FEASIBILITY OF A PILOT STUDY TO ASSESS
THE SAFETY AND ANTIPYRETIC EFFICACY OF ACETAMINOPHEN IN
CRITICALLY ILL PATIENTS

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE IN NURSING

in

The Faculty of Graduate and Postdoctoral Studies

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

December 2016

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Abstract

Preliminary, mostly small observational studies, suggest that febrile intensive care unit (ICU) patients may be at higher risk of acetaminophen-associated hypotension and that acetaminophen may be a less effective antipyretic in this population than previously thought. A pilot double-blinded, randomized controlled trial was conducted to examine four questions: (a) what is the feasibility of conducting this study, (b) is there a difference in incidence of clinically significant hypotensive events, and/or blood pressure in the four hours post intervention between febrile, non-brain injured patients who received either a single dose acetaminophen or a placebo, (c) is there a difference in fever burden between participants who received the treatment versus placebo, and (d) what are the relationships between heart rate, blood pressure, core temperature, and fever burden? Over nine months, 83% of the 950 admitted ICU patients were screened, 100 patients were eligible but due to logistical challenges, only 27 were invited to participate, of which 17 refused. Only six of the 10 participants completed the study, and of those five were randomized to the acetaminophen group. The eligibility rate increased from 10.0% to 16.3% ($p = 0.016$) after small changes to the inclusion criteria were made. The sample size was too small to draw conclusions regarding the utility of outcome measures, participant safety, or the hemodynamic or antipyretic effects of acetaminophen; however, no participant had a safety event. Participants had variable heart rate, blood pressure, and fever patterns. There was little or no discernable antipyretic effect of acetaminophen in the five participants who received the drug. Additionally, strong linear relationships were detected between mean pre-post intervention differences in fever burden and mean arterial pressure (MAP) as well as core temperature and heart rate ($p = 0.003$ for both).
Mean difference in MAP increased by 2.20 mmHg for every 1 °C-hour increase in net change in fever burden ($R^2 = 0.906; 95\% \text{ CI } [1.214, 3.186])$. Mean difference in heart rate increased by 4.840 beats/minute for every 1 °C increase in mean difference in core temperature ($R^2 = 0.905; 95\% \text{ CI } [2.665, 7.014])$. 
Preface

This research project was originally conceptualized by the author. The study was submitted, revised and re-submitted to a number of research competitions before receiving funding from the 2014 Vancouver Coastal Health Research Institute (VCHRI) Team’s Grant Award for the “safety and efficacy of acetaminophen in the intensive care unit (SEA-ICU) study” and the 2015 UBC School of Nursing Internal Research Award. The author was solely responsible for all writing involved in the various grant applications; however, the research proposal was developed in collaboration with the SEA-ICU research team (Dr. William Henderson, Allana LeBlanc, Jennifer Yang-Wong and Dr. Gregory Mah) and the thesis committee (Dr. Leanne Currie, Dr. Martha Mackay and Dr. William Henderson). The author was also solely responsible for writing this thesis, under the supervision of the thesis committee.

Ethics approval was received on February 25, 2015 from the University of British Columbia Research Ethics Board (Approval Number #H13-01160) and kept valid until it was closed on November 2, 2016. The study was conducted at Vancouver Hospital’s ICU from May 28, 2015 until January 20, 2016.
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<tr>
<td>AAH</td>
<td>Acetaminophen-associated hypotension</td>
</tr>
<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>AUC\textsubscript{0-2h}</td>
<td>Area under the curve for a 2 hour period</td>
</tr>
<tr>
<td>AUC\textsubscript{0-6h}</td>
<td>Area under the curve for a 6 hour period</td>
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<tr>
<td>BAT</td>
<td>Brown adipose tissue</td>
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<tr>
<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>ECG</td>
<td>Electrocardiography</td>
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<td>EMBASE</td>
<td>Excerpta Medica database</td>
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<tr>
<td>ETCO\textsubscript{2}</td>
<td>End tidal carbon dioxide</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IPA</td>
<td>International Pharmaceutical Abstracts</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>L/min</td>
<td>Litre per minute</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Positron-emission tomography and computer tomography</td>
</tr>
<tr>
<td>PiCCO®</td>
<td>Pulse index continuous cardiac output</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>rm-ANOVA</td>
<td>Repeated measures analysis of variance</td>
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<tr>
<td>RN</td>
<td>Registered nurse</td>
</tr>
<tr>
<td>SA</td>
<td>Sino-atrial</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SOFA</td>
<td>Sequential organ failure assessment</td>
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<tr>
<td>SPSS-23</td>
<td>Statistical Package for Social Sciences Inc. version 23</td>
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<tr>
<td>VGH</td>
<td>Vancouver General Hospital</td>
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<td>WOS</td>
<td>Web of Science</td>
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Acknowledgements

There are many people who contributed, both to my development as a nurse researcher and directly to this project. First, let me thank my thesis committee who were instrumental in guiding this research project. Without their insight this project would never have been achievable or become something that is hopefully a valuable contribution to our collective knowledge. My adviser, Dr. Leanne Currie was key in both maintaining high standards yet also keeping this ambitious study realistic. Dr. Martha Mackay’s critical eye was, and continues to be, invaluable for ensuring clarity and scientific rigor. When my friend, colleague and ICU intensivist, Dr. William Henderson encouraged me to pursue my ‘little’ research question in our ICU lunchroom, little did I know he would be seeing me through my Master’s program.

I also have to extend my thanks to my ICU team at VGH, all of whom are I consider as my friends as well as outstanding colleagues. This study simply could not have happened if it not for every one of them. First, I must thank Allana LeBlanc and Jennifer Yang-Wong who were there for the first poor drafts of the research proposal and who repeatedly told me, “if this is what you like, just go and get your Masters already!” The best of friends are the ones who will kick you in the pants when you need it. Our pharmacist, Dr. Gregory Mah completed our multidisciplinary research team and whose contributions and constructive feedback only strengthened the quality. Special thanks is also needed for our research coordinator, Denise Foster, for every bit of support and research knowhow she offered. Our team of ICU Intensivists were incredibly supportive of this project and freely offered their advice. I must also thank the very best ICU team I
will ever have the pleasure of working with; I wish there was space to list everyone. This
study would never have happened if it were not because of the VGH ICU Team.

I would also like to thank both Vancouver Coastal Health Research Institute (VCHRI) and the UBC School of Nursing (SON) for both their financial, practical and logistic support of this and many other studies. First, VCHRI not only provided funding to conduct this study, but also through the Team’s Grant Award, they enable direct care clinicians to ask questions, build a team and pursue uncovering the answers. Similarly, the UBC SON also provided funding to allow this study to be published in an open source journal so it can be shared with a wider audience of clinicians and researchers.

I would like to offer special thanks to the research participants in this and past studies who bravely chose to be a part of clinical research in the critical care setting. We do everything possible to ensure research is conducted both safely and ethically; however, this pales in comparison to the courage possessed by ICU patients and their families who chose to contribute themselves to research during the most precarious moments of their lives. The words “thank you” are too small. All I can offer is a commitment to ensure we learn as much as possible from the contributions you made, and share that knowledge as widely as possible.

If you are a clinician or researcher and you are reading this document, this was written for you. I hope it is of value to your work, and thank you for helping me fulfill our collective commitment to the people we care for.
Dedication

There is an extraordinary group of people that I am lucky to share this journey, and my life with; I wish to dedicate this work to my family. My parents, Paramjit Singh Toor and Hardev Kaur Toor, raised me so I never saw limits in my life. Once I embarked on this journey, my parents found a 1001 ways to provide logistic support to make the pursuit of Masters degree possible. My brothers, sisters, cousins, nieces and nephews graciously understood when I skipped out on too many family events (including Star Wars: The Force Awakens) to pursue this project. I am also lucky to have the wisest, kindest and most supportive husband in the world. Not only did Gurpreet selflessly incorporated this degree into our lives, having him as my dedicated technical support person was a life saver when I accidently smashed my computer or unintentionally corrupted all the thesis files. Finally I dedicate this thesis to my children, Gulzaar and Rohan, who grew up thinking having a grad student mom was normal. They pitched in and sacrificed without even knowing it. I am sure they thought all the take-out pizza was just a bonus, but it really was to bring a little sanity to our crazy life. This project was not my work, it was our shared achievement as a family. Thank you.
Chapter 1: Introduction

Background

Between 25.5% and 45% of patients admitted to the intensive care unit (ICU) develop a fever (Kiekkas et al., 2010; Laupland et al., 2008; Niven, Stelfox, Shahpori, & Laupland, 2013). Fever is a beneficial response to injury or infection because it enhances immunological function (Bartfai & Conti, 2010), regulates the inflammatory process (De Maio, 2014; De Maio & Vazquez, 2013), and impairs microbial function (Mackowiak, 1981; Mackowiak, Marling-Cason, & Cohen, 1982; Moore et al., 2013). Fever has also been associated with lower mortality rates for some critically ill patients (Lee et al., 2012; Schulman et al., 2005). These benefits come at a high metabolic cost; heart rate (Morrison, 2011; Morrison, Nakamura, & Madden, 2008) and oxygen consumption increase by approximately 10% for every degree Celsius increase in core temperature (Manthous et al., 1995). This increased metabolic demand is especially noteworthy for critically ill patients who often require life-supportive therapies, such as mechanical ventilation and hemodynamic support, and are, therefore, severely limited in their ability to compensate. Even small increases in metabolic demand may lead to physiologic instability (Drewry & Hotchkiss, 2013). When fever occurs, acetaminophen is the preferred antipyretic therapy because it has been recognized as a safe and effective drug (Bertolini et al., 2006; Egi & Morita, 2012; Hammond & Boyle, 2011; Jefferies et al., 2011; Lee et al., 2012; Niven, Léger, Stelfox, & Laupland, 2012; Niven, Stelfox, & Laupland, 2013; Prescott, 2000).

Antipyretic therapy is recommended for certain critically ill populations such as those with acute brain injury (including traumatic head injury and stroke), severe
respiratory impairment, or severe cardiac dysfunction. Antipyretic therapies are favoured with acute brain injury because fever is associated with worse neurological recovery in these patients (Badjatia, 2009; Bohman & Levine, 2014; Perman, Goyal, Neumar, Topjian, & Gaieski, 2014). Patients with severe respiratory compromise require high levels of oxygen and ventilator support to maintain homeostasis. Treatments that reduce metabolic demand, such as sedation and fever suppression, can help to restore the oxygen supply-demand balance (Mohr & Doerschug, 2013; Niven, Léger, Stelfox, et al., 2012). Similarly, patients with severe cardiac dysfunction require high levels of hemodynamic support, yet may still not be able to meet basic physiologic demands. Antipyretics decrease metabolic demand, thereby potentially restoring homeostasis (Mohr et al., 2011; Niven, Léger, Stelfox, et al., 2012; Schortgen et al., 2012).

However, researchers have not come to consensus on the best practice for managing fever in critically ill patients who do not have an acute brain injury. Arguments continue both for fever suppression to reduce metabolic demand (Mohr & Doerschug, 2013; Schortgen et al., 2012) and against fever suppression to maximize the immunologic benefits of fever (Drewry & Hotchkiss, 2013; Lee et al., 2012; Schulman et al., 2005). Those who support fever suppression during critical illness argue that a critically ill patient is already severely compromised, often requiring life-supportive therapies to meet basic metabolic needs; the additional metabolic and cardiac demands induced by a fever further threaten the patient’s physiological stability (Mohr et al., 2012; Mohr & Doerschug, 2013; Schortgen et al., 2012). Those who oppose routine fever suppression argue that maximizing immunologic performance may be the key to survival when critical illness is due to, or complicated by, a severe infection (Drewry &
Hotchkiss, 2013; Lee et al., 2012; Schulman et al., 2005; Young, Saxena, Beasley, et al., 2012; Young, Saxena, Eastwood, Bellomo, & Beasley, 2011). For example, antipyretic drugs may cause harm because, first, they blunt the fever-dependent processes of immunomodulation and second, they mask changes in the febrile response, potentially delaying recognition of new infections and/or antibiotic therapy failure (Drewry, Fuller, Bailey, & Hotchkiss, 2013). The heterogeneity of critical illness adds complexity to this debate. Many different disease processes can lead to a critical illness; additionally, patients may have one or more comorbidity uniquely impacting their physiologic response to illness. At some times or for some patients, maximizing immune function by allowing a fever may have greater benefit, while at other times, reducing metabolic demands by suppressing fever may be advantageous (Jefferies et al., 2011; Niven, Stelfox, & Laupland, 2013). This has created challenges to the development of practice recommendations for or against antipyretic therapy. Thus, to date, researchers have not presented any agreed-upon recommendations for when to suppress or not to suppress fever in critical illness (Dellinger et al., 2013; Jefferies et al., 2011; Niven, Stelfox, & Laupland, 2013). With no guidelines, clinicians are left to weigh the benefit of reduced metabolic demand against the risks of antipyretics on a case-by-case basis (Vera, Zapata, Gich, Mancebo, & Betbese, 2012).

While acetaminophen has been shown to be safe and effective for the general population, new evidence is emerging that contradicts the perceived safety and antipyretic efficacy for critically ill patients. Preliminary research has suggested that acetaminophen may be associated with an unexpected, clinically significant and potentially life-threatening reduction in blood pressure if not corrected quickly (Boyle,
Hundy, & Torda, 1997; Boyle et al., 2010; Cruz, Garutti, Díaz, & Fernández-Quero, 2002; de Maat, Tijssen, Brüggemann, & Ponsen, 2010; Hersch, Raveh, & Izbicki, 2008; Krajčová, Matoušek, & Duška, 2013; Mackenzie, Forrest, Thompson, & Marsh, 2000; Mrozek et al., 2009; Vera et al., 2012). Additionally, other studies have suggested that acetaminophen is a less effective antipyretic in the critically ill population than expected (Gozzoli et al., 2004; Greenberg, Chen, & Hasday, 2010; Mackenzie et al., 2000; Poblete, Romand, Pichard, König, & Suter, 1997; Vera et al., 2012). Clinicians must reconsider the potential risks of acetaminophen against its antipyretic efficacy in light of this new evidence.

