THE DESIGN AND ANALYSIS OF AN INFORMATICS INFRASTRUCTURE TO SUPPORT CLINICAL DECISION MAKING IN THE MANAGEMENT OF OPIOID PCA INFUSIONS FOR PALLIATIVE PATIENTS

by

Justin D. Clutter

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The thesis of **Justin D. Clutter**

has been approved by the following supervisory committee members:

Katherine A. Sward	, Chair	**7/ 15/ 2015** Date Approved
Guilherme Del Fiol	, Member	**7/ 15/ 2015** Date Approved
John Franklin Hurdle	, Member	Date Approved

and by **Wendy W. Chapman** , Chair/Dean of

the Department/College/School of **Biomedical Informatics**

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

Though medical advances in the last century now allow us to forestall death, many patients suffer from significant symptoms as they battle severe disease. Opioid medications are particularly effective when treating pain in these patients and infusion by the patient controlled analgesia (PCA) paradigm is commonly used in patients with severe disease. While PCA allows rapid titration yet individualized adjustment of opioid dose, it involves complex, high-stakes decisions. Unfortunately, clinicians complain that it is often difficult or impossible to find the data needed to make these decisions. A relevant data display could support clinical decisions by providing real-time up-to-date clinical data at the point of care.

Literature synthesis and multiple modeling techniques were used to quantify the domain. An inductive, qualitative approach, including graphical mapping techniques, was used to build a foundational domain information model which was subsequently validated using a survey of domain experts. A gap analysis was performed, mapping concepts from the information model to the emerging HL7 FHIR standard.

Modeling revealed a complex workflow, highlighted the bottleneck in information flow to providers at the point of care, and supported the premise that a relevant data display would be beneficial. The gap analysis showed that currently existing FHIR resources are capable of representing all relevant concepts from the domain information model needed for decision making in this complex use-case. Potential problems with FHIR implementation were identified and recommendations to address these are presented.

“We must all die. But that I can save him from days of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind than even death himself.”

Dr. Albert Schweitzer

June, 1914

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CHAPTER 1

STUDY OVERVIEW

1.1 Introduction

Despite tremendous medical advances over the last century, many patients with serious, life-threatening illnesses experience significant untreated pain as a consequence of disease or disease treatment. The clinical specialty of Palliative Care emerged to meet this need, focusing on management of complex and difficult symptoms, including severe and intractable pain, in patients with serious and life-limiting illnesses. Over the last 20 years, numerous approaches have been developed to combat pain in these patients. One particular modality shows much promise: Patient Controlled Analgesia (PCA). Originally developed to manage post-operative pain, PCA has been applied to pain management for very sick and terminal patients. A striking advantage of PCA is that it involves patients in their care, allowing them to titrate their pain relief to what *they* feel is an adequate balance of analgesia versus medication side effects. At times the patient may prefer more analgesia despite side effects such as sedation; at other times he or she may choose less analgesia. Thus PCA management is a real-world example of patient-centered medical care.

Because the modality allows rapid titration of opioid dose to the level the *patient* considers comfortable, parenteral opioid infusion administered by a PCA pump has become a commonly utilized modality in palliative settings. Rapid titration of opioid infusions is a complex task, however, and requires an accurate and comprehensive understanding of numerous clinical factors. Complicating this situation, Palliative Medicine specialists often

work as consultants, and it is not unusual for Palliative Medicine providers to manage as many as a half dozen PCAs on any given day with multiple providers involved in the care for each patient over the course of treatment. Therefore, managing and communicating information germane to PCA management is a critical element in the patient's care.

Despite advances in electronic health records, the information needed to titrate and manage opioid infusions can be difficult to locate and aggregate in a meaningful way. There is little or no literature evaluating the adequacy and quality of data, with respect to managing PCAs, available to clinicians at the point of care. Anecdotally, however, clinicians complain that they lack adequate data to make optimal titration decisions.

Automating the aggregation and presentation of relevant information holds the potential to address the problem of missing or difficult- to-locate information. An emerging HL7 standard, Fast Healthcare Interoperability Resources (FHIR, pronounced "Fire"), may be able to facilitate development of such a data aggregation tool. FHIR is intended to provide a granular, modular way to exchange data, with less overhead than traditional HL7 implementations. It is intended to address real clinical needs and is designed for flexible custom workflows, web based APIs, mobile applications (apps), cloud computing, and medical device integration.[1] The potential of FHIR to support such emerging technologies has been widely embraced, but as a newly emerging standard the actual extent to which it will succeed in these endeavors remains to be demonstrated.

1.2 Purpose and Aims

Clinical decision making in the management of opioid PCA infusions for palliative patients is a complex task. Clinicians are challenged by lack of information on which to base decisions, and difficulty locating the information when it does exist. **The purpose of this research was to examine the feasibility of using a standards-based informatics**

approach to manage information relevant to the use-case of managing opioid infusions in palliative settings. The aims were:

1. To understand the information needs and data requirements informing decision making in palliative care PCA management through:
    a. Development of an information model based on in-depth analysis of the use case.
    b. Validation of the information model through formal expert review.
2. To examine the potential feasibility of using the emerging FHIR standard for the specialized use case of palliative care PCA management. A gap analysis was conducted by mapping model elements to FHIR resources.

1.3 Significance

Despite the anecdotal reports of clinicians, who claim that they lack information needed to manage PCAs, we could find no literature evaluating the adequacy or quality of information available to clinicians at the point of care in this use case. The information required to make decisions regarding opioid titration *may* exist within electronic health record (EHR) systems, but the mere existence of information in the EHR is irrelevant if it is not ***available*** when and where needed. **If needed information is present but scattered throughout the EHR, buried amongst thousands of other pieces of data, it is *effectively* absent as the effort required to retrieve it exceeds that which a clinician can or will expend.** An automated system could 8provide an ideal solution to this problem, as such a system could find data quickly and efficiently, aggregate that data into useful information, then display it in an easily assimilated format for use in decision making.

Automating the aggregation and presentation of relevant information holds the potential to improve PCA management for palliative care in two key ways. First, such a

system would reduce the cognitive burden on clinicians, allowing them to focus on management decisions rather than expend considerable time and effort searching for information. Second, such a system would supply a more consistent, complete, and accurate set of data on which to base management decisions. By reducing cognitive load and providing a more complete and accurate set of information that is presented in a uniform way at the point of decision-making, one could expect a reduction in human errors and in turn improved patient outcomes and safety.

1.4 Innovation

Automated systems to locate and aggregate data have been successfully applied to such tasks as trending labs and clinical data, providing a level of decision support through data presentation.[2] However, very little if any decision support appears to have been developed for more subjective symptom phenomena, particularly the palliative care subject area, despite pain being a nearly universal phenomenon.

FHIR, an emerging HL7 standard intended to support rapid development of mobile apps and modules that can enhance EHR functionality, is currently of high interest in the informatics community. This project informs the design of an infrastructure upon which an EHR module providing decision support for management of opioid titrations could be built. The obvious first step would be a visualization tool, but the study also paves the way for development of a more elaborate, active clinical decision support system (CDSS) that could provide suggestions to providers in real-time at the point of decision making. The benefit extends beyond this one use case; if FHIR is found to be robust enough to meet this challenge, it suggests the standard can be successfully applied to other similarly complex subject areas in clinical care.

1.5 Organization of This Manuscript

The subsequent chapters of this manuscript are organized as follows. First, a literature review regarding palliative medicine, pain management, and the information management challenge provides background information and context for the study. The three subsequent chapters describe: foundational work and targeted literature summary to understand the information needs within the clinical domain, Aim 1 (methods, results, and discussion), and Aim 2 (methods, results, and discussion). Finally, a concluding chapter discusses and summarizes the work.

CHAPTER 2

THE CLINICAL CONTEXT

Examination of the clinical context begins with an overview of the development of palliative care as a discipline and a philosophy of care. Literature regarding late-life pain and management of pain crises, including patient controlled analgesia (PCA) and opioid medications, further elucidate the clinical issue that is the focus of the research use case. Finally, the information management challenge is described.

2.1 Historical Introduction

In the early part of last century, amazing advances in anesthesia, surgery, and antimicrobial therapy paved the way for a revolution in medical care.[3,4] In the latter half of the century, amazing technological advances gave birth to the modern ICU (intensive care unit) with various modes of life support that further revolutionized medicine.[5–7] This revolution in medicine had a profound impact on society, as the life expectancy drastically increased over this time.[6] As one after another dreaded killers was conquered by medical science, the last pages of the lives of Americans became a very different story. We no longer died from rapidly fatal conditions, such as infection and trauma, but rather fell victim to slow, insidious killers like chronic diseases of the heart, kidneys and lungs, and cancers.[4,8,9] Before this great revolution, the work of physicians was to “care” for the sick and dying, but after this revolutionary change, the focus of western medicine had become to “cure” disease.[4,6,9–11] Despite this new goal, all patients eventually die. The change, however was

that death now often followed a prolonged battle with disease, and patients often spent many of their last days in hospitals or nursing facilities receiving intensive treatments, supported by various machines.[10–19] This shift in focus from care to cure left much suffering unaddressed, while at the same time modern treatments often increased the suffering which patients endured as they lived out the ends of their lives.[17(pp14-30),19–23]

2.2 Palliative Care

2.2.1 Definition of Palliative Care

Recognizing that the suffering of patients was often overlooked by "modern" medicine, in the mid 1900's a few pioneers began to champion the application of medical science and technology blended with a human approach to provide relief to those suffering at the close of their lives.[24,25] Their work and research lead to the modern movement of palliative care. The concept of palliative care has evolved over the last half century, but the emphasis on relief of suffering has remained. The World Health Organization's (WHO) definition of Palliative Care states:

> Palliative care is an approach that improves the quality of life of patients and their families facing the problem [sic] associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.[26]

The National Consensus Project for Quality Palliative Care (NCP) describes palliative care as both a philosophy of care and a system of care delivery. It is critical to understand that the term "palliative care" can represent these two distinct concepts – a philosophy of care and a system of care delivery. This second concept, palliative care as a structured system of care delivery, is perhaps best illustrated by the multi-disciplinary team approach to delivering care. Hospice care, an inpatient consultative palliative care team, and outpatient palliative care teams in an oncology clinic all provide examples of the highly

structured systems for delivering care as described by the NCP. These systems of delivery are composed of multiple elements including various professionals, dedicated locations, and unique financing models, which are bound together into a functioning care-delivery system by associated specialized processes. These systems of care delivery are very visible to clinicians, patients, and families, so it is common to hear people say "they have called in palliative care" or "we moved him to palliative care," equating palliative care with these concrete parts of the system of care delivery. While this concept of palliative care is more visible, it is the less visible concept from the NCP definition, of palliative care as a philosophy, which is integral to this work.

A philosophy of care is a paradigm or approach to caring for patients, "a framework of care goals and values to help you make the best choices."[27] In contrast to a system of care that describe the mechanisms by which care is rendered, a philosophy of care drives what should be done and how.[28,29] A philosophy of care can direct either the entirety of a patient's care, or can be influential over just one narrow segment of the care. In the latter case it must integrate with other philosophies of care. The full NCP definition of palliative care is:

> The goal of palliative care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. Palliative care is both a philosophy of care and an organized, highly structured system for delivering care. Palliative care expands traditional disease-model medical treatments to include the goals of enhancing quality of life for patient and family, optimizing function, helping with decision making, and providing opportunities for personal growth. As such, it can be delivered concurrently with life-prolonging care or as the main focus of care.[30(p6)]

The first phrase, "the goal of palliative care is to prevent and relieve suffering," is an excellent yet concise statement of the palliative philosophy. While these goals are simple and certainly not unique to palliative care, they form the core of palliative care as a philosophy. Similar to the WHO definition of Palliative Care, this definition relies heavily on the idea of improving or maximizing quality of life. In the palliative philosophy of care,

suffering is more than physical pain. Dame Cicely Saunders, one of the early pioneers of Palliative Medicine, was one of the first physicians to weave this broad definition of suffering into her work. In describing her role as a palliative physician, she describes suffering as a multifactorial and unique experience, intrinsic to an *individual* patient. She stated the physician's role is to address

> things that can add up to a general state of misery as a disease in itself … a complex of physical, emotional, social, and spiritual elements. The whole experience for a patient includes anxiety, depression, and fear; concern for the family who will become bereaved; and often a need to find some meaning in the situation, some deeper reality in which to trust.[31(p1600)]

The Canadian Palliative Care Association likewise took a broad view of suffering while clearly focusing on the individual when they defined palliative care as

> a philosophy of care that provides a combination of active and compassionate therapies intended to comfort and support patients and families who are living with a life-threatening illness, being sensitive and respectful of their religious, cultural, and personal beliefs, values, and traditions.[32(p342)]

The goals of palliative care as a philosophy of care, then, are based on a broad definition of suffering with a distinct focus on the *individual* patient.

2.2.2 Scope of Palliative Care

While considerable confusion exists over what palliative care is – a system of care *and* a philosophy of care – the scope of palliative care is often even more misunderstood. Perhaps some of this confusion results from observing the highly structured system of care delivery and not recognizing, appreciating, or understanding the less visible philosophy of care that underlies that system of delivery. Many mistakenly believe that palliative care should be reserved for those in the last few hours or days of life, in keeping with a very restricted definition of a “terminal” condition. Others wrongly equate palliative care with hospice care which, in the United States, is defined by the Medicare Hospice Benefit, which requires that a patient no longer be seeking curative treatment.[33–36] The result is that many

believe palliative care to be a distinct and separate form of care, incompatible and incongruent with curative treatments.

This narrow view of the scope of palliative care is at odds with how nearly every palliative care organization and those working in the field view the discipline.[33,37–41] The WHO definition of palliative care lists a series of attributes of palliative care, including:

> [Palliative care] is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.[26]

Several statements in the first chapter of The National Quality Forum's (NQF) National Framework and Preferred Practices for Palliative and Hospice Care Quality provide a well-stated scope of Palliative Care that provides further details:

> Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social, and spiritual needs and facilitating patient autonomy, access to information, and choice.
>
> Of particular importance, palliative care services are indicated across the entire trajectory of a patient's illness and its provision should not be restricted to the end-of-life phase.
>
> Palliative care can be delivered concurrently with life-prolonging care or as the main focus of care. … Palliative care continues from the time of diagnosis as long as the conditions and their treatments pose significant burdens until a reversal is achieved or death results.[42(p vi)]

Another NQF document, Policies and Tools for Hospice and Palliative Care Programs, similarly broadens the concept of end of life care stating,

> "End-of-life care" is not bounded by a specific prognosis; rather, it involves the recognition of the irreversibility of a life-limiting medical condition(s) that will likely result in death.[43(p16)]

As do these, most modern, widely-accepted definitions of palliative care describe it as appropriate for patients who are facing "life threatening" or have "life-limiting" illnesses. This intentionally includes patients months or even years prior to death. The time for palliative care begins long before the time immediately preceding death, those few hours to

days referred to as the “actively dying” stage of life.[36,42,44,45] The key concept is that a palliative philosophy is appropriately applied to ***any*** patients facing life-limiting or life-threatening diseases, *irrespective* of either how long they have yet to live or whether they are still actively being treated for their life-limiting condition. The NQF explicitly denounces the idea of limiting palliative care based on a temporal prognosis, stating that palliative care may be appropriate “from the time of diagnosis.”

2.3 End of Life Pain

2.3.1 A Unique Problem Requiring a Unique Response

While suffering is a complex state and encompasses much more than physical symptoms, pain has been a particularly troubling symptom with which mankind has wrestled for centuries.[46–49] In 1931 Albert Schweitzer summarized the situation in his day by stating, “pain is a more terrible lord of mankind than even death itself.”[50] It is not surprising then, that pain was specifically targeted by early pioneers of palliative medicine.[25,31,41,51–53] Unfortunately, despite this work, Dr. Schweitzer's statement still remains true today; studies show that physical pain remains one of the most feared symptoms when patients think about death and dying,[5,54–59] and many patients still experience considerable pain toward the ends of their lives.[21,57,60,61]

Rather than endure pain, the goal is for seriously ill patients is to remain in a state of analgesia, the state of insensitivity to (or loss of the ability to feel) pain ,yet to simultaneously remain conscious.[62] This goal of insensitivity to pain can be approached in many different ways and when compared to other philosophies of care, there are features of a palliative approach to managing pain that set it apart from the approaches of other disciplines. It must be emphasized that treatment plans, protocols, practices, and approaches appropriate in one setting may not be applicable to other settings. What may be acceptable

and appropriate in a palliative setting may be completely inappropriate in other settings and vice versa. One must, therefore, be cautious to apply the palliative approach to pain management only to appropriate patients. Patients facing life-limiting illnesses differ in a number of important ways from patients in other settings; understanding those differences is important to understanding the palliative approach to pain.

2.3.1.1 Unique Feature - Pain Intensity

Patients dealing with life-limiting illnesses face unique types of pain and pain syndromes. As disease progresses, in many cases the pain escalates as well. Disease so profound that it threatens to overwhelm the patient despite all medical interventions often causes pain which increases to levels far more intense than the pain experienced from routine acute injuries or chronic pain syndromes. This escalation all-too-frequently results in a situation referred to as a "pain crisis," described in a 2008 JAMA article as a situation

> in which the patient reports severe, uncontrolled pain that is causing the patient, family, or both severe distress. The pain may be acute in onset or may have progressed gradually to an intolerable threshold (as Determined by the patient), but requires immediate intervention. National Comprehensive Cancer Network pain management guidelines identify a pain emergency as an event in which patients have severe pain (a numerical estimate of at least 7 on a 10-point scale) that **requires rapid opioid titration to provide analgesia.** [emphasis mine] [63(p1458)]

The same articles goes on to state:

> There are no epidemiological data to suggest how commonly pain crises occur. Our own experience at Memorial Sloan-Kettering Cancer Center suggests that of about 120 inpatient consultations a month, our Pain and Palliative Care Service is called for what is identified as a pain crisis by the referring physician as frequently as 20 to 30 times a month.[63(p1458)]

Typical estimates of terminal patients experiencing significant pain are between 36 and 75%,[64] with a recent meta-analysis using stringent criteria suggesting around 65%.[65] One study of patients with cancer found that 89% of them experienced moderate to severe pain with over 50% having moderate to severe pain at least "often" over the course of their

illness.[66] Any regimen, then, needs to be able to cover a wide range of pain, from minor every-day aches and pain to the most severe and excruciating pains

2.3.1.2 Unique Feature - Pain Fluctuation

In addition to the severe nature of pain experienced by palliative patients, the types of pain caused by end-stage or terminal disease typically varies in intensity over the course of the disease.[67] Disease progression can lead to steady increases over time or pain may quickly increase to crisis level in a short period. Palliative patients often have variations in the short-term, such as over a day. Sometimes these fluctuations are caused by certain activities throughout the day (such as changing position), but fluctuations in pain intensity may appear to occur randomly. As such, palliative patients need a regimen capable of providing a steady level of analgesia to cover their "baseline" pain but also able to provide temporary increases in analgesic effect to cover short-term "breakthrough" pain.[68–70] Developing a regimen that provides analgesia across a wide range of intensities, yet one that is flexible enough to adapt *quickly* to rapid changes in pain intensity, is often challenging.

2.3.1.3 Unique Feature – Life Expectancy

Due to their life-limiting illnesses, patients in palliative contexts obviously have a shorter life expectancy than patients in other contexts. As such, long-term side effects and long-term risks associated with certain medications or pain regimens are of lesser concern to these patients. More importantly, for patients with a short prognosis there is a sense of urgency to relieve their pain quickly so they can make the most of what time they have left. This concern applies especially to patients in acute pain, such as those suffering from a pain crisis. The faster medication can be safely titrated, the better: speed is of the essence. In fact, a longstanding metric for hospice is whether pain relief is achieved within 48 hours or less of onset (or admission to hospice);[71,72] this is becoming a metric for palliative care

services as well.[73] Methods of pain relief employed in palliative settings, then, must have both a rapid onset and the ability to be rapidly titrated in order to maximize the amount of "good" time the patient has.

2.3.1.4 Unique Feature – Physical Limitations

Given their severity, life-threatening diseases often impose significant physical limitations. As a result, many patients are either homebound or require great effort to leave their homes. Frequent travel to clinics or hospitals can pose severe hardship, adding to the patients' suffering. Even within their homes, progressive physical limitation makes it important to keep treatment regimens simple and limited to what can be carried out with a minimum of effort. As serious disease evolves it is common to have progressive organ dysfunction, such as liver or kidney failure. This makes medication regimens with complex pharmacokinetics and pharmacodynamics difficult to manage and prone to failure due to side effects, adverse reactions, or medication interactions. The combination of advancing disease, weakness, and organ dysfunction further makes patients poor candidates for procedural or surgical intervention for pain.

2.3.1.5 Unique Feature – Psychosocial Factors

An important, yet often overlooked, factor in the care of patients facing life-limiting illnesses is the impact the disease has on their psychosocial situation. Such illness creates multiple psycho-social barriers for the patient. Seriously ill patients lose control of much in their lives and face incomprehensible losses; understandably this often leads to severe emotional distress and an emotionally fragile state. Anything that can be done to give suffering patients a sense of empowerment can be immensely beneficial.[63] Involving the patient as much as possible, including setting goals of analgesia and in decisions about timing and amount of doses, can be extremely empowering to patients.[74] In addition to the

impairment caused by emotional distress on patients and caregivers, dementia and delirium in patients and caregivers, even if mild, significantly impact the ability to comply with analgesia regimens. Complex regimens are not an option; the regimen must be simple and straightforward. Perhaps most importantly, though, many of these patients are on a fixed income with extravagant medical expenses, so simple, highly effective, yet low cost regimens are needed.

2.4 Opioid Medications for Palliative Pain Management

So, then, what is needed is a fast-acting and rapidly titratable means of providing analgesia over a wide range of doses that can be self-administered easily by the patient with minimal physical and mental effort, can be used in the case of physical deterioration and organ failure, and is inexpensive. While this is a tall set of orders, one of the oldest classes of medications, opioids, holds the promise to fulfill many of these demands.

2.4.1 History of Opioid Use

Though the opium poppy has been used medicinally for the last 30,000 years,[75] a turning point occurred in the 1800s when advances in chemistry allowed purification of potent opioids on a large scale. Thomas Sydenham, a 17th-Century English physician, called laudanum, made of sherry, opium, saffron, and cloves, "the most valuable drug in the world."[75] Given such acclaim and availability, use of opioids became widespread and by the turn of the century problems of overuse were apparent. In 1914 the U.S. government stepped in to deal with the problem, enacting the Harrison Act,[76] and suddenly this previously widely used class of medication became something feared, both by the public and practitioners.[75,77] Opioids became associated with stereotypical images of "street addicts" and their use was quickly confined to the "periphery of society."[75,76] By the mid 1900s, the prevailing mindset in the U.S. was that opioids should be used as a modality of

"last resort," one reserved only for those "who were clearly dying."[53] Coupled with the rise of suffering at the end of life, this reluctance to use such an effective medication needlessly perpetuated much pain and suffering. In 1986, in response to increasing concern over unrelieved pain, the WHO established an "analgesic ladder" to guide use of pain medications.[78] This model was originally designed for use in treating cancer pain[78–80] but became a de facto standard for management of many types of pain.[80–82] While the WHO ladder improved the treatment of pain in many settings by increasing *appropriate* use of opioids,[78,80] considerable fear and stigma still surround opioid use today, even for patients nearing life's end.[75,83–86]

2.4.2 Concerns about Opioid Use

Though opioids *must* be managed carefully, as there are dangers in both their short and long term use, the risks are no reason to avoid this highly effective class of medications in palliative patients. There are certainly significant ill effects that develop over months to years of opioid use, but these are rarely an issue in palliative settings, as patients either are not expected to have a prognosis long enough to realize those side effects or the nature of the disease is so severe that compared to the suffering, the side effects, are negligible.[87] The more immediate risks posed by opioids, however, are important to consider and manage appropriately.[88–90] One common concern is that opioids are potentially habit-forming; another is that if not used carefully, opioids can be dangerous, even deadly.

