

# Dimensions of Patient Safety Culture in Family Practice

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## Abstract

Safety culture has been shown to affect patient safety in healthcare. While the United States and United Kingdom have studied the dimensions that reflect patient safety culture in family practice settings, to date, this has not been done in Canada. Differences in the healthcare systems between these countries and Canada may affect the dimensions found to be relevant here. Thus, it is important to identify and compare the dimensions from the United States and the United Kingdom in a Canadian context.

The objectives of this study were to explore the dimensions of patient safety culture that relate to family practice in Canada and to determine if differences and similarities exist between dimensions found in Canada and those found in previous studies undertaken in the United States and the United Kingdom. A qualitative study was undertaken applying thematic analysis using focus groups with family practice offices and supplementary key stakeholders.

Analysis of the data indicated that most of the dimensions from the United States and United Kingdom are appropriate in our Canadian context. Exceptions included *owner/managing partner/leadership support for patient safety, job satisfaction and overall perceptions of patient safety and quality*. Two unique dimensions were identified in the Canadian context: *disclosure and accepting responsibility for errors*.

Based on this early work, it is important to consider differences in care settings when understanding dimensions of patient safety culture. We suggest that additional research in family practice settings is critical to further understand the influence of context on patient safety culture.

## Background

Since the release of the Institute of Medicine report *To Err Is Human: Building a Safer Healthcare System* (Kohn et al. 1999), more attention has been paid internationally to the issues surrounding patient safety. The safety of healthcare has been shown to be influenced by its organizational culture (Nieva and Sorra 2003; Schutz et al. 2007; Wachter 2004), which is the pattern of assumptions, values and norms within an organization (Schein 1990) and is the primary driver of safety (Ruchlin et al. 2004). If the organizational culture does not support patient safety, unsafe care will continue to occur (Baker and Norton 2001; Gaba et al. 2007; Pace 2007; Pronovost and Sexton 2005; Singer et al. 2007; Wachter 2004; Westrum 2004).

Organizational culture is a broad construct composed of many subsets of culture, one of which is safety (Clarke 1999; Hofstede 1980; Reiman and Oedewald 2004). The focus on safety culture began in the nuclear power and aviation industries (Health and Safety Commission 1993) and is now recognized as an important component in the delivery of healthcare (Blegen et al. 2009; Clarke 1999; Fleming and Wentzell 2008; Gaba et al.

1994; Ginsburg and Tregunno 2007; Hofstede 1980; National Patient Safety Agency [NPSA] 2006; Reiman and Oedewald 2004; Stock and Mahoney 2008). NPSA defines safety culture as one in which “both the individuals and the organisation are able to acknowledge mistakes, learn from them, and take action to put things right...[It] is open and fair, and one that encourages people to speak up about mistakes” (2006: 17, 21). It also has been suggested that “safety culture is a critical element necessary to achieve reductions in medical errors and adverse events” (Stock et al. 2007: 375). To improve patient safety, a shift in culture from “blame and shame” to “just and trusting” is required (Reason 1997).

In order to improve patient safety culture, it is necessary to be able to interpret and measure it. To date, the majority of research on patient safety culture interpretation and measurement has focused on acute care settings. Singla et al. (2006) performed a systematic review of existing instruments or tools developed in the United States to measure patient safety culture in acute care. They found 13 instruments identifying 23 dimensions of patient safety culture. These dimensions were grouped into six broad categories: management/supervision, risk, work pressure, competence, rules and miscellaneous. One of these instruments, the Stanford Instrument (Singer et al. 2003), was modified to fit the Canadian acute care context (York University n.d.).

### **Family practice settings differ from acute care in organizational structure, administrative and clinical processes and the reason for and type of visits.**

Family practice settings differ from acute care in organizational structure, administrative and clinical processes and the reason for and type of visits. In family practice, a formalized organizational structure with set policies and procedures is rare; services such as specialist care, laboratories and diagnostic imaging are off site; there is less control over the patients' environments (Hammons et al. 2002; O'Beirne and Sterling 2009; Schutz et al. 2007); the turnaround of results is much slower; and patients are more likely to be seen for chronic issues rather than conditions of high acuity (Dovey et al. 2002a, 2002b).

