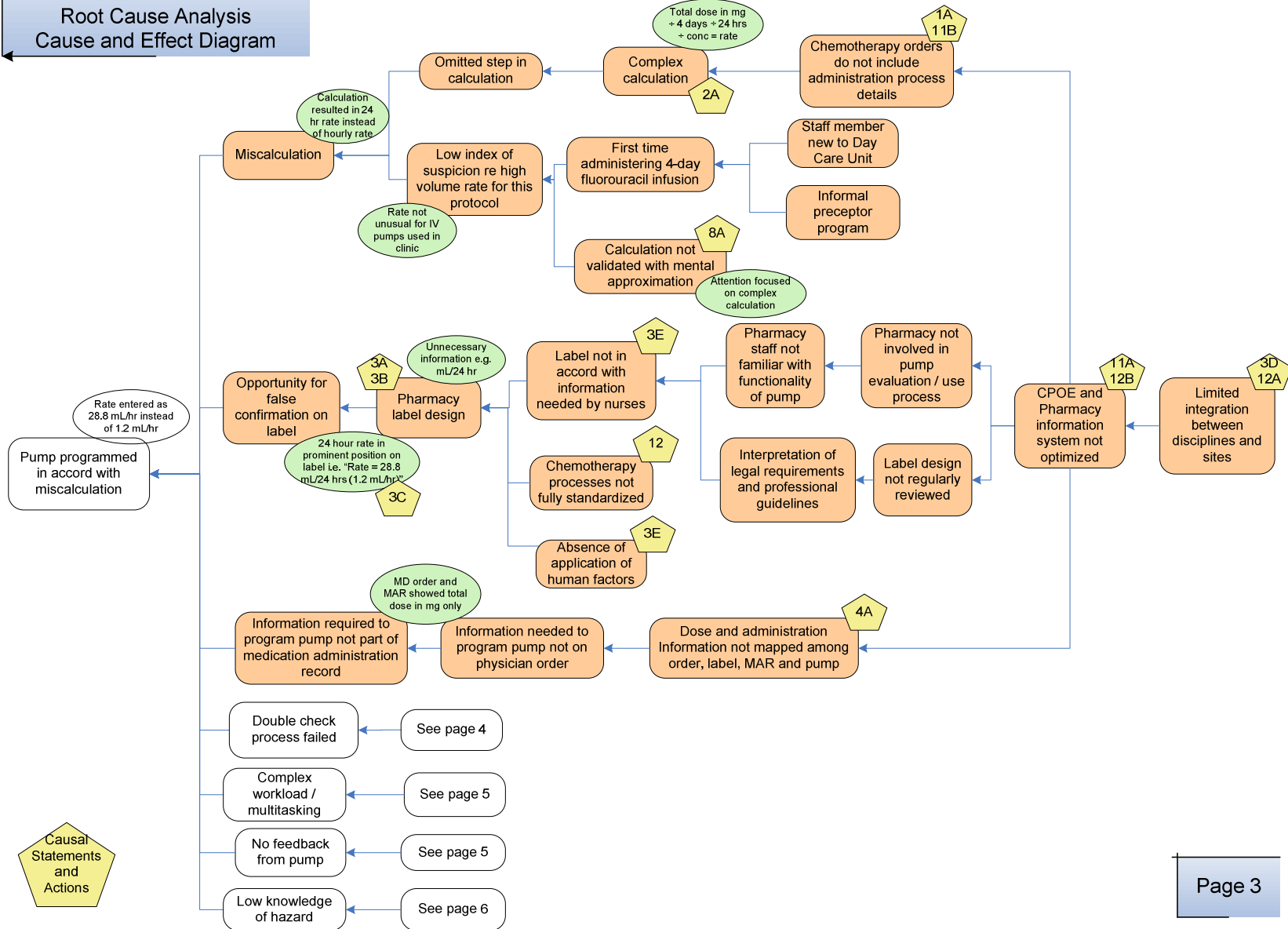
Root Cause Analysis  
Cause and Effect Diagram