Opioids do induce chemical dependence and they are frequently abused. However, it is well established that the natural chemical dependence that accompanies repeated use of opioids over time does not correlate with increased levels of abuse.[91] In patients in palliative and hospice settings where opioids are used liberally to treat pain, the incidence of misuse/abuse of opioids has been found to be no greater than the rate of abuse seen in the

general public.[31,92–95] Overall there has not been evidence linking increased rates of addiction to *appropriate* medical use of opioids in individuals who otherwise were not predisposed to (or have previously had) problems with addiction.[84,92,96,97] It is vitally important, however, to keep in mind that this statement is predicated on the *appropriate* use of opioid medications. The use of analgesic medications for any purpose other than relief of physical symptoms (i.e. pain or dyspnea) is misuse; use of opioids to numb emotional pain (so called "chemical coping") or for their euphoric properties (to get "high") is misuse and indicates *heightened* risk of escalating abuse or possible later addiction. If prescribers do not police the use of opioids appropriately and allow use of higher doses than needed to achieve analgesia, or if they allow or enable indiscriminate use of opioids, the risks of abuse and addiction do likely increase considerably. The importance of prescribers managing opioid regimens with vigilance cannot be over-emphasized. This author has personally witnessed significant problems develop on many occasions, sometimes with devastating results, when prescribers have failed to keep the purpose of opioid regimens focused on analgesia. Merely being in a palliative setting provides no protection against the dangers of *improper* use of opioids.[98,99]

The second concern, that opioids are "dangerous" medications, is a concern frequently taken out of proportion. Many classes of medication and many procedures used in routine daily medical care in clinics, hospitals, and patients' homes involve risk. What protects patients from harm in such cases is the skill and dedication of the provider managing the regimen or performing the procedure.[67,100–102] Though not the only danger, the most feared short-term complications of rapid escalation are sedation and respiratory depression with either potentially even leading to death.[103–105] With skill developed through appropriate training and experience combined with the appropriate level of attention dedicated to the case, even complex rapid titrations of opioids to exceptionally high doses

can be managed safely.[97,106–111]

2.4.3 Properties of Opioids That Are Advantageous for Palliative Settings

Despite the concern with opioids, they have a number of unique properties that allow them to effectively meet the needs for an analgesic in palliative settings. Opioids have a very wide therapeutic range, from very small to massive doses. In fact, one of the key attributes of opioids is that many opioids (the mu-agonists) have no therapeutic ceiling. This means if any current dose is ineffective in a particular individual, in the absence of precluding opioid-induced side effects, it is safe to raise the dose irrespective of how high that dose is.[17(p317),90,102,106,107,112–114,115(p81)] Opioids also have a relatively rapid onset. While typical oral forms of opioids not engineered to be long-acting or slow-release reach their full analgesic potency within an hour, when given by the parenteral route (intravenous or subcutaneous injection), most opioids begin taking effect within a matter of minutes and reach full potency within a half an hour or less.[17,67,114,116] This rapid onset allows titration to large doses within a matter of hours.[63,117–119] While each opioid has a unique pharmacokinetic profile, traditional opioids (i.e. morphine, hydromorphone, oxycodone) have half-lives of about 2-4 hours, allowing them to be titrated down over a few hours, should that be needed. Most opioids also have relatively benign side effects and metabolite profiles and, when managed by skilled professionals, can be successfully used despite declining health and organ failure.[102,114,120–122] Even in the last hours or days of life as the body shuts down, opioids can safely provide analgesia through the point of death. Opioids are also relatively easy to administer in a patient's own home either by oral dosing or an infusion. Long-acting oral forms of many opioids are available, allowing an entire day's worth of very potent analgesia to be simplified into one to three doses of scheduled oral

medication. This allows even high dose infusions to be converted to oral regimens providing the same level of analgesia but involving only a few pills per day. While there are opioids that are quite expensive, many opioids have generic forms available, and overall opioids are arguably one of the least expensive classes of analgesics available.[102,118,123–125]

Opioids, then, are ideal analgesics for many patients in palliative settings. While many palliative patients are served well by opioid regimens, each situation must be individually evaluated to determine the best analgesic strategy. When rapid relief is required, such as in a pain crisis, parenteral infusions of opioids is often the method of choice to gain control of pain quickly in palliative patients. However, infusions require needles, lines, and pumps which are cumbersome, have more potential failure points, and impair mobility.[126] For these reasons, when rapid titration is not required, it is routine to use oral opioid regimens, which provide the same level of analgesia but are simpler, less intrusive, and cheaper for the patient.[80] The common fluctuations in pain intensity between extremes seen in palliative patients, however, necessitates a very adaptable regimen for palliative patients, and it is not uncommon for a patient to be switched back and forth between parenteral and oral dosing, as the patient's pain requires. These conversions and rapid titrations are very complex and require considerable skill and expertise to accomplish safely.[63,108,109,111,127–130]

2.4.4 Subjective and Individual Nature of Pain

Physical pain is a subjective experience, an aggregated mental perception that results from, and is shaped by, a multitude of sensory perceptions and internal processing.[102,131–133] While an analysis of pain as a phenomenon is beyond the scope of this work, that it is subjective has a direct bearing on this work. A tenet of palliative care is that pain is a perception truly knowable only to the patient who is experiencing it; pain is what the patient

says it is.[4(p329),17(p301),107,131]

Many physical factors affecting both a patient's perception of pain and their responsiveness to opioids vary from one individual to the next. Opioid binding receptor profiles vary from one individual to the next, as do metabolism and clearance mechanisms.[67,114,134–136] Additionally, the pain transmission pathways and integration centers in the body are very plastic and adapt to intrinsic and extrinsic events, varying in response to many factors. The phenomenon of “wind up” (when repeated or continuous painful stimuli over time lead to higher and higher perceived levels of pain), and the development of tolerance (when the same dose of opioid becomes less effective with continued repeated use), are examples. Both of these factors vary significantly between different individuals.[134]

Equally important in the perception of pain are a host of psychological and emotional factors including mood, perception of disease progression, and social situation.[67,88,134,137] Because of this, two individuals with physiologically similar events may perceive vastly different levels of “pain.” It is only expected, then, that the amount of medication required to achieve “analgesia” will vary between individuals.[97,134,138,139] Further, even the same patient may have markedly different analgesic needs at different times as any of the factors involved in creating the experience of pain change.[97] Years of research have failed to discover overall “optimal” doses of various opioids, instead showing that individuals have very different opioid requirements across a broad range of doses, reinforcing the idea that pain cannot be approached with boiler-plate regimens, but rather each episode must be approached individually.[97,106,134,140,141]

2.4.5 An Answer to the Need for Individualized Parenteral Opioid Regimens

The need for highly individualized pain regimens, especially when using opioid analgesia, has long been known. Early pioneers of palliative medicine advocated involving patients in their pain management by ordering rather liberal doses titrated upwards, sometimes by patients themselves, until patients remained in a state of analgesia.[52] Involving patients in this way proved successful for adjusting analgesia to pain that evolved rather slowly or had a stable pattern of fluctuation, but for complex patients such as those requiring high doses or rapid titration, the system was cumbersome. While use of parenteral opioids leveraged rapidly acting medications, the process of a patient summoning an attendant and discussing the need for medication, followed by the multiple steps involved in an attendant checking orders, obtaining the medication, and then finally administering it, was anything but smooth, and often involved considerable delays.[96,106] Though a patient could request a dose "as needed," many factors beyond his or her control affected the timing and dose of medication delivered leading to delays and inadequate analgesia.[106,142] The patient provided input, but was not truly in control of the analgesia regimen.[142,143]

With the advance of technology in the 1960's, a possible solution appeared when several anesthesiologists independently began experimenting with the idea of post-operative patients controlling their own analgesia using automated pumps. Philip Sechzer is often credited as the first to develop the idea in early 1965 when he had patients directly signal a device which, in response, provided them with doses of medication.[144,145] In 1968 Sechzer published preliminary findings,[146] and in 1970 he published a report of his "Patient-controlled analgesic-demand system."[145] Other pioneering anesthesiologists of that time were experimenting with similar systems, including William Forrest in Palo Alto, California,[144,147,148] Michael Keeri-Szanto in London, Ontario,[144,149–151] and J.S. Scott in Leeds,

United Kingdom.[144,150] While Sechzer's main interest was in using this device for research, Keeri-Szanto continued to push the concept into the clinical realm,[144,150] advocating its widespread use throughout the hospital.[151] Eventually, the concept of patient-controlled analgesia (PCA) became a mainstream modality for pain control, and by the 1980s was used frequently in post-operative settings.[96,97,150–152] Though by strict definition, PCA is a paradigm, the term has become synonymous with IV infusion pumps having some triggering device that a patient uses to signal the pump to deliver a dose of medication.[97] As technology evolved, pump sophistication grew such that multiple parameters regarding doses and timing could be set, pumps delivered continuous infusions along with the demand doses, and parameters such as requested doses, delivered doses, and total medication delivered were recorded. By 1990, the use of the PCA paradigm had started to make its way into oncology practice,[148,153–158] and by the mid 2000s opioid PCA use was firmly entrenched in palliative medicine.[126,159,160]

This paradigm shift truly allowed the patient, as opposed to the physician, nurses, or family, to be in control of the amount of analgesic received. While general constraints are put in place by the prescriber, within those bounds the patient determines when and how many doses of analgesia they receive. This accomplishes several goals. First, it can empower the patient, giving them some sense of control.[161] Second, it aids in the rapid titration of a parenteral opioid regimen.[159,160,162] By observing the number of attempts a patient makes of the infusion pump and correlating that with their pain scores, the prescriber gains an understanding of the effects of increasing doses. As the clinician increases either the basal infusion rate or the size of the bolus doses delivered in response to patient requests, eventually the patient will begin to space out their demands for bolus doses and rate their pain lower. This indicates one is approaching blood concentrations of opioid consistent with a state of analgesia.[97] Thirdly, the PCA paradigm incorporates an important safeguard

against possible opioid overdose. The great concern in opioid titration is an overdose resulting in death, usually caused by hypoxia from respiratory depression. If managed appropriately by a skilled provider knowledgeable about opioid use and medication kinetics, the regimen is structured such that before a patient reaches a point of respiratory depression, they become somnolent and thus no longer able to request additional bolus doses.[96] Without further boluses, the opioid level will decrease (or at least cease to rise) and the blood opioid concentration should not reach levels that cause respiratory depression.[67,163] Despite this theoretic safeguard, adverse events, and even fatalities, do occur.[100,103,164–167] Even when performed by skilled, experienced, and attentive providers, managing opioid infusions by any method, including by PCA, is a complex processes, thus prone to error.

2.5 The Informatics Challenge

Because it meets many of the described needs in patients suffering from life-limiting illness, opioid infusion using a PCA paradigm has become widely accepted as the preferred modality to achieve rapid relief of pain in palliative settings.[118,159,143] The process typically involves giving loading doses, rapid titration, a period of smaller adjustments to hone the level of analgesia, then, when analgesia is established, often a conversion to an oral regimen.[168] Given the complexity and potential dangers involved in rapid dose escalation, PCA infusions **require skilled providers to make frequent high-stakes decisions throughout the process.** They are therefore typically carried out under close supervision, usually in a hospital or other inpatient setting.[142,164,165,169,170] To maintain the safety of the patient when using a PCA infusion, it is important that those managing the infusion have accurate and appropriate clinical information on which to base decisions. Anecdotally, palliative experts complain they frequently do not have adequate data to make decisions in these complex situations. This author has likewise often struggled with this lack of data

over the course of the last ten years of his work as a palliative specialist. In the past in settings dedicated to palliative care, such as a dedicated inpatient unit or a hospice, some of the needed data was available on large, paper flowsheets. As EHRs have become increasingly common, paper flowsheets have been replaced by computers. Data *may* be culled from these systems, but this is a process beset by many challenges. In these best-case scenarios, the data needed for decision making must be *actively* sought by looking to various places in the EHR; it is rarely presented in a clear, concise, organized manner. Before the provider can analyze and synthesize, he or she must spend considerable time searching and jotting down notes. In other cases, such as general hospital wards, the ICU, or outside the hospital, data availability is even worse, and there are actual or functional data "holes" such that despite searching, data cannot be found.

One would assume that experts who are comfortable in managing these cases know ***what*** data they need and will actively seek it out despite challenges, as they reason through the process of clinical decision making. It may be another story for providers managing opioid titrations who, due to insufficient training and experience, are not "experts." One can only speculate whether they will know specifically what information to look for and then search deeply enough to find it. For either the expert or novice, having to search multiple locations throughout the record, even *if* the data are in predictable locations (which is rarely the case), creates a fractured and circuitous workflow. Such inefficient, complex workflows increase the cognitive load and thus the potential for errors.[171–175]

While the data required to make decisions regarding opioid titration *may* exist within EHR systems, providers complain that they often cannot find or struggle to find the needed information. Within an EHR, if specific fields for the information needed for decision-making when managing opioid titrations are lacking, such capacity should be relatively straight-forward to add either at the local installation level or at the vendor level.

Presupposing that capacity to store needed data elements exists within the EHR but is not used, education and accountability regarding accurate and appropriate documentation could ensure necessary data are stored within the EHR. However, none of this ensures ***availability*** of necessary data to the clinician when making decisions. If needed data is scattered throughout the EHR, buried amongst thousands of other pieces of data, the effort required to retrieve it can exceed that which clinicians can or will expend. The mere existence of information is not helpful if the provider is unable to access the information; in those cases it is as if the information does not exist.[176–178] In situations where information is difficult to find or access, the data are *effectively* absent to the clinician, and it is likely that decisions will be made without use of all desirable information.[179,180] For providers to make potentially high-stakes management decisions without adequate information presents at least a barrier to high quality pain care ,even if it does not always result in errors and harm to patients.

An automated system, in contrast, could be designed to find data quickly and efficiently, aggregate that data, then display it in a visual form that a human operator could easily assimilate and use in decision making.[173,181–183] While there are exciting advances coming, such as the development of “smart pumps,” we could find no literature evaluating the adequacy or quality of data available to clinicians at the point of care, or methods or projects to improve on the perceived lack of data when managing PCAs. This study was designed to partially address that knowledge gap.

CHAPTER 3

FOUNDATIONAL EXPLORATORY WORK

3.1 Initial Evaluation: Modeling

3.1.1 Information Transactions

When considering the clinical scenario of opioid infusion by PCA pump in palliative patients, and how to improve upon the potential problem of data availability, the first step was formally describing the involved information transactions. This modeling exercise was carried out based on the author's nearly 10 years of experience managing PCAs as a specialist in palliative medicine, and with informal input from other specialty palliative providers.

Initial modeling efforts revealed a highly complex system of information flow for managing opioid PCA regimens in palliative settings. This model of information flow may be seen in Figure 3.1. To simplify and structure the model, a high-level model of information flow was created using BPMN techniques; it is shown in Figure 3.2. This BPMN model was then used to create a general model of data flow in the health care system as seem in Figure 3.3; the generalizability of this model was shown by its adaptation to the flow of patient preference information within the healthcare system and subsequent presentation as a poster at the AMIA 2013 annual convention.[184]

The model of information flow shown in Figure 3.2 describes three sources of information, indicated by dark/shaded areas. First, the patient serves as an important primary source of information. There are common and accepted ways to obtain data from

the patient: typically a health care worker questions and physically assesses the patient. When there is a PCA infusion pump in use, the data it captures and stores becomes a second valuable source of information, as shown by the shaded swim land labeled “PCA Pump” in Figure 3.2. PCA pumps routinely keep an electronic record of many parameters including, for instance, doses given, doses requested, and interval total medication given. Routine practice in clinical settings is that nursing staff interrogate the pump at periodic intervals, physically write down the information, and later reenter data into the EHR or paper chart. While many pumps have the capability of exporting the data they collect in a structured format, for instance, into an EHR, currently this functionality seems not to be utilized by institutions or EHR systems;[185–188] no formal research, investigation, or reports could be found on actual application of this potential. In addition to reducing workload on nursing staff, interfacing PCA pumps with EHRs could increase the amount and improve the quality of data available within the EHR. Such interfaces should prove relatively straightforward to create as the data in PCA pumps are discrete numeric and text-string data. However, even if such interfaces do improve the quantity and quality of data *available* in the EHR, merely being in the EHR does not ensure data are accessible to providers. The EHR, then, represents the third source of data in this model. Data are repeatedly gathered from the patient and the PCA pump and entered into the EHR. Other primary data, such as results from laboratory, radiographic, and other tests, as well as reports of various kinds, also find their way into the EHR. Further, as healthcare providers document their findings, thoughts, and impressions, the volume of this “synthesized” information present in the EHR grows. This longitudinal record of both primary and synthesized data makes the EHR a valuable source of information.

From the model (Figure 3.2) it can be seen, however, that without the ability to move this information in real-time to the point of care when it is needed, the information

cannot have an impact on clinical care or outcomes. The complaint of providers that they lack necessary information at the point of care appears consistent with the lack of a mechanism to accomplish the identified "weak link" of movement between the EHR (or other clinical data store) and the provider at the point of care. Given the complexity of the task of managing and titrating opioid infusions in palliative settings, this is concerning, as it is well established that increased complexity of a system increases the number of failure points and thereby increases the odds of failure.[189–193] This finding affirmed that this is an area to which application of a CDSS that could efficiently aggregate and present data to a provider could provide significant benefit.

3.1.2 UML Modeling

To further evaluate the interactions of various individuals involved in the flow of PCA pump-related data, and to narrow the scope of the project to something feasible and realistic, several Unified Modeling Language (UML) diagrams were created. UML (http://www.uml.org) is an international standard (specification) for how to model application structure, behavior, and architecture as well as workflow processes and data structure. Figure 3.4 is a UML context diagram showing the key actors and systems at a high level. Of interest were the interactions between the health care providers and EHR, as seen in the use case diagram in Figure 3.5, and more specifically, the individual who is managing the opioid PCA infusion, called "prescriber" in Figure 3.6. While the prescriber interacts with the EHR in several ways, of particular interest is the retrieval and display of patient data pertinent to opioid PCA management decisions.

3.1.3 Visualization Prototyping

A fundamental question at this point was whether physicians would prefer a visual display of data aggregated by a CDSS to the current practice of navigating to various

locations in the EHR to extract the data themselves. To informally evaluate this question, drawing on nearly a decade of managing complex opioid titrations, this author began to experiment with various ways to visualize data he felt important when managing complex opioid PCA regimens in palliative settings. The results were the mock screen in Figure 3.7. This mock screen was informally shown to 4 other seasoned experts in palliative medicine at 2 other institutions; the informal response was overwhelmingly positive. All providers said such a screen displaying this data in a visual format would be incredibly useful. One provider insisted on keeping a copy of the mock screen for her records. Though informal, this overwhelmingly positive response indicated that this *type* of display was not threatening and might be a benefit to providers.

3.2 Targeted Literature Review

A literature search was performed to identify evidence-based methods and/ or guidelines for PCA management to be used as the basis of a CDSS. As management of opioid PCAs is a task almost exclusively in the domain of health practitioners, PubMed was the database of choice. Multiple approaches were used to generate search terms: key-word, text-title word, and MeSH (Medical Subject Heading) term searching. MeSH terms are formal, hierarchically arranged subject headings developed by the NLM (National Library of Medicine) and applied by the NLM to published medical literature at the time of cataloging. As MeSH terms are arranged in a tree-like structure based on increasing specificity, identifying terms that referred to opioid infusion, opioid analgesia, PCA, and other concepts of interest was accomplished by directly perusing the MeSH tree. Publications on the PCA paradigm are plentiful, with a few early articles in the 1960's, more in the 1970's, and then a significant increase in publication in the 1980's and into the 1990's. In the body of literature amassed there was considerable research about the effectiveness of

opioid PCA, use and comparison of particular agents, and many other topics related to pain research and pharmacology. However, neither primary research on h*ow* to manage and make decisions regarding titration of an opioid PCA regimen in *clinical* settings nor evidence-based guidelines for such management were found. The closest artifact to such evidence was the National Comprehensive Cancer Network (NCCN) guidelines, which are an evidence-infused consensus statement from an expert panel.[168] There is no shortage of expert opinion on how to manage a PCA expressed in the literature. Interestingly, expressed expert opinions seemed to be consistent, frequently citing accepted practice as justification. This suggested that as the PCA paradigm developed from the 1960's through the early 1980s, consensus regarding appropriate *management* of PCAs in clinical settings developed and became accepted practice before the PCA paradigm became a topic of intense *clinical* research. Understandably, as a PCA pump is a means of delivering an opioid regimen, it seems reasonable to apply many of the well accepted guidelines of opioid titration to this use case as well, but again, the basis for suggesting *how* a clinician should titrate opioids appears largely to be based on standard accepted practice rather than specific studies. To deepen the search and in hopes of uncovering evidence-based foundations for the expert opinion so readily offered, the citations of many of the publications retrieved on PubMed searching were themselves retrieved and reviewed. Again, little primary evidence to guide a clinician in making decisions regarding adjustment and titration of opioid PCA infusions could be found. Other interesting observations from the body of literature retrieved showed that early research and publications through the 1980s were limited to the post-operative setting. In the late 1980's and early 1990s articles began to appear discussing and evaluating the application of the PCA paradigm to the setting of cancer and medical illness. As they appear late in this time course, most articles on the topic of opioid PCA use in palliative settings tend to assume how to manage an opioid PCA is a-prior knowledge and

that in general, some 'standard' practice is followed.

3.3 Exploration of Mechanisms to Represent Data

A technical infrastructure is required to support a *relevant information display-based* CDSS, including a system to convey data from the storage location within the heath information system to the provider's display. Certainly such a CDSS could be a native application within an EHR, in which case proprietary terminology bindings and data representation methods would suffice. This would, however, tightly couple the CDS application to the single system to which it is native, likely limiting its use to only that single parent application, as well as making it difficult to use any outside data sources. This is a well-known problem for which the informatics community has been seeking a solution for quite some time.[194,195] Currently, there is considerable interest in modular design for EHR systems to enable more customization and wider re-use of innovative ideas and tools. Building CDS aids in a modular, EHR-agnostic fashion allows them to interface with multiple EHR platforms, achieving a much wider impact than if build on a single, proprietary system. Critical to accomplishing this modular architecture is a standardized method to pass data between modules without losing clinical meaning. Technical standards such as FTP and TCP/IP could easily transmit the data, but representation of transmitted data has yet to be standardized. FHIR, an emerging standard from HL7, is intended to fill this gap, resulting in improved real-world clinical interoperability. Basic design features of FHIR include flexibility and simplicity with a formal extension process. Extension allows FHIR to accommodate clinical data falling outside of its native ability to represent data and information.

3.4 Summary of Exploration

While it was already appreciated that managing an opioid PCA infusion is a complex task, this initial modeling work revealed that the requisite information flow to support this task is complex in its own right and is heavily reliant on humans as the conduit of data, a situation which creates multiple *potential* failure points. The obvious question was whether this deficiency could be addressed by a CDS application which would aggregate necessary data with the goal of displaying that data to clinicians in a simple, easily understandable manner.

The lack of a clear evidence-base to serve as a foundation for a CDS application posed the first challenge: determining what *are* the data needed. As expert opinion seemed to consistently reference the same concepts, and as research articles based their protocols on similar assumptions about the same concepts, it seemed that there were common, underlying, guiding principles. It was therefore hypothesized that an inductive approach might be used to quantify the data and information which seemed to underlie expert decision making, and thus could provide the needed basis for the proposed theoretical CDS application.

The second challenge, identified directly from the modeling, was *how* to convey the needed information from an EHR or other health data store to the proposed relevant data display CDSS. Preliminary exploration of the HL7 FHIR specification suggested it might provide a solution. How well and how easily FHIR could be used to accomplish this task was felt to hold the potential to suggest how well it could be applied to other such domains.