Family practice also differs in relation to the types of incidents reported and in the strategies and interventions used to improve patient safety. In family practice, most incidents are related to failure or delay in diagnosis, failure or delay in referral, medication contraindication, medication prescription errors (Dovey et al. 2003; National Patient Safety Agency 2006) and test results management (Elder et al. 2009). In acute care, interventions and strategies focus on standardizing operating procedures in

order to mitigate incidents. In family practice, interventions and strategies focus on “diagnosis, medication prescribing, dispensing and administration, and communication within practices, between different professions and between primary and secondary care” (National Patient Safety Agency 2006: 20).

Given the substantial differences in care settings, it is important to understand if and how differences influence or alter dimensions of patient safety culture. Unfortunately, very little work has been published on measuring patient safety culture in family practice. In the United States, three groups have developed sets of dimensions for family practice (Agency for Healthcare Research and Quality n.d.; Modak et al. 2007; Schutz et al. 2007), tied to respective questionnaires. Also, a framework of dimensions has been developed in the United Kingdom (Kirk et al. 2007). The dimensions from the three US sources and the UK source were similar but not identical. In the Canadian context, patient safety culture dimensions for family practice have not been developed. However, major distinctions exist within their incentives and management structures for family practice. In the United States, most of the family practice delivery is privately funded and delivered through managed care. In the United Kingdom, the delivery is primarily publicly funded and organized into “primary care trusts” (National Health Service 2009). In Canada, family practice care delivery is publicly funded and privately delivered. This variance in governance of family practice among the US, UK and Canadian contexts suggests that further exploration is required to better understand what dimensions are and are not appropriate for measuring patient safety culture in Canadian family practice.

As outlined, there are considerable gaps in knowledge concerning the dimensions of patient safety culture that need to be addressed specific to the family practice setting in the Canadian context. The remainder of this article discusses how investigation into these gaps has begun.

### **Purpose and Objectives**

This study is part of a much larger program of research that focuses on patient safety in family practice – Medical Safety in Community Practice (MSCP; O'Beirne and Sterling 2009). The purpose of the MSCP research is to collect incident information from family practices located within Alberta Health Services, Calgary Zone, and to collaborate with these practices to develop, implement and evaluate risk management strategies to increase patient safety. The overarching purpose of the study presented in this article was to explore patient safety culture within family practice settings in order to enhance the understanding of this relatively under-studied setting. Primary objectives were (1) to begin to determine the dimensions of patient safety culture for family practice in Canada and (2) to subsequently determine if differences and similarities exist between dimensions found in

Canada and those found in previous studies undertaken in the United States and the United Kingdom.

## Methods

This qualitative case study involved identifying the dimensions of patient safety culture of relevance to family practice in Canada. A convenience sample of five clinics was chosen from the MSCP program. These clinics were invited via telephone to participate in the focus groups for this study. Two clinics accepted the invitation. One of these clinics was well entrenched in the patient safety study; the other was new to the study. A third focus group was held that involved informed stakeholders, including patient safety experts and family physicians, staff and patient advocates (members of a panel in the MSCP program). These focus groups were what Stewart and Shamdasani (1990) described as “compatible and heterogeneous” because they had a diversity of practitioners and professionals with a common interest in patient safety. A semi-structured script was used to guide discussion on the dimensions that participants felt were important to patient safety culture.

The focus groups were facilitated by one of the research team members and ran for one hour or less. Each group had between four and six participants. In total, five physicians, one nurse, six office staff members, one health-care administrator and one layperson participated. All focus groups were tape-recorded. After the first focus group, participants suggested adding a definition of *patient safety culture*, and this was provided for the remaining groups. By the third focus group, no new information was emerging.

Tape recordings were transcribed, data coded and field notes used to supplement and clarify the data (Morse and Field 1995). Three researchers individually performed thematic analyses (Morse and Field 1995) on the focus group transcripts. The existing dimensions from the United States and United Kingdom were used as one lens for analysis; however, analysis remained open to identify new and emergent perspectives from the study participants. When comparing results, themes and dimensions of patient safety culture were convergent among

the reviewers. The discussion and revision of themes focused primarily on how these similar concepts were named. A final review of emergent themes and dimensions of patient safety culture was undertaken by five researchers, serving to further triangulate results and allow for additional reflective interpretation of the study participant data. If the wording was different but the concept the same, the language used in the US study (Agency for Healthcare Research and Quality n.d.) was adopted.