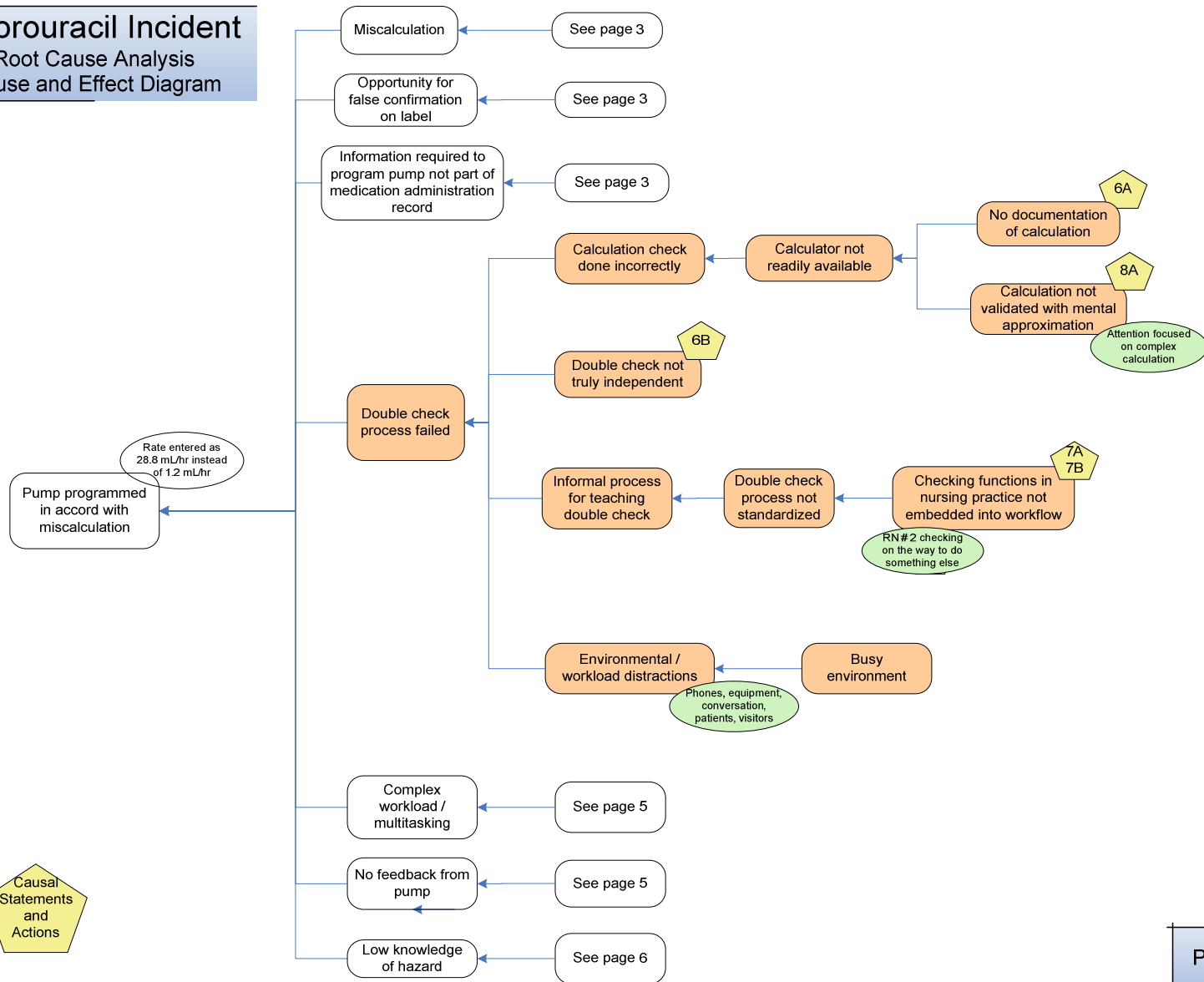
# Fluorouracil Incident

## Root Cause Analysis Cause and Effect Diagram

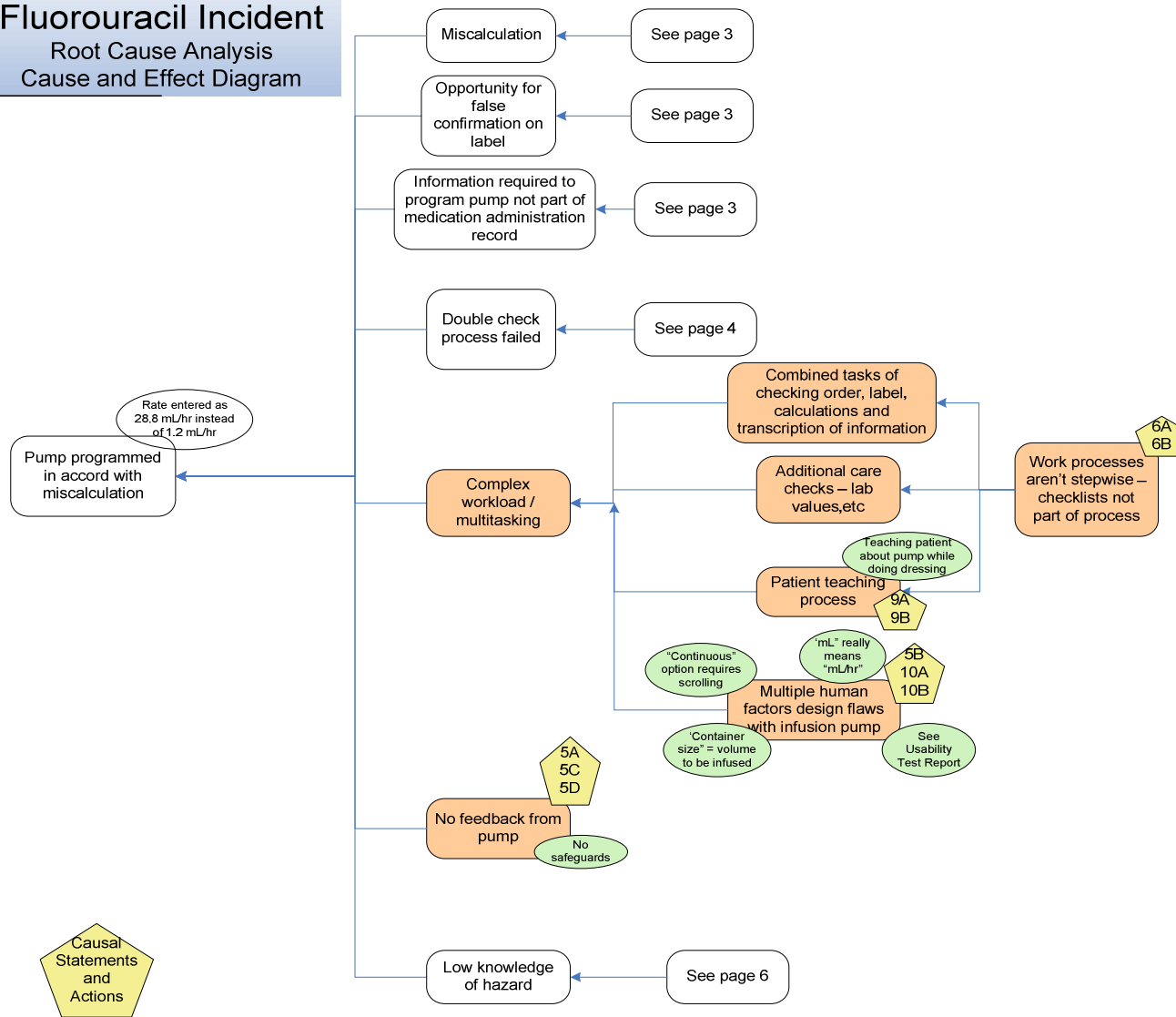


# Fluorouracil Incident

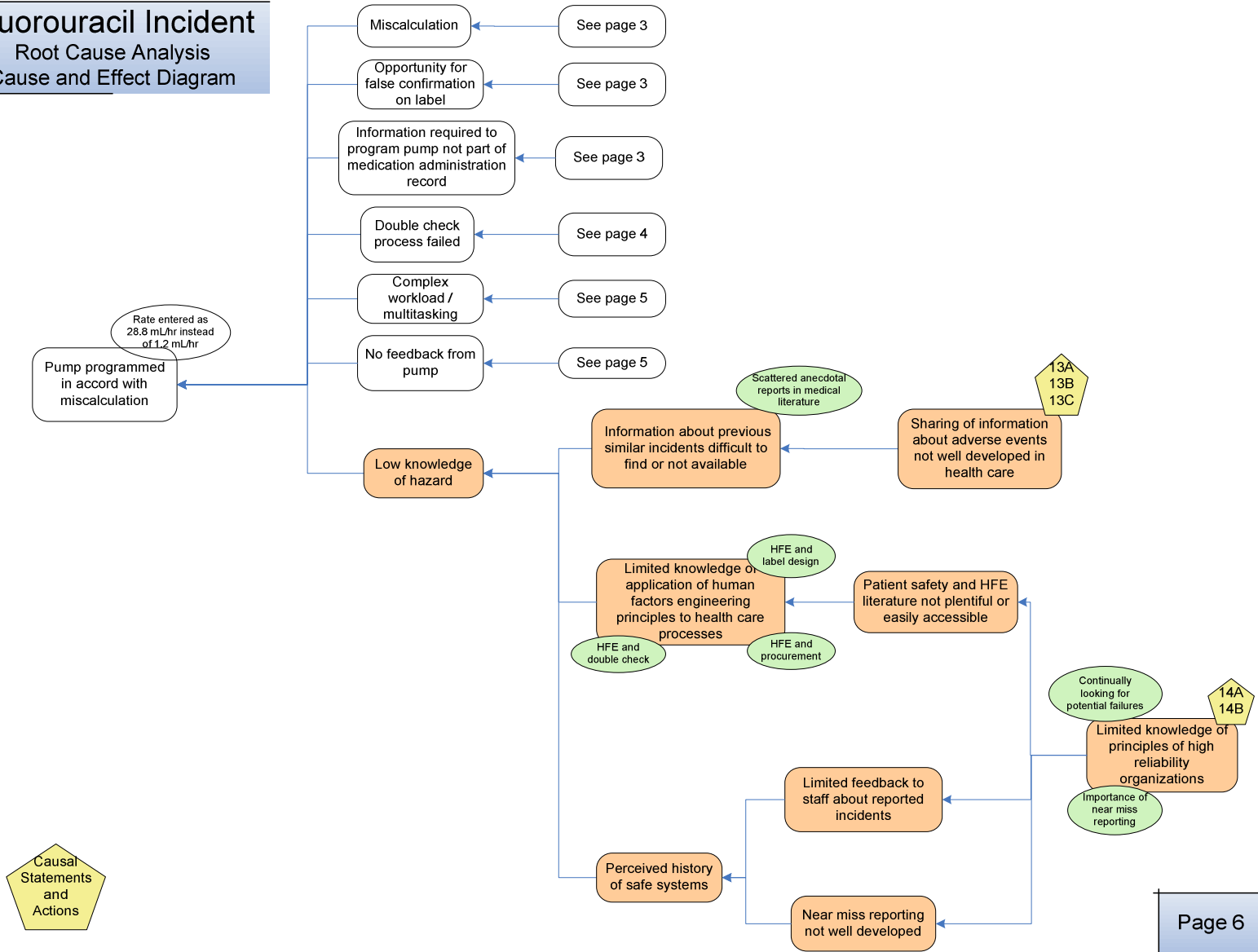
## Root Cause Analysis Cause and Effect Diagram



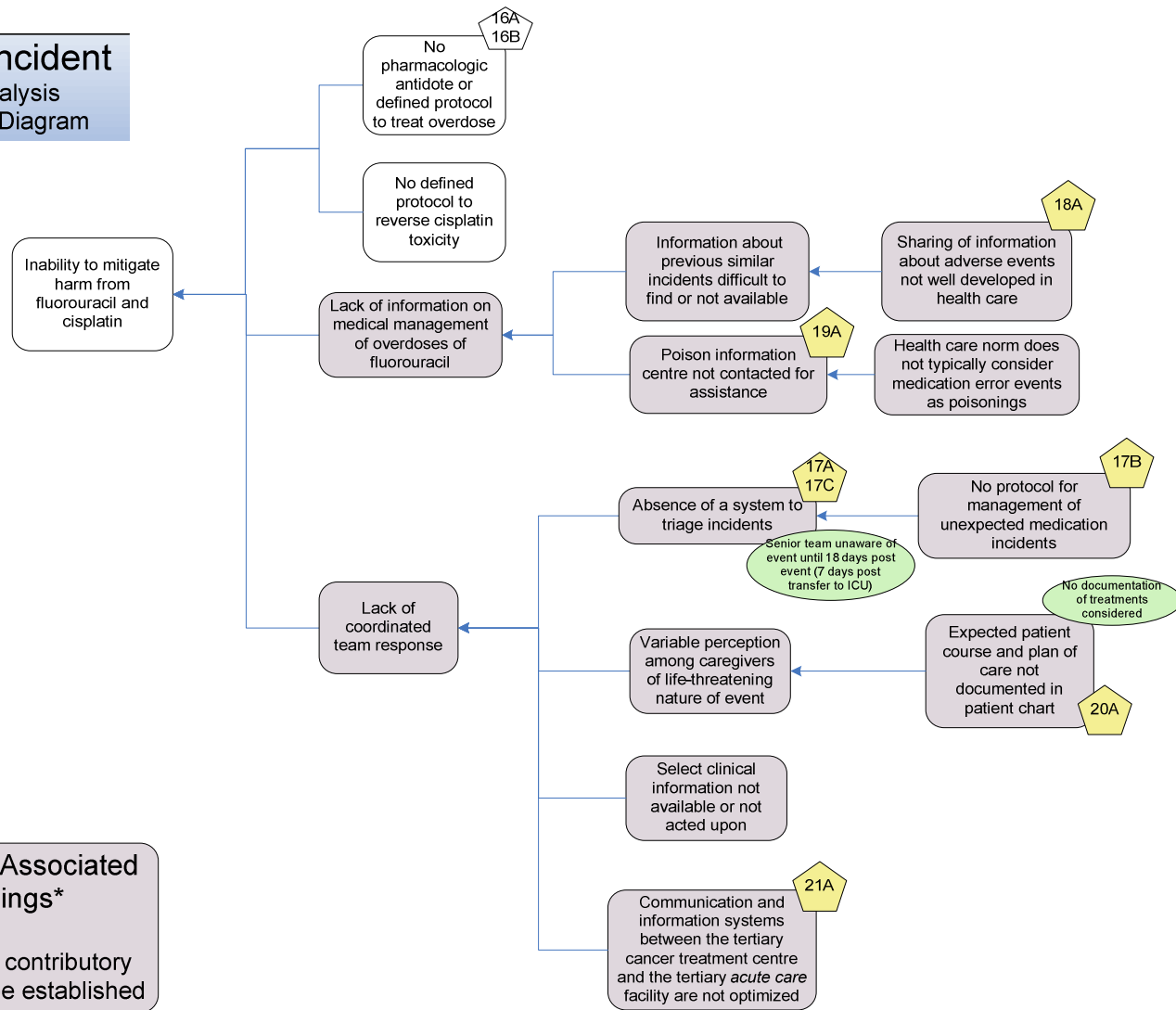
# Fluorouracil Incident Root Cause Analysis Cause and Effect Diagram



# Fluorouracil Incident Root Cause Analysis Cause and Effect Diagram



# Fluorouracil Incident Root Cause Analysis Cause and Effect Diagram



**Important Associated Findings\***  
\* Causal or contributory link cannot be established

# Fluorouracil Incident Root Cause Analysis Findings:

## Causal Statements (in order of priority)

1. A medication order without information to guide administration (e.g., total volume and rate to be programmed into the pump) resulted in reliance on a complex calculation to generate the missing information.
2. Reliance on complex calculations involving multiple dimensions (specifically mg divided by days, divided by hours, divided by concentration, to determine rate) increased the likelihood that a calculation error would occur during preparation to administer a fluorouracil infusion.
3. The medication label contained unnecessary information (e.g., “mL/24h”), and did not incorporate human factors engineering design principles (e.g., prominence of critical information), all of which increased the opportunity for false confirmation of “mL/24h” as “mL/h”.
4. Critical information that nurses need to administer medications correctly is not mapped (e.g., information available, sequence of information, use of common terminology) between the medication order, the medication administration record, the pharmacy label, and the pump, which increased the complexity of programming the infusion pump.
5. The infusion pump did not have programming safeguards<sup>4</sup> and did not provide feedback to the operator (e.g., duration of infusion), which decreased the likelihood that the miscalculation would be detected.
6. The lack of a process to ensure truly independent double checks<sup>5</sup>, with documentation of independent mathematical calculations, decreased the likelihood that the miscalculation would be detected.
7. Existing structures for checking responsibilities in nursing practice are not standardized and do not embed checking functions into nursing work routines, which increases the possibility of an incomplete check.
8. Lack of use of mental approximation to validate calculations decreased the likelihood that the miscalculation would be detected before the infusion pump was programmed.
9. Provision of patient teaching information, including pump functionality, without a review of pump data input, resulted in a missed opportunity for the practitioner to detect the incorrect pump data input (incorrect rate).