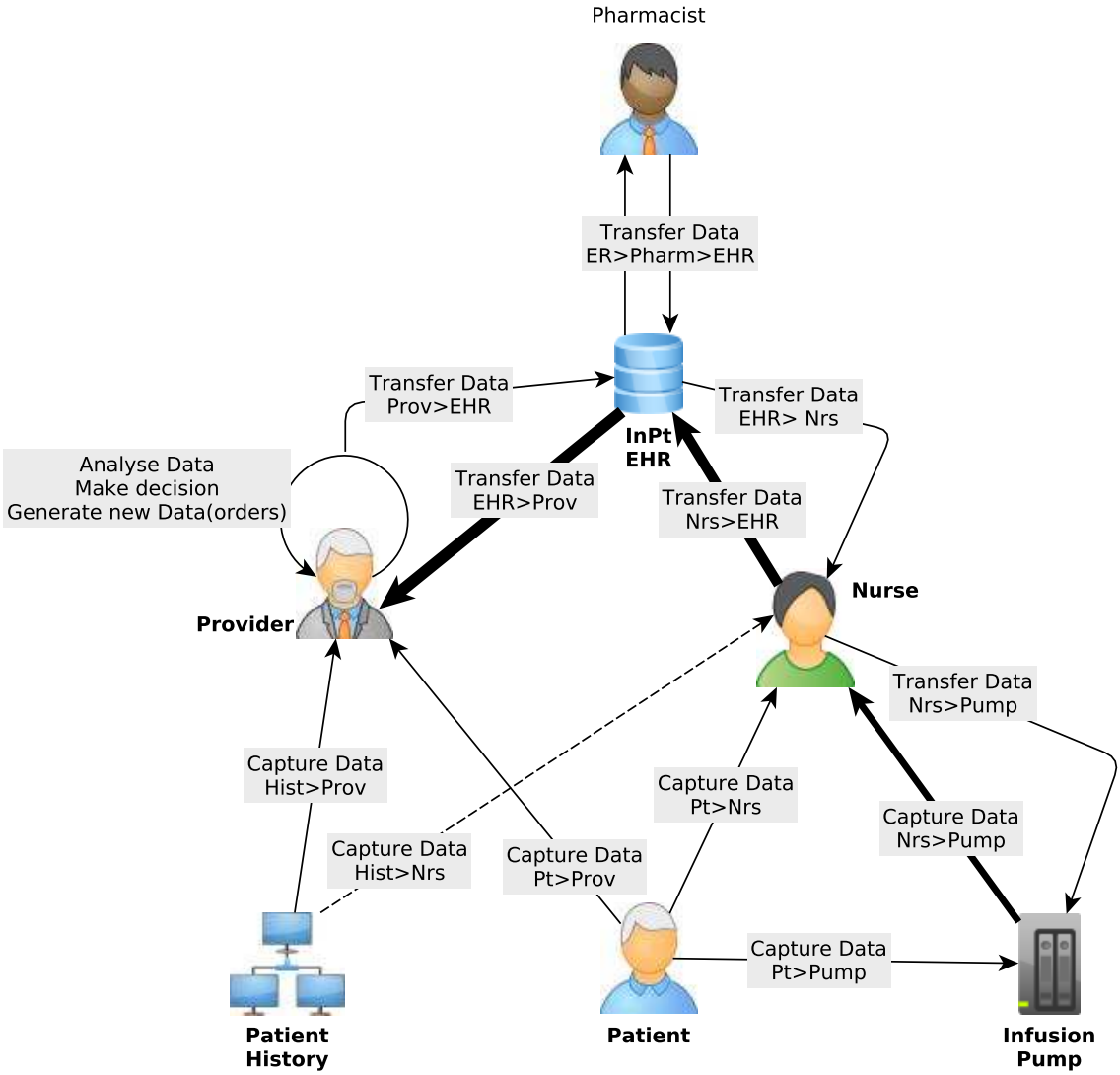


Figure 3.1 - Information flow in the context of a PCA pump

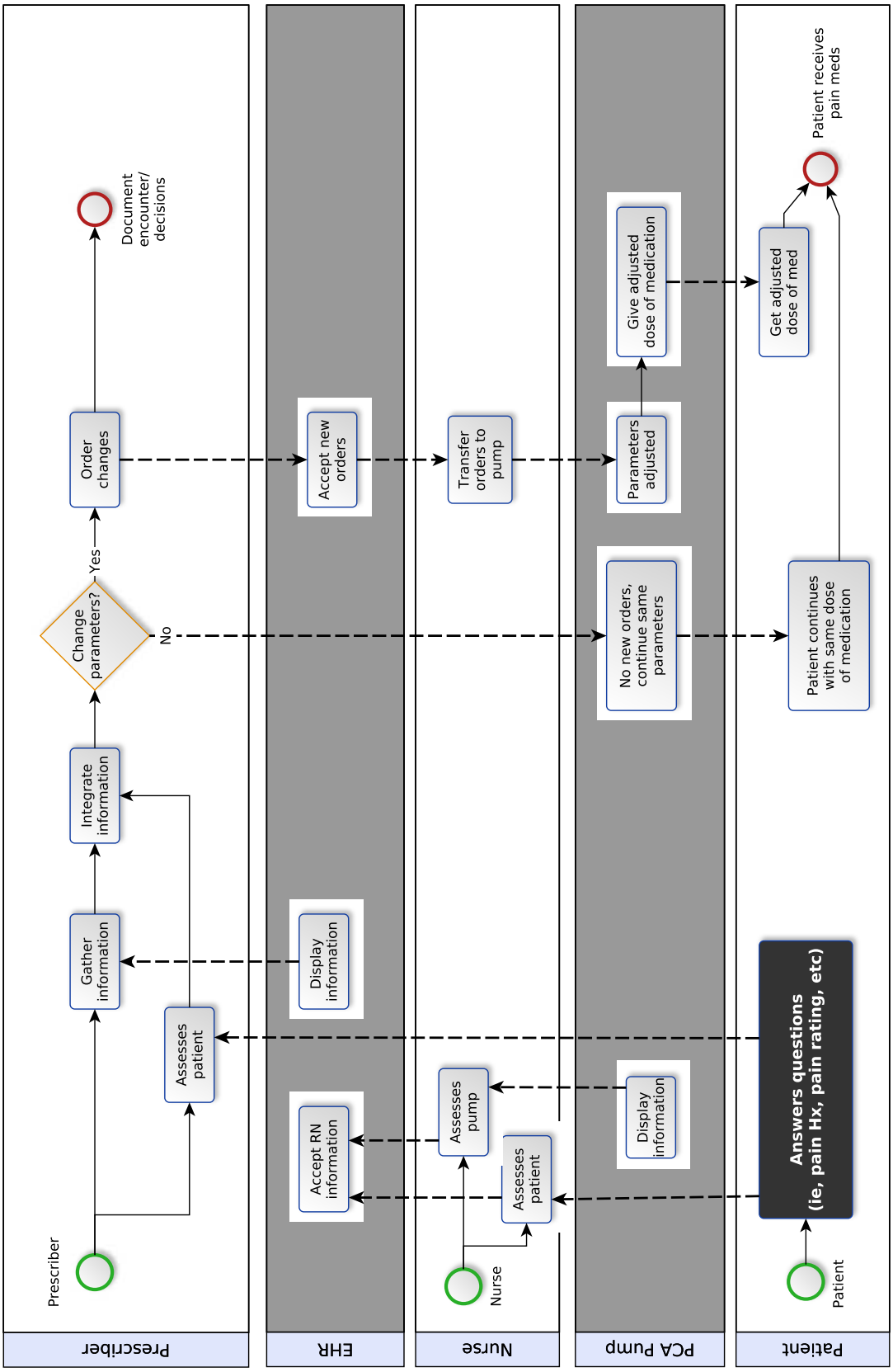


Figure 3.2 - High level PCA information flow

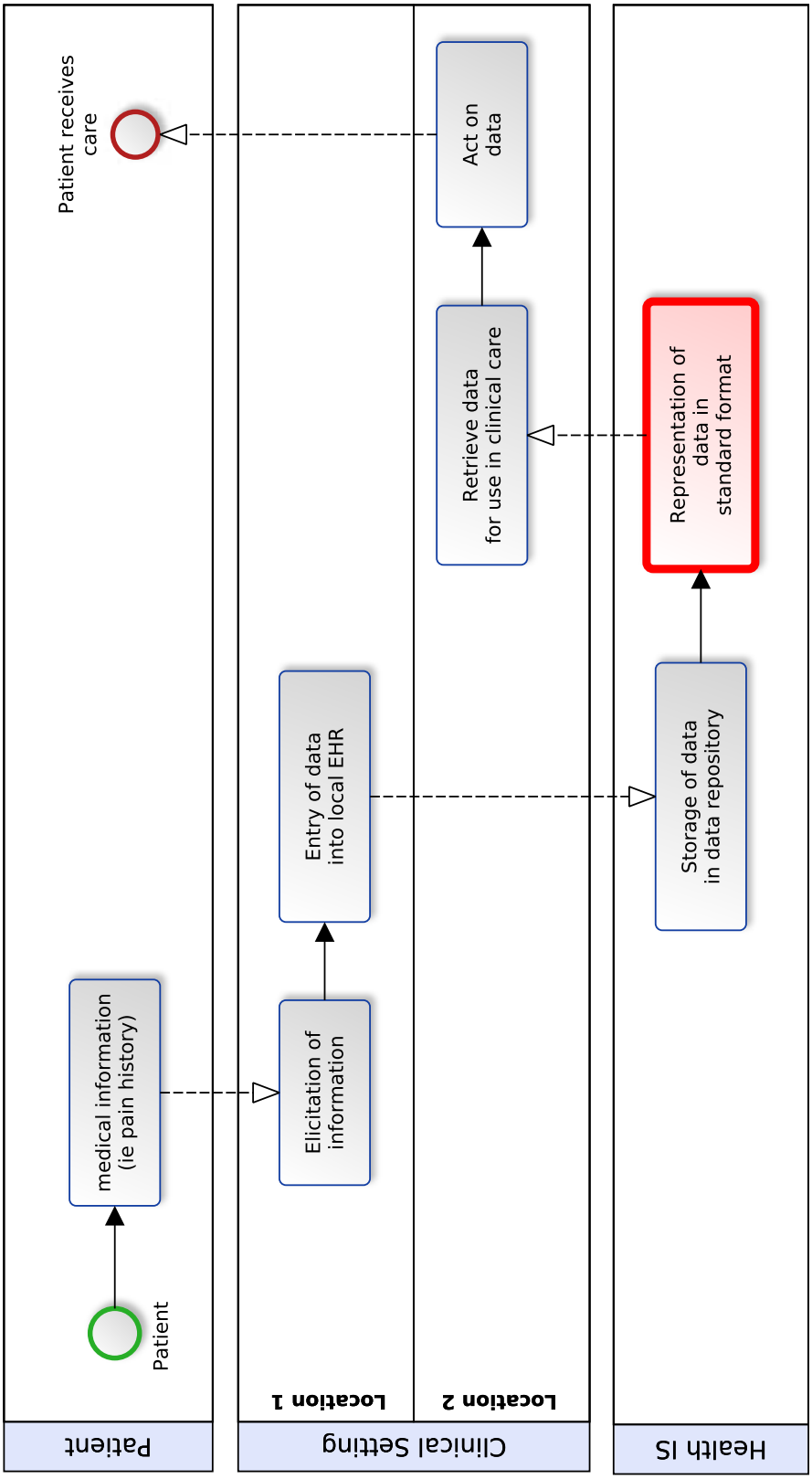


Figure 3.3 - High level health information flow

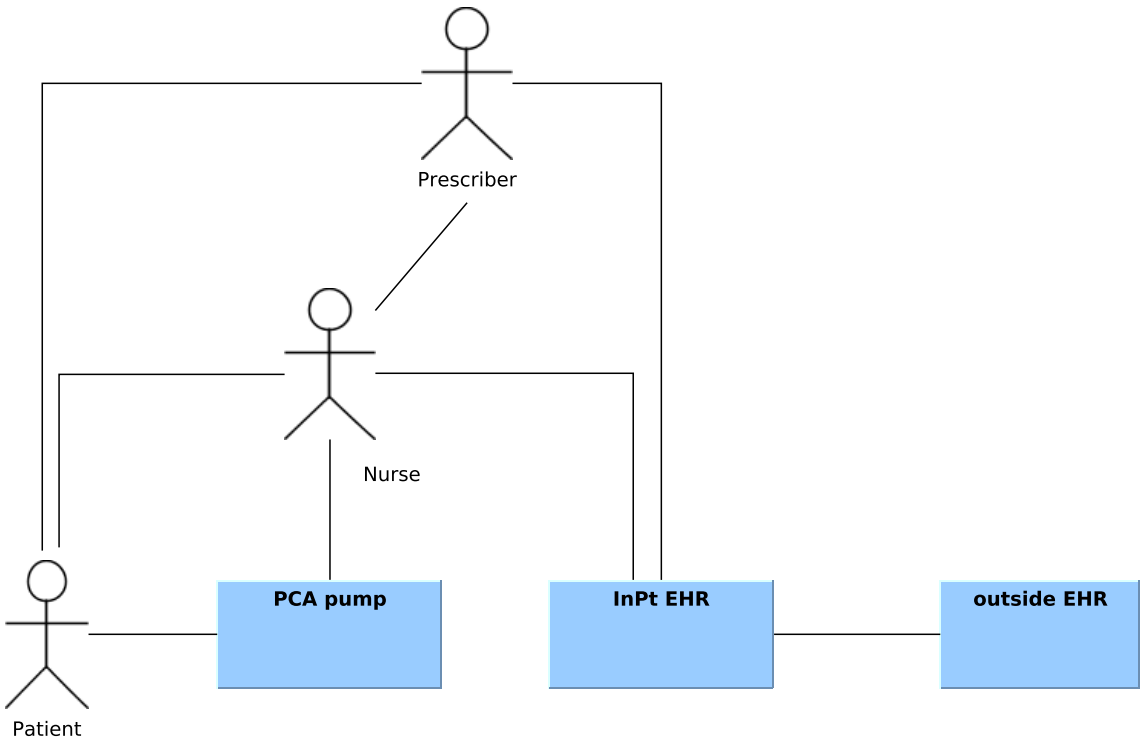


Figure 3.4 - UML context diagram: opioid PCA infusion

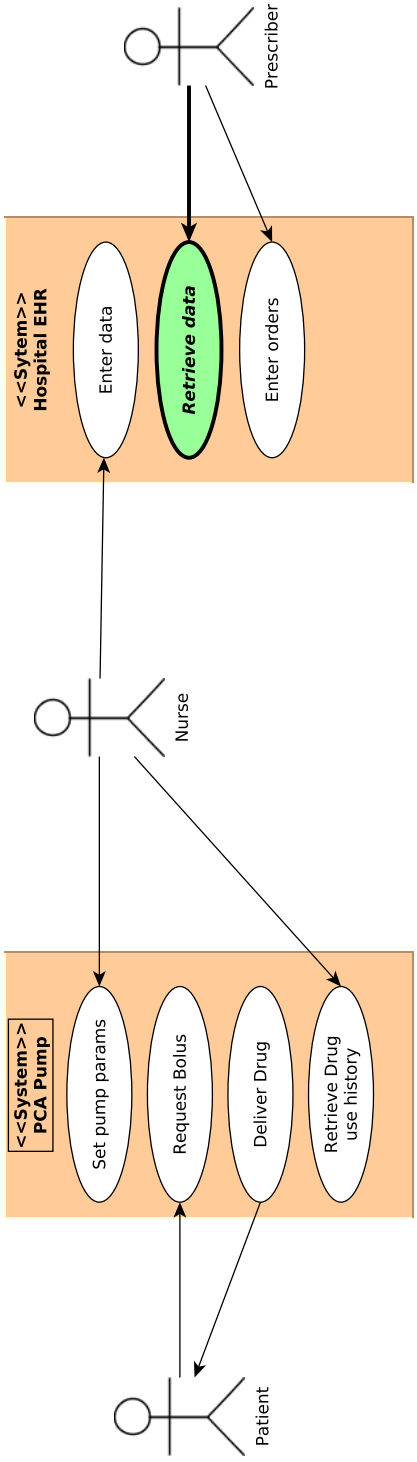


Figure 3.5 - UML use-case diagram: opioid PCA infusion

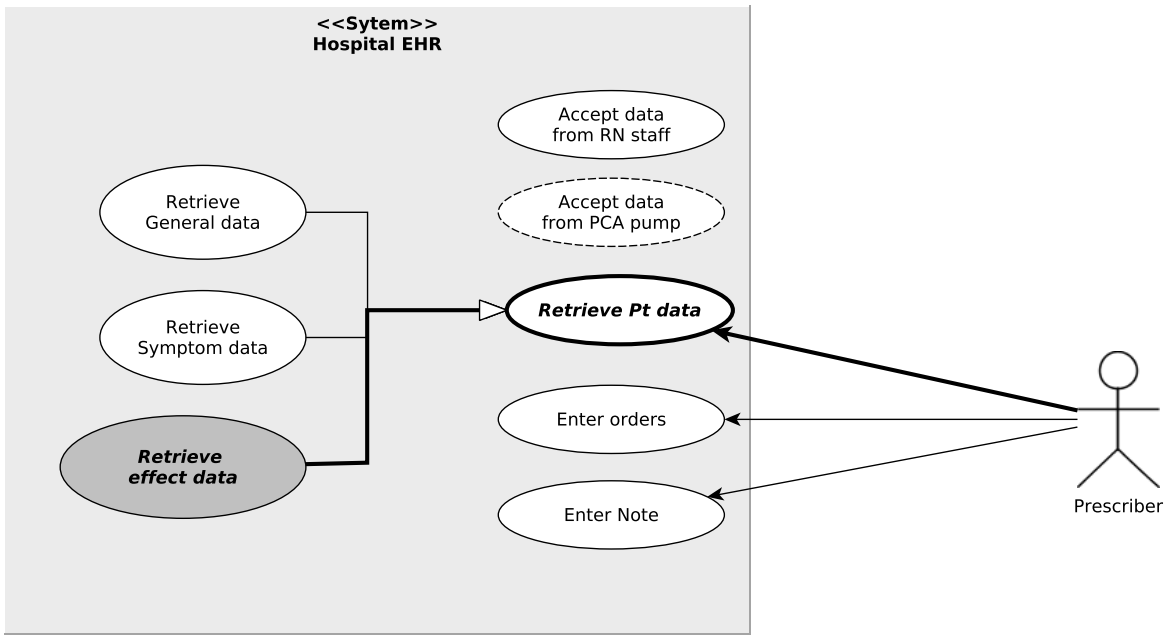


Figure 3.6 - UML detailed use-case diagram: prescriber-EHR interactions

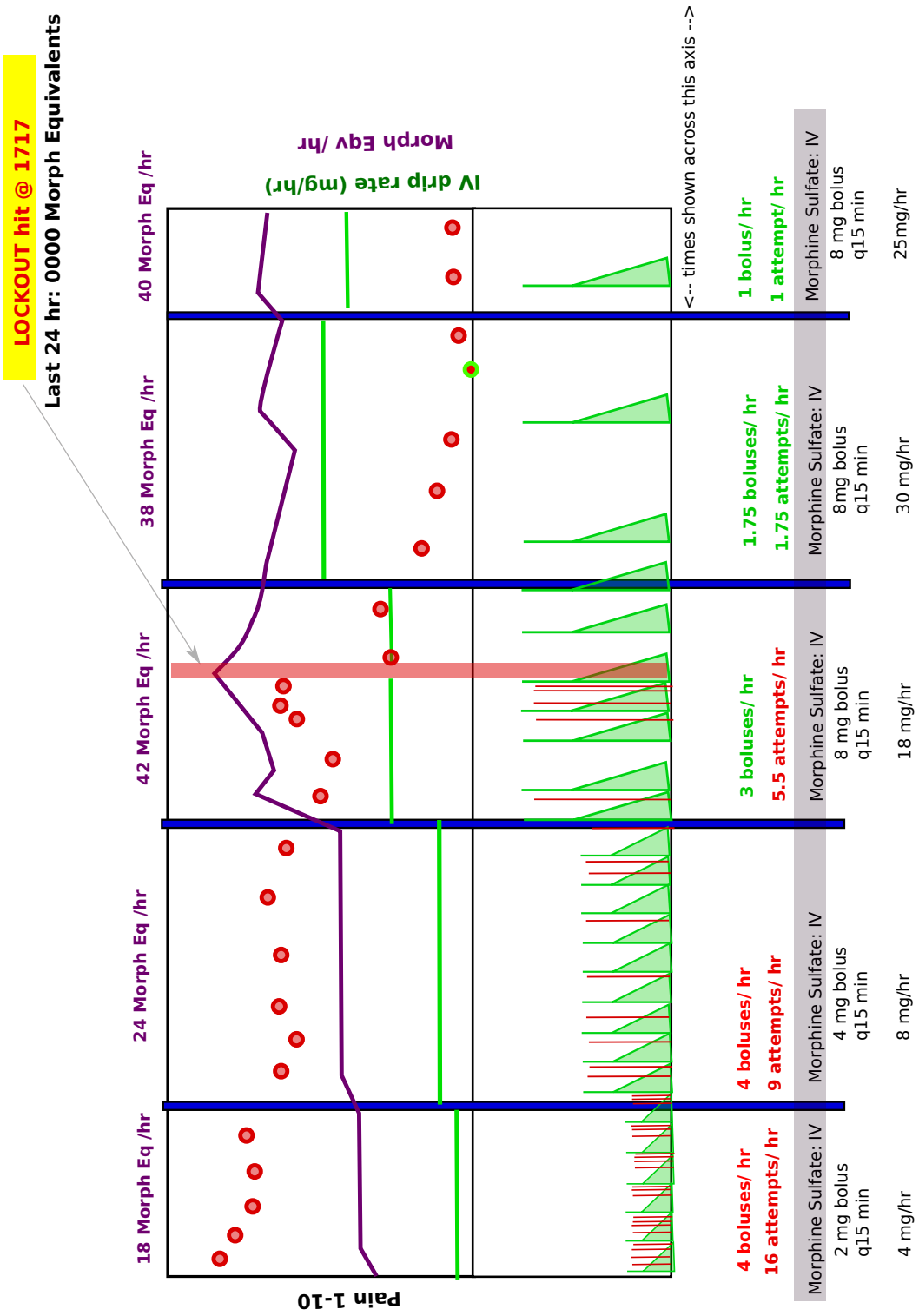


Figure 3.7 - Proposed EHR visualization of PCA pump data

CHAPTER 4

UNDERSTANDING THE DATA

4.1 Background

The goal of Aim 1 was to develop a solid understanding of the information that providers use to make management decisions regarding opioid PCA infusion regimens for palliative patients. As the ultimate goal was to develop a decision support tool, in keeping with traditional informatics practice, an information model was developed and used to accomplish this aim. A tool that supports decision making by providing data at the point of care should not display *all* data, but rather should display the *relevant* data - data that are actually needed at that point in time.[2,175,196,197] In keeping with that principle, the information model was not developed to provide a comprehensive or exhaustive list of *all* data and information elements involved in management of an opioid PCA, but to reflect those *typically* and *frequently* used by practitioners managing opioid PCA regimens in palliative settings.

Aim 1 was accomplished in two phases. In Phase 1 a systematic literature review and analysis was used to derive a list of concepts involved in decision making and ultimately an information model. In phase 2, the concepts on the model were validated by surveying domain experts.

4.2 Phase 1: Defining the Data and Information Elements

4.2.1 Methods

4.2.1.1 Design

Phase 1 began with a systematic literature review. Graphical mapping techniques were then used to summarize, synthesize, and organize concepts from the literature.[198,199] From an initial free-form mind map that represented all instances of concepts identified in the literature, a concept map displaying the unique data and information elements was abstracted. This concept map was then formalized into an information model.

4.2.1.2 Sampling

The sample for the systematic literature review included three distinct types of artifacts: published journal articles formed the core of the review, textbooks and guidebooks provided additional academic sources, and clinical protocols from several health institutions provided real-world practical data. The sample sources are shown in Table 4.1 and a diagram showing the process is shown in Figure 4.1.

An initial search of journal articles was performed using the PubMed database. As *management* of opioid regimens is limited to the domain of health care practitioners, PubMed was the only literature database used in initial searching. To identify articles published from 1950 to the present, searches using simple text, key-word, and title-words were performed based on combinations of the terms “patient controlled analgesia,” “PCA,” “palliative,” and “palliative care.” Articles of interest were those that discussed or described the clinical use of opioid medications given by parenteral (intravenous or subcutaneous) infusion using a PCA paradigm. Particular attention was paid to articles with a palliative focus, but as the PCA paradigm developed out of the anesthesia domain and post-operative setting, this was not a strict criterion lest foundational articles be missed. The bibliographies

of articles were reviewed and relevant works cited there, if not already present in the corpus of identified articles, were obtained. This process was followed until results of searches began to show high overlap with articles already included in the corpus. Finally, the abstract or full text of the article was reviewed for relevance.

Well known, well respected, and oft quoted palliative texts and guidebooks were reviewed. For these materials, sections dealing with either PCA use or opioid management were identified, extracted, and included in the corpus. As opioid PCA regimens are a specialized type of opioid analgesia regimen, sections on opioid management were also included.

The last category of material included in the systematic review was clinical protocols. Several healthcare institutions around the country were contacted with a request for protocols dealing with palliative use of opioid PCA regimens. Interestingly, palliative experts at several institutions responded that they had no protocols in their institutions that they felt should be used as evidence in a project such as this. As with the texts and guidebooks, sections of protocols related to opioid infusion management in general were included, as PCA regimens are a specialized subset of opioid regimens.

4.2.1.3 Data Collection Methods - Annotation

The protocol for annotation and the number of sources to be used was determined prior to beginning the review. In this protocol, a single reviewer (this author) reviewed sources in electronic form, and tagged any mention of a data or information element associated with management, adjustment, or assessment of an opioid PCA regimen. As typical of qualitative inquiry, this reviewing and tagging procedure continued until a state of saturation was reached. We defined saturation for this project as when, after review of the initial set was complete, 3 or more consecutive new sources were reviewed but revealed no

new elements. At the point this criterion was met, it was assumed all major concepts used for decision making in the domain had been identified and the set of tagged data elements was considered complete.

Tagging of sources, extraction of tagged data, manipulation of extracted data, and qualitative review of data was carried out electronically, so considerable document processing and manipulation was required. A pipeline approach was used to facilitate data extraction and qualitative review by combining several different applications in series. This pipeline is illustrated in Figure 4.2.

The first step in the process was to obtain the full text of each source. For sources such as textbooks, handbooks and protocols that were available only as a paper copy, sections identified as relevant to the scope of this project were scanned to create an electronic file. "ScanTailor,"[200] a free document processing application, was used to process initial scanned images. With this application, image files can be combined, cleaned, aligned, straightened, cropped, then saved as high-contrast, monochrome, multi-page PDF files. For documents obtained in electronic format other than PDF, various tools were used to convert them to PDF format, including "LibreOffice Writer,"[201] the "Ghostscript"[202] and "ImageMagick"[203] command line tools for Linux, and others. In order to be processed in the pipeline, all PDF files needed to have a text layer; files created from scans or other images lack this layer. For any PDF file that did not already have a text layer consisting of the full-text of the article, one was created using the optical character recognition (OCR) feature of the application "PDF-Xchange Viewer."[204] Once all files were available in the PDF format with the required text layer, they were ready for annotation.

Annotation was carried out using an Android tablet (an Acer a200). Files to be annotated were transferred to the tablet by FTP over WiFi (using an FTP server called "FTPServer"[205] on the tablet and the FTP client "Filezilla"[206] on the PC) or using an

application called “Dropsync.”[207] Dropsync allows true, bi-directional synchronization of files between specified directories on any PC and an Android tablet device via a Dropbox[208] account.

Once transferred to the tablet, the reviewer opened and read each source with one of two applications, “Repligo Reader”[209] or “ezPDF Reader.”[210] When any mention of data or information regarding adjustment or management of a PCA regimen was identified, he annotated it with the high-light annotation tool of the PDF reader. When annotation of each source was completed, the source was transferred to the Dropbox account or PC to await the extraction of tagged elements.

The way in which Repligo Reader and ezPDF Reader create annotations in the PDF file is a *critical* feature that makes possible the later techniques in this pipeline. Both applications can create highlight annotations by copying the highlighted text to a secondary location in the PDF text layer where it is stored as a discrete annotation object.

4.2.1.4 Analysis – Mind Mapping

The open source application Docear[211] was used to extract and analyze the annotations to produce a mind map. A mind map is a flexible, free-form approach to diagrammatically representing concepts and relationships where concepts are represented as nodes arranged into a tree structure with relationship links and other metadata represented visually.[212] Docear is self-described as an “Academic Literature Suite.” It combines fairly robust mind-mapping capabilities with features of typical reference managers. Docear can extract annotations from a PDF file by first creating a node to represent the parent PDF file then creating a child node for each annotation object stored in the PDF text layer. Each node's label is set to whatever text was saved in that annotation object by the PDF reader when the annotation was created. Once extracted, nodes may be moved, grouped, sorted,

and enriched by the addition of tags, graphical icons or other metadata. Each node extracted by Docear is individually tagged with information referencing the annotation's location in the source PDF. This allows a user to search for, sort, and count nodes based on their source document as well as to open the source PDF to the precise location of the annotation in the document even after considerable manipulation to the structure of the mind map.

After annotations from a source were imported into an initial mind map, simple drag-and-drop functionality was used to move, organize, and group elements into categories. Within each category, nodes were organized into a hierarchical structure. For example, if "GI side effects" was identified in one source and "nausea" was identified in another, a category of "side effects" could be created with the node "GI side effect" as a child and then the "nausea" node placed as a child under "GI side effect." Once all annotations from the initial set of sources had been organized, saturation was assessed.

To assess saturation, 4 additional protocols were reviewed, annotated, and imported into the mind map, using the process previously described. Each element in the 4 protocols was successfully mapped to an existing concept and no new elements were identified. This met the pre-established definition of saturation. Additional journal articles were then reviewed, annotated, and imported to the mind map. In the first article reviewed to assess saturation, a concept not currently represented on the map was identified. While this element was a new concept, it did fit into an existing category. After this, 4 additional articles were sequentially reviewed, annotated, and annotations were imported into the mind map. All elements identified in those articles mapped to concepts currently represented in the mind map with no new elements identified. This fulfilled the prespecified definition of saturation. The list of protocols and articles used to assess saturation is shown in Table 4.2.

Having reached a state of saturation, this mind map was considered complete. It represented evidence-based data and information elements involved in managing an opioid

PCA organized into a hierarchical model. Each node corresponded to one mention of a data or information element used in making decisions when managing an opioid PCA infusion in the evidence corpus.

4.2.1.5 Early Synthesis – Concept Mapping

The initial mind map was then used to create a concept map. A concept map is a formalized version of a mind map that can be used by system designers and ontology developers. A concept map highlights unique concepts and the structure is often guided by a "focus question" or some sort of theoretical framework.[213] The focus question was, "How would a palliative medicine clinician search for these data and information elements?" It was common to have multiple instances of the same element, such as "respiratory depression," in the mind map as many concepts were mentioned numerous times in the evidence. All instances of identical concepts on the mind map were aggregated into a single node in the concept map. Similar concepts on the mind map were likewise collapsed into single nodes if it was determined that they represented synonyms of the same underlying clinical concept. Being careful to retain the categorization into groups identified in the prior mapping exercise, adjustments were made to the structure to locate similar concepts into closer proximity within the map. The result was a graphic map representing each unique data or information element used in managing an opioid PCA.

4.2.1.6 Final Synthesis – Information Model

Nodes from the concept map were examined and transferred to a spreadsheet, creating a list of unique data and information elements. This list, along with the concept map, was then used to build an information model that represented those data and information elements that are important when managing an opioid PCA infusion based on concepts reported in the literature over a period of over 50 years (1960 to present). This

information model further formalized the concept map, representing the concepts as real-world objects,[214] in this case, as data might be organized within a typical electronic health record.

4.2.2 Results

4.2.2.1 Sample Description

Initial searches identified 315 potential journal articles, of which 225 remained after review of articles or abstracts and application of the inclusion and exclusion criteria. Throughout the 1970's there was slowly increasing interest in PCA with sporadic publications, though the concept was called by a variety of different names. Articles in this time frame were found most often by following citations in later articles. In the late 1980's there was a dramatic increase in the number of publications. Figure 4.3 shows a graph of the number of PubMed-indexed articles published per year when searching on the “patient controlled analgesia” used as either a general text string, a title/abstract term, or a MeSH term.

As the model being developed was intended to be representative but not necessarily exhaustive, a representative set of literature consisting of 2 major texts in the field, 5 handbooks and guidebooks, 10 articles specifically selected to be high yield, and 1 protocol were selected for initial analysis. Sources were selected based on the potential yield, which was subjectively determined by the comprehensiveness, the length of journal article (with preference to longer articles assuming they would contain more detail and data), and the frequency that the source was cited by other sources. A second set of sources to determine if saturation had been reached was selected and is described below.

4.2.2.2 Mind Map

When complete, the mind map revealed 4 general categories into which all identified elements could be placed. The categories were: (1) elements related to the patient, (2) elements related to the treatment plan, (3) elements related to the medication being given, and (4) elements related to the pump settings / prescription. Further organization revealed varying levels of subdivisions, depending on the category. These subcategories are shown in Docear's outline form in Figure 4.4. The entire mind map was quite large, at approximately 12 feet tall if printed using a standard font. A small segment of the mind map to show the structure is shown in Figure 4.5.

4.2.2.3 Concept Map

In creating the concept map, three categories were retained and directly transferred from the mind map: elements related to the treatment plan, elements related to the medication being given, and elements related to the pump settings / prescription. From elements in the mind map related to the patient, three distinct categories of elements were created in the concept map. This resulted in 6 categories: (1) patient adverse event data, (2) patient pain data, (3) patient context data, (4) treatment data, (5) medication data, and (6) pump data. While this minor restructuring in form in which the data was presented increased the ease with which researchers could examine concepts and relations between concepts, it had no clinical implications. The full concept map may be reviewed in Appendix A.

4.2.2.4 Information Model

The information model represented all elements from the concept map as objects in a hierarchical arrangement. There were two main categories, *information related to treatment* and *information related to the patient*. Under each category was a cascade of more specific

information elements. For example, AdverseEvent is an example of patient-related information which included the more specific topic of adverse GI_Effects, which in turn included instances of nausea, vomiting, and constipation. The information model can be seen in Figures 4.6, 4.7, and 4.8 .

4.2.3 Discussion

Many patients with serious, life-threatening illnesses experience significant, complex, and difficult symptoms as a consequence of the disease or disease treatment. The clinical specialty of Palliative Medicine emerged to meet this need. Treatment approaches such as parenteral opioid infusion administered by PCA protocols are important interventions in the palliative medicine toolbox that can relieve suffering and improve quality of life. Managing an intervention like opioid infusion via PCA pump is a complex, high-stakes endeavor, particularly when doses need to be titrated rapidly in response to severe pain. Unfortunately, palliative medicine clinicians have complained that they lack adequate data to make optimal titration decisions; that the information is either not present in the record or is too difficult to locate. Automating the aggregation and presentation of relevant information holds the potential to address the problem of missing or difficult-to-locate information. Preliminary work revealed that the information flow to support this task is complex, and there has been little or no literature evaluating the adequacy and quality of data available to clinicians at the point of care, with respect to managing PCAs. Therefore, the first step in designing an informatics solution to this clinical problem was to identify the data and information needed for clinical decision making in the identified use case of using opioid infusion via PCA pump in the palliative care context. For aim 1, phase 1, an evidence-based information model was developed, based on a systematic review of the literature.

This first phase of aim 1 began with broad literature evaluation and data extraction, which was followed by sequential creation of progressively more formalized models. The mind map represents a comprehensive set of elements gleaned from a representative set of published literature and PCA protocols, organized into a loosely hierarchical structure. The concept map consolidated and condensed this raw data into a more manageable form, retaining but refining the hierarchical structure. The final step was creation of an information model for the clinical use case of opioid PCA infusion management. This information model depicted data and information elements involved in this clinical domain, representing them as objects organized into hierarchical groupings of increasing specificity.