## Results

The analyses of our review of existing literature and our own data highlight several important results. Thirteen dimensions of patient safety culture relevant to family practice in our Canadian cases were identified. Table 1 illustrates the dimensions and compares them with those in the US and UK studies. Each of these dimensions is further described in Table 2, which provides

**Table 1. Patient safety culture dimensions in family practice: comparison of US and UK cases with Canadian cases**

Dimension*	US and UK Cases	Canadian Cases
Organizational learning	X	X
Communication about error	X	X
Staff training	X	X
Teamwork	X	X
Patient care tracking/follow-up	X	X
Communication openness	X	X
Patient safety and quality issues	X	X
Office processes and standardization	X	X
Information exchange with other settings	X	X
Work pressure and pace	X	X
Overall ratings on quality and patient safety	X	X
Owner/managing partner/leadership support for patient safety	X	
Job satisfaction	X	
Overall perceptions of patient safety and quality	X	
Disclosure		X
Accepting responsibility for error		X

\*Dimensions from the three US sources (Agency for Healthcare Research and Quality [AHRQ] n.d.; Modak et al. 2007; Schutz et al. 2007) and one UK source (Kirk et al. 2007) were similar but not identical, and we chose the wording of AHRQ.

**Table 2. Dimensions, descriptions and examples for the Canadian cases**

Dimension	Description of Dimension	Narrative Example
Organizational learning	Illustrates the level of learning that occurs from incidents within the practice, and work to improve those problems	"Well, in my opinion, it's hard to anticipate every aspect of the type of mistakes that can be made, but when a mistake is brought forward, something is done to address it so it hopefully does not happen again. And it's not disregarded."
Communication about error	Shows the openness of the practice members to admitting errors and discussing them with others	"Creating an atmosphere where people feel comfortable bringing forward mistakes."
Staff training	Reflects how well the office ensures staff members are trained in what they are required to do	"In-service training in various aspects of what the staff are doing would definitely help."
Teamwork	Identifies respect, working relationships and helping others in the work load as part of teamwork	"The idea of teamwork is hugely important. The people that contribute are present at the decision; co-operate in that collegial world of encounter."
Patient care tracking/ follow-up	Measures the extent offices perform proper follow-up and tracking of patients	"Well, having test results going astray is big, especially when something has been missed. If there was something important in the results..."
Communication openness	Reflects how open all members of the office are in voicing their opinion and accepting others	"I think it's important that everyone feels free to contribute their ideas because everyone has a different role and, maybe, just a different way they do about things."
Patient safety and quality issues	Reflects things that can happen in medical offices that affect patient safety and quality of care (e.g., access to care, medication and medical records)	"In a perfect healthcare setting would be timely access to a physician, appropriate evaluation, proper medication and compliance by the patient and also appropriate laboratory investigation and follow-up on that."
Office processes and standardization	Identifies procedures, processes, workflow and standardization	"It is creating processes within our medical environments that allow patients or clients to move through these processes in a positive manner."
Information exchange with other settings	Captures how often the office has had problems exchanging accurate, complete and timely information with external settings (laboratory, diagnostic imaging, specialists)	"Because the clinic does not notify us when they've received our referral ... we are now attaching a cover that says please respond that you have received this referral. They haven't returned our faxes, but we just started that last week."
Work pressure and pace	Explores distractions and volume of work	"If the environment you are working in is too distracting, it's unsafe."
Overall ratings on quality and patient safety	Measures overall ratings on patient-centred, effective, timely, efficient and equitable healthcare	"Part of patient safety is getting the most up-to-date evidence-based care."
Disclosure	Reflects disclosure of error to the patient	"Patients are confident in knowing that if something gets missed, it will be brought to their attention ... it's not hidden from them; it's disclosed."
Accepting responsibility for error	Illustrates that individuals can accept that they made an error	"I think it's important if you have made a mistake to say, 'I'm sorry, I made a mistake,' because mistakes happen and it's not that you purposely try to make mistakes during your day at work."

some examples of the Canadian perspectives found in the data.