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<sup>4</sup> Pump safeguards can include pre-programmed dose ranges with ability to prevent programming doses outside the range, or pre-programmed rates that prevent programming a rate outside the range

<sup>5</sup> See Appendix 6: Glossary of Terms, Independent double-check

10. Human factors design flaws in the infusion pump (e.g., inconsistent terminology, difficult-to-find menu choices) increased the complexity of programming the pump and the associated cognitive load, which in turn reduced the likelihood that incorrect pump data input would be detected.
11. The variation in clinical practice of preparing and administering chemotherapy medication, including the use of different infusion pumps at the two tertiary cancer treatment centres of the provincial cancer board, makes it difficult to build detailed common medication order sets for the shared computerized prescriber order entry and pharmacy information systems, which limits the ability to include specific details (e.g. total volume and rate) in the electronic medication order.
12. Limited integration and standardization between the two tertiary cancer treatment centres of the provincial cancer board prevents optimization of the shared computerized prescriber order entry and Pharmacy information systems.
13. Information about previous events with high-dose fluorouracil protocols is difficult to find or not available, increasing the likelihood that opportunities for prospective implementation of system safeguards went unrecognized.
14. Limited knowledge about the culture of “high-reliability organizations” and the application of human factors design principles to enhance the safety of health care environments, decreased the likelihood that hazards present in the processes related to ambulatory administration of fluorouracil infusions would be recognized.
15. The treatment protocol design for nasopharyngeal carcinoma which utilizes 4 days of high-dose fluorouracil prepared and administered in one infusion bag, combined with a single high dose of cisplatin, increased the likelihood that programming the infusion pump with incorrect data would result in the patient’s death.
16. The absence of a pharmacologic antidote or defined treatment protocol for fluorouracil overdose increased the possibility that a significant overdose of fluorouracil would result in the patient’s death.

## Important Associated\* Findings

1. The absence of a system to triage medication incidents, and thereby to assess the need for intervention, decreased the likelihood of a coordinated team approach to patient care in response to an incident.
2. Relevant learning from previous events with high-dose fluorouracil protocols is difficult to find or not available, reducing the index of suspicion regarding the potential for a fatal outcome, as well as an inability to learn from “what’s been tried before”.
3. A poison information centre was not considered as an additional information resource in the initial management of the fluorouracil overdose.
4. The expected course and plan of care were not documented in the patient’s health record, which reduced the likelihood that the life-threatening nature of the incident would be clearly communicated to all team members, which in turn led to variable perceptions of the level of clinical monitoring and intervention needed.
5. Continuity of medical care between the tertiary cancer treatment centre and the tertiary *acute care* facility is not optimally supported by communication and information systems.

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\* causal link cannot be established



## **Incidental Findings**

As noted earlier, incidental findings are factors that have been assessed as having little bearing on the outcome of the case under analysis, but that are relevant to the general quality and safety of patient care.

### **Combined use of electronic and manual systems**

The tertiary cancer treatment centre currently operates with a mixed electronic and manual system. This mixed system creates additional workload for pharmacy and nursing staff and increases the potential for transcription errors and miscommunication of information. Despite the use of an electronic ordering system, manual pre-printed orders are utilized along with the electronic orders. Administration of medications is documented on manual nursing flow sheets, handwritten medication administration records (MARs) and in the electronic system.

The computerized prescriber order entry (CPOE) system does not interface with the pharmacy information system; this creates additional work and opportunity for error for transcription and miscommunication of information for pharmacy staff as orders must be entered into the pharmacy information system. In reviewing this case, it was learned that a miscalculation occurred when the pharmacist initially reviewed the order in the clinic. This resulted in the generation of an incorrect label when the pharmacy technician entered the order information into the pharmacy information system. The miscalculation was detected by the pharmacy technician when the volume of fluorouracil to be added to the infusion bag calculated by the pharmacist did not match the volume calculated by the computer system.

### **No predefined dose limits in CPOE system or pharmacy information systems**

No predefined dose limits are incorporated in the CPOE and pharmacy information systems. Predefined dose limits can be set up to automatically generate alerts for physicians and pharmacy staff when usual doses are exceeded. Systems can also be set up to block entries that exceed the maximum dose in the system or to require the user to enter the rationale for a higher dose.

### **Informal preceptor program for unit-based orientation and training**

Although the formal orientation program is highly structured, the unit-based orientation process for new staff members relies on an informal preceptor program. The double check process is also taught as part of this informal preceptor program, but not as part of the formal orientation program.

### **Busy Environment**

The high level of activity in the Day Care Unit and the resulting environmental distractions increased the cognitive load for programming and checking functions related to medication administration. The organization has completed a strategic plan to address planning for increased patient volumes.

### **Misconception that folinic acid might act to reduce effect of fluorouracil**

Several specialists consulted by ISMP Canada during preliminary research into the case, as well as intensive care unit (ICU) staff at the tertiary *acute care* facility, initially identified folinic acid as an agent that might be helpful to reduce the effect of fluorouracil. However, when staff at the tertiary *acute care* facility contacted the poison information centre they were advised that

folinic acid should not be used in this situation. Folinic acid is sometimes used in combination with fluorouracil to enhance effectiveness of fluorouracil; the combination *increases* the risk of toxic effects.

### **Look-alike / sound-alike drug names: folinic acid and folic acid**

A common look-alike / sound-alike medication error involving folinic acid and folic acid occurred at the tertiary *acute care* facility early in the patient's ICU admission. Orders that were intended to refer to folinic acid were written as "folate", which resulted in the dispensing and administration of folic acid, which was neither helpful nor harmful. These orders were discontinued after information was received from the poison information centre indicating that treatment with folinic acid was not appropriate.

### **Role and training of the outpatient clinic nurses in checking and verifying chemotherapy orders and laboratory data**

The role and training of the outpatient clinic nurses in checking and verifying chemotherapy orders and laboratory data varies and is not standardized. Written guidelines are needed to ensure that expectations for checking of chemotherapy orders and lab data are clearly outlined for nurses in the clinic, to ensure that patients do not proceed to the Day Care Unit for medication administration until all required checks have been successfully completed.

### **Misunderstanding about pharmacists' role in clinical monitoring in outpatient clinics**

Although pharmacists routinely monitor patient laboratory results and will intervene if such results indicate that a patient should not receive chemotherapy, this monitoring is done only if laboratory results are available when the medication order is being reviewed. If laboratory work is pending, the results are not routinely followed up by pharmacy staff. There is opportunity to create a more structured and coordinated process for monitoring laboratory data that includes ensuring that chemotherapy for patient administration is delivered to the patient care area only *after* laboratory results have been verified.

### **Clinical role of inpatient pharmacists not optimized**

The inpatient pharmacists do not routinely participate in clinical rounding activities and have limited opportunity to provide pharmaceutical care.

### **Multitasking requirement for pharmacy technician entering medication orders**

The pharmacy technician responsible for order entry of medication orders into the pharmacy information system is also required to triage phone calls coming into the dispensary. The order entry desk is located in a central area with multiple distractions. Some organizations have created quiet areas for order entry to reduce the opportunity for distraction during this critical step in processing medication orders.

### **Use of abbreviations and symbols on pre-printed orders**

A number of dangerous abbreviations and symbols are used on pre-printed order forms, e.g., "5FU" for "fluorouracil", "MgSO<sub>4</sub>" for "magnesium sulphate", use of "<" and ">" for "greater than" and "less than". A copy of a "Do Not Use" list of dangerous abbreviations prepared by ISMP Canada is available at:

<http://www.ismp-canada.org/download/ISMPCanadaListOfDangerousAbbreviations.pdf>.

### **Management of Dihydropyridine Dehydrogenase (DPD) deficiency**

It is unknown if the patient had a dihydropyridine dehydrogenase (DPD) deficiency; such a deficiency would have increased her sensitivity to fluorouracil. The prevalence of DPD deficiency in the American population is 4-7%.<sup>6</sup> Serious toxic effects, including death, have been reported in DPD-deficient patients receiving fluorouracil, even at low doses.<sup>7</sup> There is currently no reliable and accessible test for DPD deficiency available. Clinical practice guidelines regarding testing and management of DPD deficiency have not been developed. Relatives of patients who have had severe *and unexpected* reactions to fluorouracil need to know that DPD deficiency is probably inherited.

### **Fluorouracil drug monograph not available in *Compendium of Pharmaceuticals and Specialties***

In the course of researching background information on fluorouracil, it was discovered that the Canadian manufacturer of fluorouracil injection, Mayne Pharma, has opted to include only a product description (instead of a complete monograph) in the *Compendium of Pharmaceuticals and Specialties (CPS)*. As the CPS is often a “first check” source of drug information for health care professionals, this omission may make it more difficult for practitioners to quickly obtain information about potential adverse effects and management of toxic effects. A copy of the product monograph is included as a package insert with each vial of product; however this does not ensure availability of information to the end user for products (such as fluorouracil) that must be premixed by the pharmacy before dispensing.

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<sup>6</sup> Ezzeldin H. Diasio R. Dihydropyrimidine dehydrogenase deficiency, a pharmacogenetic syndrome associated with potentially life-threatening toxicity following 5-fluorouracil administration. *Clinical colorectal cancer*. 2004. vol.4, no.3, 181-9.

<sup>7</sup> DPD Deficiency. Available at: <http://dpdenzyme.com/index.htm>

## Causes and Recommended Actions

This report identifies opportunities for implementation of system safeguards and safety enhancements. Certain of the specific findings are applicable to all health service organizations and the recommendations are directed to several components and levels of health care systems, both nationally and internationally.

Causal Statement Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept) <sup>8</sup>	Time Frame	Responsibility
1	<b>A medication order without information to guide administration (e.g., total volume and rate to be programmed into the pump) resulted in reliance on a complex calculation to generate the missing information.</b>				
	1A	Include critical information required for medication administration as part of standardized order sets in manual and electronic medication orders. For example, if optimal programming of the ambulatory infusion pump requires data input of “total volume” and the “rate of infusion”, these data should be available in the medication order.	Control	Intermediate	Pharmacy and Therapeutics Committee

<sup>8</sup> “Eliminate”, “Control”, and “Accept” refer to options for safety strategies: *eliminate* or remove the hazard, provide safeguards to *control* the risk, or *accept* the risk (rarely a reasonable choice).