A data or information model forms the foundation of any robust CDS application and increasingly it is recognized that this foundation should be laid using rigorous, standardized approaches; traditionally there are three sources from which to build such a model: expert opinion, predictive models (based on clinical data), and published literature.[2] In cases like this where formal, universally accepted guidelines to direct care are lacking, evidence-based medicine (EBM) approaches, such as systematically reviewing published evidence as done here, provides one mechanism to form guiding principles from valid, relevant information.[215,216] In this domain, a body of evidence existed in the form of well-respected articles, texts, and guidebooks. Though perhaps not true in every case, for most clinical domains there likely is such evidence available even if there are not clear guidelines already synthesized. This project was strengthened by the inclusion of real-world protocols but such protocols, might or might not be available for other domains, depending on the specific domain and focus question at hand.

The overall approach used in this project was in no way tied to the domain and could easily be used in any other similar domain where there is adequate evidence to form a corpus for element identification and extraction. This work used mind mapping, an

accepted qualitative approach,[198,217,218] to apply principles of evidence-based medicine to build the requisite foundation for the proposed CDS application. Building the information model from the ground up using articles and texts ensured that the foundation for this CDS would be evidence based. Incorporating real-world protocols ensured that the information model would be relevant to practicing clinicians. The systematic approach, including broad literature searching and extraction of elements until a formally defined point of saturation was reached, supplied a degree of rigor to this process.

The tools (see Figure 4.2) and techniques used in this project are domain agnostic, as well, and thus should be generalizable to other complex clinical domains. While considerable work was required to locate, evaluate, and implement suitable tools to develop the pipeline used in this project, once developed, the actual use of that pipeline was straightforward. The task of amassing clinical evidence is common and likely necessary for any work to build the foundation of a CDS. The process of annotating source documents is a common task in qualitative analysis. Based on the author's limited experience and his discussion with other researchers experienced in qualitative work, the tools and techniques used here seemed no more difficult, and perhaps less difficult to use than other qualitative analysis tools and techniques; the time required also seemed consistent with typical qualitative work. The simplicity of Docear's mind mapping features, however, was anecdotally noted by both this author and an experienced qualitative researcher to be, while adequate for this type of work, considerably simpler than traditional qualitative software. Easier use combined with the negligible hardware and software costs compared to other software make the approach and the tools developed for use in this project an attractive option for those seeking to build similar foundational infrastructures for CDS applications in other clinical domains.

A limitation of this portion of the work was that the review and annotation was

primarily carried out by a single person. This limitation was mitigated by two factors. First, the work was conducted by a domain expert board certified in as a sub-specialist in palliative medicine with extensive experience managing PCAs across a wide spectrum of care locations from outpatient settings to tertiary medical center ICUs. This individual also has informatics training. It was felt considerable expertise and intimate familiarity with the domain were important to ensure correct interpretation and preservation of semantic meaning when identifying, manipulating, and analyzing the data and information elements. Second, the work was reviewed in detail, at least weekly, by a second individual who also had a background in clinical care (nursing), some experience with palliative care and PCA management, and extensive informatics experience.

4.3 Phase 2: Validating the Evidenced-Based Model

4.3.1 Methods

The models synthesized from published evidence and clinical protocols represent data and information believed to be important in management of opioid PCAs in palliative settings. However, published literature, protocols, and guidelines may differ from actual clinical practice.[219–225] The information model was reviewed by the investigator, a domain expert in palliative management of opioid PCA infusions, and by other clinicians, and the model appeared to show all data needed to manage an opioid PCA infusion in palliative settings. This informal review suggested the model had at least face validity. More rigorous evaluation of other forms of validity was undertaken.

4.3.1.1 Design

Model validation was approached similar to a content validity assessment. Content validity, the extent to which all facets of a theoretical construct are represented within a set of items in a measure,[226] would confirm that the elements obtained from the prior phase

encompassed the real-world data and information needs of providers managing opioid PCAs in palliative settings. Content validity differs from and complements face validity in that the evaluation process is more formalized, and is conducted using recognized subject matter experts.[226]

4.3.1.2 Data Collection Methods

Content validity of the model was assessed through expert review using an approach based on a Modified Delphi technique.[227] The Delphi method is a widely used and well accepted method of evaluating consensus from a group of experts; the modified approach differs from "traditional" Delphi methods in that the process begins with a list of elements rather than asking the experts to construct the list of elements themselves.[227,228] The Delphi method typically involves multiple rounds of questionnaires that seek to discover then progressively refine items until consensus is reached. Because the purpose for this study was simply to assess the perceived completeness of the *existing* information model, and because this model was evidence-derived, a single round was anticipated to be sufficient.[227]

4.3.1.3 Sampling

Participants in a Delphi study are expected to be domain experts. Although there is not consensus around the metrics for what constitutes an expert, the participants are expected to be trained and competent in the clinical domain of interest.[227] There is also no standard way to determine the number of participants required for a Delphi study, although many experts recommend that researchers use the minimum number of subjects necessary to sufficiently encompass the requisite area of expertise.[227] Like usability evaluations, Delphi studies with less than 10 participants are not unusual, particularly when the domain is well constrained.[227]

Target participants for this study were health care providers who managed and/or

prescribed opioid PCA regimens in palliative settings. Given the narrow clinical focus of the domain of interest and the relatively small national pool of experts available, target size was 3-7 experts. Using a convenience sampling approach to recruitment, providers known to the author to be experts in the field were contacted and asked if they were willing to participate. Given the length of the survey (103 data elements) and that the potential participants were busy expert clinicians, we anticipated that less than half of those invited would respond, so 14 experts were invited to participate. The survey remained open for 6 weeks.

4.3.1.4 Survey Design

After Institutional Review Board approval, the expert review and validation was conducted using an on-line survey administered using the REDCap survey system, which is hosted at the University of Utah. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[229]

The survey was constructed similarly to other Delphi studies. A single vignette was presented to the survey respondents to help focus responses on the use case of interest. The vignette described a patient in an inpatient setting who was experiencing pain from a life-limiting, but not *immediately* terminal, disease. For each element from the information model, a question was created, asking the expert to rank that element's importance for clinical decision making regarding opioid PCA regimen management on a 5-point Likert-type scale (not important, of minor importance, important, very important, extremely important). In this way 44 basic elements were presented to all participants. Using decision

logic based on responses to these basic items, up to fifty-nine additional elements could be presented. For example, when a survey participant indicated that “vital signs” was at least important (≥3), he or she was presented with the list of individual vital signs (pulse, blood pressure, etc.) from the information model. If the participant marked “vital signs” as less than important(1 or 2), he or she was not presented any of the child elements for evaluation. This lead to a possible total of 103 questions that could be presented to participants if all decision logic was triggered. At the end of the section, participants were presented an open text box to list any data or information elements that they felt were important but that did not appear on the list, or give other comments about elements. A representation of the section of the survey used for this work, formatted for print, is presented in Appendix B.

4.3.1.5 Analysis Plan

The purpose of the survey was to assess the extent to which domain experts considered the list of data and information elements to be important for clinical decision making for the described use case. Although the Likert-type question design asked participants to consider the level of importance, the primary question was simply, which elements ranked at least “important” (response of 3) versus those rankings less than “important” (response of 2 or 1).

The primary analytic method was simple descriptive statistics. For each of the data and information elements, the average (mean) ranking across the respondents was used to determine which elements were important (mean of 3 or higher). Similarly, standard deviation (SD) provided an initial estimate of response consistency, using the heuristic that SD of 1 or below represented high levels of consensus, and greater SD represented lower levels of consensus. Although the use of mean and standard deviation may be viewed as “incorrect” from a strict technical standpoint by some because the scale produces ordinal

data, these are the most common metrics reported in the literature for Likert-type items,[230] and it has been repeatedly demonstrated that traditional statistical metrics are robust and appropriate for these analyses.[231]

In addition, we used percent agreement and intra-class correlation (ICC) to evaluate consensus across some of the sets of items. ICC is an alternative to the more common metric for determining agreement between raters, *kappa*. The *kappa* metric assumes the data are categorical, whereas weighted *kappa* and ICC can be used for ordinal (or higher) data; the ICC is a special case of weighted *kappa.* An advantage is that, whereas *kappa* is used to evaluate correspondence between two raters, ICC evaluates correspondence across multiple raters. A potential limitation is that ICC is computed as a ratio of between-rater and within-rater variability, and so can only be computed for sets of items (not for individual questions). Similarly to *kappa* and correlation coefficients, ICC values can range from -1 to +1.[232]

Like *kappa*, there are no hard and fast thresholds for interpretation. It is common for opinion-based items to have lower correspondence (agreement in the range of .4 to .6), whereas significant agreement on objective measures typically is viewed as values above 0.7.[232] Cohen, the developer of the *kappa* and related statistics, suggested that values as low as .41 may be acceptable for health research, particularly with subjective items. He suggested the Kappa result be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.[233] Given the subjective nature of this evaluation, and that agreement on the exact level of importance was not the primary purpose of this analysis, we used these liberal thresholds for interpretation. While it is possible that, depending on how the software calculates ICC, the values may be negative, it is difficult to interpret the meaning of negative ICC values. Some interpret negative values like a correlation, with negative simply showing the direction of the relationship between ratings

by different experts; others interpret negative ICC to mean that the variation across items for a single rater is greater than the variation between raters (that is, that the items in the set may not be tightly linked); and still others interpret a negative ICC to mean that the true correspondence between raters is low.[234] When a negative ICC was obtained we examined the raw data to aid interpretation.

4.3.2 Results

The validation (expert review) survey was completed by 5 participants (36% of those invited). Data were analyzed using Microsoft Excel and Statistical Package for Social Sciences (SPSS, version 22) software. Demographic characteristics suggested that the participants were clinical experts in the relevant domain, as shown in Table 4.3. Four of the participants were physicians and one was a nurse practitioner; all were experienced clinicians with palliative care experience. Three of the participants ranked their ability to manage opioid PCA regimens as “Competent” and two ranked their ability as “Expert” level.

The average ranking and standard deviation for each element of the 103 elements is shown in Table 4.4. There was substantial agreement among the experts, overall, with an Intra-class Correlation (ICC) of 0.78 (95%; Confidence interval [CI] 0.71 – 0.84). No additional data or information elements were suggested. The majority of elements (96; 93%) received average ratings corresponding to important (ranking of 3), very important (ranking of 4), or extremely important (ranking of 5) for clinical decision making. For these elements, there was moderate agreement between expert rankings for these 96 elements with an ICC of 0.60 (95% CI 0.46-0.71). Eight elements (7.8%) had unanimous agreement across all 5 experts as being extremely important. Those extremely important elements are shown in Table 4.5.

While most of the items listed on the survey received average ratings of at least 3 (“important”) across all 5 experts, there were 7 elements (7% of the total) where the average ranking for the element was “less important” (2), or “unimportant” (1) in terms of influencing clinical decision making about PCA dose adjustments. Those elements are shown in Table 4.6. The ICC for this set of 7 lower ranked items was -0.16 (95% CI -0.22 to 0.94); the negative ICC is difficult to interpret. While some may interpret this as low agreement, the raw data and standard deviation suggest acceptable agreement between experts for these low-ranked elements, and only genetic profile had a standard deviation of higher than 1.

Disagreement between experts for a a number of items was noted. There were 13 items (12.6%) where the standard deviation was greater than 1; the ICC for these items was 0.12 (95% CI -0.96 to 0.69) which indicates was little if any agreement. For example, one of these items, “patient goals of care,” was rated highly by most experts (average rating 4.2 out of possible 5), but one expert rated this item as “not important,” the lowest level of importance, for decision making. Functional status was similarly ranked as not important by one expert, but at least “important” by the others. One expert rated the patient’s genetic profile as extremely important, whereas the others rated genetic profile as not important or of minor importance.

Experts agreed on the importance of items such as interventional and adjuvant therapies, but were in less agreement on the importance of non-analgesic pain interventions aimed at the underlying cause of pain. There appeared to be no consensus about patient I/O's (fluid “ins and outs”), as this element was ranked differently by every participant. The items for which there was lower consensus among experts (SD>1) are shown in Table 4.7.

4.3.3 Discussion

The expert review of the information model supports content validity. There was substantial overall agreement (ICC = .78) for the absolute ratings of importance. There was unanimous agreement from these experts about the most important items and no new data or information elements were suggested by the experts. There was some variation in ratings of the level of importance, and a few items with lower agreement about the absolute importance rankings (*SD* between experts greater than 1 for the item). A small number of items were identified as less important (mean rating < 3) but no item was ranked as completely unimportant (mean rating < 2). Some variability in the absolute rankings about level of importance was not surprising, given the subjective nature of the question and lack of evidence in the literature about what data elements are important for this use case. Overall, the findings support the idea that the items in the information model are viewed by expert palliative medicine providers as important for clinical decision making in the use case.

4.4 Summary Discussion of Aim 1

Together phase 1 and 2 suggest that the novel approach developed to identify, extract, and analyze data elements from literature and protocols was successful. The method, which allowed annotation of standard PDF files (a common file format in which many full-text journal articles are readily available) to be carried out on a low cost and highly portable tablet device, was a great benefit to this qualitative approach. The entire process handled the volume of PDF files with no difficulty. Docear, the application used to extract, sort, and categorize the annotations, easily handled a sizable mind map with over 1,500 nodes. There were no problems with file or application instability when managing a mind map of this size, even on a PC several years old and with modest hardware

specifications. Physical size of the mind map would have presented a considerable challenge if a 'hard copy' of the mind map was needed; it would be approximately 12 feet tall if printed using a standard font size. However, the zooming and panning features in Docear combined with robust search capabilities and the ability to independently collapse and expand any branch of the mind map, allowed for relatively easy navigation, manipulation, and editing of the mind map, even one of this large size.

The pipeline developed for this project may have application to a wider group of qualitative research studies. The relative simplicity and portability of the process combined with the extremely low cost of required hardware and software make this an especially attractive method for projects with limited budgets. Graphical mapping techniques, including mind mapping and concept mapping, are accepted methods of analysis and data organization in a number of fields.[198,217,235–237] This project proved that basic categorizing and organizing of elements in a branching hierarchy can easily be accomplished by mind mapping, even when dealing with a large number of individual concepts. This suggests that mind mapping as a method of initial knowledge engineering in health informatics is a reasonable candidate methodology to consider when the need arises to extract elements from published primary sources to build an information model.

The 4 general categories in the initial mind map emerged quickly and data and information elements were easily categorized into one of them. As extraction progressed, elements in each of these 4 categories lent themselves easily to further categorization into sub-categories, yielding a hierarchy with little ambiguity or overlap between categories. Data and information elements fit rather easily into these categories and sub-categories and there was very little strain or difficulty in the process of adding new elements to the existing mind map as it developed. Many elements appeared multiple times, both within single sources and across multiple sources, leading to the subjective feeling that data from all

sources were relatively consistent and that they reinforced common concepts. The free-form mind map was easily and progressively formalized, first to a concept map and then an information model, by means of aggregating nodes that had semantic similarity.

The expert review (survey) provided evidence of content validity for the model. That no additional element were suggested by the experts indicated that the extent of coverage was fairly complete; that is, the model was a reasonably comprehensive list of the applicable data and information elements needed for clinical decision making for the use case. The purpose of Aim 1 was to develop a representative, rather than comprehensive, list of elements to build a foundation for a display-oriented CDS application. Overall, the results of this portion of the work indicated that the inductive process was a successful strategy and the information model produced by this aim was evaluated as sufficiently representative of the use case.

Table 4.1
Citations for initial set of evidence used to create mind map

Type	Citation
Article	Cherny NI. Opioids and the management of cancer pain. European Journal of Cancer Supplements 2005;3(3):61-75.
Article	Ciaralli I. Patient-controlled analgesia. Paediatrics and Child Health 2009;19, Supplement 1:S83-S84.
Article	Pasero C, McCaffery M. Safe use of a continuous infusion with IV PCA. J. Perianesth. Nurs. 2004;19(1):42-45.
Article	Ladak SSJ, Chan VWS, Easty T, Chagpar A. Right Medication, Right Dose, Right Patient, Right Time, and Right Route: How Do We Select the Right Patient-Controlled Analgesia (PCA) Device? Pain Management Nursing 2007;8(4):140-145.
Article	Campbell L. Guidelines for the Implementation of Patient-Controlled Analgesia. Dis-Manage-Health-Outcomes 1998;4(1):27-39.
Article	Grass JA. Patient-controlled analgesia. Anesth. Analg. 2005;101(5 Suppl):S44-61.
Article	Etches RC. Patient-controlled analgesia. Surg. Clin. North Am. 1999;79(2):297-312.
Article	NCCN. NCCN clinical Practice Guidelines in Oncology: Adult Cancer Pain. 2014.
Article	Swanson G, Smith J, Bulich R, New P, Shiffman R. Patient-controlled analgesia for chronic cancer pain in the ambulatory setting: a report of 117 patients. J. Clin. Oncol. 1989;7(12):1903-1908.
Article	Ripamonti CI, Bandieri E, Roila F. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(suppl 6):vi69-vi77.
Textbook	Doyle D. Oxford Textbook of Palliative Medicine. 3rd ed. / edited by Derek Doyle ... [et al.].. Oxford ; New York: Oxford University Press; 2005.
Textbook	Walsh D, ed. Palliative Medicine. 1st ed. Canada: Saunders; 2009.
Guidebook	Storey P. Primer of Palliative Care. American Academy of Hospice and Palliative Care; 2006.
Guidebook	Storey P, Knight CF, Schonwetter RS. Pocket Guide to Hospice/Palliative Medicine. American Academy of Hospice and Palliative Care; 2003.
Guidebook	Pujol L, Katz N, Zacharoff K. The PainEdu.org Manual. Inflexxion; 2007.
Guidebook	Fine P, Kestenbaum M. The Hospice Companion: Best Practices for Interdisciplinary Assessment and Care of Common Problems During the Last Phase of Life. Oxford University Press; 2008.
Guidebook	Wrede L. Symptom Management Algorithms; A Handbook for Palliative Care. Intellicard; 2002.
Protocol	Hospice of the Bluegrass Medication guide.

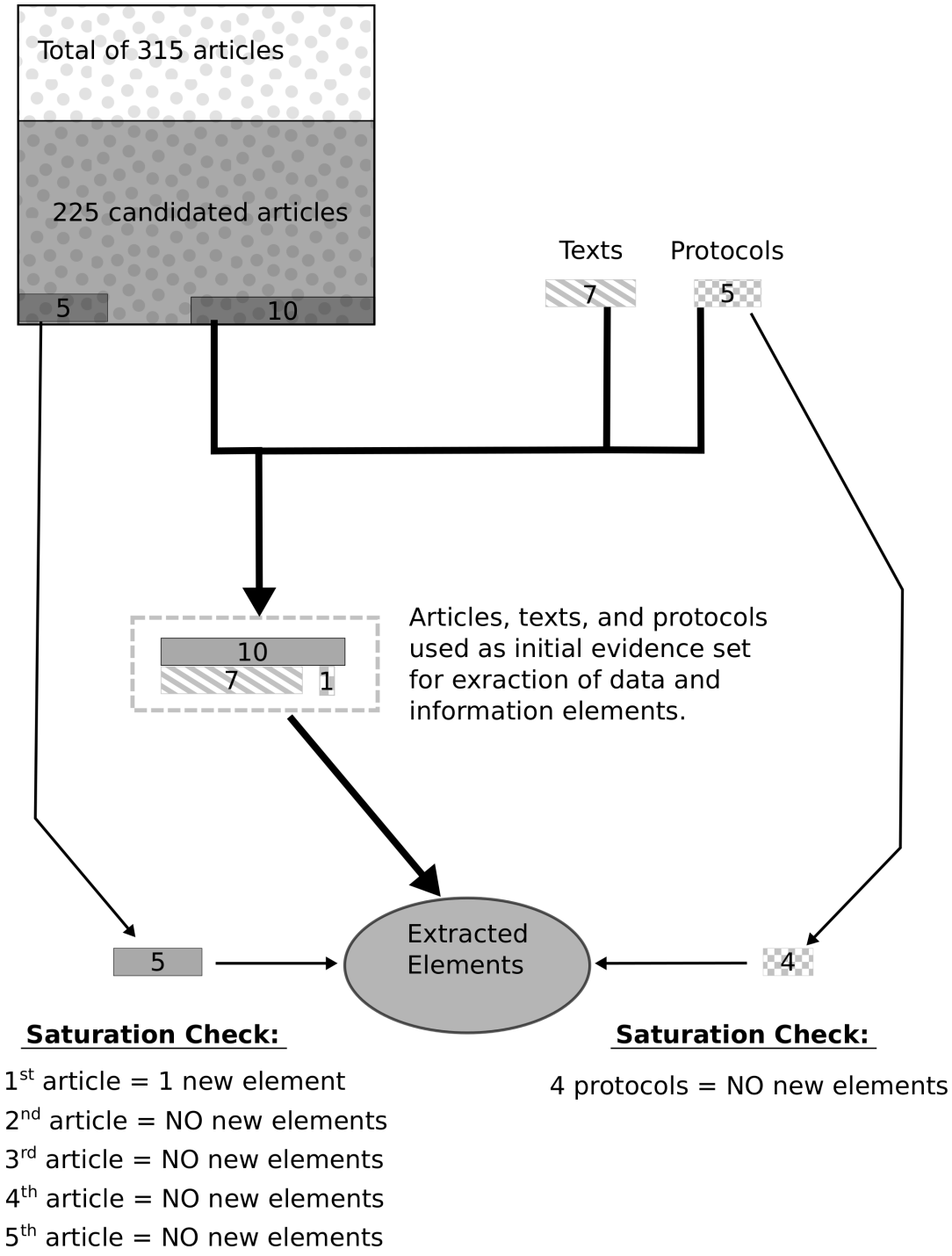


Figure 4.1 - Aim 1 phase 1 procedure: Extraction and assessment of saturation

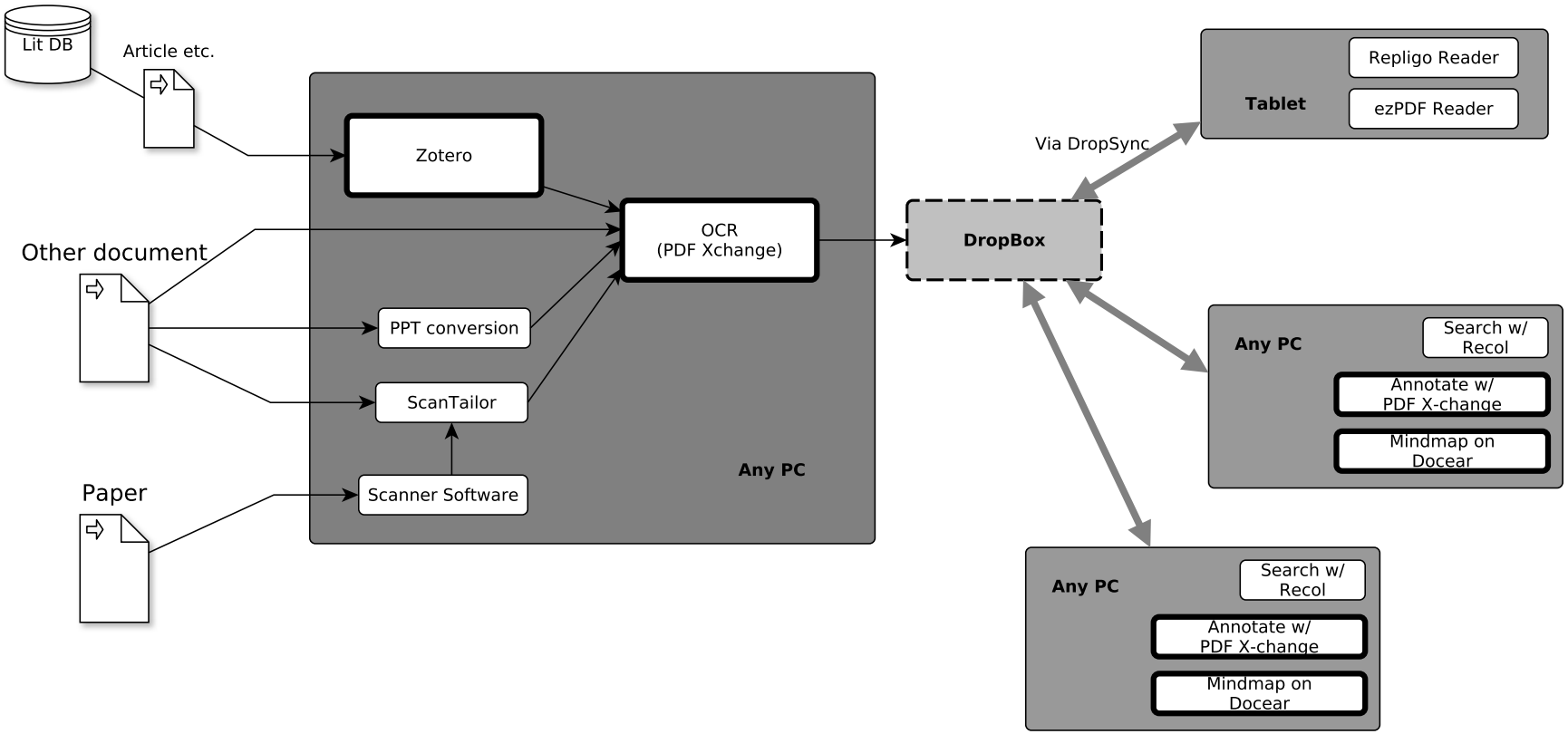


Figure 4.2 - Pipeline for annotation
Documents are obtained from sources at the left and
processed using the indicated tools, moving to hte right.

Table 4.2
Evidenced used to assess saturation

Type	Citation
Article	Dev R, Del Fabbro E, Bruera E. Patient-controlled analgesia in patients with advanced cancer. Should patients be in control? J Pain Symptom Manage 2011;42(2):296-300.
Article	Mercadante S. Opioid titration in cancer pain: A critical review. European Journal of Pain 2007;11(8):823-830.
Article	Chumbley G, Mountford L. Patient-controlled analgesia infusion pumps for adults. Nurs Stand 2010;25(8):35-40.
Article	Meuret G, Jocham H. Patient-controlled analgesia (PCA) in the domiciliary care of tumour patients. Cancer Treat. Rev. 1996;22 Suppl A:137-140.
Article	Mercadante S. Intravenous morphine for management of cancer pain. Lancet Oncol. 2010;11(5):484-489.
Protocol	San Diego Patient Saftey Council. Patient Controlled Analgesia (PCA) Guildlines of Care for the Opioid Naive Patient. 2009
Protocol	MountainStar Healthcare PCA protocols. MountainStar Healthcare, UT. 2014.
Protocol	St. Joseph Hospital PCA protocol. St. Joseph Hostpital, Lexington, KY. 2008.
Protocol	OHSU PCA protocol/ orderset. OHSU, Portland, OR. 2014.