As Table 1 shows, three patient safety culture dimensions in family practice found in the US and UK cases were not found in the Canadian context: *owner/managing partner/leadership support for patient safety, job satisfaction and overall perceptions of patient safety and quality*. Two new dimensions were identified: *disclosure* and *accepting responsibility for errors*.

The data reported here explore the dimensions of patient safety culture in Canadian family practice settings in comparison with data found in the US and UK studies. Several interesting findings warrant discussion and further examination.

## Discussion

The dimensions found in family practice in Canada identified in Table 1 suggest that there is considerable consistency of patient safety culture dimensions in our Canadian cases when compared with the US and UK cases; but, there also appear to be some differences. Eleven of the existing dimensions were relevant in the Canadian context, three were not identified and two new dimensions were discovered.

There are many possible reasons for these differences. The absence of the dimension *owner/managing partner/leadership support for patient safety* could be due to the difference in governance found in these countries. In Canada, clinics are run more as a partnership, without an overlying organizational structure. It is difficult to explain the absence of the dimension *job satisfaction* in the Canadian study, but it is interesting to note that this dimension was also not found in studies of acute care in Canada (York University n.d.). It is possible that, in this study, job satisfaction was captured as an attribute (subcategory) under other dimensions such as *office processes and standardization*. *Overall perceptions of patient safety and quality* may simply have been too broad a dimension to emerge separately in our cases. This is an area that needs further exploration.

Two new dimensions were found to be relevant in Canadian family practice settings: While *disclosure* is closely aligned with the existing dimension *communication about error*, it concerns communicating outside the clinical team to patients and families. *Accepting responsibility for error* appears to be unique and distinct, going beyond communicating about an error to admitting fallibility. These new dimensions may have arisen as a consequence of recent media coverage and emphasis in Canada on disclosure and accepting responsibility (Health Quality Council of Alberta 2006; Windwick et al. 2007). Perhaps these dimensions were missing in the US and UK cases due to the earlier timing of the studies.

It is important to stress both the strengths and limitations of the study findings. Potential limitations to the study include the following: (1) participants may not have felt comfortable enough to openly express themselves in front of their colleagues, although this risk was minimized through careful facilitation of

the focus groups; and (2) the small sample size from one city did not include all types of family practices (ranging from a single family physician practice with few employees and little organizational structure to multi-physician, multi-employee practices with some organizational structure). The major strength of the study is that it adds early and additional knowledge to understanding dimensions of patient safety culture in family practice, and it is the first of its kind in a Canadian setting.

Given that this is one early study with only a few Canadian cases, clearly more research is required to confirm and extend this initial exploratory case analysis. However, considering the significant consistency of dimensions found in common with those in the earlier US and UK studies, there is some promise for transferable lessons more generally for family practice in Canadian settings.

**It is important to consider context when adapting existing tools created in other jurisdictions.**

This study identified 13 dimensions relevant to patient safety culture in Canada. Based on this early work, it is important to consider context (country and setting) when adapting existing tools created in other jurisdictions. The dimensions found in this study will be used to develop a tool to measure patient safety culture in family practice in Canada. With this tool, we will be able to estimate patient safety culture and measure changes in culture after the implementation of safety or quality interventions.

While our work makes important contributions to understanding the dimensions of patient safety in family practice settings, additional exploration and evaluative research are needed. We encourage others to add to our empirical and theoretical knowledge of the role that culture plays in the capacity to develop and sustain patient safety in Canadian family practice settings. We also suggest that additional comparative research would provide valuable insight into how best to understand and measure the influence of patient safety culture in different countries with varying organizational arrangements for care and, especially, among distinct care settings.