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
2	<b>Reliance on complex calculations involving multiple dimensions (specifically dose in mg divided by days, divided by hours, divided by concentration, to determine rate of administration) increased the likelihood that a calculation error would occur during preparation to administer a fluorouracil infusion.</b>					
		2A	Standardize administration procedures for the high-dose fluorouracil infusion protocol; include this information and the critical calculations required as part of electronic order sets and/or pre-printed manual orders. For example, the volume and rate of infusion could be standardized for all doses. Alternatively, the concentration of the final solution could be standardized. In both cases, calculations needed for drug administration, incorporating the patient-specific dose, can then be incorporated into the order.	Eliminate	Immediate	Pharmacy and Therapeutics Committee
3	<b>The medication label contained unnecessary information (e.g., “mL/24 h”) and did not incorporate human factors engineering design principles (e.g., prominence of critical information), all of which increased the opportunity for false confirmation of “mL/24 h” as “mL/h”.</b>					
		3A	Standardize communication of orders for infusion of medication to refer to rates as “mL per hour” instead of “mL per 24 hour”.	Eliminate	Intermediate	Pharmacy and Therapeutics Committee
		3B	Remove “mL per 24 hour” rate information from medication labels, medication administration records and other communications about medications to be administered by infusion.	Control	Immediate	Pharmacy and Therapeutics Committee

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		3C	Disseminate an international warning about the use of “mL per 24 hour” rate and the use and/or manufacture of infusion pumps that require “mL per 24 hour” rates. (Researchers are asked to consider the impact of “mL per 24 hour” rate information [instead of “mL per hour” information] in treatment protocols and the associated impact when protocols are implemented widely in clinical practice.)	Control	Immediate	ISMP international network and World Health Organization, Health Canada
		3D	Develop a mechanism to ensure adequate consultation with multiple front-line staff regarding medication use. For example, create a multidisciplinary team that includes front-line practitioners from both tertiary cancer treatment centres in the provincial cancer board to review medication administration and other issues and make recommendations to the provincial Pharmacy and Therapeutics Committee.	Control	Intermediate	Pharmacy and Therapeutics Committee Facility, Advisory Committees, pharmacy and nursing leadership

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		3E	Have a multidisciplinary team review pharmacy-generated medication labels in the context of medication administration requirements. Consider human factors design principles to improve readability (e.g., prominence of critical information, font size, contrast, white space). <sup>9 10</sup>	Control	Intermediate	Pharmacy and Therapeutics Committee, pharmacy and nursing leadership
4	<b>Critical information that nurses need to administer medications correctly is not mapped (e.g., information available, sequence of information, use of common terminology) between the medication order, the medication administration record, the pharmacy label and the pump, which increased the complexity of programming the infusion pump.</b>					
		4A	To reduce the cognitive load related to programming infusion pumps, design medication orders, medication administration records, and medication labels to ensure that critical information is available and provided in a logical sequence with consistent terminology.	Control	Intermediate	Pharmacy and Therapeutics Committee, pharmacy and nursing leadership

<sup>9</sup> Designing Labels with the End-User in Mind. ISMP Canada Safety Bulletin 2002; 2 (9).

<sup>10</sup> Institute for Safe Medication Practices: Principles of designing a medication label for injectable syringes for patient specific, inpatient use. Available at:

<http://www.ismp.org/Tools/guidelines/labelFormats/injectionSyringe.asp>. Accessed: March 27, 2007.

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
5	The infusion pump did not have programming safeguards <sup>11</sup> and did not provide feedback to the operator (e.g., duration of infusion), which decreased the likelihood that the incorrect rate would be detected.					
		5A	In the absence of “smart pump” technology for ambulatory infusion pumps, use pumps with safeguards such as controlled-rate delivery (e.g., elastomeric pumps or preset maximum rates for mL/h pumps, where this functionality is available).	Control	Intermediate	Nursing and pharmacy leadership and Medical Physics Department

<sup>11</sup> Pump safeguards can include pre-programmed dose ranges with ability to prevent programming doses outside the range, or pre-programmed rates that prevent programming a rate outside the range.



Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		5B	Ask that international standards be developed for infusion pump terminology and functionality.	Control	Long term	ISMP Canada, Canadian Patient Safety Institute, Canadian Standards Association (CSA), International Organization for Standardization (ISO), World Health Organization (WHO), AdvaMed <sup>12</sup>
		5C	Ask the manufacturers of ambulatory infusion pumps to consider designing and manufacturing pumps with added safeguards (e.g., built-in software libraries) for ambulatory infusion of chemotherapy drugs.	Eliminate	Long term	ISMP Canada Canadian Patient Safety Institute, AdvaMed

<sup>12</sup> AdvaMed is an international device industry representative group: [www.advamed.org](http://www.advamed.org).

Causal Statement Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
	5D	Ask the manufacturers of ambulatory infusion pumps to enhance the ambulatory infusion pumps to include calculation and display of infusion duration based on programmed values.	Control	Long term	ISMP Canada Canadian Patient Safety Institute, AdvaMed
6	<b>The lack of a process to ensure truly independent double checks<sup>13</sup>, with documentation of independent mathematical calculations, decreased the likelihood that the miscalculation would be detected.</b>				
	6A	Incorporate checklists and calculations into medication order forms and medication administration records to embed check procedures where required.	Control	Intermediate	Pharmacy and Therapeutics Committee, pharmacy and nursing leadership

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<sup>13</sup> An independent double check is a process in which a second practitioner conducts a verification. Such verification can be performed in the presence or absence of the first practitioner. In either case, the most critical aspect is to maximize the independence of the double check by ensuring that the first practitioner does not communicate what he or she *expects* the second practitioner to see, which would create bias and reduce the visibility of an error. Institute for Safe Medication Practices Canada January 2005. Adapted with permission from: Institute for Safe Medication Practices (US). The virtues of independent double checks – they really are worth your time! ISMP Safety Alert. 2003 March 6;8(5).

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		6B	Design a structured process for conducting and documenting independent double checks and incorporate training related to this process into the staff orientation and recertification program.	Control	Immediate	Pharmacy and Therapeutics Committee, nursing leadership, Education Department
7	<b>Existing structure for checking responsibilities in nursing practice are not standardized and do not embed checking functions into nursing work routines, which increases the possibility of an incomplete check.</b>					
		7A	Consider a pilot project to evaluate the feasibility of pre-assigning responsibility for checking functions as part of standard work routines (e.g. for teams of 2 or 3 nurses).	Control	Intermediate	Nursing leadership
		7B	Ask researchers in nursing practice to conduct and publish studies on implementation of independent double checks into nursing practice routines.	Control	Long term	Nursing practice researchers, Canadian Institutes of Health Research, National Cancer Institute of Canada

Causal Statement Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
8	<b>Lack of use of mental approximation to validate calculations decreased the likelihood that the miscalculation would be detected before the infusion pump was programmed.</b>				
	8A	Include mental estimation as part of training and orientation about check processes.	Control	Immediate	Nursing and pharmacy leadership, Education Department
9	<b>Provision of patient teaching information, including pump functionality, without a review of pump data input resulted in a missed opportunity for the practitioner to detect and correct the incorrect pump data input (incorrect rate).</b>				
	9A	Include review of pump data input screens as part of the pump teaching process for patients so as to provide a final opportunity for practitioners to review data input and possibly detect incorrect programming.	Control	Immediate	Nursing leadership, Education Department
	9B	Ask the manufacturers of ambulatory infusion pumps to provide an information display screen on such pumps that summarizes critical information.	Control	Long term	ISMP Canada, Canadian Patient Safety Institute

Causal Statement Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
10	<b>Human factors design flaws in the infusion pump (e.g., inconsistent terminology, difficult-to-find menu choices) increased the complexity of programming the pump and the associated cognitive load, which in turn reduced the likelihood that incorrect pump data input would be detected.</b>				
	10A	Review the confusing aspects of the pump programming sequence for the infusion pump with all hospital staff who use the pump and during training of new staff (e.g., must scroll to find “continuous” option, “mL “ means “mL/h”, “container size” means volume to be infused).	Control	Immediate	Nursing leadership, Education Department
	10B	For the purchase of new infusion pumps, prospectively identify design and workflow issues by: <ul style="list-style-type: none"> <li>• Using a multi-site, interdisciplinary team to select infusion pumps</li> <li>• Applying human factors engineering principles</li> <li>• Conducting usability testing with 4-6 end users</li> </ul>	Control	Long term	Nursing and pharmacy leadership, Medical Physics Department
11	<b>The variation in clinical practice during preparation and administration of chemotherapy medication, including the use of different infusion pumps at the two tertiary cancer treatment centres of the provincial cancer board, makes it difficult to build detailed common medication order sets for the shared computerized prescriber order entry and pharmacy information systems, which limits the ability to include specific details (e.g., total volume and rate) in the electronic medication order.</b>				
	11A	Standardize preparation and administration processes for chemotherapy to ensure the consistency needed to build detailed common medication order sets for the shared computerized prescriber order entry and pharmacy information systems.	Control	Intermediate	Pharmacy and Therapeutics Committee

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		11B	Develop standardized order sets for the computerized prescriber order entry and pharmacy information systems that reflect the administration information needed by nurses.	Control	Intermediate	Pharmacy and Therapeutics Committee
12	<b>Limited integration and standardization between the sites prevents optimization of the shared computerized prescriber order entry and pharmacy information systems.</b>					
		12A	Take advantage of the significant opportunities for enhanced standardization between sites that use common information systems. For example, standardize options among chemotherapy protocol orders to permit inclusion of additional details in the medication order and allow the creation of pre-defined order sets for each chemotherapy protocol in the pharmacy information system.	Control	Intermediate	Pharmacy and Therapeutics Committee, Population Health and Information
		12B	Enhance the information system to provide a direct interface between the computerized prescriber order entry and the pharmacy information systems.	Control	Long term	Pharmacy and Therapeutics Committee
13	<b>Information about previous events with high-dose fluorouracil protocols is difficult to find or not available, increasing the likelihood that opportunities for prospective implementation of system safeguards went unrecognized.</b>					
		13A	Disseminate widely the de-identified findings of the current root cause analysis (e.g. through a high-impact, peer-reviewed oncology journal).	Control	Intermediate	Medical staff and senior leadership

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		13B	Ask the editors of high-impact oncology journals, such as the <i>Journal of Clinical Oncology</i> , to invite submissions of case reports of similar incidents to create a body of knowledge related to fluorouracil overdose.	Accept	Intermediate	ISMP Canada, medical staff and senior leadership
		13C	Ask the World Health Organization to develop a world-wide taxonomy and minimum data set and provide a transparent database to allow the various existing reporting programs to submit data, collected at the local level, for shared international learning.	Accept	Immediate	ISMP Canada, Canadian Patient Safety Institute
14	<b>Limited knowledge about the culture of “high-reliability organizations” and the application of human factors engineering design principles to enhance the safety of health care environments decreased the likelihood that hazards present in the processes related to ambulatory administration of fluorouracil infusions would be recognized.</b>					
		14A	Improve awareness of the attributes of high-reliability organizations through ongoing education efforts and implementation of high-visibility- safety-promotion activities.	Control	Intermediate	Senior leadership
		14B	Develop a Medication Safety Self-Assessment® program specific to systemic therapy to assist oncology practitioners in identifying areas of risk particular to this specialized field.	Control	Long term	ISMP Canada in collaboration with oncology practitioners

Causal Statement Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
15	The treatment protocol design for nasopharyngeal carcinoma which calls for 4 days of high-dose fluorouracil therapy prepared and administered in one infusion bag, combined with a single high dose of cisplatin, increased the likelihood that programming the infusion pump with incorrect rate information would result in the patient's death.					
		15A	Research delivery options for administration of cisplatin and fluorouracil within the chemotherapy protocols for head and neck cancer, considering the potential for harm in the event of an infusion pump-related medication incident.	Control	Intermediate	Canadian Institutes of Health Research, National Cancer Institute of Canada, oncology researchers



Causal Statement Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
16	The absence of a pharmacologic antidote or defined treatment protocol for fluorouracil overdose increased the possibility that a significant overdose of fluorouracil would result in the patient's death.				
	16A	Establish the development of treatment protocols for cases of inadvertent overdose of anti-neoplastic drugs as a patient safety research priority.	Control	Long term	Canadian Institutes of Health Research, National Cancer Institute of Canada, Poison Information Centres, oncology researchers
	16B	In the absence of a defined treatment protocol for fluorouracil overdose, recommend that poison information centres and health service organizations include provision of aggressive supportive care (e.g., intravenous hydration and forced diuresis, timely administration of growth factors and prophylactic antibiotics) in the immediate treatment regimens for such overdoses.	Control	Immediate	Poison Information Centres, Oncology Treatment Centres

## Important Associated Findings and Recommended Actions

Associated findings are factors associated with the care of the patient that form the basis for additional recommended actions but for which a definite causal link with the defined event could not be established.