When critically ill patients who are febrile receive acetaminophen, some may be unable to compensate for the normal thermoregulatory mechanisms initiated to reduce fever, such as vasodilation and sweating (Boyle et al., 2010; Krajčová et al., 2013). Critically ill patients are at risk for acetaminophen-associated hypotension (AAH), which is a sudden, clinically significant episode of hypotension after receiving antipyretic medication. Seven observational studies that used varying doses and routes of administration for acetaminophen reported that between 10% and 48% of critically ill patients developed hypotension severe enough to require treatment (Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; de Maat et al., 2010; Hersch et al., 2008; Mackenzie et al., 2000; Picetti et al., 2014; Vera et al., 2012). In contrast, four studies did not detect a significant change in blood pressure, but the authors of these studies either did not report the febrile status of the participants (Mrozek et al., 2009) or reported that the majority of participants were afebrile at the time they received antipyretic therapy (de Maat et al., 2010; Forouzanfard, Henin, Kadou, Colin, & Mols, 2012).
Current evidence regarding the antipyretic efficacy of acetaminophen in the critically ill population is limited. Five studies have been conducted with patients who were receiving care in the ICU (Gozzoli et al., 2004; Greenberg et al., 2010; Mackenzie et al., 2000; Poblete et al., 1997; Vera et al., 2012) and five studies have been conducted in patients with acute brain-injury (Dippel et al., 2003; Dippel et al., 2001; Kasner et al., 2002; Morgan, 1990; Sulter, Elting, Maurits, Luijckx, & De Keyser, 2004). Differences in methodology, measurement, intervention, and sample characteristics make it difficult to compare the results or even determine the efficacy of acetaminophen in these patient populations; however, several researchers suggest that acetaminophen may be a less effective antipyretic than once thought (Dippel et al., 2003; Gozzoli et al., 2004; Greenberg et al., 2010; Mackenzie et al., 2000; Vera et al., 2012), and that critically ill patients may have a more variable response to acetaminophen than anticipated (Greenberg et al., 2010; Sulter et al., 2004; Vera et al., 2012). Further investigation is needed.

**Problem Statement and Significance**

There are no definitive recommendations for fever management for non-brain-injured critically ill patients; therefore, clinicians must weigh the immunological benefits of fever against its metabolic costs to guide their decisions for individual patients. Acetaminophen is the antipyretic therapy of choice to reduce fever and restore the oxygen supply-demand balance because it is considered a safe and effective drug (Canadian Pharmacists Association [CPS], 2015; Hammond & Boyle, 2011; Jefferies et al., 2011). Recent studies conducted in critically ill populations challenge these assumptions. First, critically ill patients may be at a unique risk of AAH when
acetaminophen is used as an antipyretic treatment (Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; de Maat et al., 2010; Hersch et al., 2008; Krajčová et al., 2013; Mackenzie et al., 2000; Mrozek et al., 2009; Picetti et al., 2014; Vera et al., 2012).

Second, acetaminophen may not be as effective at reducing fever in critically ill patients compared to other patient populations (Gozzoli et al., 2004; Greenberg et al., 2010; Mackenzie et al., 2000; Poblete et al., 1997; Vera et al., 2012). A more rigorous examination of the safety and efficacy of acetaminophen is needed. Health care professionals who are caring for critically ill patients need to know both the risks of hypotension posed by acetaminophen and the expected efficacy in order to make sound clinical decisions regarding care.

**Purpose**

The original plan for this thesis was to conduct a pilot double-blinded randomized controlled trial (RCT) of a single dose of acetaminophen (650 mg) in the adult, non-brain-injured, febrile critically ill population to examine both AAH and antipyretic efficacy of acetaminophen in the critically ill population and a pilot trial was planned. However, when it became apparent that not enough participants could be enrolled in the planned time frame, assessment of feasibility became the primary goal of this thesis. Therefore the objectives of this study were first, to determine the feasibility of conducting a study which could examine both the incidence of AAH and the antipyretic efficacy of acetaminophen in the febrile critically ill population; second, to examine if, and to what extent, acetaminophen is associated with hypotension in the febrile critically ill adult patient; and third to quantify the antipyretic efficacy of acetaminophen in this population.
Research Questions

In this study, four research questions were examined. The primary research question was:

**Research question 1.** What is the feasibility of conducting a double-blinded RCT to examine both the safety and antipyretic efficacy of a standard dose of acetaminophen given to the adult, febrile, non-brain-injured critically ill patient?

The secondary research questions were:

**Research question 2.** Does 650 mg acetaminophen, administered enterally, increase the number of clinically significant hypotensive events in ICU patients (excluding brain injury, liver dysfunction or burn patients) who have a fever?

**Research question 3.** Does acetaminophen 650 mg reduce fever burden in the 6 hours after administration in febrile, non-brain-injured adult ICU patients more than placebo?

Since there were too few participants enrolled to address the secondary research questions, the original statistical analysis plans were invalid and therefore abandoned. Instead the secondary research questions were used to guide the study design and the examination of feasibility. The vital sign data was presented as a case series report and a fourth research question was added post hoc:

**Research question 4.** What is the relationship between heart rate, blood pressure, core temperature and fever burden?

Summary

For most critically ill patients, there are no guidelines for when to treat fever; therefore, clinicians must weigh the immunological benefits against its metabolic costs on
a case-by-case basis (Hammond & Boyle, 2011; Hammond et al., 2013; Jefferies et al., 2011). While acetaminophen is reputed to be a safe and effective antipyretic (Bertolini et al., 2006; CPS, 2015; Prescott, 2000), several small, primarily observational, studies have suggested that acetaminophen may pose the risk of AAH (Boyle et al., 1997; Boyle et al., 2010; de Maat et al., 2010; Hersch et al., 2008; Krajčová et al., 2013; Mackenzie et al., 2000; Picetti et al., 2014; Vera et al., 2012) and also may not be as effective an antipyretic as previously thought (Gozzoli et al., 2004; Greenberg et al., 2010; Mackenzie et al., 2000). The original intent of this thesis was to conduct a pilot RCT to examine both the hemodynamic and antipyretic effects of acetaminophen in the febrile adult non-brain-injured critically ill population. When it became clear that sample size was not going to be achieved in the given time frame, the focus on the thesis became feasibility of such a study and the secondary findings are reported as a case series.
Chapter 2: Literature Review

Fever and its management have been debated through the ages. Over the past 60 years, acetaminophen has become the drug of choice to reduce fever. It is frequently prescribed to patients in the intensive care unit (ICU) because of its reputation as a safe and effective antipyretic. This belief is primarily based on research conducted with non-critically ill patients. New evidence is challenging whether or not this long-held belief applies to the critically ill population. In this chapter a review of the literature is presented. First, a review of the concept of fever, current understanding of thermoregulation, and acetaminophen as the most widely used antipyretic today is discussed. Then, a review of how thermoregulation and the antipyretic action of acetaminophen may make critically ill patients be uniquely vulnerable to hemodynamic instability is presented. Finally, a summary of the literature search criteria and a synthesis of the evidence are presented.

Fever

The concept of fever has changed over time. Fever was once a broad idea, in which notions of disease, infection, inflammation, sensory perceptions, hemodynamic changes, and body temperature were bundled into the single word ‘fever’ (Estes, 1991; Seneta, Seif, Liebermeister, & Dietz, 2004; Stein, 1991). The advent the modern thermometer, which helped to quantify fever, also influenced the conceptual understanding; fever became more narrowly understood as a rise in core temperature rather than a disease in itself, or a complex physiologic process that impacted the whole system (Haller, 1985; Seneta et al., 2004). While the thermometer advanced scientific thinking and offered safer and more effective care to those experiencing a fever, health
care professionals no longer appreciated that the febrile response, through the normal processes of thermoregulation, has an effect on the cardiovascular system.

Thermoregulation

Like a household thermostat, the hypothalamus determines a targeted set point for the core body temperature (i.e., the hypothalamic set point; Bartfai & Conti, 2010; Eberwine & Bartfai, 2011). The hypothalamus also receives sensory messages indicating temperature measurement from throughout the body (Bartfai & Conti, 2010; Eberwine & Bartfai, 2011; Kurz, 2008). When the hypothalamus senses a discrepancy between the hypothalamic set point (i.e., set temperature) and the body temperature, then the hypothalamus activates the appropriate cold or heat defences to re-establish homeostasis. Thermoregulation is a vital physiologic process of homeostasis (Kurz, 2008). Hyperthermia is a life-threatening failure of thermoregulation; however, thermoregulation remains intact during fever (Bartfai & Conti, 2010; Eberwine & Bartfai, 2011). Fever is a regulated increase in the hypothalamic set point into the febrile range; as a result, the febrile temperature is maintained by the same cold and heat defences as in normal thermoregulation (Bartfai & Conti, 2010). The components of thermoregulation (i.e., the hypothalamus, heat defences and cold defences) are discussed in greater detail next.

Hypothalamus. The hypothalamus is the body’s thermoregulatory centre that both determines the hypothalamic target for core body temperature and regulates a number of effector mechanisms to maintain the hypothalamic set point (Eberwine & Bartfai, 2011; Kurz, 2008; Morrison, 2011; Morrison et al., 2008). Most often, normal body temperature is between 36.5 °C and 37.5 °C (Drewry et al., 2013; Kurz, 2008).
Cold or heat defences are initiated when there is as little as a 0.2 °C discrepancy between the core temperature and the hypothalamic target (Kurz, 2008). Heat defences, such as vasodilation and sweating, are triggered when the core temperature is higher than the target. Conversely, the hypothalamus will trigger cold defences such as vasoconstriction, activation of brown adipose tissue (BAT), or shivering when core temperature is below the targeted hypothalamic set point. Minimizing variations in core temperature is important because human cellular physiology has evolved to function best within a narrow range.

The only difference in the process of thermoregulation during fever is that the hypothalamic set point is reset into a febrile range (i.e., 38.3 °C to 41.0 °C; Niven, Léger, Stelfox, et al., 2012). The febrile response is activated whenever the body experiences large tissue injury, or an infection (Bartfai & Conti, 2010). Bacteria, viruses and/or injured cells either act directly as pyrogenic mediators, or indirectly through the release of pyrogenic mediators into the blood stream as a part of the inflammatory response (Bartfai & Conti, 2010; Conti, Tabarean, Andrei, & Bartfai, 2004). These pyrogenic mediators stimulate the outer membrane of the hypothalamus to release a protein called cyclooxygenase into the hypothalamus. Cyclooxygenase acts to reset the hypothalamic set point into a febrile range. Normal heat and cold defenses are then activated to maintain core body temperature at the new febrile set point until the febrile response resolves and cyclooxygenase is no longer being released into the hypothalamus (Bartfai & Conti, 2010).

**Heat defences.** If the core temperature is higher than the hypothalamic set point, the blood vessels near the skin surface can dilate and shift as much as 8 L per minute
(L/min) of blood to the surface of the skin (Kurz, 2008; Wyss, Brengelmann, Johnson, Rowell, & Niederberger, 1974; Wyss, Brengelmann, Johnson, Rowell, & Silverstein, 1975). To put this into perspective: resting cardiac output is between 4 to 5 L/min (Katori, 1979; Wolff, 2007), so an increase to 8 L/min is a significant shift in blood flow. Research has also shown women increase cardiac output to 7 L/min during pregnancy (Robson, Hunter, Boys, & Dunlop, 1989) and an active person can increase cardiac output to as much as 20 L/min or more during strenuous physical exercise (Åstrand, Cuddy, Saltin, & Stenberg, 1964); therefore, a cardiac output of 8 L/min is well within normal human cardiac capacity. This shift in blood flow may not be as easily tolerated in critically ill patients who are hemodynamically vulnerable.

When vasomotor control is inadequate to reduce core temperature, vasodilation can be augmented by perspiration (Mora-Rodriguez, Del Coso, Aguado-Jimenez, & Estevez, 2007; Wyss et al., 1974). Sweating, especially when coupled with vasodilation, dissipates a great deal of heat (Mora-Rodriguez et al., 2007; Wyss et al., 1974). It is a life-saving mechanism during heat-stress, but it comes with a cost in hypotonic fluid loss. During heat stress, humans can produce between 1.0 to 1.8 L per hour of perspiration (Gagnon, Jay, Reardon, Journeay, & Kenny, 2008; Kurz, 2008; Pugh, Corbett, & Johnson, 1967; Wyss et al., 1974). Without re-hydration during heat-stress, humans can reach profound dehydration within 1 hour (Kurz, 2008; Mora-Rodriguez et al., 2007; Pugh et al., 1967).

**Cold defences.** The first mechanism of cold defence is vasoconstriction; it reduces blood flow to the skin (i.e., the largest organ) to as little as 0.5 L/min (Kurz, 2008). This shunting of blood away from the surface increases the insulating properties
of the skin (Kurz, 2008). When vasoconstriction is insufficient at conserving heat, the body has two additional mechanisms to augment heat production, BAT and shivering (Eberwine & Bartfai, 2011; Morrison, 2011). Until recently, there was an enduring belief that BAT disappeared in early childhood in humans (Lean, 1989; van Marken Lichtenbelt et al., 2009). The identification of BAT in adults was an accidental discovery that was revealed during the hunt for tumour cells, when integrated positron-emission tomography and computed tomography (PET-CT) scans with marked a glucose called $^{18}$F-fluorodeoxyglucose became available (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). Dark areas on a PET-CT scan indicate high glucose utilization, common to both tumour cells and cold-stressed BAT. Figure 1 is an image of one of the original scans confirming active BAT in adults (van Marken Lichtenbelt et al., 2009).