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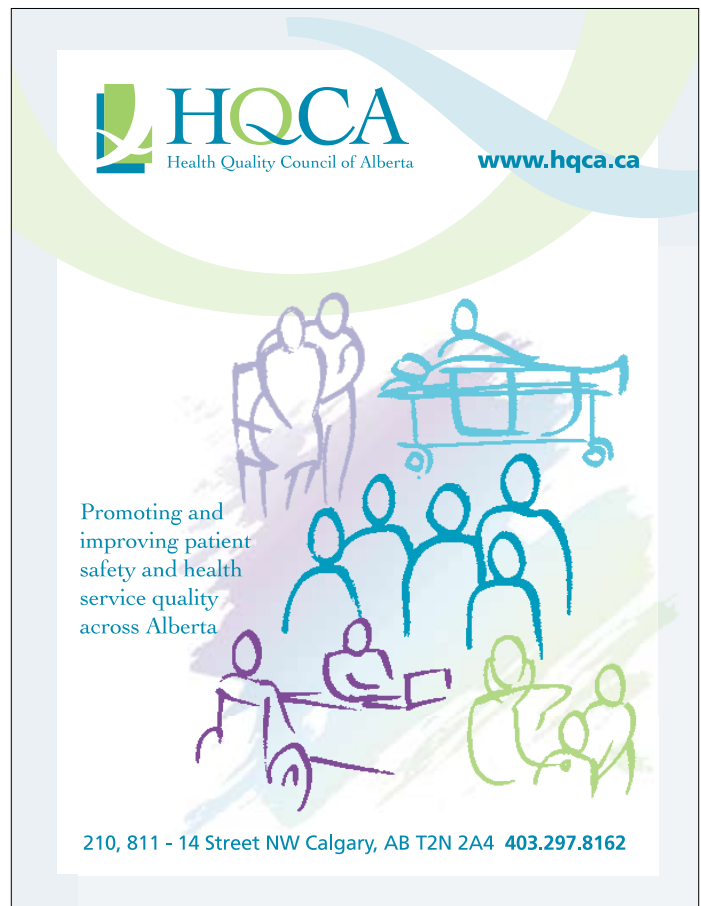
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### CONTRAINDICATIONS

FRAGMIN should not be used in patients who have the following:

- Hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) (see **WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS, Pregnant Women**), or to other low molecular weight heparins and/or heparin or pork products
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an *in vitro* platelet-aggregation test in the presence of FRAGMIN is positive
- Septic endocarditis (endocarditis lenta, subacute endocarditis)
- Uncontrollable active bleeding
- Major blood-clotting disorders
- Acute gastroduodenal ulcer
- Cerebral hemorrhage
- Severe uncontrolled hypertension
- Diabetic or hemorrhagic retinopathy
- Other conditions or diseases involving an increased risk of hemorrhage
- Injuries to and operations on the central nervous system, eyes and ears
- Spinal/epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100-120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding

### SPECIAL POPULATIONS

#### Pregnant Women:

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Cases of Gasping Syndrome have been reported in neonates when benzyl alcohol has been administered in amounts of 99-404 mg/kg/day. Manifestations of the disease include: metabolic acidosis, respiratory distress, gasping respirations, central nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

There are also postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

**Teratogenic Effects:** As with other low molecular weight heparins (LMWH), FRAGMIN should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

**Non-teratogenic Effects:** There have been postmarketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including FRAGMIN, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving FRAGMIN should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if FRAGMIN is administered during pregnancy.

#### Nursing Women:

It is not known whether FRAGMIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to nursing women.

#### Pediatrics:

The safety and effectiveness of FRAGMIN in children have not been established.

#### Geriatrics:

Elderly patients receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing intervals and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (e.g., <45 kg) and those predisposed to decreased renal function is recommended.

#### Patients with Extreme Body Weight:

Safety and efficacy of low molecular weight heparins in high weight (e.g., >120 kg) and low weight (e.g., <46 kg) patients have not been fully determined. Individualized clinical and laboratory monitoring are recommended in these patients.



## Safety Information

### WARNINGS AND PRECAUTIONS

#### Special Warnings and Precautions

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see **Special Populations, Pregnant Women**).

#### General

**FRAGMIN should NOT be administered intra-muscularly.**

FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACTIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR

WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

#### **Cardiovascular**

**Use in Patients with Prosthetic Heart Valves:** Cases of prosthetic valve thrombosis have been reported in these patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see **WARNINGS AND PRECAUTIONS, Patient Selection Criteria, SPECIAL POPULATION, Pregnant Women**).