Associated Finding Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
17	<p><b>The absence of a system to triage medication incidents and thereby to assess the need for intervention decreased the likelihood of a coordinated team approach to patient care in response to an incident.</b></p>				
	17A	<p>Develop a triage process for incident review to ensure timely medical review of incidents with a high potential to cause patient harm, regardless of severity rating on the incident report. The triage process needs to include guidelines on the type and degree of variance that should trigger notification of oncologists and pharmacists.</p>	Control	Immediate	<p>Patient Safety Officer, senior leadership, Facility Advisory Committees</p>

Associated Finding Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
		17B	Create a rapid response team that can be quickly convened to provide assistance in managing medication incidents with potential for serious harm.	Control	Immediate	Patient Safety Officer, senior leadership, Facility Advisory Committees
		17C	Develop consensus guidelines on what constitutes an “overdose” or “infusional variance”. For example, an overdose might be defined as a dose that is 10% greater than the correctly calculated dose and an “infusional variance” might be defined as an infusion administered over an interval that is 25% different from the intended time.	Control	Long Term	Canadian Institutes for Health Research, National Cancer Institute of Canada Poison Information Centres and oncology-related research

Associated Finding Number	Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
18	Relevant learning from previous events with high-dose fluorouracil protocols is difficult to find or not available, reducing the index of suspicion regarding the potential for a fatal outcome, as well as an inability to learn from “what’s been tried before”.				
	18A	Ask the World Health Organization to develop a world-wide taxonomy and minimum data set and provide a transparent database to allow the various existing reporting programs to submit data, collected at the local level, for shared international learning.	Control	Immediate	ISMP Canada, Canadian Patient Safety Institute
19	A poison information centre was not considered as an additional information resource in the initial management of the fluorouracil overdose.				
	19A	Develop a protocol for dealing with potentially serious medication incidents that includes the need to consider contacting the regional poison information centre.	Control	Immediate	Pharmacy and Therapeutics Committee, Facility Advisory Committees

Associated Finding Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
20	The expected course and plan of care were not documented in the patient's health record, which reduced the likelihood that the life-threatening nature of the incident would be clearly communicated to all team members, which in turn led to variable perceptions of the level of clinical monitoring and intervention needed.					
		20A	<p>In the setting of a high-risk drug overdose, a detailed consultative note from a medical oncologist (or the prescribing physician if the overdose involves a non-chemotherapy drug) should be added to the patient's health record and also should be communicated through direct contact with front-line medical and nursing personnel who are involved in the patient's care. The consultation should outline:</p> <ul style="list-style-type: none"> <li>• the patient's underlying medical problem;</li> <li>• the intended treatment and the treatment actually administered;</li> <li>• the potential immediate and short-term toxic effects (including those that are common and mild as well as those that are serious and rare);</li> <li>• the specific monitoring and therapeutic measures required, including schedules for monitoring and;</li> <li>• when appropriate, drugs and doses.</li> </ul>	Control	Immediate	Medical staff, senior leadership, Facility Advisory Committees

Associated Finding Number		Action Number	Recommended Action(s)	Type of Action (Eliminate, Control, Accept)	Time Frame	Responsibility
21	<b>Continuity of medical care between the tertiary cancer treatment centre and the tertiary <i>acute care</i> facility is not optimally supported by communication and information systems.</b>					
		21A	Enhance the communication and information systems for transitions of care between the tertiary cancer treatment centre and the tertiary <i>acute care</i> facility.	Control	Long term	Senior leadership tertiary cancer treatment centre and tertiary acute care facility

## Appendix 1: Reports of Similar Incidents with Fluorouracil

A search was conducted for information about similar incidents. Sources of information included national and international medication and device incident reporting programs, as well as case reports in the medical literature and internet. 231 incident reports involving fluorouracil and/or ambulatory infusion pumps were reviewed. Incidents similar to the one under analysis are summarized below.

Patient Outcome	Event Date	Pump	Device Problem	Description	Information Source
Death	2/2/00	I-Flow Corp. Home-pump Eclipse infusion pump	Overdelivery	The patient received 4400 mg of fluorouracil over 2 hours instead of 4 days (175 mL/h used instead of 2 mL/h) due to fluorouracil placement in wrong infusion pump for outpatient use	FDA MAUDE, US medication error reporting program
Death	10/6/00	Smith medical MD CADD-Legacy Plus ambulatory infusion pump	Overdelivery due to misprogramming	The patient was to receive 10,000 mg of fluorouracil over 120 hours (or a 5-day period). The pump was incorrectly programmed at 83.3 mL/h instead of 83.3 mg/h and the infusion completed in less than 3 hours.	US medication error reporting program
Death	10/27/00	Baxter Healthcare Corp. Sabrateck Homerun ambulatory infusion pump	Overdelivery	The patient received 10,400 mg of fluorouracil within 2 hours instead of the expected 5 days. The patient became florid, septic and expired.	FDA MAUDE
Death	11/18/03 (report date)	Deltec CADD Legacy Plus ambulatory infusion pump	Wrong pump	The patient received 6000 mg of fluorouracil over 4 hours instead of 4 days because CADD-Legacy Plus pump was used instead of CADD-Legacy 1 pump.	FDA MAUDE
Death	2005	Eclipse	Overdelivery	The patient was to receive unspecified dose of fluorouracil over 48 hours but it was completed in 45 minutes	Google
No adverse event	8/2/05	Smith medical MD CADD-Legacy Plus ambulatory infusion pump	Overdelivery	The patient was to be given 1750 mg/day infusion of fluorouracil over 96 hours. But the infusion completed within a day because the pump was programmed at 48 mL/h instead of 2 mL/h. [i.e. fluorouracil administered over 4 hours instead of 96 hours. Note: Patient received	FDA MAUDE

<b>Patient Outcome</b>	<b>Event Date</b>	<b>Pump</b>	<b>Device Problem</b>	<b>Description</b>	<b>Information Source</b>
				1/3 cisplatin dose only.]	
Death	1/4/06	Smith Medical MD CADD-Legacy Plus ambulatory infusion pump	Wrong pump	Legacy Plus pump was used instead of Legacy 1 pump and the patient received the total dose of Fluorouracil in one hour.	FDA MAUDE
Death	Unknown	Unknown	Overdelivery	The patient received a 4-fold overdose of Fluorouracil and died 11 days later.	FDA MAUDE



## Appendix 2: Usability Test Report on AIM Plus and Chemotherapy IV Bag Label

**Location:** An Ontario oncology clinic

**Date and Time:** November 2, 2006; 1300-1500h

### Participant Background (6 participants, 5 full scenarios)

- 1) RN (registered nurse), APN (advanced practice nurse), CPL (clinical practice leader) Chemotherapy Unit
- 2) RN, MN, Clinical Educator
- 3) RN, APN/CPL, General Treatment Services
- 4) RN, APN, inpatient medical/radiation oncology
- 5) RN, home chemotherapy infusion program
- 6) RN, BScN, Nurse in home infusion program
  - RN #4 did first half of scenario and was interrupted, RN #6 did second half

### Items (Props) and Setting

- Participant seated at a countertop (chair level) in an office within the clinic
- AIM Plus Infusion Pump (battery powered)
- IV mini-bag with tubing and AIM Plus-specific cassette (already primed) and labelled with home infusion fluorouracil (de-identified)
- Portable calculator and pad of paper with pen

### Scenario

- Nurse is briefed on rationale for their participation in trying to use the pump and that they have not used this type of pump before, but have used a similar pump for chemotherapy (1 min)
- Nurse is told the following set-up (3 min)
  - The nurse has already brought the patient into the home infusion clinic chair
  - The chart has been reviewed and the proper lab values confirmed and the medication information on the bag label confirmed
  - The nurse comes back to their work area to program and assemble the pump
  - No paper guides are available for the infusion pump
  - The test director provides virtual help in a stepped fashion from general to specific
- Usability test mostly guided by IV bag label (10 min)
- Debrief (2-3 min)

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### Key Resources

Dumas JS, Redish JC. *A Practical Guide to Usability Testing*. London, UK: Intellect, 1999.

Etchells E, Bailey C, Biason R, et al. Human factors in action: Getting pumped at a nursing usability laboratory. *Healthc Q*. 2006 Oct;9 Spec No:69-74.

Gosbee J. Comparative Usability Test of Four Single Channel Infusion Pumps. *VA Technical Report*. Washington DC: Department of Veterans Affairs. 2002.

Graham MJ, Kubose TK, Jordan D, Zhang J, Johnson TR, Patel VL. Heuristic evaluation of infusion pumps: implications for patient safety in intensive care units. *Int J Med Inform*. 2004;73:771-779.

## **Observed scenario at tertiary cancer treatment centre (as an overview of what was replicated)**

An observation was made of the steps taken by one Day Care nurse to replace a fluorouracil IV bag for a patient in week 5 of 6 of his regimen. The observer also asked questions of the nurse and a few questions of the patient (during times when it would not be interrupting key actions).

Once the patient was checked in, the nurse assembled four items together on the top of her workspace counter (approximately from left to right):

- 1) AIM Plus pump
- 2) Labelled IV bag with attached tubing
- 3) Hand-held sized calculator
- 4) Paper chart (including the blue MAR sheet for documentation of administration).