![Cold Exposure Thermoneutral Conditions](image)

**Figure 1.** Brown adipose tissue activity in the thermoneutral and cold-exposed adult.

BAT accounts for a great deal of heat production (Cannon & Nedergaard, 2012; Ouellet et al., 2012). BAT decreases with age, although it can persist until late adulthood (Saely, Geiger, & Drexel, 2012; Yoneshiro, Aita, Matsushita, Okamatsu-Ogura, et al., 2011) and is adaptable in that it increases function in winter (Au-Yong, Thorn, Ganatra, Perkins, & Symonds, 2009). It is well regulated (Cannon & Nedergaard, 2012; Eberwine & Bartfai, 2011; Morrison, 2011; Saely et al., 2012) and is activated whenever the core temperature is lower than the hypothalamic set point, (i.e., when peripheral vasoconstriction is insufficient, and core body temperature continues to fall below the hypothalamic set-point; Eberwine & Bartfai, 2011). This is also the same process that occurs during the febrile response (Eberwine & Bartfai, 2011).

BAT is brown because it is highly innervated and vascular (Ouellet et al., 2012; Saely et al., 2012). BAT activity is tightly regulated by the hypothalamus (Eberwine & Bartfai, 2011; Morrison, 2011). When BAT is stimulated, specialized mitochondria contained within BAT can generate 300 times more heat than any other cell in the body (Ouellet et al., 2012; Yoneshiro, Aita, Matsushita, Kameya, et al., 2011). BAT requires a great deal of blood flow for two reasons: (a) to supply the tissue with fuel and (b) to flush out the newly heated blood, distributing it to other areas of the body (Saely et al., 2012). The hypothalamus also concomitantly stimulates the sino-atrial (SA) node of the heart to increase heart rate and contractility; therefore, increased heart rate and contractility occur simultaneously whenever BAT is activated, including during a fever (Eberwine & Bartfai, 2011; Morrison, 2011; Morrison et al., 2008). Thus, the discovery of BAT in adults helps to explain the relationship between fever and the heart.
The body will stimulate shivering when BAT activation is insufficient to generate enough heat to maintain the core body temperature, (Horvath, Spurr, Hutt, & Hamilton, 1956; Kurz, 2008; Newstead, 1987). Shivering begins when the core body temperature is 1 °C to 2 °C below the thermoregulatory set point (Rodriguez et al., 1983). While shivering is effective at significantly increasing heat production, it comes with a high metabolic cost: shivering increases oxygen consumption and metabolic demand because all muscles of the body rhythmically contract to generate heat (Horvath et al., 1956; Kurz, 2008; Rodriguez et al., 1983).

**Summary of thermoregulation.** Thermoregulation is a vital physiologic process of homeostasis that is controlled by the hypothalamus (Kurz, 2008) and remains intact in the febrile state. Fever is a regulated increase in the hypothalamic set point into the febrile range; as a result, the febrile temperature is maintained with the same cold and heat defences as in normal thermoregulation (Bartfai & Conti, 2010). When the core temperature is below the hypothalamic set point, vessels to the skin constrict, shunting blood away from the surface; BAT is stimulated to generate heat, and if this is insufficient, the body begins to shiver (Morrison, 2011). When the core temperature is above the desired set point, heat defences such as vasodilation and perspiration effectively augment heat loss (Kurz, 2008). While these hemodynamic changes are significant, they are well within the normal capacities of healthy, hydrated adults. However, these changes may not be as easily tolerated in critically ill patients. The physiological process of thermoregulation remains intact in the febrile state. This normal thermoregulatory function may make febrile critically ill patients uniquely vulnerable to acute hypotension after receiving antipyretic medication.
Acetaminophen

Today, fever is recognized as an immunologically beneficial but metabolically expensive host response (Eyers, Jefferies, Shirtcliffe, Perrin, & Beasley, 2011; Hammond & Boyle, 2011; Jefferies et al., 2011; Laupland, 2009; Niven, Stelfox, & Laupland, 2013; Su et al., 2005). Some scientists continue to explore and argue for the benefits of fever, such as enhanced immune-response or impaired bacterial replication (Drewry & Hotchkiss, 2013; Eyers et al., 2011; Lee et al., 2012; Su et al., 2005; Young, Saxena, Bellomo, et al., 2012), whereas others have warned that fever causes harm, especially for those most vulnerable, and therefore should be suppressed (Mohr et al., 2012; Schortgen et al., 2012). The decision to treat fever is based on balancing the metabolic costs of fever against its physiologic benefits. Many would argue that treatment to reduce fever, especially amongst the critically ill, is a logical decision.

Acetaminophen has become the antipyretic drug of choice because it is considered safe and effective. After its initial release in the 1950s acetaminophen gained in popularity, yet it did not overtake acetylsalicylic acid (ASA) as the number one antipyretic choice until the 1980s, when ASA was linked to Reye’s syndrome in children (Jahr & Lee, 2010; Mills, 1991; Monto 1999; Prescott, 2000), which can be fatal or result in brain injury (Glasgow, 2006; Monto 1999; Sarnaik, 1999). As previously outlined, the febrile response is regulated by the release of cyclooxygenase into the hypothalamus, which results in the up-regulation of the hypothalamic set point (Bartfai & Conti, 2010; Eberwine & Bartfai, 2011; Romanovsky et al., 2005). Acetaminophen blunts the febrile response because it is a cyclooxygenase inhibitor that acts on the hypothalamus (Yeh & Reddy, 2012). Acetaminophen is known to induce hepatotoxicity (CPS, 2015; Lexi-
Comp, n.d.), but other adverse effects such as neutropenia, thrombocytopenia, and hypersensitivity reactions are noted to be very rare (CPS, 2015; Lexi-Comp, n.d.). When acetaminophen is given orally, the onset of antipyretic action occurs within 1 hour (peak levels at 48 minutes) but the duration of its antipyretic effect is 6 hours or greater (Lexi-Comp, n.d.). Acetaminophen is not commonly known to affect hemodynamic status (CPS, 2015; Jahr & Lee, 2010; Mackenzie et al., 2000; Lexi-Comp, n.d.; Yeh & Reddy, 2012).

To date, the research evaluating the safety and antipyretic efficacy of acetaminophen has primarily been conducted in non-critically ill patients. What limited evidence there is in the critically ill population suggests acetaminophen may not be as hemodynamically inert as once thought (Boyle et al., 1997; Boyle et al., 2010; Krajčová et al., 2013; Mackenzie et al., 2000). A brief overview of how the interactions of fever, antipyretics and thermoregulation in the critically ill population may act as the biophysiologic basis for the hemodynamic effects of acetaminophen in the critically ill are presented in the next section.

**Physiologic Vulnerability in Critical Illness**

Critical illness induces a state of metabolic vulnerability. Serious injury or infection, which causes critical illness, also induces higher metabolic demands in order to heal broken tissue and/or mount an immunologic response. This increase in metabolic demand is coupled with a limited capacity to meet these demands. Critically ill patients often suffer from impaired gas exchange both in the lungs and tissues because of the global inflammatory response (O’Brien, Ali, Aberegg, & Abraham, 2007). Fever further increases both metabolic and cardiac demands by as much as 10% for every 1 °C increase
in core temperature (Manthous et al., 1995; Morrison, 2011). Fever can tip a metabolically vulnerable critically ill patient toward physiologic instability, which is why clinicians often administer antipyretics such as acetaminophen.

Critically ill patients also exist in a state of hemodynamic vulnerability. When the inflammatory response is induced systemically, global peripheral vasodilation that leads to leaky capillary membranes creates a maldistribution of circulation; blood is shunted away from vital organs, preload to the heart is decreased, and, if not treated, can lead to life-threatening hypotension (O’Brien et al., 2007). Even when hypotension is reversed, critically ill patients have limited capacity to compensate for changes in hemodynamics, such as those induced during thermoregulation. Potentially, when acetaminophen is given to a febrile critically ill patient, cold defences that increase core temperature (vasoconstriction and BAT activity, coupled with SA-node stimulation) halt, and heat defences (vasodilation and perspiration) are stimulated. Some evidence suggests that the onset of the antipyretic action of acetaminophen may pose a risk of hypotension in the febrile critically ill population. The research articles related to these risks are summarized in the next sections.

Safety and Antipyretic Efficacy of Acetaminophen in the Critically Ill

Two literature searches were conducted to identify gaps in the literature to inform the research questions. The first search addressed what is known about the phenomenon of AAH, and the second search addressed the antipyretic efficacy of acetaminophen in the critically ill population. The same databases were searched but different search strategies were used. These two literature reviews are presented separately.
Search Criteria for Acetaminophen-Associated Hypotension

Few limitations to the search criteria were applied because AAH is not a phenomenon reported in the recent drug manual CPS (2015) suggesting that limited published literature was available on this topic. Inclusion criteria included any original research articles including randomized controlled trials (RCTs) and other interventional studies, and prospective or retrospective observational studies that examined any route or dose of acetaminophen. Case reports were excluded because there were enough articles at a higher level of evidence. Other restrictions included limiting reports to adult human studies and those published in English, French or Spanish because translation resources for French and Spanish were available. Additionally, the publications needed to report on at least hourly measurement of the participants’ vital signs after acetaminophen and for a minimum of 30 minutes after treatment.

Five databases were searched: Cumulative Index to Nursing and Allied Health (CINAHL), MEDLINE, the International Pharmaceuticals Abstracts (IPA), Excerpta Medica database (EMBASE), and the Web of Science (WOS). All databases, with the exception of IPA, were searched twice, in May of 2014 and in July of 2015. IPA was excluded from the second search because it was no longer available through the University of British Columbia’s Library system in July of 2015. No articles that met the inclusion criteria were identified through IPA in May 2014. The following search terms and Boolean operators were used: “acetaminophen” OR “paracetamol” AND “hypotension.” The search terms “acetaminophen” OR “paracet*” AND “hypoten*” were used with WOS database because it does not use medical subject heading (i.e., MeSH) terms to code journal articles. Finally, a hand search of reference lists from the captured
literature was conducted and eight additional articles for secondary screening were identified.

This search strategy resulted in a total of 749 articles (see Figure 2). After removing duplicates and conducting a preliminary screening of titles and abstracts for relevance, 65 articles were retained for secondary screening of the full article including reference lists. After completing the secondary screening, 52 articles were excluded from the review. A total of 13 original research articles were included in this review (Avellaneda et al., 2000; Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; de Maat et al., 2010; Forouzanfard et al., 2012; Gozzoli et al., 2004; Hersch et al., 2008; Krajčová et al., 2013; Mackenzie et al., 2000; Mrozek et al., 2009; Picetti et al., 2014; Vera et al., 2012). When possible, authors were contacted to clarify study details.
Synthesis of Acetaminophen-Associated Hypotension Research

Two case reports of acetaminophen-related hypotensive events in which patients did not report other signs of allergy (Brown, 1996; MacKenzie, 1981) were published before Boyle et al. (1997) reported the first formal investigation into this phenomenon. Boyle et al. (1997) conducted a small \( n = 27 \) prospective, observational study examining the incidence of hypotension in critically ill adults who received
acetaminophen orally. The majority of participants received acetaminophen for fever ($n = 23$) and the remaining for pain control (Boyle et al., 1997). Investigators detected an average 10% decrease in systolic blood pressure (SBP) and a 7% decrease in mean arterial pressure (MAP) at 30 to 120 minutes post-acetaminophen ($p < 0.01$; Boyle et al., 1997). This difference was detected despite nearly one third (8/27) of participants having received treatments for acute hypotension post-acetaminophen: three received fluid boluses, two received vasoactive infusions and three received both a fluid bolus and vasoactive drugs. Their study had several limitations (Boyle et al., 1997). It was a small, single-centre observational study; in addition, the study had no control group, no blinding and no randomization therefore it had a high risk of bias (Boyle et al., 1997).

In more recent years, other research teams, from primarily European countries, conducted mostly observational studies that examined the incidence of hypotension after acetaminophen in the critically ill population (Avellaneda et al., 2000; de Maat et al., 2010; Forouzanfard et al., 2012; Hersch et al., 2008; Mackenzie et al., 2000; Vera et al., 2012). Recently, investigators have also begun expanding into different ICU sub-populations such as critically ill patients with acute brain injury (Picetti et al., 2014) and post cardiac surgery (Avellaneda et al., 2000; Krajčová et al., 2013). Recent studies have also explored physiological mechanisms that are suspected to contribute to AAH (Boyle et al., 2010; Krajčová et al., 2013; Mrozek et al., 2009). The incidence of AAH ranged widely (0-48%), showing the heterogeneity between studies. These studies differed in methodology, sample size, sample characteristics, incidence of fever, dose and route of acetaminophen. The definition of hypotension itself varies between studies; however most report hypotension in two ways: (a) differences of SBP, MAP, and diastolic blood
pressure (DBP) between the treatment and comparison group, and/or (b) incidence of hypotension requiring treatment with fluid bolus, vasoactive infusions, or both.

Both I. M. Mackenzie et al. (2000) and Avellaneda et al. (2000) conducted retrospective chart reviews. I. M. Mackenzie et al. (2000) examined 191 episodes of acetaminophen administration in 53 ICU patients and also found hypotension requiring treatment occurred in 26.2% (50/191) of the cases. In their study, I. M. Mackenzie et al. (2000) made comparisons in two ways: (a) with baseline data immediately prior to receiving acetaminophen and (b) with “matched controls” (p. 1408), which the authors defined as data from the same patient that was either 8 or 24 hours, before or after the intervention period in which no acetaminophen was given. I. M. Mackenzie et al. (2000) did not record any incidents of hypotension (either as hypotension requiring treatment or change in SBP, DBP or MAP) for the matched controls. Avellaneda et al. (2000) reviewed the charts of 72 uncomplicated cardiac surgery patients post-extubation to compare the hemodynamic effects of the following: 1,000 mg acetaminophen intravenous (IV), 30 mg ketorolac IV and 2,000 mg metamizol IV. Avellaneda et al. (2000) also made comparisons with the participant’s baseline data. While no information was reported about the incidence of fever amongst participants or treatments for hypotension post intervention, the researchers did report a modest but statistically significant decrease in SBP and DBP \( (p < 0.01) \) in the acetaminophen group when compared to their baseline data (Avellaneda et al., 2000). While these studies had moderate sample sizes, again there were no randomization, blinding, or control groups.