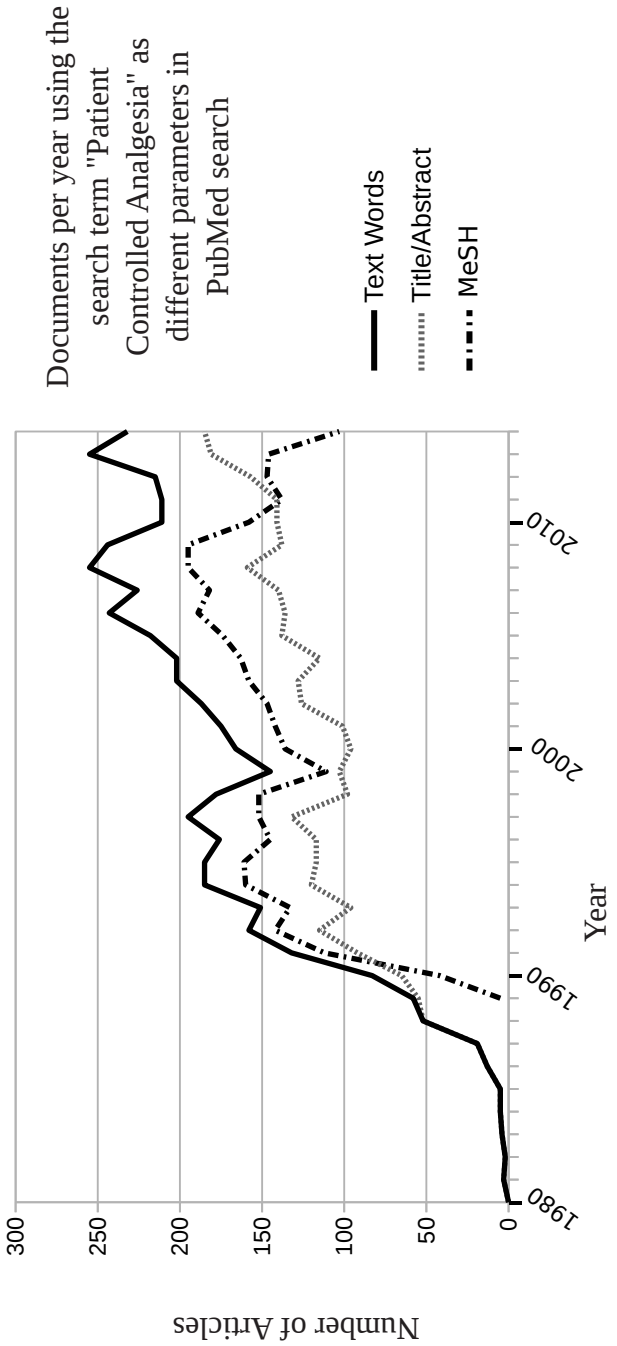


Figure 4.3 - PCA articles in PubMed

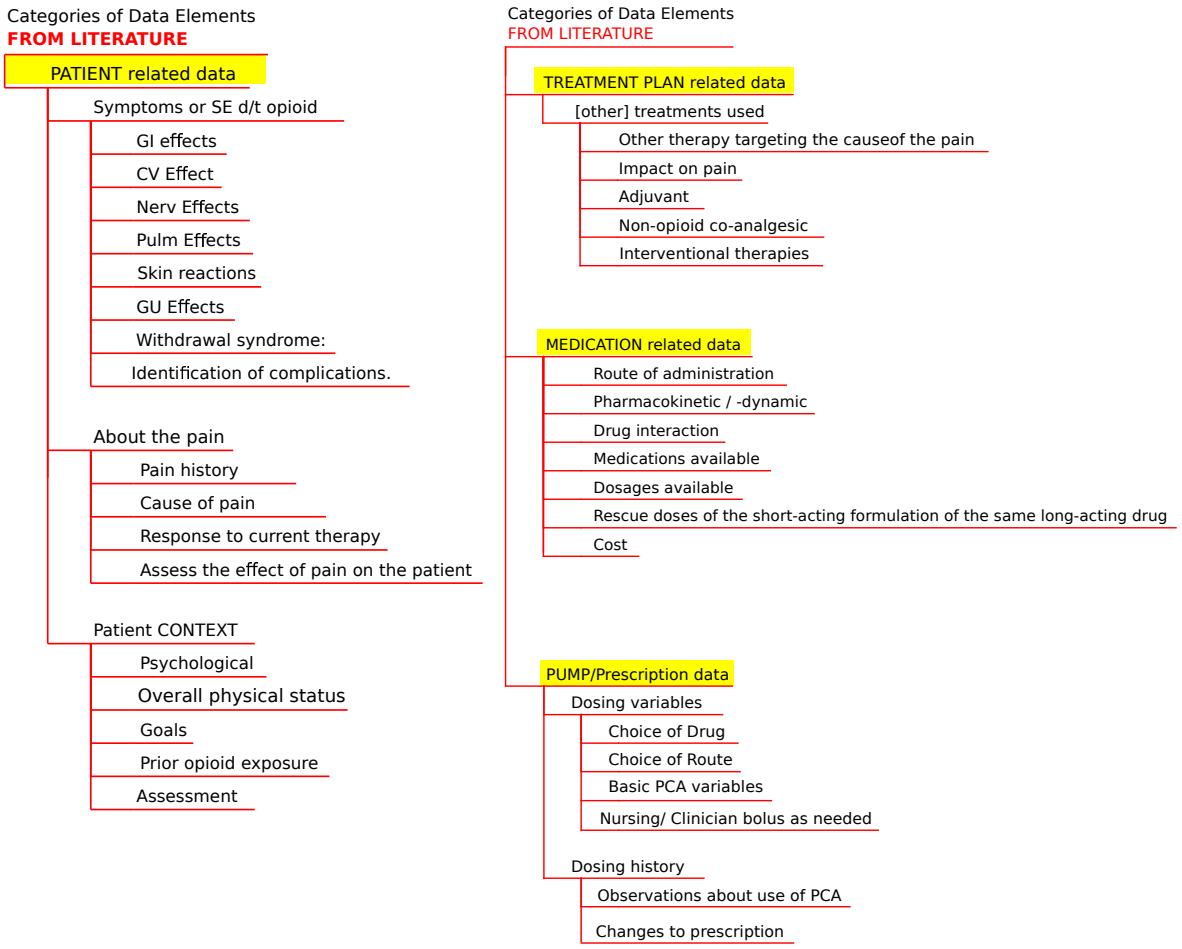


Figure 4.4 - Mind map sub-categories
(Printed in Docear's outline format.)

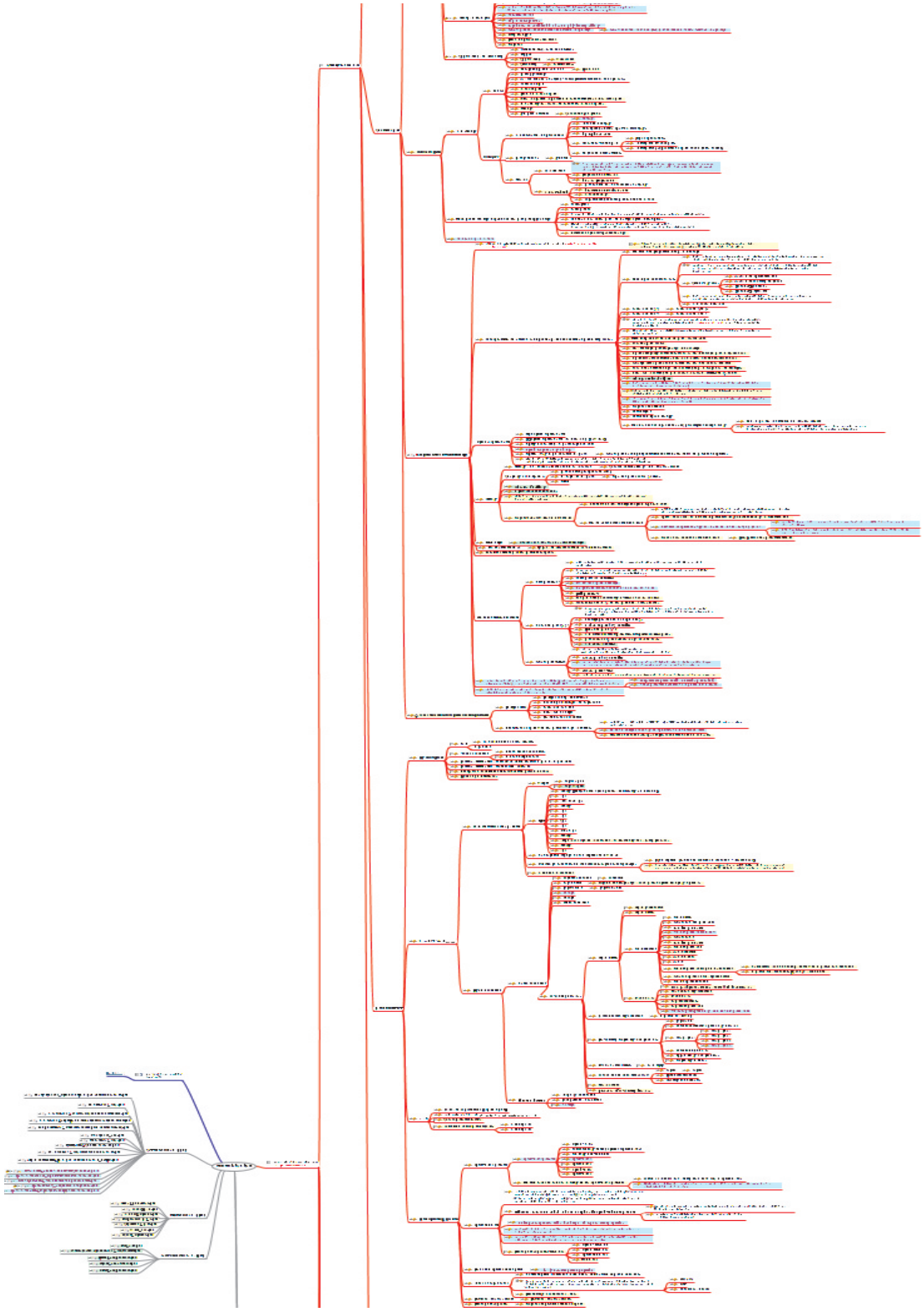


Figure 4.5 - Mind map
This is a screen capture of a small section of a Docear mind map showing the structure of a mind map.
(Actual mind map is over 12 feet long.)

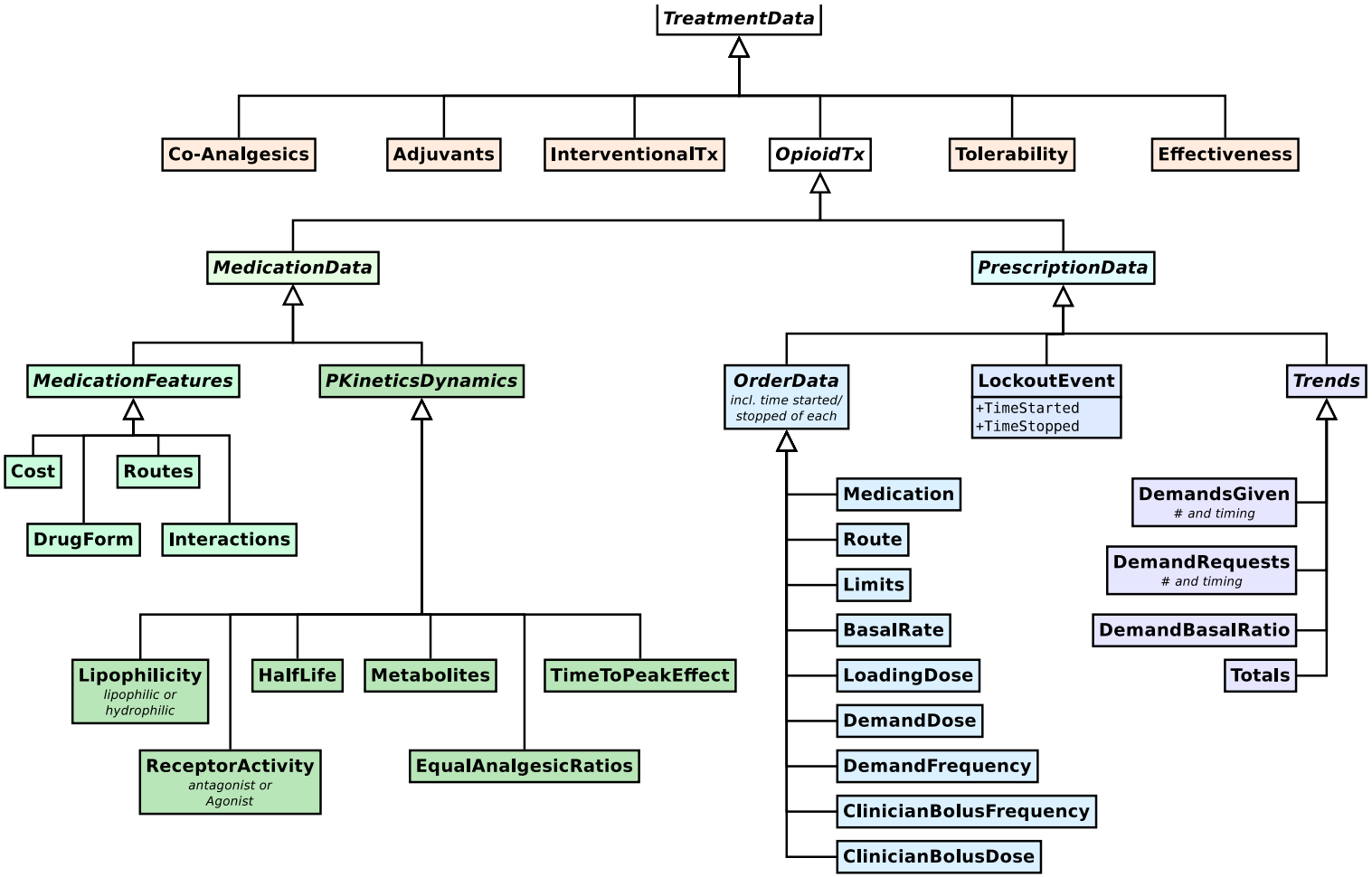


Figure 4.6 - Information model - treatment data

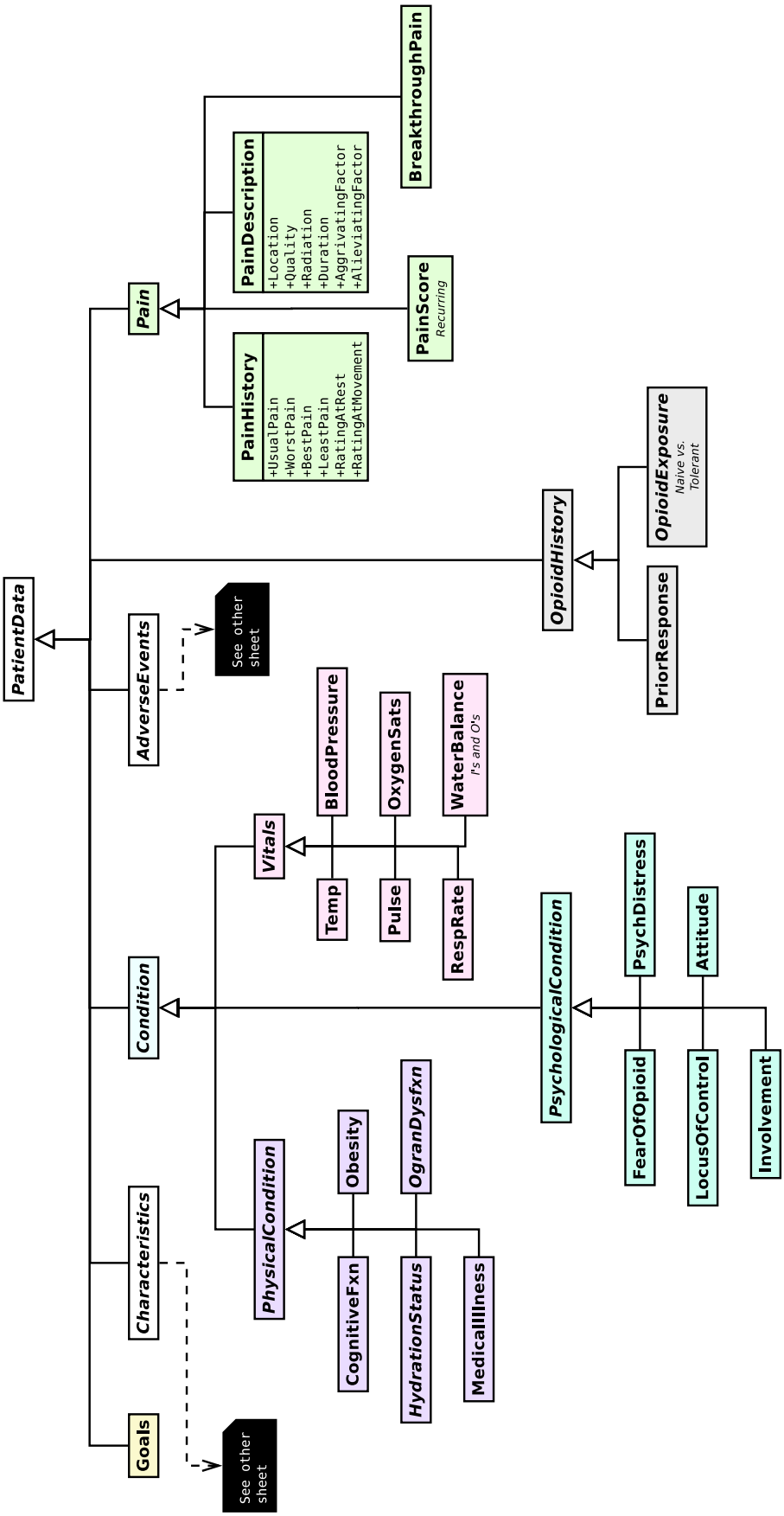


Figure 4.7 - Information model - patient data part 1

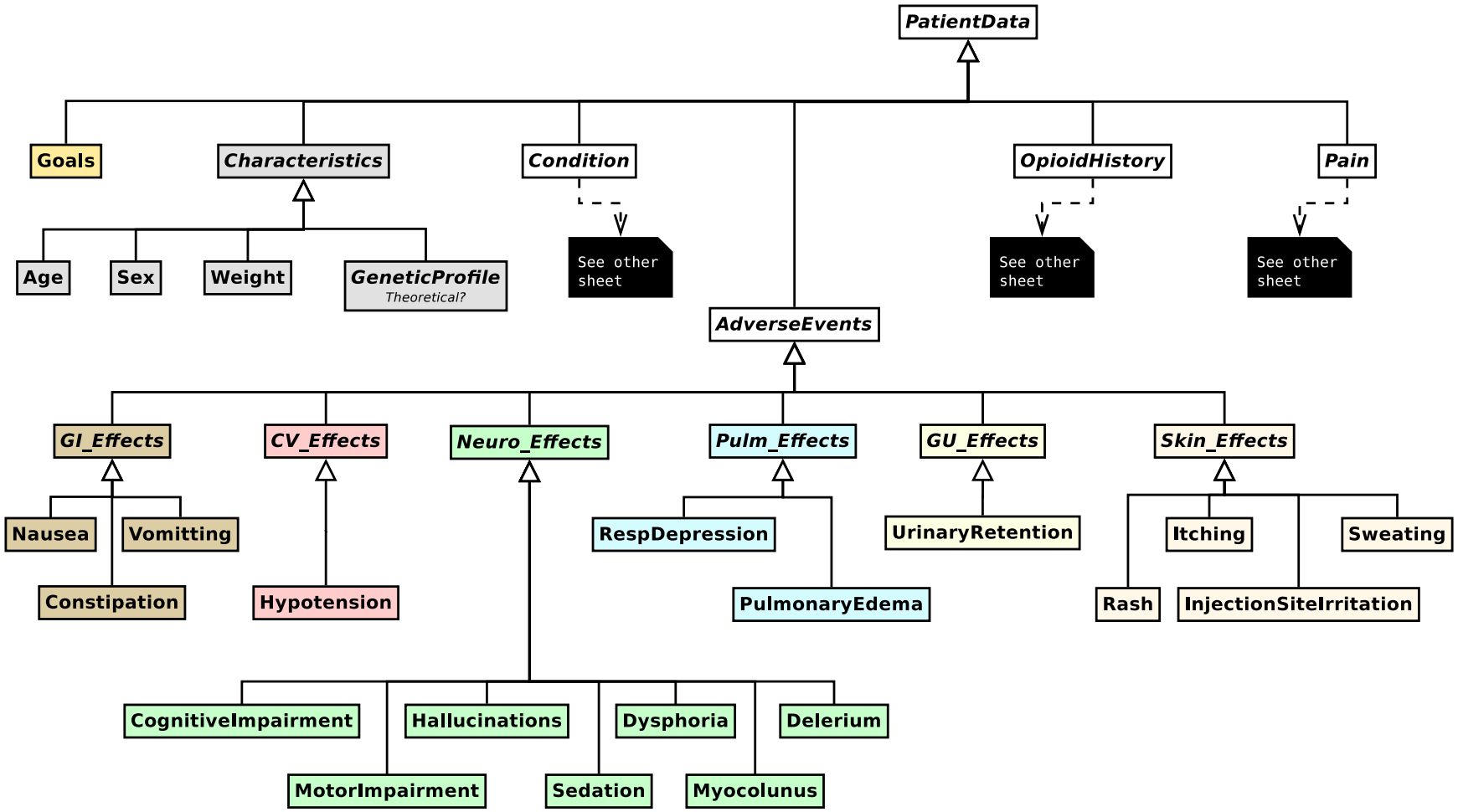


Figure 4.8 - Information model - patient data part 2

Table 4.3
Survey demographic data

	Years in practice	Years in Palliative Medicine	Years of experience managing PCA regimens	Estimated number of PCA regimens managed per year
	22	12	12	50
	33	33	25	100
	6	6	6	36
	10	10	6	3
	8	8	8	5
mean	15.8	14.25	11.25	38.8
Stadard Deviation	11.5	12.6	9.2	39.7

Table 4.4
Average ranking for elements in the survey

Element:	MEAN	STDEV
Patient's ability to understand and use the PCA	5	0
Patient's ability to comprehend the PCA device and paradigm	5	0
Size of the PCA demand dose ordered	5	0
Ordered frequency of PCA demand doses	5	0
History, timing, and pattern of use of demand doses	5	0
Basal infusion rate	5	0
Information about opioids given by other than PCA (ie loading or clinician doses, or concomitant orders)	5	0
24 hour (or other interval) total opioid given	5	0
Whether patient is opioid naive or tolerant	4.8	0.45
Patient's response to opioids before this episode	4.8	0.45
The effectiveness of the current pain regimen	4.8	0.45
The tolerability of the current pain regimen	4.8	0.45
Patient's cognitive functioning	4.8	0.45
Patient's physical condition (ie organ dysfunction, functional status, etc.)	4.8	0.45
Cause of pain	4.8	0.45
Effect of the pain on the patient and his/her life	4.8	0.45
Myoclonus	4.8	0.45
Delirium	4.8	0.45
Impaired cognitive function	4.8	0.45
Name of drug in use	4.8	0.45
Route of opioid administration	4.8	0.45
Calculated and trend data about PCA use (totals, demand patterns, etc.)	4.8	0.45
Clinician bolus that are/were ordered or available	4.8	0.45
Administered clinician boluses	4.8	0.45
Concurrent orders for oral opioids	4.8	0.45
Use of ordered oral opioids	4.8	0.45
Number and timing of demand doses given	4.8	0.45
Currently used interventional therapies	4.6	0.55
Renal function	4.6	0.55
Patient's description of the pain	4.6	0.55
Nausea	4.6	0.55
Vomiting	4.6	0.55
Impaired motor function	4.6	0.89
Respiratory depression	4.6	0.89
Time when particular PCA parameters started/stopped	4.6	0.55
Loading doses given	4.6	0.89
Number and timing of demand dose requests	4.6	0.55
Interactions with other medications	4.6	0.55
The particular opioid's kinetics	4.6	0.55
Equianalgesic ratios	4.6	0.89

Table 4.4 - Continued

Element:	MEAN	STDEV
Currently used co-analgesics	4.4	0.55
Currently used adjuvant therapies	4.4	0.55
Pain scores/ratings over course of treatment	4.4	0.55
Patient's rating of pain under different circumstances (ie best, worst, typical...)	4.4	0.55
Patient's self-rating of pain when moving	4.4	0.89
GI symptoms/side effects	4.4	0.89
Constipation	4.4	0.89
Ratio of demands made to demand doses given	4.4	0.89
Time to peak effect	4.4	0.55
Metabolites and features of metabolites	4.4	0.89
Patient's goals of care	4.2	1.79
Age	4.2	0.84
Non-analgesic treatment directed at the cause of the pain	4.2	1.3
Currently prescribed bowel regimen (laxatives, stimulants, etc.)	4.2	0.84
Patient's vital signs	4.2	0.45
Hepatic function	4.2	0.84
Episodes of breakthrough pain	4.2	0.84
Location of the pain	4.2	0.84
Quality of the pain	4.2	0.84
Aggravating factors	4.2	0.84
Alleviating factors	4.2	0.84
Patient's self-rating of usual pain	4.2	0.84
Patient's self-rating of pain at its worst	4.2	0.84
Patient's self-rating of pain at its least	4.2	0.84
Patient's self-rating of pain at rest	4.2	0.84
Pulmonary symptoms/side effects	4.2	0.84
Hallucinations	4.2	0.84
Sedation	4.2	1.1
Dose forms available (other routes, dosages, etc.)	4.2	0.84
Patient's psychological condition	4	0.71
Respiratory rate	4	1
Duration of the pain	4	0.71
Neurologic symptoms/side effects	4	1
Urinary retention	4	0.71
Dysphoria	4	1
What "limits" (1hr, 4hr, etc.) are set	4	1.41
If or when limits were reached (and pump locks out)	4	1
Patient characteristics such as age, weight, sex	3.8	0.45
Weight	3.8	0.84
Pulseoximetry	3.8	0.84
Baseline cognitive status	3.8	0.84
Respiratory function	3.8	0.84

Table 4.4 - Continued

Element:	MEAN	STDEV
Radiation of the pain	3.8	1.1
Half-life	3.8	1.1
Receptor profile (agonist, agonist-antagonist, etc.)	3.8	0.84
Hypotension	3.6	0.89
Pulmonary edema	3.6	0.89
Blood pressure	3.4	0.89
Functional status	3.4	1.52
Skin symptoms/side effects	3.4	1.14
Underlying cardiopulmonary disease	3.2	1.3
Hydration status	3.2	1.3
Rash	3.2	0.84
Hydrophilic/hydrophobic and Lipophilic/Lipophobic characteristics	3.2	1.1
I/O's (fluid "ins and outs")	3	1.58
Injection site irritation	3	1
Itching	2.6	0.55
Cost of drug	2.6	0.55
Pulse	2.4	0.89
Sweating	2.4	0.55
Patient's genetic profile potentially affecting opioid metabolism, effect, or side effects	2.2	1.64
Sex	2.2	0.45
Temperature	2.2	0.84

Table 4.5
Elements rated "extremely important" by all experts

Patient Context Elements:

Patient's ability to **comprehend** the PCA device and paradigm
Patient's ability to understand and **use** the PCA

Pump Related Elements:

Size of the PCA demand dose delivered
Ordered frequency of PCA demand doses
History, timing, and pattern of use of demand doses
Basal infusion rate
Information about opioids given by other than PCA
24 hour (or other interval...) total opioid given

Table 4.6
Elements ranked as less important

Element	Mean	SD
Symptom/ Adverse Event Related Elements:		
Itching	2.60	0.55
Sweating	2.40	0.55
Pulse	2.40	0.89
Temperature		
Cost of medication	2.60	0.55
Patient Characteristics:		
Patient's sex	2.20	0.45
Patient's genetic profile, potentially affecting opiod metabolism, effect, or side effects	2.20	1.64

Table 4.7
Elements with low agreement

Element	Mean	SD
Symptom/ Adverse Event Related Elements:		
Skin symptoms	3.40	1.14
Sedation	4.20	1.10
Pain Related Elements:		
Radiation of the pain	3.80	1.10
Patient Context Related Elements:		
Patient's genetic profile, potentially affecting opiod metabolism, effect, or side effects	2.20	1.64
Patient goals of care	4.20	1.79
I/O's (Fluids “ins and outs”)	3.00	1.58
Functional status	3.40	1.52
Hydration status	3.20	1.30
Underlying cardiopulmonary disease	3.20	1.30
Treatment Related Elements:		
Non-analgesic treatment directed at the cause of the pain	4.20	1.30
Medication information related elements:		
Drug half-life	3.80	1.10
Drug hydrophilic/hydrophobic and lipophilic/lipophobic characteristics	3.20	1.10
Pump Related Elements:		
What limits (1hr, 4hr, etc.) were set	4.00	1.41

CHAPTER 5

FHIR TO REPRESENT PCA DATA

5.1 Background

The overall goal of aim 2 was to assess the adequacy of the emerging HL7 standard FHIR to represent the data elements used by the proposed CDS application. Theoretically, the CDS application could be system-agnostic if it could be developed with a system-independent way to request and receive the needed data. The FHIR standard is an emerging standard intended to allow such cross-platform use of data.