The nurse prepared the IV pump-specific tubing by cutting off the downstream plastic clamp (so it does not dig into patient); and adding another piece of tape onto the air-fluid filter to the small piece of tape placed by pharmacy. The tape has been used in the clinic for the AIM pump tubing since one or more IV tubing sets have leaked at this tubing-filter connection.

The IV bag label was checked against the order in the chart at an earlier preparation step. For the following steps the nurse oriented the bag to read the multi-line label and used the calculator to check total dose, daily dose, and hourly dose calculations for internal consistency. The nurse did not use a piece of paper to write it out; the algebra was done in her head and the math on the calculator. The nurse did not make any checkmarks on the label or an order sheet.

The nurse held the pump at an angle towards her to better see the screen and quickly went through several screens on the pump in order to:

- 1) Start a new program
- 2) Choose "continuous" category (#5) on the second of two screens of options
- 3) Choose "mL" from three choices including "mg/mL" and "µg/mL" (note it does not read "mL/h" on this screen;
- 4) Enter the rate in mL/h on the next screen by looking at the mL/h rate on the label (she did not reorient 90 degrees to look at the new green label that also has the rate)
- 5) Enter total volume in next screen and then finish some other screens, "save" the program, and then review the settings. Code then entered to "lock" out the programming keys/functions.

Once the above steps were complete, the nurse signed the blue chemo MAR type sheet next to the fluorouracil listing.

Another nurse 20 feet away was then asked to do a chemo check. The second nurse held the pump in her hand, and selected the option to review the saved program. This nurse checked the rate and volume to infuse against the white (old) label, and also did not seem to use or read the new green label. This second nurse also signed the blue MAR sheet.

The first nurse then took the pump, tubing, IV bag, and belt pack (for patient to carry the pump and bag) to the table next to the seated patient. She reviewed the name of the medication and duration of flow (7 days) from the IV bag label, and the flow rate on the IV pump with the patient.

Figure 1. Label for Fluorouracil infusion.

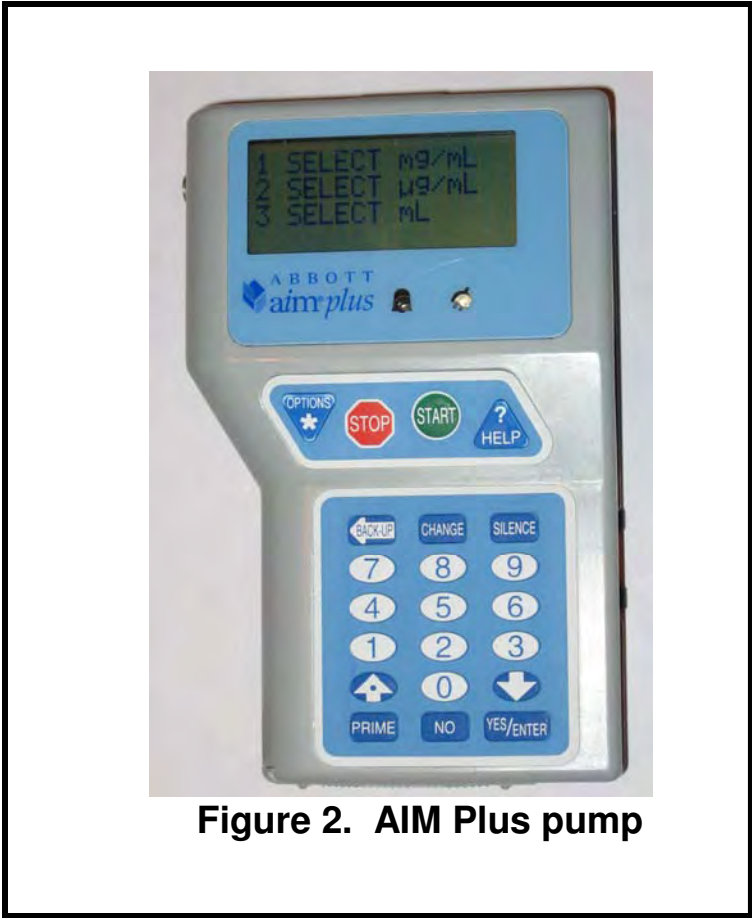


Figure 2. AIM Plus pump

# Usability Test Observations

Participant	Observations
1	<p><b>OVERALL: Some delay finding a few buttons, but no incorrect data input</b></p> <ul style="list-style-type: none"> <li>- Reviews IV bag label and does calculations on paper and calculator to see if day, 4 day and rate are consistent with each other</li> <li>- With some delay, figures out how to put cassette and tubing and snap them in place on the pump (2-3 fumbling around with the snap button on side)</li> <li>- Presses “start” button to power on, 30 sec to look at all five sides; eventually sees slide button on side</li> <li>- Comments that the system is doing self test</li> <li>- Goes through early menus looking at screen intently; holding pump at 30 degree angle in order to best see screen</li> <li>- Assumes “mL” option under “continuous” option is “mL/h” and chooses this option (#5)</li> <li>- Looks at IV bag quickly to identify rate to enter (1.2 mL/h near the 24 h rate)</li> <li>- Wonders aloud how to review settings, then finds option and reviews easily</li> <li>- Shows “patient” how to tell if pump is working and that fluid level should go down</li> <li>- Initially finds pump confusing but less so as she works with it – comments that pump was straight-forward to use</li> </ul>
2	<p><b>OVERALL: Nearly had incorrect data input with mg/h vs mL/h confusion</b></p> <ul style="list-style-type: none"> <li>- Reviews IV bag label and does calculations on paper and calculator to see if day, 4 day and rate are consistent with each other</li> <li>- Quickly puts cassette and tubing and snaps them in place on the pump</li> <li>- Presses “start” button to power on, but quickly sees and uses slide button on side</li> <li>- Goes through early menus, holding pump at 30 degree angle in order to best see screen</li> <li>- Does not “see” that “mL” option under “continuous” option is “mL/h”, so chooses “mg/mL” option to input values from bag. From this point gets different screens than “mL/h”, but it is possible to enter the bag label values this way too</li> <li>- Enters 45.5 for mg/mL, but looks and does not see for 20 seconds the up arrow button is also the decimal button</li> <li>- Wonders aloud about mg/h entry, then types in 28.8, but quickly says “oops” and changes to 54.6 mg/h (milligrams per hour)</li> <li>- Wonders what to put in for “container size” question; then sees total volume on the bag label and assumes the IV pump is asking for this value</li> <li>- No other issues with remainder of scenario</li> <li>- During debrief, participant comments on               <ul style="list-style-type: none"> <li>• Label is okay and good buttons on IV pump</li> <li>• 28.8/24 h is what I first saw for rate, so I wrongly put that in for mg/h</li> <li>• Is used to entering mg/h as rate</li> <li>• Not easy to see that some screens require the scroll down button to see options</li> <li>• Arrow button serving also as decimal button is confusing</li> </ul> </li> </ul>
3	<p><b>OVERALL: Had incorrect data input with mg/h vs mL/h confusion</b></p> <ul style="list-style-type: none"> <li>- Puts cassette and tubing and snaps them in place on the pump first</li> </ul>

Participant	Observations
	<ul style="list-style-type: none"> <li>- Reviews IV bag label and does calculations on paper and calculator to see if day, 4 day and rate are consistent with each other</li> <li>- Presses “start” button to power on, but needs several hints to see and use power button</li> <li>- Goes through early menus, holding pump at 30 degree angle in order to best see screen</li> <li>- First she enters the “continuous” (#5) option, but states she wants to enter mg per hour like she usually does for infusions.</li> <li>- With hints, she hits back button to get programming options again and chooses “mg/mL”</li> <li>- Tried to put in 1.2 mL/h (not mg/h), but data was not accepted and display showed message that the value needed to be a minimum of 5 mg/h.</li> <li>- When prompted for “container size”, it took awhile to know this query meant total volume</li> <li>- No other issues with remainder of scenario</li> <li>- During debrief, participant commented on: <ul style="list-style-type: none"> <li>- Always does mg/h for pumps like this when using them for pain control</li> <li>- Does not like that button for up arrow is also decimal point</li> <li>- On/off switch hard to find</li> <li>- mL vs mg/mL choice was confusing, should display choice as “mL/h” not “mL”</li> <li>- Bag label items should follow sequence and use terminology of the pump</li> </ul> </li> </ul>
4 (2-part.)	<p><b>OVERALL: Confusion with power &amp; arrow-decimal buttons</b></p> <p>PART ONE (participant #4)</p> <ul style="list-style-type: none"> <li>- Looks at label and uses calculator to confirm total volume, dose, rates</li> <li>- Much mumbling and redo of calculator entries when wrong data entered</li> <li>- Finally says, “this label is almost like it has too much information on it”</li> <li>- Tries to put cassette in and cannot use the side button to open or snap in place with multiple hints, and finally it had to be put into place by the test director</li> </ul> <p><i>[the participant was then called away and had to stop]</i></p> <p>PART TWO (participant #6)</p> <ul style="list-style-type: none"> <li>- Presses “start” button to power on, but needs three hints to see and use power button</li> <li>- Scrolls fast to “continuous” option #5 and chooses it</li> <li>- Very quick to choose “mL” option</li> <li>- Tried three times with no luck to enter 1.2, since she expected to enter in from right to left and did not know the up arrow was the decimal button she needed to push</li> <li>- Quickly went through the remaining screens and questions and reviews with no problem</li> <li>- Debrief: Nothing to add</li> </ul>

Participant	Observations
5	<p><b>OVERALL: Incorrect data input: 28.8 mL entered as rate and this went undetected throughout session</b></p> <ul style="list-style-type: none"> <li>- Presses “start” button to power on, then looks for 15 or seconds to find power button</li> <li>- Puts cassette and tubing and snaps them in place on the pump with some difficulty (30s)</li> <li>- Is confused when the self-test takes 20 seconds and wonders why it took so long</li> <li>- Scrolls down and enters the “continuous” (#5) option</li> <li>- Trying to see how to enter a decimal button</li> <li>- Enters 28.8 for rate (not 1.2)</li> <li>- When prompted for “container size”, took 60 sec to figure out this query means total volume</li> <li>- Rate double checked during review and stated aloud it was “28.8 mg/h”, and it corresponded to the IV bag label</li> <li>- Upon discussion, she said that usual process was mg/h for pumps she used, so this needed mL/h and she was shown #5 continuous option with “mL” as mL/h option</li> <li>- <b>Puts in 28.8 mL/h as the rate entry, while saying aloud 28.8 mL per hour</b></li> <li>- Assistant played role of double check nurse and asked her to confirm that the rate should be 28.8 mL/h, and again the participant stated it was the correct rate</li> <li>- Assessor asked another way for her to state the total volume was 130 mL or so, and that 28.8 mL/h made sense for four days of infusion – she said yes</li> <li>- During debrief, participant was shaken to recognize the actual rate was 1.2 mL/h <ul style="list-style-type: none"> <li>- Uses CADD that is always programmed in mg/h</li> <li>- “It’s all “jumbled” on the label”</li> <li>- everything she looked for, she had to look twice</li> </ul> </li> </ul>