**Use in Unstable Coronary Artery Disease:** When thrombolytic treatment is considered appropriate in patients with unstable angina and non-Q-wave myocardial infarction, concomitant use of an anticoagulant such as FRAGMIN may increase the risk of bleeding.

#### **Gastrointestinal**

FRAGMIN should be used with caution in patients with a history of gastrointestinal ulceration.

#### **Hematologic**

**Hemorrhage:** Bleeding may occur in conjunction with unfractionated heparin or low molecular weight heparin use. As with other anticoagulants, FRAGMIN should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

**Platelets/Thrombocytopenia:** Platelet counts should be determined prior to the start of treatment with FRAGMIN and, subsequently, twice weekly for the duration of treatment. Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. Its incidence is unknown at present.

Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia or platelet defects.

During FRAGMIN administration, special caution is necessary in rapidly-developing thrombocytopenia and severe thrombocytopenia (<100 000/ $\mu$ L). A positive or unknown result obtained from *in vitro* tests for antiplatelet antibody in the presence of FRAGMIN or other low molecular weight heparins and/or heparins would contraindicate FRAGMIN.

#### **Hepatic**

FRAGMIN should be used with caution in patients with hepatic insufficiency, as these patients may have potentially higher risk of hemorrhage.

#### **Peri-Operative Considerations**

##### **Spinal/Epidural Hematomas:**

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

When a higher dose (5000 IU s.c.) of FRAGMIN is administered for thromboprophylaxis in conjunction with surgery, no spinal/epidural invasion should be performed for at

least 12 hours following the last dose of FRAGMIN and the next dose should be held until at least 12 hours after the anaesthetic procedure. Alternatively, when a lower dose (2500 IU s.c.) of FRAGMIN is administered, the dose can be initiated 1 - 2 hours prior to surgery. FRAGMIN injection should be given after spinal/epidural anaesthesia and only if the anaesthesiologist considers the spinal/epidural puncture as uncomplicated. Indwelling catheters should not be removed or manipulated for at least 10 - 12 hours following the last dose of FRAGMIN.

**Use in Knee Surgery:** The risk of bleeding in knee surgery patients receiving low molecular weight heparins may be greater than in other orthopedic surgical procedures. It should be noted that hemarthrosis is a serious complication of knee surgery. The frequency of bleeding events observed with FRAGMIN in orthopedic surgery patients is derived from clinical trials in hip replacement surgery patients. The physician should weigh the potential risks with the potential benefits to the patient in determining whether to administer a low molecular weight heparin in this patient population.

**Selection of General Surgery Patients:** Risk factors associated with postoperative venous thromboembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, and age 60 years or above.

#### **Renal**

FRAGMIN should be used with caution in patients with renal insufficiency.

Patients with impaired renal function should be carefully monitored because the half-life for anti-Xa activity after administration of low molecular weight heparin may be prolonged in this patient population. Dose reduction should be considered in patients with severe renal impairment.

#### **ADVERSE REACTIONS**

##### **Adverse Drug Reaction Overview**

Clinically significant adverse reactions observed with use of FRAGMIN and other low molecular weight heparins include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions.

##### **Post-Marketing Adverse Reactions**

In post-marketing experience, the following undesirable effects have been reported:

**Bleeding:** Intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hemorrhage have been reported occasionally leading to fatality

**Blood and Lymphatic System:** thrombocytopenia, thrombocythemia

**Skin and Subcutaneous Tissue Disorders:** skin necrosis, alopecia, rash

**Immune System Disorders:** immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications), anaphylactic reactions

**Injury, Poisoning and Procedural Complications:** spinal or epidural hematoma

#### **DRUG INTERACTIONS**

##### **Drug-Drug Interactions**

FRAGMIN should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, non-steroidal anti-inflammatories and thrombolytic agents because of increased risk of bleeding. Acetylsalicylic acid (ASA), unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarctions.

##### **Drug-Food Interactions**

Interactions with food have not been established.