In the past, applications such as this proposed CDSS would have been developed within the EHR itself, tightly coupling the application to a single EHR system. Now, many in health IT are exploring methods to loosely couple CDS applications to EHR systems. In such new paradigms, interfaces and CDS applications are modular and can be deployed on multiple systems and platforms. This could allow users to have a customized experience meeting their specific needs regardless of the underlying platform. Such modularity requires standardization of the connections between the underlying system and the user-facing modules, such as applications and interfaces. FHIR is one mechanism proposed by which these modules could connect to, or interface with, an existing EHR.

In the past, other standards to meet this need have suffered from being difficult to use due to being highly complex, or from being overly simplistic and therefore not able to accurately represent the data at a granular and specific enough level to adequately fulfill the clinical need. FHIR has been developed to address both of these concerns. The FHIR

paradigm is based on packaging data within resources which are general and flexible, allowing a small number of resources to represent a wide variety of health data types. This constrained initial set of resources theoretically allows ease of use and implementation. While the set of existing resources are expected to meet the needs of 80% of clinical use cases, FHIR has a formal extension process to fill the gap where existing FHIR resources don't adequately represent needed data.[1] There are likely many clinical scenarios where representation of some of the necessary data will require extension, and applications supporting these use-cases need to have full interoperability with existing systems.

As the ease of both use and extension of FHIR will impact its adoption, it is important to assess both early on in its development. If use or extension is difficult, FHIR may offer little benefit over current standards. To showcase and test this new standard, a number of prototype applications have been developed that make use of common data and, anecdotally, FHIR appears easy to use. However, FHIR is still untested in many domains with a paucity of published literature describing its formal use and application.

In order to assess FHIR's robustness, a gap analysis was performed to probe how well the standard could be used as a mechanism to transfer information represented in the model developed in aim 1 from a data store, such as the EHR, to the theoretical opioid PCA CDSS proposed. The goal was to determine, with respect to this use case, what gaps existed in the existing FHIR resources (i.e., data or information that could not be adequately represented by existing FHIR resources and thus required extension), and to assess the ease with which those gaps could be filled by extension.

5.2 Methods

5.2.1 Enrichment of the List of Data Elements

In order to perform the gap analysis of FHIR, a formal list of the elements used for decision making when managing an opioid PCA was required. The information model created from the literature in Aim 1 was the starting point. This evidence-based model included a wide variety of concepts, from discrete numeric data to complex concepts representing general states of health. To further quantify elements prior to mapping and to increase the granularity of shared understanding about them, descriptive metadata about each piece of information were added. This shared understanding was expected to increase the accuracy of subsequent mapping. The enrichment activity was performed by two reviewers in collaboration. Both reviewers had extensive clinical experience in the use of opioid regimens and the PCA paradigm, as well as formal informatics training and experience. First, several categories of metadata and the coding scheme were developed. Each element was then transferred from the information model to a spreadsheet where metadata was added.

The first attribute added was the level of information as described in the DIKW theoretical framework. This hierarchy has roots as far back as the 1930 but gained popular attention in the late 1980s and early 1990s.[238,239] This framework stratifies information across a pyramid structure with meaning increasing from the lowest layer to the highest layer. See Figure 5.1. Data, the lowest level, consists of symbols which can be described objectively without interpretation. The next higher level, labeled Information, is composed of data that are interpreted or structured. Knowledge, the third layer, is information that has been synthesized and formalized. The highest layer is Wisdom, which is knowledge applied in context to answer the question, “why.”[240,241] Each element was marked with a “D”, ”I”, “K”, or “W” corresponding to the level of meaning that best described the element. For

instance, the element “pain score” referred to simple, discrete, numeric data without contextual information or interpreted meaning. While a score *may* be attributed meaning by the provider, *representing* a numeric pain score requires only the numeral itself (the scale on which the rating is needed for *interpretation*, but with respect to the score itself, only the numeral is required). The element “pain score” was therefore assigned a DIKW level of “D” for data. In contrast, the element “hypoxia” was an interpretation *about* the oxygen saturation and required comparison of a given score against a known standard to determine whether the condition or state of hypoxia was present. Hypoxia was therefore ranked as “I.” Elements requiring more complex processing and conveying a higher level of meaning, such as the element “presence of breakthrough pain: end dose failure” were labeled “K” for knowledge. A very few elements were quite complex, requiring a deep understanding of the context and meaning, so were categorized “W” for Wisdom.

Next, each element was categorized according to a 'data type.' The data types were state, occasion, or recurring. State was defined as an ongoing condition of a patient such that the moment of observation is only one point of many instances when the patient would likely be in that condition. The state is expected to exist over a much longer time period than the moment of the single observation. Examples of states included dehydration, constipation, reported typical pain at rest, cause of the pain, age, sex, renal function and opioid naïve/tolerant. States vary in their degree of permanence. The state of a patient's sex would be rather permanent, while 'dehydration' might be a state which could change over hours. In contrast, an element which describes the patient's condition or actions at a given *single* point in time, with no intended inference that the condition exists at any other time than that moment, was considered an occasion data type. Occasion data *can* be applicable to a patient over a considerable period of time, though the condition is not *necessarily* considered to exist before that or after the observation. The focus is that at the moment of

documentation of the occasion element, the patient had or did not have the characteristics of the data element in question. Occasion data define what a patient is doing, or something that is happening at the instant it is happening. Examples of elements of the occasion type include most symptoms, such as an episode of nausea or vomiting, an episode of hallucinations, and the presence of sweating. Elements of the recurring type were defined as those measurable concepts for which some value exists at *any and all* points in time, with the observed value indicating the value at the instant of observation. Measurement and documentation of recurring type data occurs frequently at set intervals often with the intent to compare values across time. An example is a patient's blood pressure – a living patient always has a blood pressure, but it is only measured periodically. Other examples of recurring type elements include weight, other vital signs (temperature, pulse, respiratory rate), and pain scores. Two other data types, constant and calculated, were added for elements that did not fit well into one of the above categories, but these were rarely used. A constant data type was defined as some characteristic that could not change; an example would be the name of a medication itself (i.e. while morphine can be given by different routes, in different doses, and at different times, it is never anything but morphine). The calculated data type was used for data or information that was mathematically derived from some other data, such as “total morphine given in 24 hours.” This could be a state the patient was in – having received a certain amount of medicine in a set time, but for clarity, it was chosen to add this data type; it was only used for data elements related to pump data.

Third, for each element in the model, a proposed method of communicating or displaying that element to the user was determined. For simple data, this was usually direct display, such as displaying individual pain scores. More complex topics, however, could be directly displayed at that complex level, or the CDSS could present more atomic data, allowing the user to infer the presence of the condition from those data. The handling of

such complex topics has a direct bearing on what information is passed to the CDS, so agreement on this handling is a *critical* step prior to mapping. For example, one element on the information model was end dose failure, a condition that occurs when a patient experiences repeated escalation in pain scores just prior to the next scheduled dose of an analgesic. A decision support system could either report that the condition of end dose failure has occurred, *or* the system could display pain scores along with dosing information and allow clinician-users to make the inference for themselves. In the latter case, the CDS itself never directly deals with the concept of end dose failure, so there is no need to map "end dose failure" to the standard. In the first case, however, where the system indicates to the user that end dose failure has occurred, two options are possible. The CDSS can either make the inference that the condition is present from required data, or it can merely relay that the condition has been documented in the clinical record to have been present. In the first case, while the data required to make the inference must be transmitted to the CDSS, the concept of "end dose failure" itself need not be mapped to the standard for transmission. In the second case, it *is* necessary to map the concept of "end dose failure" to the standard.

Once the decision had been made as to whether the CDSS would require the concept itself to be transmitted from the data source or whether the raw data would be transmitted and the inference made by the user or logic within the CDSS, elements were marked accordingly. Those elements felt to be best handled by transmission of the complex concept itself from the data store were marked with a "D" for directly displayed; elements for which inference, either by the clinician or the CDSSS, was thought to be appropriate were marked "I" for inference.

Finally, based on metadata generated for each element so far, a proposed target location of specific data or information in the clinical data source for the element was then determined and listed for each element. For elements typed as 'data' in the DIKW

framework with a proposed direct method of display, the target location was usually a single field in the clinical data store where the piece of data was expected to be found. For more complex concepts, especially those for which multiple pieces of data could be used to infer the concept, the entry listed was the location(s) of the basic data on which that complex concept could be inferred.

5.2.2 Mapping to FHIR – Gap Analysis

Once metadata had been added to the elements from the information model, this list of elements was mapped to resources in the FHIR standard to perform the gap analysis. Two reviewers separately and independently mapped each element to a FHIR resource. For those elements that were listed as inferred and relied upon, other more atomic concepts or data, the FHIR resource chosen was that which would best transmit that basic data to calculate or infer the element in question. Once individual mappings had been established, the two authors compared their mappings and reviewed the results, resolving any discrepancies by consensus. A third reviewer, an expert in standards and their application with considerable experience with other HL7 standards, was selected to arbitrate any remaining discrepancies which could not be resolved by consensus of the two reviewers.

5.3 Results

Initial inspection of the information model revealed 102 distinct pieces of data or information. Consensus regarding types and categories of metadata and the values for the metadata for each element was easily reached between the two reviewers. Enrichment with metadata related to DIKW level, data type, method of display, and location in the health data store resulted in the final enriched list of elements to be mapped to FHIR seen in Table 5.1.

The reviewers mapped all elements except an element related to genetic data, and the element “presence of appropriate treatment targeting the cause of the pain.” When

comparing mappings, the reviewers found that they had nearly identical thoughts on these two elements: the *concepts* themselves were too vague to make a determination of which FHIR elements to use. These 2 elements were left in the data set for analysis and considered elements for which the reviewers agreed on mapping.

Of the 102 elements, in independent review the reviewers picked the same FHIR resource to represent the element in 88 cases. This yielded an overall percent agreement of 86% with a Cohen's Kappa of 0.776. On closer review, 5 of the 14 discrepancies were due to a new FHIR resource that was added to the draft standard *after* the first reviewer performed his mappings, but before the second reviewer had mapped the elements. This new FHIR resource, “DeviceObservationReport,” was used by the second reviewer for data that could be readily obtained through an interface between the PCA pump and the EHR. The reviewer who mapped prior to the addition of this more specialized resource chose Observation. If one looks at the 97 elements which this anomaly did not affect, the percent agreement was around 91% and the Cohen's Kappa was 0.83.

Of the 14 elements which were mapped differently on independent review, the two reviewers easily reached consensus on all elements and did not need to discuss any mappings with the identified third reviewer. Table 5.2 lists the elements mapped, each reviewer's individual mapping choices, and the final agreed-upon FHIR resource.

Once agreement had been reached regarding the FHIR resource used to represent each of the elements, a model representing use of FHIR resources by the CDSS was developed. This model is displayed in Figure 5.2 as an architecture-style diagram illustrating the interactions of various parts of the health IT system involved in storing, requesting, accessing, transmitting, and consuming data to make possible the CDSS as proposed.

5.4 Discussion

Results indicate a very high level of agreement between the two individuals mapping the elements from the information model to FHIR. Using levels proposed by Cohen, a Cohen's Kappa of 0.773 for all 102 elements suggests "substantial agreement." If one excludes the 5 elements affected by the addition of a new resource to the FHIR standard during the study, between the time when each reviewer performed independent mappings, a Cohen's Kappa of 0.83 is regarded by Cohen as "near perfect agreement."[233] This is *highly* significant agreement as by the nature of this data set, the so-called "prevalence paradox" probably causes the Cohen's Kappa statistic to estimate agreement conservatively.[242,243]

In initial mapping, there were two elements the which both reviewers independently felt could not be mapped to FHIR. Prior to discussion, for these elements, both reviewers felt this had little to do with FHIR but rather to do with the vague nature of these 2 elements themselves. Both reviewers felt that "genetic data" does not currently have a place in clinical practice – the underlying concept is, at best, theoretical with nebulous and uncertain meaning, and there is not a consistent or accepted way to represent or communicate such data in clinical practice. While it is a fascinating subject for research and no doubt involved in the variability of response to opioids seen in different patients, neither author is aware of any test or specific genetic information or testing that presently plays a part in clinical management of opioid regimens. As such, this concept does not represent real, current data that could be used. The reviewers also independently noted that the element "Presence of appropriate treatment targeting the cause of the pain" was a problematic concept for a CDSS to capture or handle. Not only does the concept of "appropriate treatment" requires intricate synthesis of dozens or more different pieces of data, which specific pieces of data are needed is highly context dependent, varying widely from situation to situation. Without further clarification or more detailed specification, this concept was felt to represent a

concept beyond the scope of a real-world CDSS at the present time. The reviewers agreed that with the exception of these two, all other elements of the information model could be easily represented by the FHIR standard.

A number of other conclusions can be reached by observing the results of the FHIR mapping activities. First, the currently available FHIR resources are relatively comprehensive. At least in this case, they completely covered the pertinent elements of the domain in question – management of opioid PCA infusions in palliative settings. Only two elements from the information model could not be mapped, but it was determined that both were complex, vague, and in fact more theoretical concepts than discrete information used in real-world practice. In fact, these particular elements had been problematic previously and were nearly discarded from the model earlier in the process. In essence, the reviewers agreed that by all practical standards, FHIR provided 100% "real-world" coverage of this use case without extension.

A second finding is not unexpected – FHIR is still evolving. This was demonstrated by the addition of a new FHIR resource, DeviceObservationReport, to the FHIR standard between the time when one reviewer mapped elements to FHIR, and when the second did. The availability of this resource to the second mapper but not the first obviously caused discrepancies in mapping activities. Evolution is to be expected of a standard still in draft format. Once the standard is finalized this should be less of a problem, as additions will be less frequent and follow a formal protocol, such as introduction at set intervals. This does highlight, though, that it will be important for institutions using FHIR to have policies and procedures in place to deal with similar updates, even once the standard becomes finalized.

Third, FHIR was found to be highly flexible with only 8 distinct FHIR resources covering all data and information elements in the model. FHIR was found to be so flexible, in fact, that there was considerable overlap between several resources, such as between the

condition and observation resources. This is a known phenomenon; that a concept or data element can be modeled using either resource is openly addressed on the FHIR web site.[244] This sort of flexibility, however, caused discrepancies in the reviewers' independent mapping, though during discussion these discrepancies were found to be the result of a lower level of either the shared understanding about the data or the concept definition, rather than any feature of the FHIR standard or FHIR resources themselves. For instance, one reviewer considered constipation a condition of the patient, documented by staff as such, and so mapped the concept to the FHIR "condition" resource. In contrast, the other reviewer felt the concept of constipation as used by the CDS should be based on the lack of a charted bowel movement over a specified interval, so that reviewer chose the FHIR resource "observation" to transmit the data needed to the CDSS which would determine if the patient met the criteria for constipation. In discussion, both reviewers were able to see the rationale behind all such discrepancies and agreed there could be more than one correct way to map the element to FHIR.

All discrepancies were easily resolved by consensus once the reviewers discussed and agreed on type of data and originating location for the data. For example, once both reviewers decided between whether the CDSS would display constipation based on the presence of a charted condition of constipation or based on logic calculating length of time between charted instances of bowel movements, consensus on the FHIR resource was easily achieved. This highlights a significant challenge for implementers, as in the real world there are often different ways of thinking about the same clinical concept. Thus while flexibility can be a strength of the FHIR standard, flexibility comes at the cost of less intrinsic explicitness within the standard.[245,246] To avoid pitfalls, it will be absolutely crucial for implementers to be very specific about data and concepts and to have a shared understanding at a very granular level of the data being transmitted prior to attempting to

use FHIR.

While the lack of intrinsic explicitness creates the potential for sub-optimal shared understanding to undermine the interoperability it promises, the flexibility of the FHIR standard appears to be a great asset. Unfortunately, adjustments to the FHIR standard itself to increase explicitness could negatively impact this flexibility. Measures to address this lack of explicitness which do not alter the standard or it's elegant design are thus preferred. Fortunately there are several steps that could be taken to address the potential problems.

First, developing detailed implementation manuals and support documents would be quite helpful. These documents should standardize how implementers make use of and interpret the FHIR standard and its associated resources. For example, such documents could give further details on when to use the observation resource versus the condition resource, which is an issue recognized on the FHIR website. HL7 has a history of producing such documents and this may well be part of the long-term plan; FHIR is currently in draft standard form and documentation should not be produced until it moves past this very malleable form.

Second, FHIR training materials should explain clearly and in simple terms the need for specificity in underlying data models themselves. An advantage of FHIR is its simplicity but this also makes its use within the grasp of individuals with little experience and less than ideal training in medical informatics. These individuals need to understand the larger process of using FHIR, including the process of creating adequate and detailed models prior to its use, so simple guides limited to FHIR itself fall short; information on using FHIR in context is desired. These resources need to be clearly worded with simple yet thorough examples as highly technical language or complex examples could be beyond the reach of those individuals who most need to understand the danger.

Lastly, a wide variety of “pre-implementation” demonstration artifacts, such as

example models, should be made available. These artifacts should give concrete examples of both good and bad development practice so as to clearly point out both the elegance of FHIR and the very real pitfalls. While not specifically related to FHIR, showing these artifacts would convey a more accurate picture of the use of FHIR in context and could highlight the absolute necessity of laying a solid ground-work *before* the application of FHIR to a project.

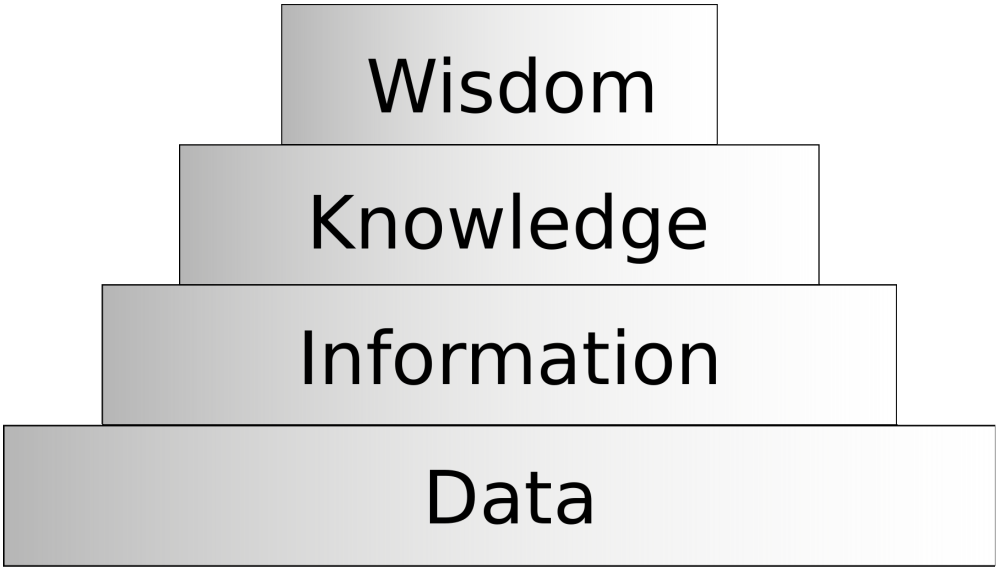


Figure 5.1 - DIKW pyramid

Table 5.1
Elements mapped to FHIR

Elements – From Pt Adverse Event Branch	DIKW level	Method of display	Based on what EHR/data store field	Data type
Presence of Nausea	I	D	charted Nausea event	occasion
Presence of Vomiting	I	D	charted Emesis event	occasion
Presence of Constipation	I	I	Trend in charted BM event	occasion
Constipation: 1 non-forced BM per day	K	I	Trend in charted BM event	state
Presence of Hypotension	I	I	trend in charted BP data	occasion
Presence of dysphoria	I	D	charted dysphoria event	occasion
Presence of Hallucinations	K	D	charted hallucination event	occasion
Presence of Myoclounus	I	D	charted myoclonus event	occasion
Presence of Delirium	K	D	charted Delirium event	occasion
Presence of Sedation	K	D	charted sedation event	occasion
Presence of Motor/cognitive impairment	K	D	charted impairment of motor/cognition event	occasion
Presence of Respiratory Depression	K	I	trend in charted RR data	occasion
Presence of Respiratory Depression: Hypoxia	I	I	trend in charted SA O2 data	occasion
Presence of Respiratory Depression: Hypercarbia	I	I	trend in charted SA CO2 (end-tidal monitor or ABG)	occasion
Presence of Pulmonary Edema	I	D	Pull from XCR report	occasion
Presence of Itching	I	D	charted itching event	occasion
Presence of sweating	I	D	charted sweating/diaphoretic event	occasion
Presence of Rash	I	D	charted rash event	occasion
Presence of Subcutaneous injection site irritation	K	D	charted site irritation event	occasion
Presence of Urinary retention	I	I	trend in charted I/O's data	occasion
Is Bowel regimen ordered? (Prokinetic)	I	D	med: [list of meds/classes]	state

DIKW level: D=Data, I=Information, K=Knowledge, W=Wisdom

Method of Dispaly: D=Direct, I=Inferred

Table 5.1 - continued

Elements – From Pt Pain Branch	DIKW level	Method of display	Based on what EHR/data store field	Data type
Pain score (self report)	D	D	charted pain score data	recurring
Reported Usual pain rating	D	D	charted pain score qualified as usual pain	state
Reported worst pain rating	D	D	charted pain score qualified as worst pain	state
Reported best pain rating	D	D	charted pain score qualified as best pain	state
Reported pain rating at rest	D	D	charted pain score qualified as usual pain at rest	state
Reported pain rating at movement	D	D	charted pain score qualified as usual pain at movement	state
Reported location of pain	D	D	charted reported location of the pain	state
Reported Pain quality	D	D	charted reported quality of the pain	state
Reported Pain Radiation (location of)	D	D	charted reported location(s) of pain radiation	state
Reported Pain duration	D	D	charted report of duration of pain	state
Reported pain aggravating factors	D	D	charted report of aggravating factors	state
Reported pain alleviating factors	D	D	charted report of alleviating factors	state
Presence of breakthrough pain	K	I	Trend in charted pain score data	state/occas
Presence of breakthrough pain: end-dose failure	K	I	Trend in charted pain score data	state/occas
Prior response to opioids	K	I	Narrative or trend in prior pain scores & med dose	state
Cause of pain	K	I	Inferred – [complex NLP if no discrete field]	state
Effectiveness of Treatment	K	I	from pain score trending in effect screen	state
Effectiveness of Treatment: severity of pain	K	I	from pain score trending in effect screen	state
Tolerability of pain	W	D	Narrative field or complex NLP	state
Affect of pain on patient	W	D	Narrative field or complex NLP	state

DIKW level: D=Data, I=Information, K=Knowledge, W=Wisdom

Method of Dispaly: D=Direct, I=Inferred

Table 5.1 - continued

Elements – From Pt Context Branch	DIKW level	Method of display	Based on what EHR/data store field	Data type
Water balance	I	I	trend in charted I/O's data	state
temp	D	D	trend in charted Temp data	recurring
HR	D	D	trend in charted Pulse data	recurring
BP	D	D	trend in charted BP data	recurring
Resp Rate	D	D	trend in charted Resp rate data	recurring
SA O2	D	D	trend in charted SA O2 data	recurring
Age	D	D	Charted Age	state
Sex	D	D	Charted Sex	state
Genetic variants	*D*	--	No known clinical value or test result represents this concept	state
Weight	D	D	Weight	recurring
Baseline cognitive Function	K	I	From charted narrative OR test (ie Folstien MMSE)	state
Hydration status:dehydration	K	I	trend in charted I/O's data -OR- condition diagnosed	state
Hydration status	K	I	trend in charted I/O's data	state
Obesity	K	I	Calculate BMI	state
Renal function	K	I	trend: BUN and Creatinine	state
Hepatic function	K	I	trend: SGOT, SGPT, GTT	state
Respiratory function	K	I	Charted %O2, %CO2, RR	state
Medical Illness	W	I	Narrative field or complex NLP	state
Functional Status	I	I	Narrative field or complex NLP	state
Opioid Naive	I	D	Calculated: eMAR data	state
Opioid Tolerant	K	D	Calculated: eMAR data	state
Opioid Tolerant: documented h/o Opioid abuse	I	D	Narrative field or complex NLP	state
Pt with fear of opioid	K	D	Narrative field or complex NLP	state
Pt locus of control	K	D	Narrative field or complex NLP	state
Pt's attitude / involvement in care	W	D	Narrative field or complex NLP	state
Patients degree of Psychological distress	W	D	Narrative field or complex NLP	state
Patient's degree of understanding of PCA	W	D	Narrative field or complex NLP	state
Patient physically capable of using PCA	W	D	Narrative field or complex NLP	state

DIKW level: D=Data, I=Information, K=Knowledge, W=Wisdom

Method of Dispaly: D=Direct, I=Inferred

Table 5.1 - continued

Element – From Treatment Branch	DIKW level	Method of display	Based on what EHR/data store field	Data type
Presence of concurrent use of Co-Analgesic	K	D	Med: [compare v list of meds/classes]	state
Presence of adjuvants currently used	W	D	Med: [compare v list of meds/classes]	state
Presence of interventional therapies (used/planned)	K	D	ICD code | compare list v. ordered procedure	state
Presence of appropriate Tx targetting the CAUSE of pain	W	I	very complex NLP	state

Elements – From Medication Data Branch	DIKW level	Method of display	Based on what EHR/data store field	Data type
Routes available	I	D	Based on eMAR, pull from local Phram DB	state
Equianalgesic Ratios	I	D	Based on eMar	state
T ½	I	D	Based on eMar	state
Time to peak effect	I	D	Based on eMar	state
Lipophillic/hdrophillic	I	D	Based on eMar	state
Recptor profile (ie. ag., ag/antag., partial...)	I	D	Based on eMar	state
Metabolites: toxic	I	D	Based on eMar	state
Metabolites: active	I	D	Based on eMar	state
Drug-Drug interactions	I	D	Based on eMar	state
Dose forms available	I	D	Based on eMAR, pull from local Phram DB	state
Cost	I	D	Based on eMAR, pull from local Phram DB	state
EKG: qt interval	I	D	pull qt interval from EKG report data	recurring

DIKW level: D=Data, I=Information, K=Knowledge, W=Wisdom

Method of Dispaly: D=Direct, I=Inferred

Table 5.1 - continued

Elements – From Pump Data Branch	DIKW level	Method of display	Based on what EHR/data store field	Data type
Medication name	D	D	charted PCA order	constant
Route	D	D	charted PCA order	constant
Demand dose size	D	D	charted PCA order	occasion
Lockout Interval	D	D	charted PCA order	occasion
Basal Rate	D	D	charted PCA order	occasion
Limit: 4hr lmiit	D	D	charted PCA order	occasion
Limit: 1 hr limit	D	D	charted PCA order	occasion
Clinician bolus	D	D	charted order – PCA or other	occasion
Time current Sig started	D	D	charted order TIMESTAMP	constant
Time current Sig stopped	D	D	charted order TIMESTAMP	constant
Loading dose	D	D	charted order – PCA or other	occasion
Demand dose Trending: # demands given	I	D	trend in charted medAdmin events (ideally, pump data)	calculation
Demand dose Trending: # demands requested	I	D	trend in charted medAdmin events v. demand requests (ideally, pump data)	calculation
Demand dose Trending: timing of demands	I	D	trend in charted medAdmin + MedRequest events (ideally, pump data)	calculation
Comparison of pain scores to Demand dose	W	I	trend in charted pain score v. charted medAdmin events	calculation
24 hour use of drug totals	I	D	Summation of medAdmin events	calculation
Info RE Other opioids in use	K	D	eMAR / charted orders	occasion

DIKW level: D=Data, I=Information, K=Knowledge, W=Wisdom

Method of Dispaly: D=Direct, I=Inferred

Table 5.2
FHIR mappings (Discrepancies shaded.)