Hersch et al. (2008), Vera et al. (2012), de Maat et al. (2010) and Forouzanfard et al. (2012) all conducted small prospective observational studies in critically ill patients
but the proportions of participants who were febrile in each study varied. Hersch et al. (2008) carried out a study in which a total of 72 acetaminophen administrations were observed in 14 febrile critically ill participants and Vera et al. (2012) included 50 febrile ICU patients who received one dose of IV acetaminophen. In contrast, the majority of participants in both de Maat et al.’s (2010) and Forouzanfard et al.’s (2012) studies were afebrile: de Maat et al. (2010) enrolled 36 participants who were given IV acetaminophen once, in which only 6 (16%) were febrile, and Forouzanfard et al. (2012) enrolled 107 participants, in which only 20 (18%) were febrile. Both Hersch et al. (2008) and Vera et al. (2012) reported a higher incidence of hypotension requiring treatment with fluid bolus and/or vasoactive infusions at 24/72 (33%) and 24/50 (48%), respectively, than de Maat et al. (2010) at 6/36 (16%) and Forouzanfard et al. (2012) at 6/107 (5%). The reported incidence of a clinically significant hypotensive event post acetaminophen was higher in studies that also reported a greater proportion of the participants who were febrile.

These six studies were conducted in a variety of intensive care settings, including both surgical and medical ICU, and shared the same limitations of small sample sizes and observational methodologies as seen in the previously mentioned studies. Collectively, these studies all reported a modest but statistically significant decrease in blood pressure (SBP and/or MAP) after patients received acetaminophen. This decrease in blood pressure was detected despite the fact that five of the six studies also reported that a proportion of participants (16–48%) received treatment for hypotension post acetaminophen (Boyle et al., 1997; de Maat et al., 2010; Hersch et al., 2008; Mackenzie et al., 2000; Vera et al., 2012). One study did not provide information about any treatments for hypotension (Avellaneda et al., 2000).
To date, two RCTs have been published; both were small, open-label studies conducted in analgesio-sedated febrile ICU patients and neither used a placebo control group (Cruz et al., 2002; Gozzoli et al., 2004). In the study conducted by Cruz et al. (2002), 60 analgesio-sedated febrile ICU patients were randomized to either receive 2,000 mg propacetamol IV (equivalent to 1,000 mg acetaminophen IV) or 2,000 mg metamizol IV. Cruz et al. (2002) excluded three (10%) of the 30 participants enrolled in the acetaminophen group from the analysis because they developed hypotension that could not be reversed with a fluid bolus alone. Despite this, Cruz et al. (2002) still detected a statistically significant decrease in blood pressure at 30, 60, and 120 minutes post intervention. In contrast, Gozzoli et al. (2004) did not detect any change in blood pressure or report any events of hypotension requiring treatment post intervention. This study may have been underpowered because only 30 participants (10 per group) were randomized to receive single treatment of either metamizol 16 mg/kg IV (max of 2,000 mg) or propacetamol 30 mg/kg IV (max of 2000 mg) or external cooling (Gozzoli et al., 2004).

Picetti et al. (2014) conducted a small prospective observational study with neuro-ICU patients (i.e., patients with traumatic brain injury, subarachnoid or intra-cerebral hemorrhage or acute ischemic stroke) and also identified a decrease in blood pressure after acetaminophen. They enrolled 32 febrile acute brain injured patients to receive a single dose of 1,000 mg acetaminophen IV (Picetti et al., 2014). They reported a decrease in MAP from 97 mmHg to 87 mmHg at 30 and 60 minutes post intervention ($p < 0.05$) even though nearly half (15/32) of the participants required an increase or initiation of vasoactive infusions (Picetti et al., 2014).
**Studies examining mechanism of action.** Mrozek et al. (2009) were the only investigators to examine for an immune-allergenic mechanism for AAH. They conducted a prospective, observational study \((n = 1,507\) doses in 127 participants; Mrozek et al., 2009). The primary objective of this study was to identify if the patients who experienced AAH were having an allergic response. To ensure they identified only patients who clearly demonstrated AAH, Mrozek et al. (2009) defined hypotension as at least a 20% reduction in SBP (in contrast to other studies where hypotension was defined as a 10% decrease in SBP). Given that they defined hypotension as a 20% decrease in SBP, it is not surprising that they also reported a low incidence of AAH at 1.33% (Mrozek et al., 2009). To explore for an allergenic mechanism, Mrozek et al. (2009) compared pre-post tryptase assays of the hypotensive-responsive group (20/1,507), but did not see levels of tryptase increase enough to confirm an allergic response. Elevated tryptase levels 6 hours after an exposure would have confirmed an allergy; however, absence of this indicator does not disprove an allergic reaction (Simons et al., 2007). Therefore, investigators were unable to confirm or completely refute if any immunological mechanisms were at play (Mrozek et al., 2009).

In 2010, Boyle et al. conducted a study similar to their 1997 study and found a similar incidence of AAH requiring treatment (33%), but this time also examined if the thermoregulatory mechanism of vasodilation played a role. Skin blood flow was assessed using a laser Doppler flowmeter. Boyle et al. (2010) made comparisons both with baseline data from the ICU patients and with a non-equivalent control group of 20 afebrile healthy volunteers. Skin blood flow increased when the antipyretic effects of acetaminophen induced the heat defences (i.e., vasodilation and sweating) in febrile
critically ill patients, but not in the control group, which was “consistent with its antipyretic action” (Boyle et al., 2010, p. 209).

Krajčová et al.’s (2013) research was the only study to directly measure systemic vascular resistance and other hemodynamic changes that potentially would occur with an episode of AAH. These researchers recruited a select group of cardiac surgery patients ($n = 6$) who were known to demonstrate hypotension (> 15% decrease in MAP) after acetaminophen for their prospective observational cross-over design study. Participants received either 1,000 mg acetaminophen IV or 50 mg ranitidine IV (as the control) every 3 hours. The researchers compared 48 acetaminophen “cycles” (p. 137) with 32 ranitidine “cycles” (p. 137). A cycle was defined as the 3 hours of data collected after the participant received either the control or study drug. A “responsive cycle” (p. 138) was defined as a cycle in which the participant demonstrated hypotension (i.e., the ≥ 15% drop in MAP). Investigators also made comparisons between responsive febrile cycles (> 38 °C; $n = 7$) and responsive afebrile cycles (<37 °C, $n = 3$). Krajčová et al. (2013) measured hemodynamic changes with a pulse index continuous cardiac output (PiCCO®) monitor which is similar to an arterial line but also can ascertain continuous core temperature, systemic vascular resistance index and pulse contour cardiac index. The researchers found a 7% decrease in MAP ($p > 0.001$) post acetaminophen but no difference post ranitidine. Hypotension occurred in 22/48 acetaminophen cycles: in the febrile ($n = 8$), afebrile ($n = 6$) and sub-febrile (37-38 °C; $n = 8$) groups. There was a non-significant trend toward a decrease in both systemic vascular resistance index and pulse contour cardiac index in the febrile acetaminophen group ($p > 0.07$); however, the
increased norepinephrine infusion rate post acetaminophen in the febrile group may have obscured hemodynamic differences (Krajčová et al., 2013).

**Variation in the reporting of presence of fever in studies to date.** Fever status amongst participants as a variable differed between studies. Eight studies (Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; Gozzoli et al., 2004; Hersch et al., 2008; Mackenzie et al., 2000; Picetti et al., 2014; Vera et al., 2012) reported that more than 75% of participants had fever at the time of receiving acetaminophen. Of these, seven studies reported a statistically significant decrease in blood pressure even though a proportion of the participants (10–48%) also received some corrective treatment for hypotension (Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; Hersch et al., 2008; Mackenzie et al., 2000; Picetti et al., 2014; Vera et al., 2012). The study by Gozzoli et al. (2004) did not detect a change in hemodynamics after propacetamol, but this study had the smallest sample size of those included in this review (n = 10). Three studies did not provide information about the fever status of participants (Avellaneda et al., 2000; Mrozek et al., 2009) or did not report if participants received treatment for hypotension after the intervention (Avellaneda et al., 2000; Krajčová et al., 2013). Two studies reported that less than 25% of the participants were febrile and the incidence of hypotension requiring treatment was reported as 5–16% (de Maat et al., 2010; Forouzanfard et al., 2012).

**Summary of acetaminophen-associated hypotension literature.** Although current evidence is inconclusive, it is likely that increased skin blood flow, decreased systemic vascular resistance index, and decreased cardiac output occur concurrently with AAH. If the study by Gozzoli et al. (2004) is included, then the incidence of hypotension
requiring treatment after acetaminophen ranges widely (0–48%), which is reflective of the heterogeneity in study methodology, sample size, dose, measurement, and other sample characteristics. Fever status amongst participants is one variable that differed between studies, but should be considered because hemodynamic changes with antipyresis are a plausible theory that needs further testing. To date, acetaminophen research conducted in the ICU has been predominantly observational in nature, and none has utilized a placebo control group. In light of this evidence, more rigorous investigation, such as a placebo-controlled RCT, with standardized methods of measuring both fever and hypotension, is warranted to determine the frequency of AAH in the ICU population, and to explore what other factors contribute to this phenomenon.

**Search Criteria for Antipyretic Efficacy of Acetaminophen in the Critically Ill**

A second literature review was conducted to answer the question, “What is the antipyretic efficacy of acetaminophen in the adult critically ill population?” In May of 2014, CINAHL, MEDLINE, IPA, and WOS databases were searched to identify studies that examined the antipyretic efficacy of acetaminophen. The subject heading terms used were: “paracetamol” OR “acetaminophen” AND “fever” OR “antipyretic efficacy” OR “efficacy” with the CINAHL, MEDLINE, and IPA databases. The search terms “acetaminophen” OR “paracetam*” AND “antipyretic efficacy” were used with the WOS database. A hand search of the reference lists of the captured literature was then performed. The following inclusion criteria were used: all types of original research such as RCTs, quasi-experimental designs, prospective or retrospective observational studies except case reports; conducting in adult human critically ill populations with fever; using any method of temperature measurement or dose or route of acetaminophen.
Figure 3. Search criteria for articles about the antipyretic efficacy of acetaminophen.

In total, 525 articles were retrieved from the initial search (see Figure 3). One article from the previous search was included because it examined both the phenomenon of AAH and the antipyretic efficacy of acetaminophen (Mackenzie et al., 2000). After duplicates were removed 153 articles remained for further screening of the titles and abstracts for relevance. A total of 143 articles were excluded because they did not meet the inclusion criteria. A total of 10 articles were included for this literature review, and
they consisted of two subgroups: five from the general ICU population and five from the acute brain-injury ICU population.

**Synthesis of Antipyretic Efficacy of Acetaminophen in the Critically Ill**

Little research has been done to examine the antipyretic efficacy of acetaminophen in critically ill patients, despite the fact that ICU patients are uniquely vulnerable to fever and may have a greater need for this evidence than the general population. Making comparisons between these 10 studies (Dippel et al., 2003; Dippel et al., 2001; Gozzoli et al., 2004; Greenberg et al., 2010; Kasner et al., 2002; Mackenzie et al., 2000; Morgan, 1990; Poblete et al., 1997; Sulter et al., 2004; Vera et al., 2012) is challenging because of the differences between critically ill patients who are, versus, are not brain-injured so the studies are summarized separately.

**Antipyretic efficacy in non-brain-injured ICU patients.** Amongst the studies conducted in the non-brain-injured ICU population (Gozzoli et al., 2004; Greenberg et al., 2010; Mackenzie et al., 2000; Poblete et al., 1997; Vera et al., 2012), none were placebo-controlled and only one (Gozzoli et al., 2004) employed random allocation of participants. Gozzoli et al. (2004) conducted a small (n = 30) open-label RCT in analgesio-sedated, febrile, mechanically ventilated patients to examine the metabolic, hemodynamic and inflammatory effects of three different antipyretic therapies: IV metamizol, IV proparacetamol or external cooling. Comparisons were with baseline data only and temperature was recorded hourly. There was a small (-0.5 °C) but statistically significant decrease in temperature from baseline at 4 hours post-intervention (p < 0.05, 95% CI [0.2 °C, 0.8 °C]).
Both Vera et al. (2012) and Poblete et al. (1997) conducted prospective studies, and both did not detect a change in temperature after administering acetaminophen. Vera et al. (2012) conducted an observational study with 150 febrile ICU patients; temperature was recorded every 30 minutes for a total of 2 hours, but only 50 patients were selected to receive 1,000 mg of IV paracetamol by the attending physician. Only 20 out of the 50 participants in the intervention arm achieved at least a 1 °C decrease in temperature by 120 minutes, which did not reach statistical significance (Vera et al., 2012). Poblete et al. (1997) conducted an open-label cross-over study that compared the antipyretic efficacy of IV propacetamol, metamizol or external cooling in 20 febrile analgesio-sedated ICU patients. They found no difference between the baseline data and post-intervention for the propacetamol group. This study may have been underpowered to detect an effect because only 11 participants were selected in the propacetamol group.