##### **Drug-herb Interactions**

Interactions with herbs have not been established.

##### **Drug-lab tests Interactions**

Interactions with lab tests have not been established.

##### **Drug-lifestyle Interactions**

Interactions with lifestyle have not been established.

To report an adverse event, please contact: **your physician, pharmacist or Pfizer Medical Information: 1-800-463-6001.**



## Administration

### DOSAGE AND ADMINISTRATION

FRAGMIN may be given by subcutaneous (s.c.) injection or by intermittent or continuous intravenous (i.v.) infusion, depending upon the circumstances. **FRAGMIN must NOT be administered intramuscularly.** Clinical trials conducted in support of clinical uses outlined below generally used subcutaneous dosing.

#### Dosing

##### *Thromboprophylaxis in Conjunction with Surgery*

The dose of FRAGMIN required for adequate prophylaxis without substantially increasing bleeding risk varies depending on patient risk factors.

##### **General surgery with associated risk of thromboembolic complications:**

2500 IU s.c. administered 1 - 2 hours before the operation, and thereafter 2500 IU s.c. each morning until the patient is mobilized, in general 5-7 days or longer.

**General surgery associated with other risk factors:** 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative, 2500 IU s.c. is given 1-2 hours before the operation, with 2500 IU s.c. given again no sooner than 4 hours after surgery, but at least 8 hours after the previous dose, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

**Elective hip surgery:** 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative 2500 IU s.c. is given 1-2 hours before the operation and 2500 IU s.c. 4-8 hours after surgery, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

The pre-operative dose may be omitted and an initial dose of 2500 IU s.c. administered 4-8 hours after the operation, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer. Omission of the pre-operative dose may reduce risk of peri-operative bleeding, however increased risk of venous thromboembolic events is possible. This option is based on the results of the North American Fragmin Trial (NAFT), which excluded patients at high risk of bleeding, i.e., documented cerebral or gastrointestinal bleeding within 3 months prior to surgery, defective hemostasis, e.g., thrombocytopenia ( $<100 \times 10^9/L$ ), ongoing anticoagulant treatment.

##### *Treatment of Acute Deep Vein Thrombosis*

The following dosage is recommended: 200 IU/kg body weight given s.c. once daily. The expected plasma anti-Xa levels during subcutaneous treatment would be  $<0.3$  IU anti-Xa/mL before injection and  $<1.7$  IU anti-Xa/mL 3 - 4 hours after injection. In order to individualize the dose, a functional anti-Xa assay should be performed 3 - 4 hours post-injection. The single daily dose should not exceed 18 000 IU. The following weight intervals are recommended to be adapted to the single-dose prefilled syringes as in the table below.

Weight (kg)	Dosage (IU)
46-56	10 000
57-68	12 500
69-82	15 000
83 and above	18 000

For patients with increased risk of bleeding, a dose of 100 IU/kg body weight given s.c. twice daily or 100 IU/kg body weight administered over a period of 12 hours as continuous i.v. infusion, can be used. The expected plasma anti-Xa levels during subcutaneous treatment would be  $>0.1$  IU anti-Xa/mL before injection and  $<1.0$  IU anti-Xa/mL 3 - 4 hours after injection.

Normally concomitant treatment with vitamin-K antagonists is started immediately. Treatment with FRAGMIN should be continued until the levels of the prothrombin

complex factors (FII, FVII, FIX, FX) have decreased to a therapeutic level, in general for approximately 5 days.

##### *Extended Treatment of Symptomatic Venous Thromboembolism (VTE) to Prevent Recurrence of VTE in Patients with Cancer*

**Month 1:** 200 IU/kg body weight given s.c. once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily.

**Months 2-6:** Approximately 150 IU/kg given s.c. once daily using the table shown below.

Weight (kg)	Dosage (IU)
$\leq 56$	7 500
57-68	10 000
69-82	12 500
83-98	15 000
$\geq 99$	18 000

**Dose reductions for chemotherapy-induced thrombocytopenia:** In the case of chemotherapy-induced thrombocytopenia with platelet counts  $<50,000/mm^3$ , FRAGMIN should be interrupted until the platelet count recovers above  $50,000/mm^3$ . For platelet counts between  $50,000$  and  $100,000/mm^3$ , FRAGMIN should be reduced by 17% to 33% of the initial dose (allowing for dosage adjustment using the pre-filled syringes), depending on the patient's weight (table below). Once the platelet count recovers to  $\geq 100,000/mm^3$ , FRAGMIN should be re-instituted at full dose.