## Summary of Findings:

- 1) **THREE of five participants entered incorrect data when programming the AIM Plus pump. One participant programmed the pump to deliver 28.8 mL/h and did not detect the incorrect rate throughout the session.\***
  - \* One participant thought the mL/h rate on the bag was mg/h and tried to enter that
  - \* One typed in **28.8** for mg/h, but quickly noted error and changed entry to **54.6** mg/h
- 2) All five participants were confused with one or more aspects of powering on, setting up, and selection of “mL/h” choice for programming the pump
  - 5/5 pushed “Start” button to power on, then 3/5 needed hints to find slide switch power button
  - 3/5 needed several seconds and hints to put tubing/cassette in place
  - 3/5 did not see or choose the “mL” option, and instead chose mg/h (with its many data inputs)
- 3) There are (at least) two other confusing features that were incidentally found in these five tests
  - 3/5 were partially to completely confused that the “arrow” button was also the decimal point button
  - 3/5 were partially confused that pump prompt “container size” was the same thing as “total volume”
- 4) One of five participants noted that other IV bag labels in her job are laid out (organized) in the same sequence and terminology as the pumps used (e.g., PCA). It was disconcerting that this label was not.
- 5) Two of the five participants used almost all of the pump functions and label with little or no problem or delay.
- 6) Four of five participants commented (qualitatively) on one or more design aspects of the pump or the IV bag label
- 7) Two of the participants who had some confusion with programming had no negative comments (qualitatively) about the design.
  - This lack of insight into design issues is very common given that the healthcare world is filled with these issues and healthcare personnel are rewarded for working around them with little complaint.

## Appendix 3: Chronological Timeline of Fluorouracil Incident

Date/Time	Item	Comment/Source
<b>May 10 – June 22, 2006</b>	Radiotherapy with concurrent chemotherapy for nasopharyngeal cancer.	Patient chart
<b>Friday, July 28</b>	Patient seen at Head and Neck clinic and chemo orders signed for July 31.	Patient chart
	Medication orders, labs, height and weight reviewed by clinic nurse. Lab results: WBC 4.8, platelets 363.	Interviews and observation during site visit
	Medication orders reviewed against medication profile, dose calculations completed by “bay” pharmacist.	Interviews and observation during site visit
	Chemo orders entered into pharmacy information system by pharmacy technician.	Interviews
	Pharmacy prepared cisplatin and fluorouracil solutions.	Interviews
<b>Monday, July 31</b> 0945h	Pt presented to Medical Day Care clinic.	Facility timeline
	Nurse #1 (RN #1) assigned to care for patient.	Interviews
1000 - 1225h	Pre-hydration and pre-medications given.	Patient chart
1225h	Cisplatin administered.	Patient chart
1340h	Post-hydration given.	Patient chart
approx 1430h	RN #1 retrieved fluorouracil and prepared programmed infusion pump on work bench using computer calculator. Performed calculation (5250 mg (total mg) divided by 4 days = 1312 mg divided by 45.57 mg/mL (concentration) = 28.8). Calculated value matched number on label. First time administering 4-day fluorouracil infusion. Concurrent workload: 4 patients to disconnect; 1 other patient to care for.	Interviews
	RN #1 requested “chemo check”.	Interviews
	RN #2 came to do chemo check on the way to another task. Could not find a calculator – did calculation mentally and on paper. Confirmed programming and locked pump.	Interviews
	Blue handwritten MAR signed off by RN #1 and RN #2.	Interviews
1500h	Fluorouracil solution initiated.	Patient chart
	Dose signed off in computer by RN # 1.	Interviews
	Patient left clinic with fluorouracil infusing and returned to XXXX House with friend.	Patient chart
1830-1900	Patient noticed pump beeped and fluorouracil infusion bag appeared to be empty.	Patient chart
1930	XXXX House volunteer drove patient and friend back to tertiary cancer treatment centre. Patient did not call prior to returning to facility.	Patient chart XXXX House interview
Tertiary cancer treatment centre evening shift	Patient seen by evening nursing supervisor who disconnected the infusion pump and flushed the line. Nursing supervisor called physician on call who advised that there was no antidote and “nothing could be done” – patient should take anti-emetics and call the clinic in the morning. Patient aware that the drug was supposed to last	Patient chart Interviews

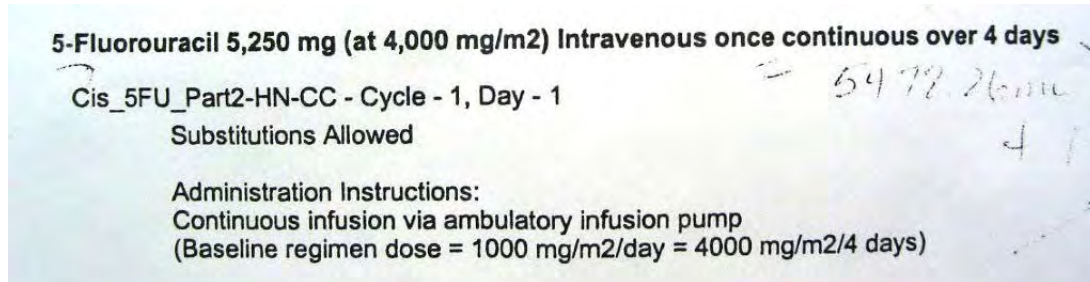


Date/Time	Item	Comment/Source
	for 4 days. Nursing supervisor counselled the patient, explaining that she had received a large amount of drug over a short time and could become very ill, emphasized the need to keep hydrated and prevent vomiting and checked to make sure patient had antiemetics at home.	
evening shift	Nursing supervisor completed paper incident report and placed it with the pump in the Day Care Clinic for follow up by the unit manager.	Interviews
approx midnight	Nursing supervisor called unit manager at home to advise of incident.	Interviews
<b>Tuesday, August 1</b> morning	Unit manager and RN #1 verified incorrect pump programming	Interviews
0900 h	Unit manager called patient and informed her that pump programming error had occurred. Advised that there could be some serious side effects and asked patient to come in. Patient was feeling well and preferred not to come to hospital. RN #1 wanted to call and apologize to patient – patient said “Tell [ ] not to worry about it.”	Incident report Interviews
	Unit manager saw attending physician in clinic. Asked if physician had heard about incident – had not yet been informed. Unit manager and physician looked at pump and reviewed programming. Unit manager explained that patient had been contacted and so far was feeling well and preferred not to come to hospital. Patient’s phone number was provided to physician who indicated intent to call patient. Unit manager called patient back to remind her to call if any sign of mouth sores.	Interviews
	Physician started literature search to determine what could be done. Checked re potential for hemodialysis, looked for predictors of what could happen.	Interviews
<b>Wednesday, August 2</b>	Physician spoke with XXXX medical oncologist/pharmacologist with special interest in fluorouracil, who confirmed literature review finding that dialysis would not be beneficial. Discussed investigational agents that might be helpful – difficult to obtain through Special Access Program and of questionable value.	Interviews
	Physician spoke with patient and asked her to come in on Thursday – still feeling well, but agreed to come in the following day. Physician wanted to “see” pt – if any concern, would immediately admit.	Interviews
<b>Thursday, August 3</b>	Physician saw patient in clinic – nausea and vomiting and some discomfort in throat. Planned admission for following day (no bed available today). Lab results: WBC 10.6, platelets 388.	Interviews
<b>Friday, August 4</b> 1430-1750h	Patient seen in ambulatory care clinic - given hydration, ondansetron, dexamethasone, metoclopramide IV. Lab results: WBC 9.4, platelets 259.	Nursing notes Patient chart
After 1800h (Long weekend)	Patient admitted to inpatient medical oncology unit.	Patient chart
<b>Friday, August 4 – Friday, August 11</b>	Inpatient monitoring and supportive treatment with IV fluids, antiemetics, antidiarrheals, specially compounded mouthwash, dexamethasone and morphine. Patient was	Patient chart

Date/Time	Item	Comment/Source
	afebrile for the duration of her admission on the inpatient oncology unit.	
<b>Friday, August 4 – Monday, August 7</b>	Patient experienced similar pain levels in her mouth, nausea with occasional emesis, and diarrhea approximately twice daily.	Patient chart
<b>Saturday, August 5</b>	Covering physician contacted the patient’s husband and advised of the pump programming error.	Facility timeline
<b>Sunday, August 6</b>	Lab results: WBC 6.2, platelets 204.	Patient chart
<b>Tuesday, August 8</b>	Increased frequency of diarrhea (5 loose bowel movements); no complaints of nausea noted.	Patient chart
<b>Wednesday, August 9</b> Evening	4 episodes of severe diarrhea; vomited twice. Lab results: WBC 0.2, platelets 83.	Patient chart
<b>Thursday, August 10</b> 0447h	Patient seen by resident on call – tachycardic (pulse ~ 140), bright green emesis with occasional bright red blood. Resident considered possibility of small bowel obstruction or cholecystitis. Stat ECG appeared normal. X-ray and bloodwork ordered to be completed urgently in the morning. X-ray indicated “striking paucity of bowel gas within abdomen ....such that the bowel is presumably fluid filled, although it could be either dilated or collapsed”. Lab results: WBC 0.1, platelets 83	Patient chart
Day shift	2 additional episodes of vomiting dark green bile; no diarrhea.	Patient chart
<b>Thursday, August 10 – Friday, August 11</b> overnight	Patient complained of bilateral numbness in hands and feet. Found to be hypotensive (BP 83/61) and tachycardic (pulse 130). Saline boluses were ordered but were not effective.	Patient chart Interviews
<b>Friday, August 11</b> 0635	BP 83/61 Lab results: WBC 0.2, platelets 13.	Patient chart
0745	Decision to transfer to intensive care unit at tertiary <i>acute care</i> facility.	Patient chart Interviews
<b>Friday, August 11 – Tuesday, August 22</b>	Aggressive treatment in intensive care unit of tertiary <i>acute care</i> facility, including: intubation, IV antibiotics, filgrastim, antifungals, electrolyte replacement. Patient gradually worsened and developed multi-system organ failure.	Patient chart (tertiary acute care facility) Interviews
<b>Friday, August 18</b>	Tertiary cancer treatment centre senior leadership notified of incident and patient condition.	Facility timeline
<b>Tuesday, August 22</b>	Patient removed from life support.	Facility timeline