The remaining two studies were retrospective chart reviews and both detected only a modest reduction in temperature (Greenberg et al., 2010; Mackenzie et al., 2000). Making comparisons between these last two studies is challenging because the method of temperature measurement is unclear or inconsistent; patients received varying doses of acetaminophen ranging from 325 mg to 1,000 mg; and the method of reporting change in temperature varied. The study conducted by I. M. Mackenzie et al. (2000) included 191 administrations of acetaminophen in 53 patients. They recorded temperature hourly for 2 hours prior to acetaminophen until 3 hours after (Mackenzie et al., 2000). Temperature change was not reported as an absolute value, but rather as a percentage change from baseline; participants had an average 1.3% decrease from their baseline temperature by 3 hours post-intervention (Mackenzie et al., 2000). The average baseline temperature was
38.3 °C, meaning a 1.3% decrease equates to 0.5 °C (Mackenzie et al., 2000). Greenberg et al. (2010) examined 166 febrile episodes in 59 ICU patients. Acetaminophen was given in 88 of the 166 febrile episodes, which allowed the team to make comparisons between the treated and untreated febrile episodes (Greenberg et al., 2010). The researchers found that temperature reduction was modestly better in the treated group compared to the untreated group (-0.86 °C versus -0.56 °C, \( p < 0.05 \)). Also, similar to the results in Vera et al.’s (2012) study, Greenberg et al. (2010) found that critically ill patients were heterogeneous in their responses to acetaminophen; high responders dropped core temperature by an average of 1.7 °C, while low responders only reduced temperature by 0.2 °C on average.

**Antipyretic efficacy in brain-injured patients.** Five studies that examined the antipyretic efficacy of acetaminophen in patients with acute brain-injury were identified (Dippel et al., 2003; Dippel et al., 2001; Kasner et al., 2002; Morgan, 1990; Sulter et al., 2004). Again, making comparisons between these studies was challenging because of differences in methodology, measurement, intervention, and sample characteristics.

Three RCTs have been conducted in patients with acute ischemic stroke and all demonstrated that acetaminophen had little or no effect at suppressing fever (Dippel et al., 2003; Dippel et al., 2001; Kasner et al., 2002). Kasner et al. (2002) conducted a study to examine the ability of acetaminophen to reduce core temperature in patients with acute stroke; participants received either 650 mg acetaminophen \( (n = 20) \) or placebo \( (n = 19) \) every 4 hours for 24 hours and core temperature was recorded every 30 minutes. One possible reason that no effect was detected in this study is that it was underpowered; as per their study protocol, three participants were excluded from the final analysis, two
from the acetaminophen group and one from the placebo group because they developed a core temperature above 38.5 °C. Dippel and colleagues contributed two studies that were similar to each other (Dippel et al., 2003; Dippel et al., 2001). The first study compared placebo with regimens of acetaminophen 500 mg every 4 hours for 5 days or 1,000 mg every 4 hours for 5 days (Dippel et al., 2001); the second study compared placebo with acetaminophen 1,000 mg every 4 hours for 5 days or ibuprofen 400 mg every 4 hours for 5 days (Dippel et al., 2003). In both studies, each arm had 24–26 participants. In the first study, Dippel et al. (2001) detected a difference in temperature (i.e., the high-dose acetaminophen group had a 24-hour mean temperature of 37.0 °C verses 37.4 °C in the placebo group; \( p < 0.05 \)) but did not detect a difference in the second study (Dippel et al., 2003).

The remaining studies were not placebo-controlled and found acetaminophen had some antipyretic action, although it is difficult to determine its antipyretic efficacy from the reported findings. Morgan (1990) conducted a small \( (n = 21) \) quasi-experimental study amongst patients with brain-injury in an ICU to examine if there was a different cooling rate when acetaminophen was given by itself \( (n = 7) \), or was augmented by external cooling \( (n = 14) \). No difference was found in cooling rates between acetaminophen with or without external cooling and all participants returned to the normal range within 2 hours (Morgan, 1990). Sulter et al. (2004) compared 132 febrile periods in 63 patients. Participants received either ASA 500 mg \( (n = 43) \) or acetaminophen 1,000 mg \( (n = 89) \) to suppress fever in acute ischemic stroke patients whose core temperature rose above 37.5 °C. They found acetaminophen to be modestly more effective than ASA at reducing fever; acetaminophen restored normothermia
 (> 37.5 ° C) for 20% (18/89) of the participants by 1 hour and 38% (34/89) by 3 hours post administration (Sulter et al., 2004).

**Summary of antipyretic efficacy of acetaminophen literature.** Determining the antipyretic efficacy of acetaminophen in the ICU population is not possible with the limited research currently available. Differences in methodology, measurement of fever, acetaminophen dosing and administration and sample characteristics limit the ability to make comparisons between the ten studies available. This evidence suggests that the antipyretic efficacy of acetaminophen in critically ill patients is highly variable (Greenberg et al., 2010; Sulter et al., 2004; Vera et al., 2012) and further investigation using rigorous study methods is needed.

**Summary**

Fever is recognized as an effective immunological response to infection or injury but fever imposes high metabolic and cardiac demands. Critical illness imposes unique challenges for patients, as it renders patients both metabolically and hemodynamically vulnerable. Antipyretics such as acetaminophen are administered to minimize the metabolic stress caused by fever; however, it is possible that acetaminophen may increase hemodynamic vulnerability. The normal thermoregulatory processes activated to reduce core temperature also causes hemodynamic changes that critically ill patients may not be able to compensate for. Clinicians who care for critically ill patients need to know both the risks and benefits of acetaminophen in order to manage fever in these patients. This review examined the evidence for AAH and the antipyretic efficacy of acetaminophen in the critically ill population. If the studies by Gozzoli et al. (2004) and Krajčová et al. (2013) are excluded because both had a sample size of ten or less, the incidence of AAH
is between 5% and 46.8% (Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; de
Maat et al., 2010; Forouzanfard et al., 2012; Hersch et al., 2008; Mackenzie et al., 2000;
Picetti et al., 2014; Vera et al., 2012). Increased skin blood flow, decreased systemic
vascular resistance, and decreased cardiac output occur concurrently with AAH (Boyle,
2011; Krajčová et al., 2013). With regard to antipyretic efficacy, while acetaminophen
has been shown to have a moderate antipyretic effect in the non-critically ill population
(Bachert, Chuchalin, Eisebitt, Netayzhenko, & Voelker, 2005; Kett, Breitmeyer, Ang, &
Royal, 2011; Maron & Ickes, 1976; Vargas, Maneatis, Bynum, Peterson, & McMahon,
1994), the results from studies conducted in critically ill patients are inconclusive. To
date, acetaminophen research conducted in the ICU mostly has used observational
methods and higher quality study designs are needed.
Chapter 3: Methods

A pilot randomized controlled trial (RCT) to evaluate both AAH and antipyretic efficacy was initiated. When it became apparent that too few participants would be enrolled within the timeline to make the planned statistical analysis valid, the primary focus of the project was changed to examining the feasibility of an RCT on this topic. The original research plan is presented later in this chapter. Data that were collected to examine the hemodynamic and antipyretic effects of acetaminophen are analyzed as a case series.

Research Question 1: Feasibility

The first research question was, “What is the feasibility of conducting a double-blinded RCT to examine both the safety and antipyretic efficacy of a standard dose of acetaminophen given to the adult, febrile, non-brain-injured critically ill patient?” Thabane et al. (2010) recommend using both qualitative and quantitative data to assess four components of feasibility: research process, research resources, data management and scientific factors.

The research processes that were examined included the screening, recruiting and data collection processes (Thabane et al., 2010; Tickle-Degnen, 2013; see Table 1). At the time of the interim analysis there was a lower than anticipated enrolment rate. In response, the decision was made to broaden the enrolment criteria to improve the eligibility rate. In order to test if these changes had any effect on the eligibility rate an additional research question and associated hypothesis was added for statistical testing (see Table 1).
Resources were defined as the time required and financial costs associated with the research materials, personnel, other logistic supports utilized in this study (Thabane et al., 2010; Tickle-Degnen, 2013). The question that addressed resources was, “Were there adequate resources allocated to address the first and second research questions?”

Table 1

*Questions Addressing the Research Processes*

<table>
<thead>
<tr>
<th>Process</th>
<th>Questions</th>
</tr>
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<tbody>
<tr>
<td><strong>Screening Process</strong></td>
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</tr>
<tr>
<td>Was the screening process</td>
<td>Was the screening process effective in identifying all eligible patients?</td>
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<td>effective in identifying all</td>
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<td>eligible patients?</td>
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<td>What were the facilitators</td>
<td>What were the facilitators and barriers to the screening process?</td>
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<td>and barriers to the</td>
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<tr>
<td>screening process?</td>
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<tr>
<td><strong>Recruitment Process</strong></td>
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<td>What was the eligibility</td>
<td>What was the eligibility rate?</td>
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<td>rate?</td>
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<tr>
<td>What were the most common</td>
<td>What were the most common reasons for exclusion from this study?</td>
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<td>reasons for exclusion from</td>
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<td>this study?</td>
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<tr>
<td>What was the enrolment rate?</td>
<td>What was the enrolment rate?</td>
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<td>What were the barriers to</td>
<td>What were the barriers to enrolment?</td>
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<td>enrolment?</td>
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<tr>
<td>Did the change in the</td>
<td>Did the change in the exclusion criteria that was enacted on November 5,</td>
</tr>
<tr>
<td>exclusion criteria that was</td>
<td>2015 have an effect on the eligibility rate?</td>
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<td>enacted on November 5, 2015</td>
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<td>have an effect on the</td>
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<tr>
<td>eligibility rate?</td>
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<tr>
<td>(H_0): The change in</td>
<td>(H_0): The change in exclusion criteria did not make a difference to</td>
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<tr>
<td>exclusion criteria did not</td>
<td>the eligibility rate.</td>
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<tr>
<td>make a difference to the</td>
<td></td>
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<tr>
<td>eligibility rate.</td>
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<tr>
<td>(H_{A1}): The change in</td>
<td>(H_{A1}): The change in exclusion criteria did make a difference to</td>
</tr>
<tr>
<td>exclusion criteria did make</td>
<td>the eligibility rate.</td>
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<tr>
<td>a difference to the eligibility rate.</td>
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<tr>
<td><strong>Data Collection Process</strong></td>
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<tr>
<td>How long did data collection</td>
<td>How long did data collection take per participant?</td>
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<tr>
<td>take per participant?</td>
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<tr>
<td>What were the barriers or</td>
<td>What were the barriers or challenges to data collection?</td>
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<tr>
<td>challenges to data collection?</td>
<td></td>
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</table>

Data management refers to the effectiveness of strategies that ensured data accuracy and completeness (Thabane et al., 2010; Tickle-Degnen, 2013). Two questions addressed data management: (a) were the data management processes effective to ensure data accuracy and completeness; and (b) what were the barriers and facilitators to effective data management?
Thabane et al. (2010) define scientific factors as the safety of the research procedures and interventions, accuracy and reliability of measurement, and an evaluation of the clinical relevance of the outcome measures. Three questions were addressed: (a) were the research and intervention procedures as safe as predicted, (b) were the methods of measurement accurate and reliable, and (c) were the outcome measures clinically relevant?

**Research Question 2: Acetaminophen-Associated Hypotension**

The second research question was, “Does 650 mg acetaminophen, administered enterally, increase the number of clinically significant hypotensive events in febrile intensive care unit (ICU) patients (excluding brain injury, liver dysfunction or burn patients)?” This question had four research hypotheses:

- **H02**: There is no difference in the number of clinically significant hypotensive events within 4 hours after intervention between treatment (i.e., 650 mg acetaminophen) and control groups (i.e., placebo).
- **H03**: There is no difference in the change from baseline of systolic blood pressure (SBP) or mean arterial pressure (MAP) between the treatment and control groups.
- **H04**: There is a difference in the change from baseline of SBP or MAP between the treatment and control groups.
- **H05**: There is a difference in the number of clinically significant hypotensive events in the 4 hours after intervention between the treatment group and control group.
• $H_04$: There no a difference in the total equi-volume of fluid administered in the 4 hours post-intervention between the treatment and control groups.

• $H_{A4}$: There is a difference in the total equi-volume of fluid administered in the 4 hours post intervention between the treatment and control groups.

• $H_{05}$: There is no difference in the total equi-dose of vasoactive infusions administered in the 4 hours post intervention between the treatment and control groups.

• $H_{A5}$: There is a difference in the total equi-dose of vasoactive infusions administered in the 4 hours post intervention between the treatment and control groups.

**Research Question 3: Antipyretic Efficacy**

The third research question was, “Does acetaminophen 650 mg reduce fever burden in the 6 hours after administration in febrile, non-brain-injured adult ICU patients more than placebo?” The hypothesis was:

• $H_{06}$: There is no difference in fever burden within 6 hours of study drug administration between the treatment group and the control group.

• $H_{A6}$: There is a difference in fever burden within 6 hours of study drug administration between the treatment group and the control group.

**Research Question 4: Relationships Between Fever, Heart Rate and Blood Pressure**

There were too few participants who completed this study to address the second or third research questions therefore these questions were used to guide the study design and inform the examination of feasibility. Instead the vital sign data is presented as a
case series and a fourth research question was added. What is the relationship between heart rate, blood pressure, core temperature, and fever burden?