Element	Reviewer 1 Mapping	Reviewer 2 Mapping	Consensus Mapping
Presence of Nausea	Observation	Observation	Observation
Presence of Vomiting	Observation	Observation	Observation
Presence of Constipation	Observation	Observation	Observation
Presence of Hypotension	Observation	Observation	Observation
Presence of dysphoria	Observation	Observation	Observation
Presence of Hallucinations	Observation	Observation	Observation
Presence of Myoclounus	Observation	Observation	Observation
Presence of Delirium	Observation	Observation	Observation
Presence of Sedation	Observation	Observation	Observation
Presence of Motor/cognitive impairment	Observation	Observation	Observation
Presence of Respiratory Depression	Observation	Observation	Observation
Presence of Respiratory Depression: Hypoxia	Observation	Observation	Observation
Presence of Respiratory Depression: Hypercarbia	Observation	Observation	Observation
Presence of Pulmonary Edema	**DiagnosticReport**	**Condition**	Inferred: DiagnosticReport
Presence of Itching	Observation	Observation	Observation
Presence of sweating	Observation	Observation	Observation
Presence of Rash	Observation	Observation	Observation
Presence of Subcutaneous injection site irritation	Observation	Observation	Observation
Presence of Urinary retention	Observation	Observation	Inferred: Observation
Is Bowel regimen ordered? (Prokinetic)	Medication prescription	Medication prescription	Inferred: Medication prescription
Pain score (self report)	Observation	Observation	Observation
Reported Usual pain rating	Observation	Observation	Observation
Reported worst pain rating	Observation	Observation	Observation
Reported best pain rating	Observation	Observation	Observation
Reported pain rating at rest	Observation	Observation	Observation
Reported pain rating at movement	Observation	Observation	Observation
Reported Pain location	Observation	Observation	Observation
Reported Pain quality	Observation	Observation	Observation
Reported Pain Radiation	Observation	Observation	Observation
Reported Pain duration	Observation	Observation	Observation
Reported pain aggravating factors	Observation	Observation	Observation
Reported pain alleviating factors	Observation	Observation	Observation
Presence of breakthrough pain	Inferred: Observation	Observation	Observation
Presence of breakthrough pain: end-dose failure	Inferred: Observation	Observation	Observation
Prior response to opioids	**Observation && MedAdmin(s)**	**condition**	Observation
Cause of pain	**Observation**	**condition**	Observation
Effectiveness of Treatment	**Observation**	**condition**	Observation
Effectiveness of Treatment: severity of pain	**Observation**	**condition**	Observation
Tolerability of pain	Observation	Observation	Observation
Affect of pain on patient	Observation	Observation	Observation

Element	Reviewer 1 Mapping	Reviewer 2 Mapping	Consensus Mapping
Water balance	Observation	Observation	Observation
temp	Observation	Observation	Observation
HR	Observation	Observation	Observation
BP	Observation	Observation	Observation
Resp Rate	Observation	Observation	Observation
SA O2	Observation	Observation	Observation
Age	***Inferred: Patient.birthDate***	**Observation**	*Inferred: Patient.birthDate*
Sex	**Patient.gender**	**Observation**	Patient.gender
*Genetic variants***	*Concept too vague*	*Concept too nebulous to map*	Concept itself not map-able
Weight	Observation	Observation	Observation
Baseline cognitive Function	Observation	Observation	Observation
Hydration status:dehydration	Condition -OR- Observation	Observation	Condition -OR- Observation
Hydration status	Observation	Observation	Observation
Obesity	Inferred: Observation(s)	Observation	Observation
Renal function	Observation	Observation	Observation
Hepatic function	Observation	Observation	Observation
Respiratory function	Observation	Observation	Observation
Medical Illness	Condition	Condition	condition
Functional Status	**Condition**	**Observation**	Observation
Opioid Naive	Condition	Condition	Condition
Opioid Tolerant	Condition	Condition	Condition
Opioid Tolerant: documented h/o Opioid abuse	Condition	Condition	Condition
Pt with fear of opioid	Condition	Condition	Condition
Pt locus of control	Condition	Condition	Condition
Pt's attitude / involvement in care	**Condition**	**Observation**	Condition
Patients degree of Psychological distress	Condition	Condition or observation	Condition
Patient's degree of understanding of PCA	Condition	Observation	Condition
Patient physically capable of using PCA	Condition	Observation	Condition
Presence of concurrent use of Co-Analgesic	MedicationPrescription.Medication	MedicationPrescription	MedicationPrescription
Presence of adjuvants currently used	MedicationPrescription.Medication	MedicationPrescription	MedicationPrescription
Presence of interventional therapies (used/planned)	Procedure && DiagnosticOrder	procedure v. order	procedure v. order
Presence of appropriate Tx targeting the CAUSE of pain	*too complex to map*	*Left blank - too complex to map*	too hard
Routes available	medication	medication	medication
Equianalgesic Ratios	medication	medication	medication
T ½	medication	medication	medication
Time to peak effect	medication	medication	medication
Lipophillic/hdrophillic	medication	medication	medication
Recptor profile (ie. ag., ag/antag., partial...)	medication	medication	medication
Metabolites: toxic	medication	medication	medication
Metabolites: active	medication	medication	medication
Drug-Drug interactions	medication	medication	medication
Dose forms available	medication	medication	medication
Cost	medication	medication	medication
EKG: qt interval	observation	observation	Observation

Table 5.2 - Continued

FHIR mapping

Element	Reviewer 1 Mapping	Reviewer 2 Mapping	Consensus Mapping
Medication name	MedicationPrescription.Medication	MedicationPrescription	MedicationPrescription
Route	MedicationPrescription.Route	MedicationPrescription	MedicationPrescription
Demand dose size	MedicationPrescription.doseQuantity	MedicationPrescription	MedicationPrescription
Lockout Interval	MedicationPrescription.timing	MedicationPrescription	MedicationPrescription
Basal Rate	MedicationPrescription.rate	MedicationPrescription	MedicationPrescription
Limit: 4hr lmiit	MedicationPrescription.maxDosePerPeriod	MedicationPrescription	MedicationPrescription
Limit: 1 hr limit	MedicationPrescription.maxDosePerPeriod	MedicationPrescription	MedicationPrescription
Clinician bolus	MedicationPrescription	MedicationPrescription	MedicationPrescription
Time current Sig started	MedicationPrescription	MedicationPrescription	MedicationPrescription
Time current Sig stopped	MedicationPrescription	MedicationPrescription	MedicationPrescription
Loading dose	MedicationPrescription	MedicationPrescription	MedicationPrescription
Demand dose Trending: # demands given	**MedAdmin**	**DeviceObservationReport**	DeviceObservationReport
Demand dose Trending: # demands requested	**observation**	**DeviceObservationReport**	DeviceObservationReport
Demand dose Trending: timing of demands	**Calc: MedAdmin**	**DeviceObservationReport**	DeviceObservationReport
Comparison of pain scores to Demand dose	**Obs.PainScore && MedAdmin**	**DeviceObservationReport**	DeviceObservationReport
24 hour use of drug totals	**Calc: MedAdmin**	**DeviceObservationReport**	DeviceObservationReport
Info RE Other opioids in use	MedicationPrescription	MedicationPrescription	MedicationPrescription

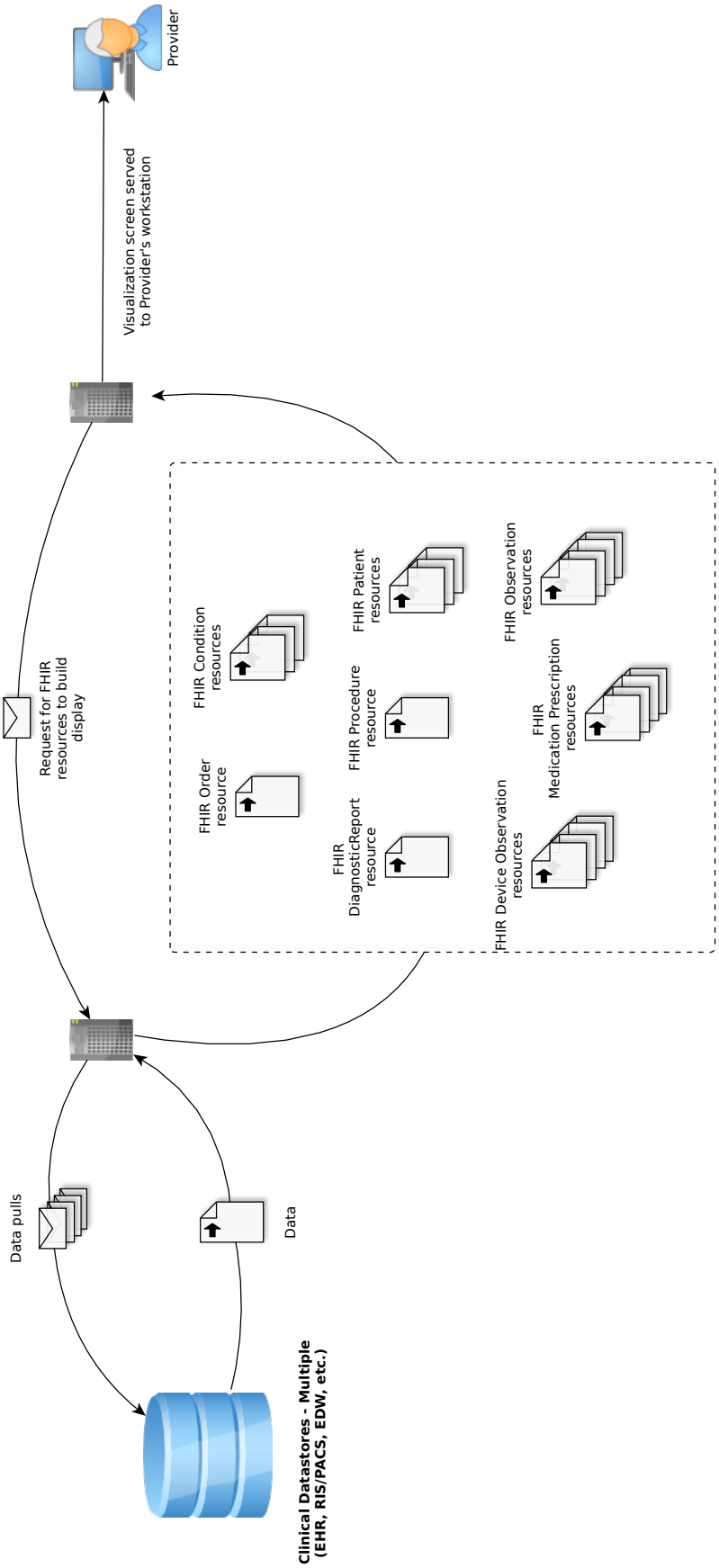


Figure 5.2 - High level CDS system architecture
All FHIR resources used by the proposed CDS system.

CHAPTER 6

CONCLUSION

6.1 Discussion of Current Work

Despite unprecedented medical advances in the last century, the problem of untreated and under-treated pain resulting from end-stage disease remains largely unaddressed. However, it is estimated that 90% of that pain could be adequately treated using *currently available* modalities.[80,247–252] The problem, then, lies not in a lack of adequate treatments or the need to make new discoveries, but in the application of available knowledge and techniques. The PCA paradigm holds the promise to improve pain control for those experiencing late life pain, however, providers using this modality have identified that accessing accurate and complete data is a challenge. As one well accepted function of medical informatics is to make the right information available to the right person at the right time, the discipline of medical informatics should be uniquely situated to respond to this challenge. A second challenge was identified in preliminary investigations: though a domain replete with loudly voiced expert opinion, this domain lacks both clear evidence-based guidance for decision making and clear articulation of the particular information needed to make decisions. The application of relatively standard techniques within the field of medical informatics proved successful at overcoming this second challenge, resulting in the creation of several key components of the infrastructure for a possible Clinical Decision Support System for the domain that could meet the first challenge.

The challenge of understanding the information needs and data requirements that

inform decision making when managing an opioid PCA, particularly in a palliative setting, was addressed by applying information extraction and mind mapping techniques to a body of evidence comprised of published literature and clinical protocols. The result was an information model which was validated by expert review using a modified Delphi technique. This validation proved the inductive approach as developed was successful. The challenge of supplying needed information to clinicians at the point of care was addressed by examining the feasibility of using the emerging HL7 FHIR standard, currently in draft form, as a means to represent requisite data. This second portion of the work suggests that existing FHIR resources are sufficient to convey concepts, information, and data required for clinical decisions making when managing an opioid PCA in a palliative context.

The successful use of informatics techniques to address these challenges is important to the field in several ways. First, the successful use of an inductive approach to build the necessary evidence base to support a CDS system has wide application across other clinical domains. Developing a firm foundational understanding of the information requirements of clinicians in a given domain is a crucial first step to building a successful CDS system. This cannot be understated. To that end, the inductive process developed for this project proved capable of handling a large body of evidence efficiently and with relatively minimal investment in hardware or software solutions. All software used were available as inexpensive stand-alone applications, as open source projects, or as free versions with limited but sufficient functionality for this project. Hardware requirements were modest, at most, and are commonly available to researchers and developers. The use of the applications in the process was fairly straightforward, and someone with moderate computer abilities could likely become proficient in their use with a minimum of effort. The use of mind mapping in particular proved to be a very useful way of dealing with the data extracted from the body of evidence, and the application Docear proved a very robust tool for the task.

In fact, after using the application heavily over a few months, this author is left with the feeling he has just scratched the surface of the capabilities of Docear.

The use of FHIR to represent data involved in a domain typically thought of as a “niche” case , here the clinical use case of opioid PCA management, evaluated FHIR's flexibility. That all data and information elements necessary for decision making when managing an opioid PCA in a palliative setting could be mapped to FHIR *without* extension demonstrates the robust flexibility of FHIR to cover even less common real-world scenarios. FHIR is being developed specifically to be easy to implement and this project affirmed that as well. Both reviewers in this project felt that the FHIR specification and resources were easy to understand and manipulate. As the standard is so new, a current question is whether the FHIR specification is robust enough to handle real-world clinical challenges. This work is one attestation that the FHIR specification is flexible enough to handle yet another clinical domain, in this case, one which is a bit off the beaten path.

Several disadvantages of FHIR were suggested by this work and, though stated earlier, do bear repeating. The reviewers involved in mapping elements to FHIR resources frequently found that even *slight* discrepancies in understanding of the concept underlying the element, or differences in opinion as to what specific data an element referred to in the storage model, resulted in differing suggestions for which FHIR resource to use. Given FHIR's extreme flexibility, it is incumbent on the individual or team building or implementing an application to develop a granular enough *shared* understanding between all involved to avoid these sorts of discrepancies. It is concerning that this lack of explicitness could result in multiple representation schemata for similar concepts, undermining the purpose of a standard. Further, as FHIR is quite easy to use, it will be within the reach of many implementers who lack experience and understanding to realize the importance of explicitness when working with complex health data. It remains to be seen whether users

will realize the need to provide explicit descriptions of data and then preserve that explicitness throughout the system; and if they don't, what problems may result. The potential for a situation where lack of explicitness undermines the utility of a standard, eroding the potential interoperability it is intended to facilitate, is certainly real. While its potential mis-application in this way is not a fault of the FHIR specification itself, it is a potential danger of which one should be aware in light of the interest and current publicity surrounding FHIR and its likely coming widespread use, and one which HL7 should address with, among other methods, robust but clear training materials and thorough examples of proper use.

6.2 Potential Future Work

This work focused on the development of the foundational infrastructure for a CDS application that could provide timely and needed information to clinicians when managing opioid PCA infusions in palliative settings. In the short-run, this work on the foundational infrastructure paves the way for work on the technical infrastructure and, eventually, the development of a functional application. The FHIR specification includes many terminology bindings based on the resource used, and the immediate next step is to evaluate how well these map to the data representing and supporting concepts in the information model developed in this project. It is also necessary to evaluate the extent to which accurate data exists within real-world EHRs and other data stores corresponding to the data and information elements needed by this CDSS. In reality, any CDS application is constrained to that data and information which is reliably available in the stores of the health information systems upon which it is deployed. Interfacing PCA pumps to the EHR could be of great benefit in this regard, as it would provide an automatic way to move information into the EHR that currently relies on humans as a conduit. Such an interface should provide

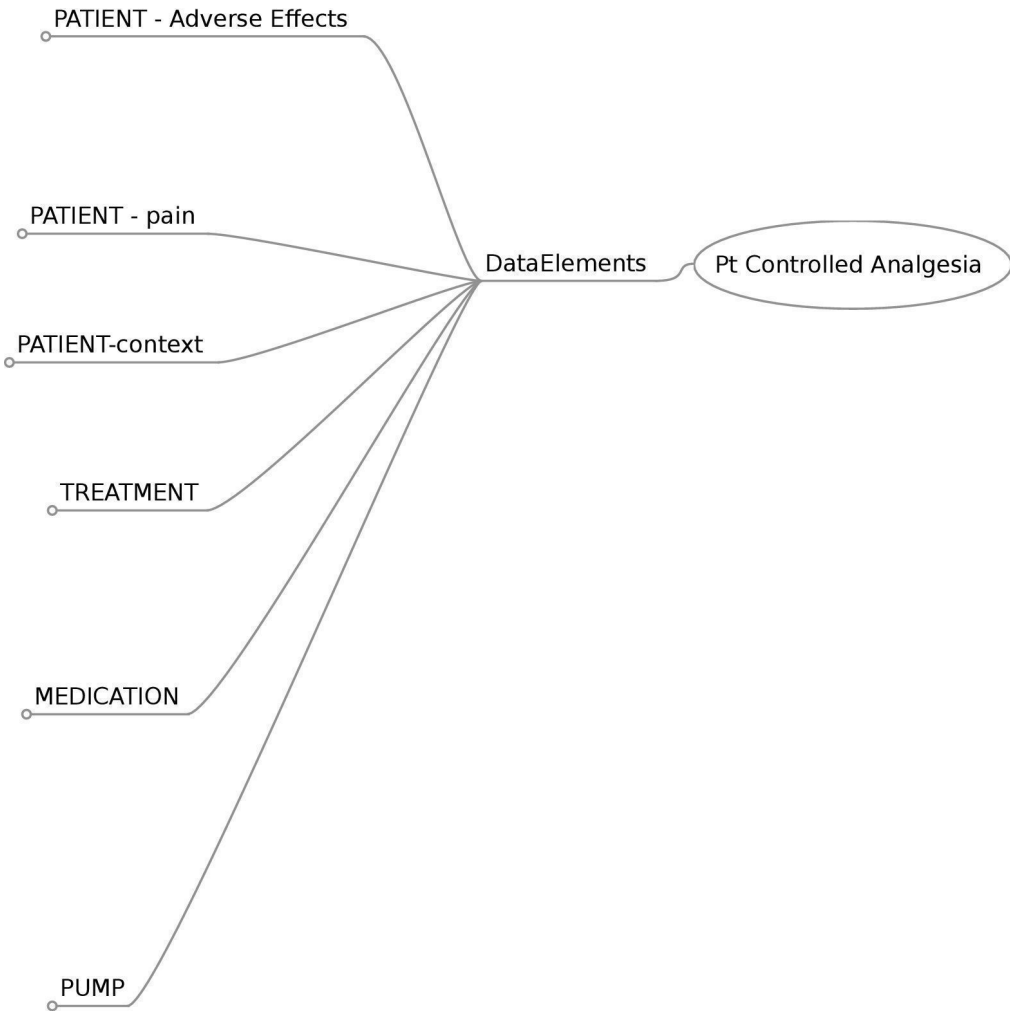
a reliable and accurate source of information for the CDS application. Once work to ensure needed information is available to the CDS, the structure of XML or JSON messages as the payload of FHIR resources needs to be developed and tested. Once this technical infrastructure is in place, it is possible to proceed to development of a functioning prototype that converts this data into a visualization screen in a manner which is is palatable to providers. Such an application should then undergo iterative testing and optimization, to determine if the ultimate goal of a CDSS, tangible improvements in the care of patients, can be realized.

While developed specifically for the use case of opioid PCA management in palliative settings, this CDS holds the potential to be useful in other settings. It was mentioned in Chapter 2 that an opioid PCA infusion regimen is a specialized mode of providing opioid therapy. In fact, many of the concepts germane to managing opioid PCAs are similar to those used in opioid management in general. While for this work the scope was kept narrow, with minor modification this CDS application could be adapted to support opioid management in many other settings. The closely related clinical scenarios of PCAs used in the post-operative setting is a logical next step, but other scenarios where opioids are administered parenterally could be supported by this application. Wider application includes the management of other methods of delivery, such as implantable pumps delivering opioid directly to the CNS, or complex oral regimens. While the system envisioned for the short-term is a passive CDS application functioning as a relevant data display, it is certainly possible to extend functionality and create an active CDS system. As this project broadly defined the information needs of expert clinicians when making decisions for this use case, all *data* needed for an active CDS system which would issue alerts, offer optional general assistance with management, and provide specific suggestions based on the patient's unique clinical situation should be present and available within the

CDS system. To extend this system and create an active system would require only the creation of decision logic and the extension of the interface.