## Appendix 4: Electronic Fluorouracil Order

### Photograph of a Printed Copy of the Electronic Fluorouracil Order:



## Appendix 5: Mitigation of Harm from Fluorouracil

1. Mitigation of harm considerations specific to fluorouracil:
  - a. Probably useful
    - i. Some sources recommend forced diuresis to improve fluorouracil elimination. While the effectiveness of this approach is not extensively documented, it is safe and prudent to admit such patients on parenteral hydration at a minimum of 2 litres per day.
    - ii. An overdose of a fluorouracil with its potential myelotoxicity should be treated with myeloid growth factor support beginning at 24 hours after the incident or as soon as possible. Growth factor treatment reduces the likelihood of neutropenia and its infectious complications and has also been shown to reduce the risk of mucositis.
  - b. Possibly useful
    - i. Oral glutamine supplements have been shown in a small randomized trial<sup>14</sup> to reduce diarrhea and surrogates of gastrointestinal toxicity in the setting of high dose fluorouracil therapy. In the clinical trial, supplements were initiated prior to drug administration, however, there is no literature on the use of this strategy in a rescue setting. If used, these supplements should be begun promptly.
    - ii. Cardiotoxicity is associated with high dose fluorouracil therapy, particularly when given in combination with cisplatin<sup>15</sup>, with short term electrocardiographic or biochemical evidence of ischemic change in more than 20% of patients. In the setting of fluorouracil overdose, baseline cardiogram and close cardiac monitoring are prudent.
    - iii. A single randomized study<sup>16</sup> of angiotensin converting enzyme therapy in patients who had been treated with high dose fluorouracil demonstrated reduced rates of development of cardiac dysfunction.
    - iv. The literature on dialysis or hemoperfusion to remove fluorouracil is limited and inconclusive. Sauer et al<sup>17</sup> report that the procedure is "possibly effective" in fluorouracil overdose, and Behesti et al<sup>18</sup> report that, when used in a regional perfusion model, up to 85% of drug can be extracted by hemoperfusion over

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<sup>14</sup> Daniele B, Perrone F, Gallo C, Pignata S, De Martino S, De Vivo R, Barletta E, Tambaro R, Abbiati R, D'Agostini L. Oral glutamine in the prevention of fluorouracil induced intestinal toxicity: a double blind, placebo controlled, randomised trial. *Gut* (2001) 48, 28-33.

<sup>15</sup> Gamelin E, Gamelin L, Larra F, Turcant A, Alain P, Maillart P, Allain YM, Minier JF, Dubin J. Acute cardiac toxicity of 5-fluorouracil: pharmacokinetic correlation. *Bull Cancer* (1991) 78, 1147-53.

<sup>16</sup> Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Martinelli G, Veglia F, Fiorentini C, Cipolla CM. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* (2006) 114, 2474-81.

<sup>17</sup> Sauer H, Fuger K, Blumenstein M. Modulation of cytotoxicity of cytostatic drugs by hemodialysis in vitro and in vivo. *Cancer Treatment Reviews* (1990) 17, 293-300.

<sup>18</sup> Behesti MV, Denny DF, Glickman MG, Bodden W, Marsh JC, Strair R, Ravikumar TS. Percutaneous Isolated Liver Perfusion for treatment of Hepatic Malignancy: Preliminary Report. *Journal of Vascular and Interventional Radiology* (1992) 3, 453-458.

charcoal cartridges. However, Keller et al<sup>19</sup> state that hemoperfusion, hemofiltration and hemodialysis "cannot be guaranteed". Charcoal hemoperfusion is an uncommon procedure and would obviously require the involvement of a nephrologist with specialized training. Given the relatively short half-life of fluorouracil (6-20 minutes), this approach would have no usefulness unless initiated within hours after an overdose.

- c. Experimental or ineffective:
  - i. A variety of agents have been reported in pre-clinical models to mitigate fluorouracil toxicity: hyaluronic acid, uridine, probucol, 5-benzyloxybenzyl-barbituric acid acyclonucleoside, 2.3.5-tri-0-acetyluridine, 5-phenylthioacyclouridine, and 5-phenylselenenyl-acyclouridine. Mechanisms to expedite and report the use of such agents in emergent clinical settings should be developed.
  - ii. Allopurinol ice balls have been used to prevent oral mucositis in patients receiving high dose fluorouracil, but two clinical trials<sup>20, 21</sup> have reported that systemic high dose allopurinol had no impact on fluorouracil toxicity.

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<sup>19</sup> Keller F, Gallkowski U, Roth W, Boese-Landgraf J. Combined haemoperfusion, haemofiltration and haemodialysis for systemic detoxification in locoregional 5-fluorouracil therapy. *Cancer Chemotherapy and Pharmacology* (1991) 29, 164-166.

<sup>20</sup> Merimsky O, Inbar M, Chaitchik S. Treatment of advanced colorectal cancer by 5-fluorouracil-leucovorin combination with or without allopurinol: a prospective randomized study. *Anti-Cancer Drugs*. (1991) 2, 447-451.

<sup>21</sup> Ahmann FR, Garewal H, Greenberg BR. Phase II trial of high-dose continuous infusion 5-fluorouracil with allopurinol modulation in colon cancer. *Oncology*. (1986) 43, 83-85.

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## Appendix 7: Glossary of Terms

### **Critical Incident:**

An incident resulting in serious harm (loss of life, limb, or vital organ) to the patient, or the significant risk thereof. Incidents are considered critical when there is an evident need for immediate investigation and response. The investigation is designed to identify contributing factors and the response includes actions to reduce the likelihood of recurrence.

*From Davies J, Hebert P and Hoffman C, Canadian Patient Safety Dictionary (Ottawa: Royal College of Physicians and Surgeons of Canada, 2003).*

### **Dihydropyrimidine Dehydrogenase (DPD) Deficiency**

Dihydropyrimidine Dehydrogenase (DPD) is an enzyme responsible for catabolism of over 85% of an administered dose of fluorouracil. Patients with decreased DPD activity are at increased risk of serious, life-threatening toxicity from fluorouracil; deaths have been reported.

*From: Diasio Robert B. Clinical Implications of Dihydropyrimidine Dehydrogenase on 5-FU Pharmacology. Oncology 2001 Supplement; 15(1): 21-27.*

### **Fluorouracil**

Fluorouracil is a fluorinated pyrimidine antimetabolite, and is used as an antineoplastic agent for the treatment of solid tumours, including breast, colorectal, gastric, and head and neck cancers. The major manifestations of toxicity are hematological, neurocutaneous (hand-foot syndrome), mucosal and digestive tract adverse effects, which are more often encountered with dose-intensified strategies, but are also seen with moderate doses.

*From: Ploylearmsaeng, Su-arpa; Fuhr, Uwe; Jetter, Alexander How may Anticancer Chemotherapy with Fluorouracil be Individualised? Clinical Pharmacokinetics. 45(6):567-592, 2006.*

### **Harm:**

Harm is defined as a temporary or permanent impairment in body functions or structures. Includes mental, physical, sensory functions and pain.

*From: Definitions of Terms. Toronto (ON): Institute for Safe Medication Practices Canada; c2000-2006. Available from: <http://www.ismp-canada.org/definitions.htm>. Developed by the Institute for Safe Medication Practices Canada, the Canadian Institute for Health Information, and Health Canada (collaborating parties for the development and implementation of the Canadian Medication Incident Reporting and Prevention System [CMIRPS]).*

### **Human Factors Engineering**

Application of knowledge about human capabilities and limits to the design of safe, efficient and comfortable systems (e.g., medical devices). This field of study is also known as ergonomics or usability engineering.

*From: Wickens C.D. Lee J., Liu Y.D.: Introduction to Human Factors Engineering (2nd Edition). Newark, NJ: Prentice-Hall, 2003*

### **Independent Double Check**

An independent double check is a process in which a second person conducts a verification. Such verification can be performed in the presence or absence of the first practitioner. In either case, the most critical aspect is to maximize the independence of the double-check by ensuring that the first practitioner does not communicate what he or she expects the second practitioner to see, which would create bias and reduce the visibility of an error.

*From: Independent Double Check Definition, ISMP Canada website, <http://www.ismp-canada.org/definitions.htm>*

### **Medication Incident:**

Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Medication incidents may be related to professional practice, products, procedures, and systems, and include prescribing, order communication, product labelling/ packaging/ nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

*Similar Term: Medication Error*

*From: Definitions of Terms. Toronto (ON): Institute for Safe Medication Practices Canada; c2000-2006. Available from: <http://www.ismp-canada.org/definitions.htm>. Adapted from the National Coordinating Council for Medication Error Reporting and Prevention, What Is Medication Error? Developed by the Institute for Safe Medication Practices Canada, the Canadian Institute for Health Information, and Health Canada (collaborating parties for the development and implementation of the Canadian Medication Incident Reporting and Prevention System [CMIRPS]).*

### **Near Miss or Close Call:**

An event that could have resulted in unwanted consequences, but did not because either by chance or through timely intervention the event did not reach the patient.

*Similar Terms: Near Hit or Good Catch*

*From: Definitions of Terms. Toronto(ON): Institute for Safe Medication Practices Canada; c2000-2006. Available from: <http://www.ismp-canada.org/definitions.htm>. Developed by the Institute for Safe Medication Practices Canada, the Canadian Institute for Health Information, and Health Canada (collaborating parties for the development and implementation of the Canadian Medication Incident Reporting and Prevention System [CMIRPS]).*

### **No Harm Event:**

An incident occurs which reaches the patient, but results in no injury to the patient. Harm is avoided by chance or because of mitigating actions.

*From: Definitions of Terms. Toronto(ON): Institute for Safe Medication Practices Canada; c2000-2006. Available from: <http://www.ismp-canada.org/definitions.htm>. Developed by the Institute for Safe Medication Practices Canada, the Canadian Institute for Health Information, and Health Canada (collaborating parties for the development and implementation of the Canadian Medication Incident Reporting and Prevention System [CMIRPS]).*

### **Root Cause Analysis:**

An analytic tool that can be used to perform a comprehensive, system-based review of critical incidents. It includes the identification of the root and contributory factors, determination of risk

reduction strategies, and development of action plans along with measurement strategies to evaluate the effectiveness of the plans.

*Canadian Patient Safety Institute, Institute for Safe Medication Practices Canada, Saskatchewan Health. Canadian Root Cause Analysis Framework, Canadian Patient Safety Institute, Edmonton: March, 2006.*

**Safety:**

Freedom from accidental injuries.

*From Kohm LT, Corrigan JM, Donaldson MS, eds. To err is human: Building a safer health system. Washington, DC, National Academy Press, 1999.*

**System:**

A set of interdependent elements (people, processes, equipment) that interact to achieve a common aim.

*From World Alliance for Patient Safety. WHO draft guidelines for adverse event reporting and learning systems. Geneva (Switzerland): World Health Organization; 2005*