**Operational Definitions**

Six key concepts require operational definitions for this study: critically ill patient, fever and new fever, clinically significant hypotension, total equi-volume fluid, total equi-dose of vasoactive infusions, and fever burden. These operational definitions are summarized in Table 2.
Table 2

*Operational Definitions and Measurement*

<table>
<thead>
<tr>
<th>Concept</th>
<th>Operational Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Significant Hypotensive Event</td>
<td>A hypotensive event (i.e., MAP below 60 mmHg) which required either an IV fluid bolus (crystalloid and/or colloid) of 500 mL or greater, initiation and/or increase in infusion of norepinephrine by at least 5 mcg/min from baseline (or the equivalent dose of other vasopressors), or both.</td>
</tr>
<tr>
<td>Critically Ill Patient</td>
<td>A patient who was admitted to the ICU at Vancouver General Hospital and had an established arterial line for continuous blood pressure monitoring.</td>
</tr>
<tr>
<td>Fever</td>
<td>A core temperature greater than 38.3 °C for at least 120 minutes, or a core temperature of greater than or equal to 39.0 °C for at least 15 minutes.</td>
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<tr>
<td>Fever Burden</td>
<td>The amount of fever a patient experienced over a period of the study as measured as an area under the curve (AUC). Fever burden is the area below the participant’s temperature curve and above a cut-off of 37.7 °C, over time in hours. Since it is a measurement of an area, that is temperature over a period of time, the unit of measure for fever burden was °C-hours. Equation 1 was used to estimate fever burden from serial temperature readings.</td>
</tr>
<tr>
<td>New Fever</td>
<td>A fever of less than 48 hours in duration, from the onset of the fever or of the ICU admission (whichever occurred later).</td>
</tr>
<tr>
<td>Persistent Hypotension</td>
<td>A MAP less than 55 mmHg for greater than 15 minutes or a MAP less than 45 mmHg for more than 5 minutes.</td>
</tr>
<tr>
<td>Total Equi-dose Vasoactive Infusions</td>
<td>Since a variety of vasoactive infusions could be administered to correct hypotension and they have varying dose effects, the total equi-dose of vasoactive infusions would be calculated by the following formula: 10 mcg/min norepinephrine ≈ 5 mcg/kg/min dopamine ≈ 10 mcg/min epinephrine ≈ 1 mcg/min phenylephrine ≈ 0.02 u/min vasopressin (Russell et al., 2008) before totalling the dose of vasoactive infusions received. §</td>
</tr>
<tr>
<td>Total Equi-volume Fluid</td>
<td>Since crystalloid fluid exerts a lower oncotic pressure than colloid fluid when administered intravenously (Finfer et al., 2004; Myburgh &amp; Mythen, 2013), total equi-volume fluid was calculated by converting all colloid volumes to the equivalent crystalloid volume at a 1:1.4 ratio prior to totalling the fluid volumes.</td>
</tr>
</tbody>
</table>

*Note. § It was not anticipated that patients receiving dobutamine and/or milrinone would be included in this study because these two drugs are uncommonly used in this ICU and when they are used, it is for patients with known or suspected cardiac dysfunction.*
Calculating fever burden as an area under the curve. The serial temperature readings of each participant were plotted on a graph to create a temperature curve with time (in hours) along the x-axis and temperature (in °C) along the y-axis. Fever burden as an area under the temperature curve was estimated using the trapezoid method with Equation 1 (Allison, Paultre, Maggio, Mezzitis, & Pi-Sunyer, 1995; Bender, 1994; Matthews, Altman, Campbell, & Royston, 1990; Tai, 1994). The area of a rectangle is calculated by multiplying the width by the height. In this equation, the width is the time difference between two points of data ($t_2 - t_1$). In the trapezoid rule, the height is determined by taking the average height (i.e., temperature) between the two time points. This is done for all serial temperature readings. Then, all the subinterval areas were added (only including areas above the 37.7 °C normal threshold) to obtain the total fever burden as an area under the curve (AUC) for the 2 hours pre-intervention (AUC$_{0-2h}$) and an AUC for the 6 hours post intervention (AUC$_{0-6h}$).

Equation 1. Fever burden.

$$FB = \sum_{i=0}^{n-1} (t_2 - t_1) \left( \frac{(Tt_2 - 37.7) + (Tt_1 - 37.7)}{2} \right)$$

In this equation:
- $Tt_1$ = the temperature at the first time point (in °C)
- $Tt_2$ = the temperature at the second (or later) time point (in °C)
- $t_1$ = the first time point (in hours)
- $t_2$ = the second time point (in hours)
- $(t_2 - t_1)$ = the interval of time between time points 1 and 2
- FB = fever burden when the temperature persisting above the normal range throughout the interval of time (i.e., $Tt_1 \geq 37.7$ °C and $Tt_2 \geq 37.7$ °C).
- The unit of measure for fever burden is °C-hours.
Original Study Design with Adaptive Changes

A pilot, double-blinded RCT was planned to address the feasibility of undertaking a larger scale study as well as the hemodynamic effects and antipyretic efficacy of acetaminophen in the adult, febrile non-brain-injured population. An adaptive design was utilized, which allowed for the possibility of prospective adaptations (e.g., preplanned stopping rules for safety and/or efficacy reasons), concurrent or ad hoc adaptations (e.g., adjustments to enrolment criteria) and retrospective adaptations (e.g., changes to the statistical analysis plan prior to unblinding of the data), which were considered during the preplanned interim analysis (Chow & Chang, 2008). An interim analysis was planned for either after the first 30 participants had enrolled or after 4 months, which ever occurred first. In this case, the 4 months occurred first.

Prospective Adaptations as Pre-Planned Stopping Rules

Participant safety was ongoing because the research team monitored for any adverse events as participants completed the study. The following four stopping rules were predefined and reviewed during the interim analysis: (a) if there was a greater than 5% incidence of any complications associated core-temperature probe insertion, monitoring, or removal; (b) if there was a greater than 5% incidence of very high fever (greater than 40.0 °C); (c) if the incidence of AAH was greater than 50% because the a priori power analysis proposed a 25% incidence of AAH with an alpha of 0.05 and power of 0.80; or (d) if there was a greater than 5% incidence of persistent hypotension.

Sample, Inclusion, and Exclusion Criteria

The target population was the non-brain-injured adult patient who was critically ill and had developed a new fever (see Table 2). As per the original statistical analysis
plan (see Appendix A), the target sample size was 62 (31 in each arm) and based on retrospective data from the ICU database, it was estimated that this could be achieved in 6 months. The inclusion and exclusion criteria were selected to ensure participants’ safety, which included having no contraindications to either receiving acetaminophen (such as liver failure); to withholding acetaminophen (such as brain injury, cardiac dysfunction or severe hypoxemia) or to having core temperature monitored; and to reduce confounding factors that may have an impact on thermoregulation (such as damage to the skin, extra-corporeal blood treatments) or drug absorption (such as gastrointestinal malabsorption). Also, enrolment was not pursued when the most responsible physician was opposed to it for any reason. Table 3 provides a full list of the inclusion and exclusion criteria at the onset of the study and Table 4 outlines the changes to the exclusion criteria that were enacted on November 5, 2015.

**Concurrent adaptations: Changes to the exclusion criteria.** By October 2015, participant enrolment was very low; therefore, during the interim analysis the research team reviewed the barriers to enrolment and made changes to the study procedures with the intent of increasing the success without compromising participant safety and minimizing any compromise to the scientific validity. As a result, two changes were made after the amendments to the ethics application were approved on November 5, 2015 (see Table 4).
### Table 3

**Initial Enrolment Criteria (May 28 to November 4, 2015)**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either currently have a fever or the potential of having a fever during this ICU admission.</td>
<td>Significant liver dysfunction</td>
</tr>
<tr>
<td>Adult patients (&gt; 18 years) admitted to ICU at VGH</td>
<td>Acute neurological injury (i.e., that is diagnosed or treated during this hospital admission)</td>
</tr>
<tr>
<td>Continuous arterial pressure monitoring in place at the time of intervention and data collection</td>
<td>Seizure disorder</td>
</tr>
<tr>
<td>To remain in the ICU for the entire study period (2 hours prior to drug administration to 6 hours post drug administration)</td>
<td>Known cardiomyopathy, elevated cardiac enzymes indicative of an acute cardiac injury, ECG changes indicative of cardiac ischemia (i.e., ST elevation/depression in 2 contiguous leads), or evidence of cardiac dysfunction.</td>
</tr>
<tr>
<td>Able to safely tolerate core temperature monitoring</td>
<td>Hemodynamic instability (requiring fluid boluses, or change/initiation of vasopressors. Patients receiving steady doses of vasopressor support may be included)</td>
</tr>
<tr>
<td>Participant/Substitute decision maker fluent in English.</td>
<td>Severe hypoxemia, (FiO2 requirements of &gt; 60% to maintain SaO2 &gt; 90% or PaO2 &gt; 70)</td>
</tr>
<tr>
<td>IN ORDER TO PROGRESS to the intervention stage, the participant must also have a core temperature ≥ 38.3 °C for 2 or more consecutive hours, or a core temperature ≥39.0 °C for 15 consecutive minutes, but not longer than 48 hours*</td>
<td>Temperature &gt; 40.0 °C for ≥ 15 minutes</td>
</tr>
<tr>
<td></td>
<td>Receiving external cooling</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis, plasma exchange, or any treatment where the blood is taken out of the body and processed</td>
</tr>
<tr>
<td></td>
<td>Acute thermal injury to skin (i.e., burn)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal malabsorption (i.e., unable to tolerate at least 40% of their daily caloric needs enterally)§</td>
</tr>
<tr>
<td></td>
<td>Receiving medications that have known antipyretic effects (acetaminophen, ibuprofen, steroids, etc.)§</td>
</tr>
<tr>
<td></td>
<td>Attending physician opposed to enrolment in the study</td>
</tr>
<tr>
<td></td>
<td>Previous participation in the study</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

*The American College of Critical Care Medicine and Infectious Diseases Society of America has defined fever as temperature > 38.3 °C (O'Grady et al., 2008). ECG = electrocardiography; ICU = Intensive Care Unit; ST = a segment on the ECG tracing; VGH = Vancouver General Hospital; SaO2 = Oxygen Saturation of Hemoglobin; PaO2 = Partial pressure of oxygen dissolved in the blood; § = these criteria were changed from what is stated here on November 5, 2015.
Table 4  
Changes Made To the Exclusion Criteria

<table>
<thead>
<tr>
<th>Before November 5, 2015</th>
<th>After November 5, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal malabsorption (i.e., patient is unable to tolerate at least 40% of their daily caloric needs enterally).</td>
<td>Gastrointestinal malabsorption was redefined to be less strict. Patients were excluded if they could not tolerate medication enterally but still could participate even if they were not receiving at least 40% of their daily caloric needs enterally.</td>
</tr>
<tr>
<td>Receiving medications that have known antipyretic effects (acetaminophen, ibuprofen, steroids, etc.). All antipyretics had to be discontinued upon enrolment into this study.</td>
<td>Participants may continue to receive acetaminophen PRN but will only continue to the intervention stage of the study if they can tolerate having acetaminophen withheld for up to 12 hours as determined by the ICU team.</td>
</tr>
</tbody>
</table>

Note. ICU = Intensive Care Unit; PRN = Per re nata (when necessary).

Setting, Screening, and Consent

The setting was a 31-bed mixed surgical and medical ICU within a university-affiliated hospital that had 24-hour on-site physician coverage. While acetaminophen was an option in the Vancouver General Hospital (VGH) ICU admission order set as well as the VGH Emergency Department’s Sepsis Protocol, the decision to administer acetaminophen was often at the discretion of the ICU registered nurse (RN). Similarly to what was reported in the literature (Greenberg et al., 2010; Lee et al., 2012; Young et al., 2011), the use of acetaminophen as an antipyretic was variable at VGH ICU.

Screening took place during weekday mornings. This unit had an RN who was employed full time as the research coordinator. The research coordinator was available Monday to Friday from 8:00 a.m. to 4:00 p.m.; however, there was no relief coverage for absences related to vacation or illness. All new patients admitted during the prior 24 hours (or 72 hours on Mondays to cover weekend admissions) were evaluated for eligibility.
To maximize early identification of participants, the research team provided 30-minute beside education sessions to the direct care staff about this study in April of 2015. Also, the “SEA-ICU laminated cards” (see Appendix B) were distributed on computer stations throughout the ICU to alert staff about this study and how to contact the research team if they identified a potential candidate or had questions. All patients who were eligible to participate in the study were invited, regardless of whether they currently had a new fever. The research team placed “SEA-ICU Recruitment Sheet” (see Appendix C) in all eligible new patients’ charts and gave the “SEA-ICU Patient Information Pamphlet” (see Appendix D) to patients and/or their family members as early as possible. This pamphlet was posted on the VGH ICU website for patient and families on the “Research in the ICU” page (Vancouver Coastal Health, 2016). When patients met the eligibility criteria, the research coordinator was contacted to obtain consent.

The VGH ICU research coordinator was employed to obtain consent from the patient when possible, or the patient’s substitute decision maker. Additionally, the author also obtained consent when the research coordinator was unavailable. A patient’s substitute decision maker was the next-of-kin who was responsible for medical decisions if the patient was unable to do so. When consent was obtained from the substitute decision maker, all attempts were made to also obtain assent from the participant, provided the participant was not delirious as indicated by an Intensive Care Delirium Screening Checklist score of less than 4 (Bergeron, Dubois, Dumont, Dial, & Skrobik, 2001). Additionally, the research team renewed consent from the participant at a later time when able.
Telephone consent was also utilized because it was anticipated that the research coordinator might have challenges in connecting with families in a timely manner because she was only available during business hours and some families visited outside of these times. If a patient was eligible, the research team offered the information pamphlet to all potentially eligible ICU patients and their family members. If the research coordinator was unable to meet with the family in person, the ICU clinical team participated in confirming that the family received the information pamphlet and agreed (verbally, to the bedside RN) to being contacted via telephone by the research coordinator to learn more about the study. The bedside RN was asked to record the family’s decision about telephone contact on the recruitment sheet. If consent had been given, the research coordinator placed the SEA-ICU Clinician Information About Enrolled Participants document (see Appendix E) and a copy of the signed consent form (see Appendix F) in the participant’s chart. Another copy of the consent form was given to the family and the original consent form was kept with the research files.

**Monitoring for Fever Upon Enrolment**

Unlike the other vital sign measures, continuous core temperature monitoring was not routine for every patient in the ICU therefore when the participant had core temperature monitoring already established such as a urinary catheter temperature probe, it was used for continuous temperature monitoring because both the oesophageal and urinary catheter sites are considered equally accurate (Lefrant et al., 2003; Lilly, Boland, & Zekan, 1980). If core temperature monitoring was not preexisting, then a member of the research team placed a temperature probe in the participant’s oesophagus for the duration of the study so core temperature could also be continuously monitored. If the
participant was afebrile at the time of enrolment, the RN caring for the participant was asked to contact the research team if and when the participant became febrile. Additionally, these participants were reviewed daily during regular screening to monitor for a new fever. If the participant was febrile and acetaminophen-naïve (i.e., had not received acetaminophen in the previous 6 hours) at the time of enrolment, then the research team proceeded with the study protocol (i.e., final safety check, randomization and intervention procedures). If the participant was febrile and but had recently received acetaminophen, then the ICU team was consulted to ensure the participant could tolerate acetaminophen being withheld for up to 12 hours. If so, the research team waited at least 6 hours from the last dose of acetaminophen before continuing with the study protocol.