Weight (kg)	Scheduled Dose (IU)	Reduced Dose (IU)	Mean Dose Reduction (%)
$\leq 56$	7 500	5 000	33
57-68	10 000	7 500	25
69-82	12 500	10 000	20
83-98	15 000	12 500	17
$\geq 99$	18 000	15 000	17

##### *Unstable Coronary Artery Disease (Unstable Angina and Non-Q-Wave Myocardial Infarction)*

120 IU/kg body weight given s.c. twice daily with a maximum dose of 10 000 IU/12 hours. The expected plasma anti-Xa levels during subcutaneous treatment would be  $>0.1$  IU anti-Xa/mL before injection and  $<1.6$  IU anti-Xa/mL 3 - 4 hours after injection. These levels were obtained from another patient population. Treatment should be continued for up to 6 days. Concomitant therapy with ASA is recommended.

##### *Deep Vein Thrombosis in Hospitalized Patients with Severely-Restricted Mobility*

In hospitalized patients with severely-restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

##### *Use in Patients with Renal Impairment*

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully.

Administration of low molecular weight heparins to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (creatinine clearance  $<30$  mL/min), which may lead to an increased risk of bleeding. This effect has not yet been determined for FRAGMIN. Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

##### *Anticoagulation for Hemodialysis and Hemofiltration*

**Chronic renal failure, patients with no other known bleeding risk:** Hemodialysis and hemofiltration for a maximum of 4 hours: dose as below, or only i.v. bolus injection of 5000 IU. Hemodialysis and hemofiltration for more than 4 hours: i.v. bolus injection of 30 - 40 IU/kg body weight followed by i.v. infusion of 10 - 15 IU/kg body weight per hour. This dose normally produces plasma levels lying within the range of 0.5 - 1.0 IU anti-Xa/mL.

**Acute renal failure, patients with high bleeding risk:** i.v. bolus injection of 5 - 10 IU/kg

body weight, followed by i.v. infusion of 4 - 5 IU/kg body weight per hour. Plasma level should lie within the range of 0.2 - 0.4 IU anti-Xa/mL.

**Dilution**

FRAGMIN solution for injection may be mixed with isotonic sodium chloride or isotonic glucose infusion solutions in glass infusion bottles and plastic containers. *Post-dilution concentration: 20 IU/mL.*

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit.

	<b>1 mL 10 000 IU</b>
<b>Isotonic NaCl Infusion</b> (9 mg/mL)	500 mL
<b>or</b>	
<b>Isotonic Glucose Infusion</b> (50 mg/mL)	500 mL

The infusion rate is 10 mL/hour. The solution should be used within 24 hours.



**Study References**

1. Canadian Centre for Occupational Health and Safety (CCOHS). Diseases, disorders and injuries: needlestick injuries. [http://www.ccohs.ca/oshanswers/diseases/needlestick\\_injuries.html](http://www.ccohs.ca/oshanswers/diseases/needlestick_injuries.html). Accessed February 26, 2010.
2. FRAGMIN Product Monograph, Pfizer Canada Inc., July 2009.

**SUPPLEMENTAL PRODUCT INFORMATION**

**Overdosage**

Accidental overdosage following administration of FRAGMIN may lead to hemorrhagic complications. FRAGMIN should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of FRAGMIN is inhibited by protamine. This effect may be largely neutralized by slow intravenous injection of protamine sulphate. The dose of protamine to be given should be 1 mg protamine per 100 anti-Xa IU of FRAGMIN administered. A second infusion of 0.5 mg protamine per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-Xa activity is never completely neutralized (maximum about 60%).

Particular care should be taken to avoid overdosage with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulphate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available. Refer to the protamine sulphate Product Monograph for further directions for use.

**Product Monograph available on request.**