APPENDIX A

CONCEPT MAP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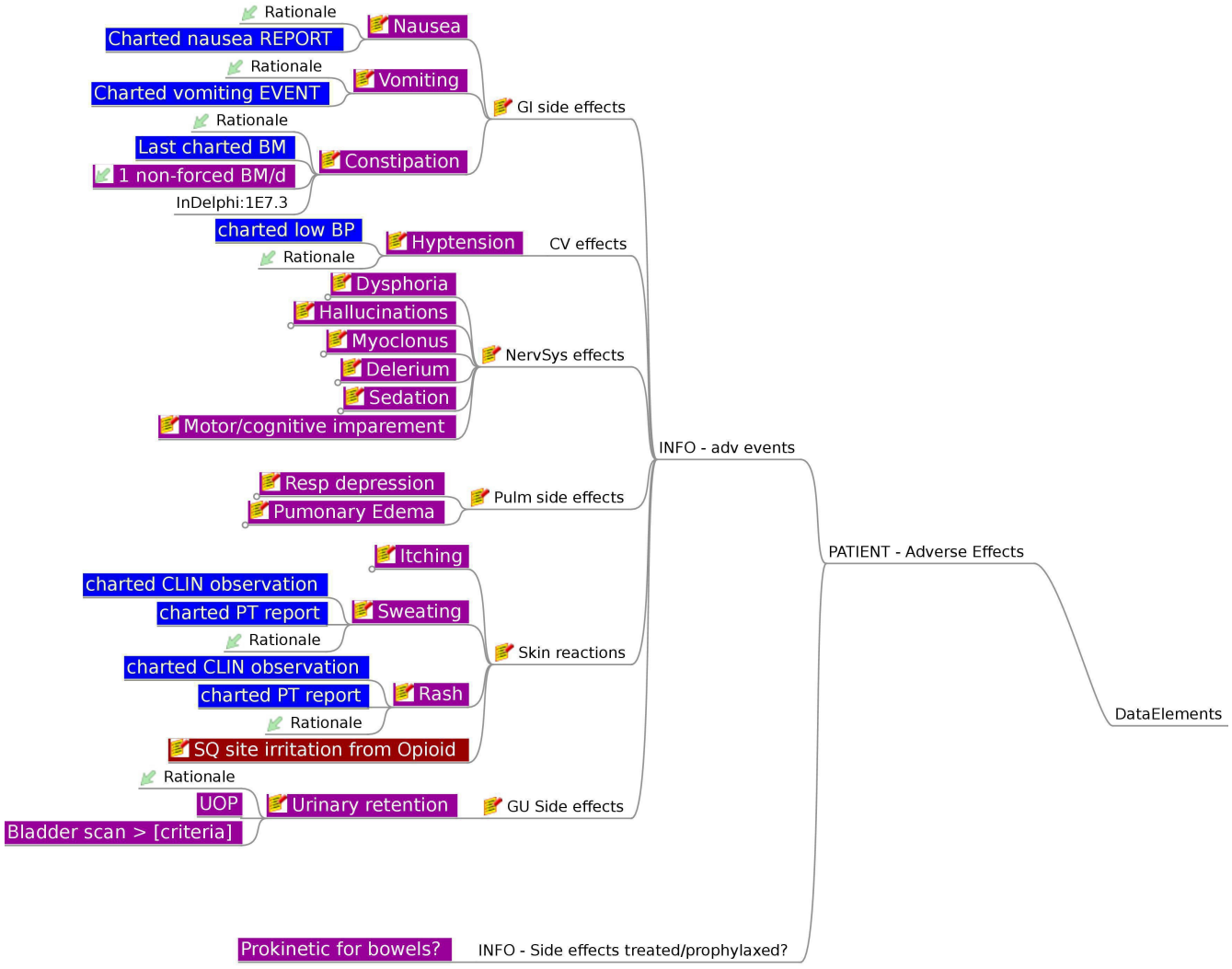
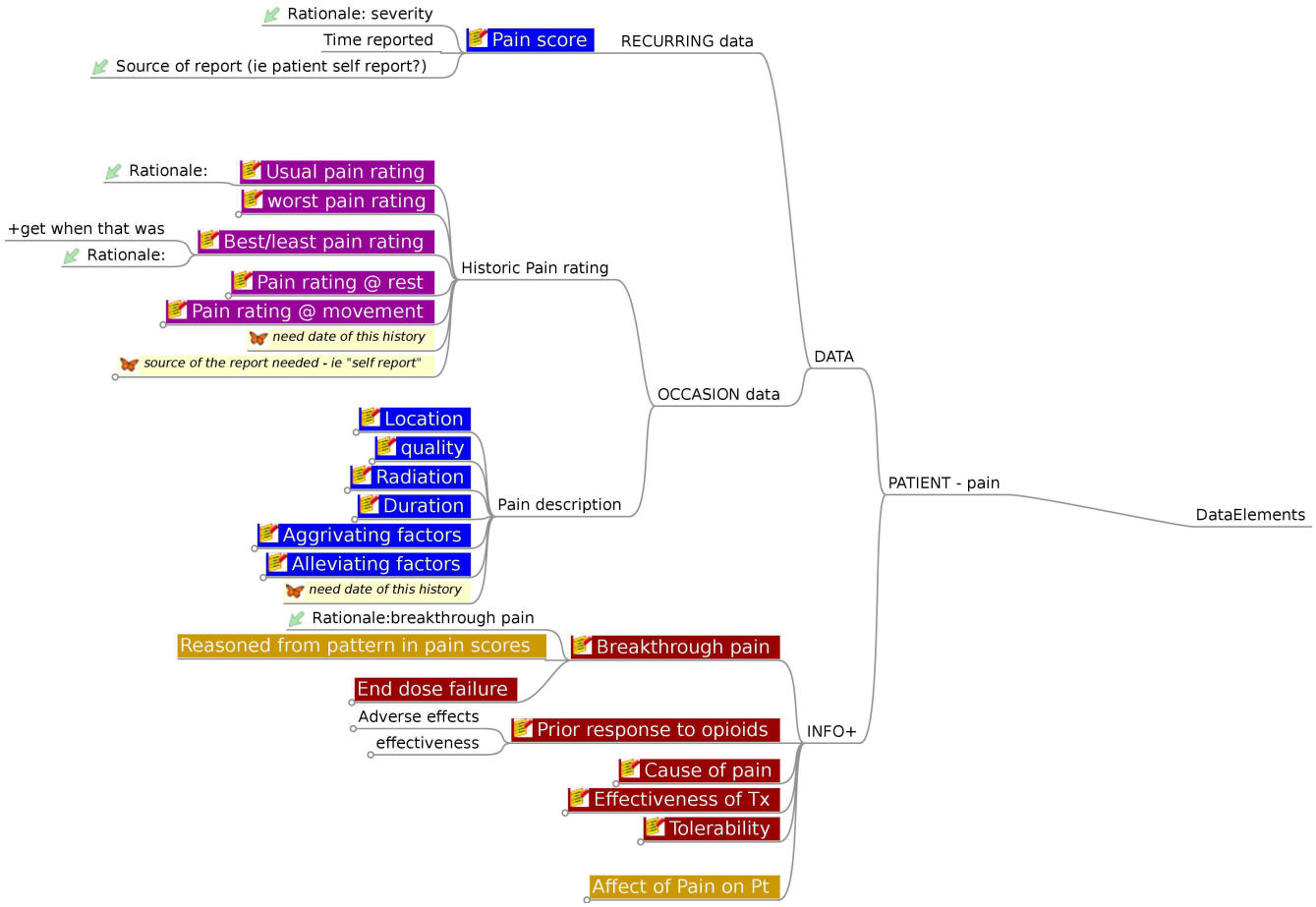
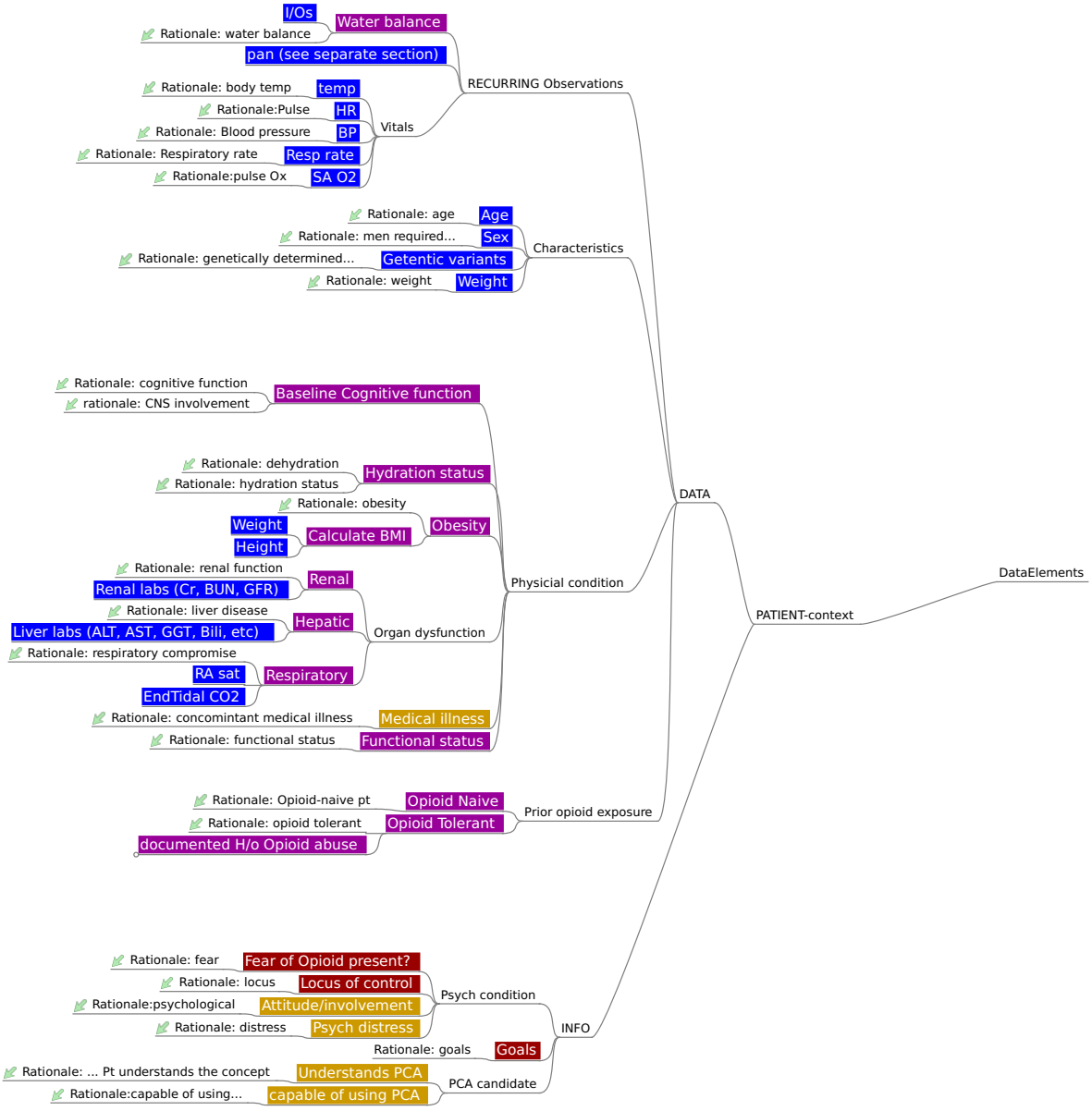
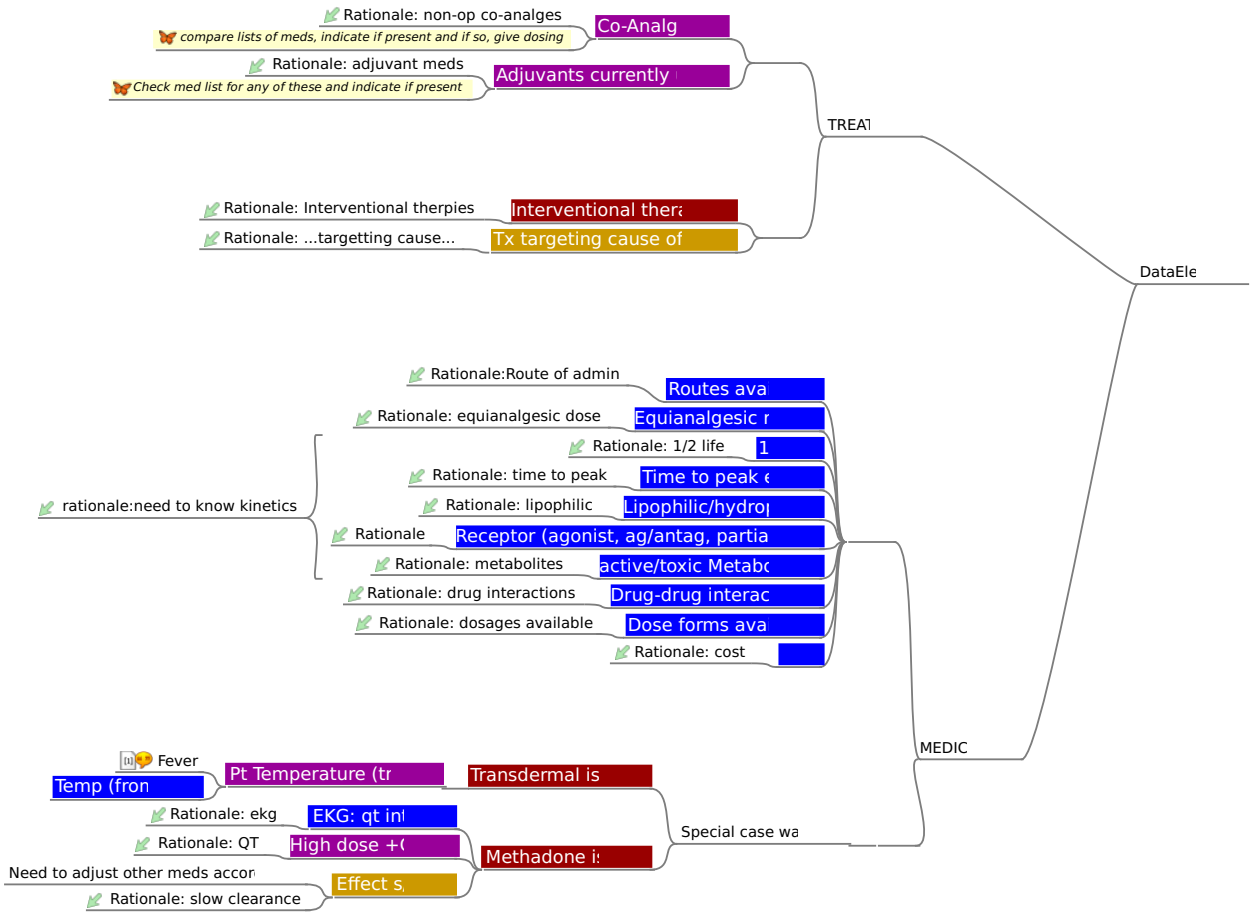
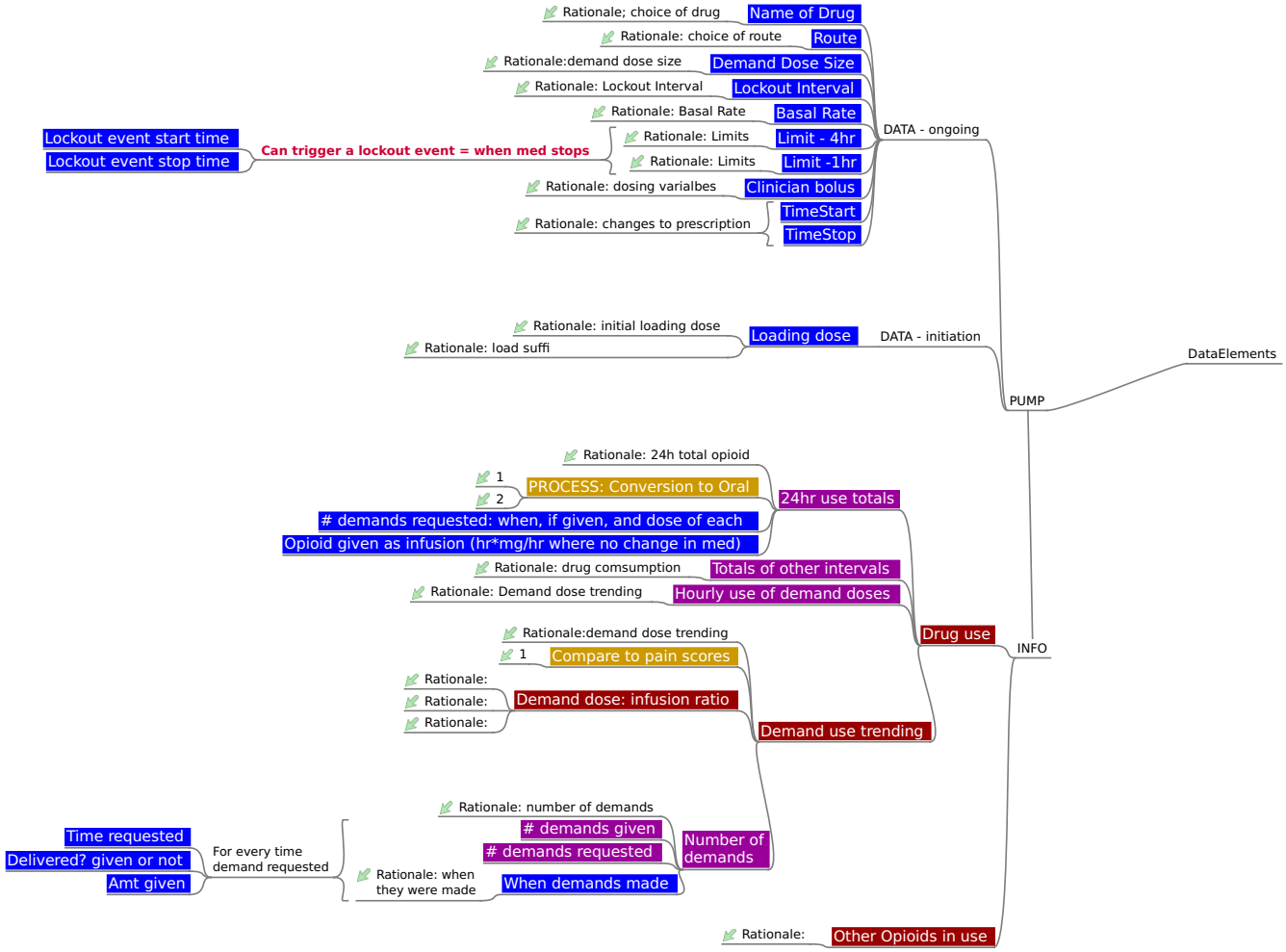
PATIENT - pain
PATIENT-context
TREATMENT
MEDICATION
PUMP
DataElements
Pt Controlled Analgesia


DataElements
PATIENT - Adverse Effects
INFO - adv events
GI side effects
Nausea
Rationale
Charted nausea REPORT
Vomiting
Rationale
Charted vomiting EVENT
Constipation
Rationale
Last charted BM
1 non-forced BM/d
InDelphi:1E7.3
CV effects
Hyptension
charted low BP
Rationale
NervSys effects
Dysphoria
Hallucinations
Myoclonus
Delerium
Sedation
Motor/cognitive imparement
Pulm side effects
Resp depression
Pumonary Edema
Skin reactions
Itching
Sweating
charted CLIN observation
charted PT report
Rationale
Rash
charted CLIN observation
charted PT report
Rationale
SQ site irritation from Opioid
GU Side effects
Urinary retention
Rationale
UOP
Bladder scan > [criteria]
INFO - Side effects treated/prophylaxed?
Prokinetic for bowels?


Rationale: severity
Time reported
Pain score
RECURRING data
Source of report (ie patient self report?)
Rationale:
Usual pain rating
worst pain rating
+get when that was
Rationale:
Best/least pain rating
Pain rating @ rest
Pain rating @ movement
Historic Pain rating
need date of this history
source of the report needed - ie "self report"
Location
quality
Radiation
Duration
Aggrivating factors
Alleviating factors
Pain description
need date of this history
OCCASION data
DATA
Rationale:breakthrough pain
Reasoned from pattern in pain scores
Breakthrough pain
End dose failure
Adverse effects
effectiveness
Prior response to opioids
Cause of pain
Effectiveness of Tx
Tolerability
INFO+
Affect of Pain on Pt
PATIENT - pain
DataElements


DataElements
PATIENT-context
DATA
RECURRING Observations
Water balance
I/Os
Rationale: water balance
pan (see separate section)
Vitals
temp
Rationale: body temp
HR
Rationale:Pulse
BP
Rationale: Blood pressure
Resp rate
Rationale: Respiratory rate
SA O2
Rationale:pulse Ox
Characteristics
Age
Rationale: age
Sex
Rationale: men required...
Getentic variants
Rationale: genetically determined...
Weight
Rationale: weight
Physicial condition
Baseline Cognitive function
Rationale: cognitive function
rationale: CNS involvement
Hydration status
Rationale: dehydration
Rationale: hydration status
Obesity
Rationale: obesity
Calculate BMI
Weight
Height
Organ dysfunction
Renal
Rationale: renal function
Renal labs (Cr, BUN, GFR)
Hepatic
Rationale: liver disease
Liver labs (ALT, AST, GGT, Bili, etc)
Respiratory
Rationale: respiratory compromise
RA sat
EndTidal CO2
Medical illness
Rationale: concomintant medical illness
Functional status
Rationale: functional status
Prior opioid exposure
Opioid Naive
Rationale: Opioid-naive pt
Opioid Tolerant
Rationale: opioid tolerant
documented H/o Opioid abuse
INFO
Psych condition
Fear of Opioid present?
Rationale: fear
Locus of control
Rationale: locus
Attitude/involvement
Rationale:psychological
Psych distress
Rationale: distress
Goals
Rationale: goals
PCA candidate
Understands PCA
Rationale: ... Pt understands the concept
capable of using PCA
Rationale:capable of using...


Rationale: non-op co-analges
compare lists of meds, indicate if present and if so, give dosing
Co-Analg
Rationale: adjuvant meds
Check med list for any of these and indicate if present
Adjuvants currently
TREAT
Rationale: Interventional therpies
Interventional thera
Rationale: ...targetting cause...
Tx targeting cause of
DataEle
Rationale:Route of admin
Routes ava
Rationale: equianalgesic dose
Equianalgesic r
Rationale: 1/2 life
1
Rationale: time to peak
Time to peak
rationale:need to know kinetics
Rationale: lipophilic
Lipophilic/hydro
Rationale
Receptor (agonist, ag/antag, partia
Rationale: metabolites
active/toxic Metab
Rationale: drug interactions
Drug-drug interac
Rationale: dosages available
Dose forms ava
Rationale: cost
MEDIC
Fever
Pt Temperature (tr
Transdermal is
Temp (fron
Rationale: ekg
EKG: qt in
Rationale: QT
High dose +
Methadone i
Special case wa
Need to adjust other meds accor
Effect s
Rationale: slow clearance


DataElements
PUMP
INFO
DATA - ongoing
Rationale; choice of drug
Name of Drug
Rationale: choice of route
Route
Rationale:demand dose size
Demand Dose Size
Rationale: Lockout Interval
Lockout Interval
Rationale: Basal Rate
Basal Rate
Rationale: Limits
Limit - 4hr
Rationale: Limits
Limit -1hr
Lockout event start time
Lockout event stop time
Can trigger a lockout event = when med stops
Rationale: dosing varialbes
Clinician bolus
Rationale: changes to prescription
TimeStart
TimeStop
DATA - initiation
Rationale: initial loading dose
Loading dose
Rationale: load suffi
Drug use
Rationale: 24h total opioid
24hr use totals
1
2
PROCESS: Conversion to Oral
demands requested: when, if given, and dose of each
Opioid given as infusion (hr*mg/hr where no change in med)
Rationale: drug comsumption
Totals of other intervals
Rationale: Demand dose trending
Hourly use of demand doses
Rationale:demand dose trending
1
Compare to pain scores
Rationale:
Rationale:
Rationale:
Demand dose: infusion ratio
Demand use trending
Rationale: number of demands
demands given
demands requested
Number of demands
Rationale: when they were made
When demands made
For every time demand requested
Time requested
Delivered? given or not
Amt given
Rationale:
Other Opioids in use

APPENDIX B

REDCap SURVEY

PCA data - Experts' opinion

Please complete the survey below.

Thank you!

The goal of this project is to better understand the information needs of providers as they manage complex opioid infusions, particularly PCA pumps in patients with life-limiting illnesses. It is hoped that this understanding will eventually lead to improvements in EHRs such that information needed in managing opioid regimens is more accessible.

Some questions may seem overly simple to a seasoned palliative care provider - most of us "know" what data we need and assume others do as well. While there is considerable expert opinion and even some research on how to manage opioid infusions and PCA regimens, extensive literature searches revealed little or no consideration of what pieces of information providers need or when that information was needed for decision-making over the course of managing an opioid infusion or PCA regimen. From an informatics perspective, this creates a gap that can negatively impact development of clinical tools, such as EHR modules and decision support applications. This study is one small part of a larger effort to fill that gap.

The survey is seeking your opinion as a provider experienced in managing opioid PCA regimens in palliative settings, so please don't feel the need to spend considerable time to determine the "right" answer to questions - the right answer for the purpose of this study is your opinion.

This study has been reviewed and approved by the IRB of the University of Utah.

Participation in this study is voluntary and consent to participate is implied by your clicking the "next page" button below and entering the survey itself.

You should have previously received and reviewed a consent letter, but if not, you may review it using the link below. You may contact the investigator or the University of Utah IRB with concerns at the addresses listed in the consent letter.

[Attachment: "PCA_ExprtSrv01_Consent.pdf"]

If you have not read the consent letter or if you have any concerns about participation, please do not enter the survey.

Before we start, we would like to know a little about your experience with managing PCAs. This will help us better understand the needs of users at various levels of experience. The following questions require some reply before you can continue, but if you feel at all uncomfortable answering any of these questions, please type "NA" instead of an answer and continue on to the survey.

What are your credentials? (i.e. physician, NP, APN, PA, RPh, etc.) _____

For how many years have you been in practice? _____
(do not include time in clinical training)

What is your clinical background / specialty? _____

For how many years have you been practicing that specialty? _____

For how long have you been managing opioid PCA regimens? _____

Approximately how many PCA regimens would you say you manage in a year? _____

Based on the following scale, how would you rate your ability to manage opioid PCA regimens: Novice - I often consult resources or other providers for help. Competent - I occasionally need to consult resources or other providers with complex issues. Expert - I rarely need help; I am the one others consult.

◯ Novice
◯ Competent
◯ Expert

There are three sections to this survey.

In the first section, you will be asked about the overall importance of certain information when managing an opioid PCA regimen. At times you may be asked about specific examples of information which you rate as important. (This is the largest section).

In the second section, you will be asked how often you use the information you indicated was important in section one. (There might be information you feel is vital to have though you use it rarely - that is fine and is part of what this study hopes to discover.)

In the third section you will be asked when during management of an opioid PCA regimen you feel the information you marked as important in section one is needed.

It is possible to save your progress, exit the survey and come back later; click the "Save and Return Later" button at the bottom of each section and follow the directions given (you will write down a code to resume the survey).

Click the "Next Page" button below to get started.

Section 1

Importance of information

In answering the questions in this section, consider the following scenario:

You are managing the disease-related pain of a patient with end-stage disease (not "actively" terminal). You have decided to manage the pain with parenteral opioids delivered via PCA pump. The patient is in a facility where you will be accessing records to obtain data and write orders in person (that is, you are not managing this PCA regimen by phone where someone else, such as a nurse, will be gathering and supplying the information to you). Please consider that other physicians may change orders to the PCA regimen, so you cannot rely just on your own memory or knowledge of prior orders.

If you are not sure, don't know, or wish not to answer an item, leave it blank.

To erase an answer, click the "reset" to the right of the answer choices.

This section uses conditional logic such that certain answers will trigger more specific follow-up questions.

In general, how important is the following general information about a patient to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
Patient characteristics such as age, weight, sex	○	○	○	○	○
Patient's goals of care	○	○	○	○	○
Patient's ability to understand and use the PCA	○	○	○	○	○
Whether patient is opioid naive or tolerant	○	○	○	○	○
Patient's response to opioids before this episode	○	○	○	○	○
Patient's genetic profile potentially affecting opioid metabolism, effect, or side effects	○	○	○	○	○

You marked patient characteristics as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Age	○	○	○	○	○
Weight	○	○	○	○	○
Sex	○	○	○	○	○

In general, how important is the following information about a patient's treatment/ careplan to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
Currently used co-analgesics	○	○	○	○	○
Currently used adjuvant therapies	○	○	○	○	○
Currently used interventional therapies	○	○	○	○	○
Non-analgesic treatment directed at the cause of the pain	○	○	○	○	○
The effectiveness of the current pain regimen	○	○	○	○	○
The tolerability of the current pain regimen	○	○	○	○	○
Currently prescribed bowel regimen (laxatives, stimulants, etc.)	○	○	○	○	○

In general, how important is the following information about a patient's condition to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
Patient's vital signs	○	○	○	○	○
Patient's cognitive functioning	○	○	○	○	○
Patient's psychological condition	○	○	○	○	○
Patient's physical condition (ie organ dysfunction, functional status, etc.)	○	○	○	○	○

You marked vital signs as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Temperature	○	○	○	○	○
Pulse	○	○	○	○	○
Respiratory rate	○	○	○	○	○
Blood pressure	○	○	○	○	○
Pulseoximetry	○	○	○	○	○
I/O's (fluid "ins and outs")	○	○	○	○	○

You marked cognitive function as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Baseline cognitive status	○	○	○	○	○
Patient's ability to comprehend the PCA device and paradigm	○	○	○	○	○

You marked physical condition as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Functional status	○	○	○	○	○
Underlying cardiopulmonary disease	○	○	○	○	○
Hydration status	○	○	○	○	○
Renal function	○	○	○	○	○
Hepatic function	○	○	○	○	○
Respiratory function	○	○	○	○	○

In general, how important is the following information about a patient's pain to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
Pain scores/ratings over course of treatment	○	○	○	○	○
Patient's description of the pain	○	○	○	○	○
Patient's rating of pain under different circumstances (ie best, worst, typical...)	○	○	○	○	○
Episodes of breakthrough pain	○	○	○	○	○
Cause of pain	○	○	○	○	○
Effect of the pain on the patient and his/her life	○	○	○	○	○

You marked description of the pain as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Location of the pain	○	○	○	○	○
Quality of the pain	○	○	○	○	○
Radiation of the pain	○	○	○	○	○
Duration of the pain	○	○	○	○	○
Aggravating factors	○	○	○	○	○

Alleviating factors	○	○	○	○	○

You marked pain scores in different circumstances (best, worst, etc.) as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Patient's self-rating of usual pain	○	○	○	○	○
Patient's self-rating of pain at its worst	○	○	○	○	○
Patient's self-rating of pain at its least	○	○	○	○	○
Patient's self-rating of pain at rest	○	○	○	○	○
Patient's self-rating of pain when moving	○	○	○	○	○

In general, how important is the following information about symptoms or adverse effects possibly related to opioids to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
GI symptoms/side effects	○	○	○	○	○
Hypotension	○	○	○	○	○
Neurologic symptoms/side effects	○	○	○	○	○
Pulmonary symptoms/side effects	○	○	○	○	○
Skin symptoms/side effects	○	○	○	○	○
Urinary retention	○	○	○	○	○

You marked GI symptoms as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Nausea	○	○	○	○	○
Vomiting	○	○	○	○	○
Constipation	○	○	○	○	○

You marked neurologic symptoms as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Dysphoria	○	○	○	○	○
Hallucinations	○	○	○	○	○
Myoclonus	○	○	○	○	○
Delirium	○	○	○	○	○
Sedation	○	○	○	○	○
Impaired motor function	○	○	○	○	○
Impaired cognitive function	○	○	○	○	○

You marked pulmonary symptoms as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Respiratory depression	○	○	○	○	○
Pulmonary edema	○	○	○	○	○

You marked skin symptoms as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Itching	○	○	○	○	○
Rash	○	○	○	○	○
Sweating	○	○	○	○	○
Injection site irritation	○	○	○	○	○

In general, how important is the following information about PCA parameters and use to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
Name of drug in use	○	○	○	○	○
Route of opioid administration	○	○	○	○	○
Size of the PCA demand dose ordered	○	○	○	○	○
Ordered frequency of PCA demand doses	○	○	○	○	○
History, timing, and pattern of use of demand doses	○	○	○	○	○
Basal infusion rate	○	○	○	○	○
Information about opioids given by other than PCA (ie loading or clinician doses, or concomitant orders)	○	○	○	○	○
What "limits" (1hr, 4hr, etc.) are set	○	○	○	○	○
If or when limits were reached (and pump locks out)	○	○	○	○	○
Time when particular PCA parameters started/stopped	○	○	○	○	○
Calculated and trend data about PCA use (totals, demand patterns, etc.)	○	○	○	○	○

You marked information about opioids being given by other than PCA as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Loading doses given	○	○	○	○	○
Clinician bolus that are/were ordered or available	○	○	○	○	○
Administered clinician boluses	○	○	○	○	○
Concurrent orders for oral opioids	○	○	○	○	○
Use of ordered oral opioids	○	○	○	○	○

You marked trends in PCA use and/or history and timing of demand doses as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Number and timing of demand dose requests	○	○	○	○	○
Number and timing of demand doses given	○	○	○	○	○
24 hour (or other interval) total opioid given	○	○	○	○	○
Ratio of demands made to demand doses given	○	○	○	○	○

In general, how important is the following information about the opioid being given to your decision-making and management of a PCA regimen?

	Not important	Of minor importance	Important	Very important	Extremely important
Dose forms available (other routes, dosages, etc.)	○	○	○	○	○
Cost of drug	○	○	○	○	○
Interactions with other medications	○	○	○	○	○
The particular opioid's kinetics	○	○	○	○	○

You marked information about kinetics as at least important. Please rate the following to provide more detail:

	Not important	Of minor importance	Important	Very important	Extremely important
Half-life	○	○	○	○	○
Time to peak effect	○	○	○	○	○
Hydrophilic/hydrophobic and Lipophilic/Lipophobic characteristics	○	○	○	○	○
Receptor profile (agonist, agonist-antagonist, etc.)	○	○	○	○	○
Metabolites and features of metabolites	○	○	○	○	○
Equianalgesic ratios	○	○	○	○	○

That's it for section 1. Before we move on to Section 2, if there are any pieces of information that you feel are important but which you did not see listed above, please feel free to type those in the box to the right.

_____

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