**Final Safety Check, Randomization, and Blinding Procedures**

Once the participant met the criteria for a new fever the research team conducted a final safety check to ensure the participant was hemodynamically stable and still eligible for the study. At this point, the research team notified the VGH Pharmacy Department during regular hours (7:30 a.m.–10:00 p.m. daily) so they could coordinate randomization, blinding, preparation and dispensing of the study medication (650 mg acetaminophen or placebo). If the participant developed a fever after hours (i.e., between 10:00 p.m. and 07:30 a.m.), the ICU team was directed to care for the participant as per their clinical judgement, but they were asked to refrain from administering acetaminophen after 4:00 a.m. if possible. The pharmacy was contacted the following morning for randomization if the participant still met the study criteria.

The Clinical Drug Trials Pharmacist was responsible for the randomization and blinding procedures. Randomization was determined by using permuted blocks of 10 to
ensure an approximate 1:1 allocation ratio between each study group. Only the Clinical Drug Trails Pharmacist was aware of the participant allocation until the analysis was completed. For the safety of the participants, emergency unblinding procedures were as follows: Sealed envelopes containing the participants’ allocation information were kept in the research coordinator’s office in a locked filing cabinet or with a research team member until the study was complete. Although it was never needed, this procedure was done to ensure that the ICU team could contact the research team and unblinding could occur within 10 minutes.

**Intervention**

Participants were randomized and received either a single capsule containing 650 mg of acetaminophen or a single capsule of placebo that was identical in appearance. This was administered via the nasogastric or orogastric tube, as per standard procedures. The ICU RN assigned to care for the participant administered the study medication.

**Measurement of Study Variables**

Vital signs such as heart rate SBP, MAP, and diastolic blood pressure (DBP) and core temperature were recorded every 5 minutes for a period of 8 hours. Data were collected starting from 2 hours prior to the intervention until 6 hours following the intervention. Also the participants’ fluid intake, output and total dose of vasoactive drugs were also recorded for the 8-hour study period.

It was standard practice to level, recalibrate, and assess function of the arterial line every 12 hours. Additionally, the arterial line was levelled, calibrated, and a square test was performed immediately prior to data collection to assure accuracy of the readings as per standard procedures. Manual blood pressure readings were also conducted to
ensure there was correlation between readings obtained from the arterial line and non-invasive cuff. Digitally recorded MAP, SBP, and DBP were downloaded and/or printed from the ICU monitors (CARESCAPE Monitor B650 made by GE Healthcare). A sample of the continuous arterial and electrocardiography waveforms were printed for visual inspection of data quality and accuracy.

Continuous monitoring of the participant’s core body temperature was achieved by Covidien Mallinckrodt esophageal temperature probe, if an equivalent core temperature probe was not already in place. These temperature probes were standard equipment at VGH ICU and, when needed, was usually inserted by the bedside RN. Temperature probe readings were compared with the standard oral temperature readings to ensure function and accuracy of the temperature probe prior to data collection. If the temperature probe reading was found to be inaccurate, it was replaced with a functioning temperature probe.

There are two confounding variables known to have an impact on blood pressure: fluid status and intra-thoracic pressure. Data pertaining to these confounding variables were gathered in order to assess if these variables had an impact on participant responses. Three types of data to evaluate fluid status were gathered: (a) fluid intake and output during the 6 hours of vital sign data collection, (b) the overall fluid balance for the day of intervention, and (c) overall fluid balance for the day prior to intervention (if available). Another contributing factor to blood pressure is changes in intra-thoracic pressure. Positive pressure ventilation is known to increase intra-thoracic pressure, thereby impeding blood flow returning to the heart (Luecke & Pelosi, 2005). Increases in intra-thoracic pressure can induce hypotension. Therefore, data pertaining to participants’
ventilator settings were recorded, if applicable, during the 6 hours of vital sign data collection. Other potential confounding variables to fever burden or hypotension include the presence of infection, antibiotic use, illness severity and co-morbidities; therefore, data about these variables were also recorded on the SEA-ICU Data Collection Form (see Appendix G).

**Retrospective Adaptations and the Final Statistical Analysis Plan**

Statistical analyses were performed using SPSS Version 23 (IBM Corp., 2014). Descriptive statistics were used to summarize recruitment data, such as screening, eligibility, consent and refusal rates to examine feasibility. Descriptive statistics were also used to summarize participants’ demographic data.

Two retrospective adaptations were made to the original statistical analysis plan prior to unblinding. First, a chi-squared test was run to compare eligibility rates before and after November 5, 2015 to address the feasibility question: “Did the change in the exclusion criteria that was enacted on November 5, 2015 have an effect on the eligibility rate?” Second, the initial statistical analysis plans to test hypotheses two to six could not be conducted because of low enrolment. Instead, these clinical data are presented in a case series report with descriptive statistics. Additionally, post-hoc exploratory statistical analysis was conducted after unblinding and a review of the summary statistics of the case series report to examine relationships between heart rate, blood pressure, temperature, and fever burden. Simple linear regression was used to test the relationships between net change in fever burden and mean difference in MAP, as well as net change in mean temperature and mean difference in heart rate.
Data Management

All data collected were manually entered from the SEA-ICU Data Collection Form into SPSS-23. A key file and log was maintained as participants were assigned a randomly generated identification number upon enrolment. All data were managed in compliance with local research ethics board regulations.

Summary

This study addressed four questions: (a) what is the feasibility of this study design to address the second and third research questions, (b) what are the hemodynamic effects of acetaminophen in the febrile ICU population, (c) what is the antipyretic efficacy of acetaminophen in this population, and (d) what are the relationships between heart rate, blood pressure, temperature and fever burden? Due to low enrolment, several changes were made. Concurrent changes were the changes to the exclusion criteria made in response to the very low enrolment. Retrospective changes, prior to unblinding, included two changes to the statistical plan: aborting the original statistical analysis plans to test the hypotheses related to the hemodynamic and antipyretic effects of acetaminophen because of the small sample size; and statistically testing if the change in exclusion criteria had an effect on the eligibility rate. Post-hoc exploratory statistical analysis was conducted after unblinding to examine the relationships between the temperature and the hemodynamic vital sign data.
Chapter 4: Results

Participants were enrolled between May 28, 2015 and January 20, 2016. No safety events occurred; therefore none of the preplanned stopping rules for safety monitoring were enacted. Changes to the exclusion criteria were made in response to the very low enrolment by the time of the interim analysis. Two changes to the statistical plan were made prior to unblinding. First, one additional hypothesis was added retrospectively, to examine if the change in the eligibility criteria had an effect on eligibility rate. Second, because the final sample size was too small to conduct the planned statistical tests addressing the second and third research question, a fourth question was added; these results were presented as a case series report. Finally, after unblinding, post-hoc exploratory analysis was done to examine the relationships between core temperature, fever burden, blood pressure, and heart rate.

Feasibility

This pilot study failed to enrol the targeted number of participants (62) to justify conducting the planned statistical tests. Hence feasibility was made the primary objective to better inform future investigations into these clinical questions. Feasibility was examined based on a framework that defines four components: “research processes, resource utilization, data management, and scientific factors” (Charlesworth, Burnell, Hoe, Orrell, & Russell, 2013, p. 1; see also Thabane et al., 2010).

Research Processes

The research process incorporates several sub-process. The screening, recruitment, consent, and data collection processes are examined next.
**Screening process.** Just over 83% (790/950) of all patients admitted to the ICU during the enrolment period were screened for eligibility. The majority of patients (n = 790) were screened only once; however, several patients were screened a second (n = 50) or third (n = 8) time if it appeared their status had changed enough to warrant rescreening. A total of 160 patients were missed; this occurred when patients were admitted and discharged when the research team or research coordinator was away. Week 1 had the highest number of patients screened (n = 52) because all ICU patients were new to this study. Conversely no patients were screened in Week 31 because the research team was away over the Christmas holiday season. If these two outliers (Weeks 1 and 31) were omitted, then the number of patients screened each week ranged from 10 to 42 (mean 24.8; standard deviation [SD] 7.7) patients. Weeks with the lowest number of patients screened (Weeks 9, 13, 14, and 30) coincided with absences of the research team and/or the research coordinator (see Figure 4).

*Figure 4. Total number of patients screened and eligible by week.*

*Note.* Week 1 begins on May 28, 2015. No screening occurred on Week 31 (December 24 to 30, 2015) for Christmas Holidays.
New patients were easy to identify by consulting with the ICU team in the morning or reviewing the unit census list. Depending on the number of new admissions, the longest time spent on screening was 30 minutes. This usually occurred on Mondays in order to capture all new patients admitted from Friday afternoon until Monday morning. Longer screening time also occurred after prolonged breaks (due to holidays or illness) to capture new patients from multiple days. On following days (i.e., Tuesday to Friday), screening took between 10 to 15 minutes.

The ICU staff education provided prior to beginning this study and the patient information pamphlet were facilitators to the screening process. The patient information pamphlet (see Appendix D) was, by far, more often utilized by the ICU team to inform themselves about the study than it was by the patients and families it was originally intended for. As a result of these two strategies, the ICU staff were familiar with the study protocol, therefore they routinely and accurately identified new patients who were potentially eligible for this study.

**Recruitment process.** Of the 848 screenings that occurred in this 9-month period, 11.8% \((n = 100)\) were found to be eligible. If the outlier weeks (i.e., Weeks 1 and 31) were excluded, then, a median of two patients, with a range of zero to seven patients, met the eligibility criteria each week. A complete list of the reasons patients were excluded is summarized in Table 5; on occasion patients met multiple criteria for exclusion. The six most common reasons for exclusion were acute brain injury \((n = 148)\), requiring regular non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen \((n = 143)\), not remaining in the ICU for the entire study period \((n = 132)\), liver dysfunction \((n = 99)\), no
arterial line \( (n = 98) \), and extracorporeal blood treatments such as continuous renal replacement therapy \( (n = 94) \).

Table 5

**Reasons Patients Were Excluded**

<table>
<thead>
<tr>
<th>Criteria for Exclusion</th>
<th>No. of Cases</th>
<th>Percentage of Total Screened ( (n = 848) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute neurologic injury</td>
<td>148</td>
<td>17.4%</td>
</tr>
<tr>
<td>Requiring NSAIDS or regular acetaminophen</td>
<td>143</td>
<td>16.7%</td>
</tr>
<tr>
<td>Not remaining in the ICU for the study period</td>
<td>132</td>
<td>15.6%</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>99</td>
<td>11.7%</td>
</tr>
<tr>
<td>No arterial line</td>
<td>98</td>
<td>11.6%</td>
</tr>
<tr>
<td>Extracorporeal blood treatments</td>
<td>94</td>
<td>11.1%</td>
</tr>
<tr>
<td>Gut malabsorption</td>
<td>73</td>
<td>8.6%</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>49</td>
<td>5.8%</td>
</tr>
<tr>
<td>Acute burn injury</td>
<td>18</td>
<td>2.1%</td>
</tr>
<tr>
<td>Cannot tolerate temperature monitoring</td>
<td>16</td>
<td>1.9%</td>
</tr>
<tr>
<td>Acute cardiac injury or dysfunction</td>
<td>15</td>
<td>1.8%</td>
</tr>
<tr>
<td>Receiving external cooling</td>
<td>14</td>
<td>1.7%</td>
</tr>
<tr>
<td>Severe hypoxemia</td>
<td>11</td>
<td>1.3%</td>
</tr>
<tr>
<td>Physician opposed</td>
<td>10</td>
<td>1.2%</td>
</tr>
<tr>
<td>Temperature greater than 40 °C</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>Does not have potential for fever</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hemodynamically unstable</td>
<td>1</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

*Note.* NSAIDS = non-steroidal anti-inflammatory drugs; ICU = intensive care unit.

**Effect of the change in the exclusion criteria.** Two criteria were changed with the intent to increase recruitment without compromising patient safety or the scientific integrity of the study: (a) acetaminophen no longer had to be discontinued upon enrolment, but rather could be given as needed to control pain and (b) patients could still be enrolled if they were not being fed via the gastric track as long as oral medications were still permitted. These changes were implemented on November 5, 2015.
The chi-squared test for independence was used to test if this change had an effect on the eligibility rate. Before November 5th, 61 out of the 608 patients screened (10.0\%) were eligible for this study. After November 5th, the eligibility rate increased to 16.3\% (39/240). Changing the eligibility criteria resulted in a statistically significant increase in the eligibility rate, $\chi^2 (1, n = 848) = 5.810, p = 0.016$, phi = 0.87.

**Consent process.** Due to the dependency on mechanical ventilation and high incidence of delirium in the ICU population, both of which impair communication with patients, the research team was unable to obtain consent directly from patients. This was not unexpected, but as a result, the research team relied on the patients’ substitute decision makers (100\% whom were family members), to engage in the consent process. However, of the 100 patients who were eligible, the research team was unable to contact 73 substitute decision makers. Once a contact was made with a substitute decision maker, the process of obtaining consent took 12 or more hours. Of the patients and families who were invited to participate in this study, 63\% (17/27) refused to participate.

Many family members did not always visit during business hours. Also, 44.4\% of all patients who were admitted to the ICU during the study period, lived outside the Lower Mainland because VGH ICU is a provincial center for many critical care services. This potentially created an additional challenge for some family members to be present during the times the research coordinator was available to invite patients and families to participate in this study. The research team attempted to use telephone consent in order to overcome this barrier; however, it was often not successful because telephone contact could only be made if families consented to this in advance. The Recruitment Sheet, which was placed in every eligible patient’s chart, informed ICU clinicians to ask and
document if the family consented to telephone contact. Additionally, the research team routinely reminded the ICU RN to ask families for permission. Despite these efforts, the ICU RN team frequently did not ask or document consent for telephone contact when families called in. Reasons stated included, the ICU RN responsible for caring for the patient was not the RN who answered the call from family, or the ICU RN forgot to request permission for telephone contact when they engaged in information exchanges with family members.

Another barrier to recruitment was that ICU patients’ clinical status, and therefore their eligibility status changed quickly. For example, the median length of stay at VGH ICU between May 2015 and January 2016 was 4.45 days ($N = 950$, quartile 1 = 2.23, quartile 3 = 9.29, interquartile range = 7.05). The median number of days a patient required mechanical ventilation was 3.25 days ($N = 950$, quartile 1 = 1.28, quartile 3 = 7.43, interquartile range = 6.14) which means half of all patients admitted to the unit were close to discharge within 78 hours. As a result many patients were close to discharge, and therefore ineligible, before contact could be made with the substitute decision makers.

When contact was made, 63% of substitute decision makers refused to participate in the study. While families were informed that they were not required to provide a reason for their refusal, most did spontaneously. Their responses fell into three categories: overwhelming fear and stress, not wanting to put the patient at any additional risk during a critical illness, or not wanting a temperature probe inserted.

**Data collection process.** It took a minimum of 9 hours per participant to complete baseline data collection, pre-post intervention data collection, and follow-up
data collection. Baseline data included both research audit information (i.e., consenting
details) as well as demographic data and took approximately 30 minutes to collect.
However, since there were so few participants enrolled, the researcher collected this
information directly from the participants’ chart. Three participants (#3, #4, and #6)
progressed to the intervention stage on the same day they were enrolled; therefore both
the baseline and pre-post intervention data were collected at one time. Collecting the pre-
post intervention data was the most time-consuming as it included the pre-intervention
safety check, calibration of measurement tools, 2 hours of pre-intervention data,
coordination of the intervention, followed by 6 hours of post-intervention data. While the
researcher was not present for the entire 8 hours of the study period, the researcher was
required to be present to coordinate the data collection and intervention for 1 to 2 hours
prior to the intervention, and to return 6 hours after the intervention to download the data.

The initial plan was to digitally download vital sign data electronically from the
patient monitors and use print-outs of vital sign data as a backup record. This was not
feasible because of issues with the Datex-Ohmeda S/5™ Collect (2003) software,
therefore only paper print-outs of vital sign data were captured. Finally, follow-up data
were collected the next day and it took 20 minutes to complete.

**Resource Utilization**

The cost of recruiting six participants who completed the study over 9 months
was $22,200.00 (see Table 6). This was inadequate to achieve the recruitment goals of
this study.
Table 6

*Financial Summary for the SEA-ICU Study*

<table>
<thead>
<tr>
<th>Items</th>
<th>Proposed Budget</th>
<th>Actual Expenditures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grant</td>
<td>In Kind</td>
</tr>
<tr>
<td><strong>Personnel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Release Time (Principal Investigator)</td>
<td>$11,100.00</td>
<td>-</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td>$5,750.00</td>
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<tr>
<td>Statistical Consulting</td>
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<tr>
<td>Pharmacy Dispensing Costs</td>
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<td>$1,344.00</td>
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<tr>
<td><strong>Materials &amp; Supplies</strong></td>
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</tr>
<tr>
<td>Miscellaneous Office Supplies</td>
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<td>$350.00</td>
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<tr>
<td><strong>Research Equipment</strong></td>
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<td></td>
</tr>
<tr>
<td>Disposable Temp. Probe &amp; Supplies</td>
<td>-</td>
<td>$793.00</td>
</tr>
<tr>
<td>Temp. Connecting Cables</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GE Healthcare Serial Cable &amp; Adaptor</td>
<td>$127.60</td>
<td>-</td>
</tr>
<tr>
<td>GE Healthcare iCollect Software</td>
<td>$744.80</td>
<td>-</td>
</tr>
<tr>
<td>Pharmacy Compounding</td>
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<td>-</td>
</tr>
<tr>
<td><strong>Communication &amp; Publication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posters &amp; knowledge translation materials</td>
<td>$750.00</td>
<td>-</td>
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<tr>
<td><strong>Total</strong></td>
<td>$22,200.62</td>
<td>$2,487.00</td>
</tr>
</tbody>
</table>

**Data Management**

There were several challenges related to digitally capturing vital sign data that interfered with ensuring data accuracy and completeness. This was due to unanticipated problems with downloading of digital vital sign data. The monitors in the ICU had recently been upgraded to allow for the capture of digital vital sign data, primarily to
support research activities. While the current system stores up to 72 hours of data, the current system does not allow for data to be digitally downloaded retrospectively. Digital vital sign data could only be captured by slaving a computer loaded with the Datex-Ohmeda S/5™ Collect (2003) software to the patient monitors and recording it prospectively. There were several issues with this software that made capturing digital data unreliable: the only way to verify if a digital recording was being captured was by stopping the recording and checking the data; and if any cables were disturbed, or the file became too large the recording would stop without issuing alerts. As a result, the only reliable method to capture vital sign data was to retrospectively print it and manually enter the data into a spreadsheet.

The issues with the software also compromised data completeness, because it meant there was no back up for capturing vital sign data. On one occasion, some vital sign data was inadvertently lost for the participant in the placebo group (Participant #1). This participant was moved from one area to another shortly after the beginning of the post-intervention period and the electronic vital sign data were unintentionally deleted. Thus, for Participant #1, vital sign data were recorded every 5 minutes for the first 35 minutes of the pre-intervention period, and then only captured retrospectively from the participant’s chart at 60 minutes intervals thereafter.

**Scientific Factors**

Assessment of scientific factors included the safety of the study, the accuracy and reliability of measurements, and the clinical relevance of the outcome measures. There were no participant safety concerns associated with use of the measurement tools,
intervention procedures, very high fever or hemodynamic instability identified in this study. Also, there were no safety issues with the administration of the study drug.

Blood pressure measurement was reliable and accurate. In all six cases, arterial lines were levelled, calibrated and checked for accuracy as per standard procedures. In all six cases, the arterial line had a satisfactory square test, overall function was evaluated as good or very good and there was agreement, on average, within 13 mmHg for systolic blood pressure (SBP) and diastolic blood pressure (DBP); and within 5 mmHg for mean arterial pressure (MAP) between the blood pressure readings obtained from the arterial line and non-invasive cuff pressures.

Temperature measurement required more attention the other hemodynamic measures but also provided reliable and accurate data. Temperature probes had to be inserted in nine of the ten participants who were enrolled. Only one participant (#6) had a preexisting urinary catheter temperature probe prior to enrolment. Either a member of the research team, or the ICU RN inserted or replaced the temperature probe as needed for ongoing monitoring. If the temperature probe was in for multiple days, it had a tendency to slip out because, even though it was taped to the endotracheal tube, the adhesive loosened over time with exposure to oral secretions. In one case (Participant #4), 40 minutes of temperature data were lost during the pre-intervention period because the esophageal probe had become dislodged. The one urinary catheter temperature probe used in this study never became dislodged.

In regards to the clinical relevance of outcome measures, most outcome measures (i.e., heart rate, temperature, SBP, DBP and MAP) are recognized as clinically meaningful vital signs that are commonly monitored continuously in the ICU setting.
Similarly these vital signs are also meaningful and frequently used in clinical research. There were two somewhat novel outcome measures used in this study: the number of clinically significant hypotensive events and fever burden. While no participant experienced a clinically significant hypotensive event, both heart rate and blood pressure were highly variable (see Figures 6 to 11). In one case (Participant #1), the ICU team frequently titrated the norepinephrine from 0 to 7 mcg/min, on the intervention day in response to changes in blood pressure. Participant #1 did not meet the criteria for clinically relevant hypotension (i.e., increase by at least 5 mcg per minute of norepinephrine) because he began the post-intervention period on 3 mcg per minute of norepinephrine infusion, which was titrated up to a maximum of 7 mcg per minute and then titrated off over remainder of the post-intervention period.

Core body temperature was also variable both between and within participants (see Figures 6 to 11). In light of this variability, other methods to quantify fever that have been used in previous studies such as peak temperature, maximum change from baseline temperature and percentage change in temperature would not have been able to fully account for this fluctuating temperature pattern. Therefore, the AUC method, to measure fever burden, was both reliable and accurate when the data were available.

**Case Series Report**

As too few participants were enrolled to justify conducting the planned statistical tests, the data are presented as a case series. This includes participant demographics, data pertaining to AAH and fever burden. All analyses were completed before the researcher was unblinded to participant allocation. Unblinding occurred on September 13, 2016, in the presence of Dr. Leanne Currie.
Sample and participant demographics. Of the ten participants enrolled in this study, four did not experience a fever while in the ICU therefore were never randomized. Only Participant #1 was randomized to the placebo arm and the other five participants were randomized into the acetaminophen arm (see Figure 5). All six participants who were randomized completed the study; however some 5-minute vital sign data were missing (i.e., only recorded hourly) for the one participant who was assigned to the placebo intervention, because of a technical failure.

Participants included four men, and two women, and their ages ranged from 29 to 76. Three participants (#2, #3, and #6) were classified as medical ICU patients and three were classified as surgical ICU patients. Participants’ acute physiology and chronic health II (APACHE II) score ranged between 16 and 30. Sequential organ failure assessment (SOFA) scores were recorded for the first five days of in the ICU and on the day of intervention (see Table 7). Half of the participants (#1, #2, and #3) required some hemodynamic support (i.e., norepinephrine) on the day of intervention; however, of those, only two were receiving hemodynamic support during the study period (#1 and #2). All except one participant (#6) were mechanically ventilated. Total fluid balance for the participants on the day of intervention ranged from -1882 ml to +2416 ml.
Figure 5. PRISMA flow diagram of recruitment results.
Table 7

**Participant Clinical and Demographic Profiles**

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Placebo</th>
<th>Acetaminophen Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participant</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172</td>
<td>168</td>
</tr>
<tr>
<td>Pre-Hospital Weight (kg)</td>
<td>102</td>
<td>115</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>34.5</td>
<td>40.7</td>
</tr>
<tr>
<td>Admitting Diagnosis</td>
<td>thoracic surgery &amp; hypoxic respiratory failure</td>
<td>cardiogenic shock</td>
</tr>
<tr>
<td>ICU Admission Classification</td>
<td>surgical</td>
<td>medical</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>SOFA Score – Day 1</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>SOFA Score – Day 2</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>SOFA Score – Day 3</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>SOFA Score – Day 4</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>SOFA Score – Day 5</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>ICU DOI</td>
<td>4th Day</td>
<td>5th Day</td>
</tr>
<tr>
<td>DOI – SOFA</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>DOI – Mechanical Ventilation (Y/N)</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DOI – Hemodynamic Support (Y/N)</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>DOI – Fluid Balance (ml)</td>
<td>+2416</td>
<td>-1882</td>
</tr>
</tbody>
</table>

**Note.** APACHE II = acute physiology and chronic health evaluation score – version II; F = female; ICU = Intensive Care Unit; M = male; N = no; SOFA = sequential organ failure assessment; DOI = day of intervention; Y = yes.

**Acetaminophen-associated hypotension.** Acetaminophen-associated hypotension (AAH) was identified using two strategies: comparing counts of clinically
significant hypotensive events and comparing vital sign data. Pre-post comparisons of fluid status and doses of vasoactive drugs are presented in Table 8. Pre-post comparisons of summary vital sign data are presented in Table 9.

No clinically significant hypotensive events were recorded for any participants (see Table 8). No participants received colloid fluids in the pre- or post-intervention period, therefore the conversion equation for equi-volume fluid was not required. Only two participants received any vasoactive infusions during the study period. Participant #1 was on low-dose norepinephrine infusion (6 mcg/min) at the beginning of the pre-intervention period and it was titrated between 0 to 7 mcg/min in response to blood pressure variability for the remainder of the data collection period. Participant #2 was on milrinone at 0.5 mcg/kg/min, which was decreased to 0.25 mcg/kg/min after the first hour in the pre-intervention period and remained at that rate for the remainder of the data collection period. No conversions were made to determine the equi-dose of milrinone because a suitable formula was not found in the literature and planned statistical tests were not conducted.
Table 8

**Acetaminophen-Associated Hypotension: Clinically Significant Hypotension**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant ID Number</td>
<td>1</td>
<td>2 3 4 5 6</td>
</tr>
<tr>
<td>Clinically Significant Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Period (2 hours)</td>
<td>--</td>
<td>-- -- -- -- --</td>
</tr>
<tr>
<td>Post Intervention Period (4 hours)</td>
<td>--</td>
<td>-- -- -- -- --</td>
</tr>
<tr>
<td>Total Fluid intake (ml)†</td>
<td>235</td>
<td>736 308 30 183 232</td>
</tr>
<tr>
<td>Pre-Intervention Period (2 hours)</td>
<td>734</td>
<td>856 682 460 707 353</td>
</tr>
<tr>
<td>Post Intervention Period (4 hours)</td>
<td>245</td>
<td>1400 952 775 230 905</td>
</tr>
<tr>
<td>Total Fluid output (ml)‡‡</td>
<td>80</td>
<td>790 218 475 140 225</td>
</tr>
<tr>
<td>Pre-Intervention Period (2 hours)</td>
<td>245</td>
<td>1400 952 775 230 905</td>
</tr>
<tr>
<td>Post Intervention Period (4 hours)</td>
<td>245</td>
<td>1400 952 775 230 905</td>
</tr>
<tr>
<td>Fluid Balance</td>
<td>+ 155</td>
<td>- 54 + 90 - 445 + 43 + 7</td>
</tr>
<tr>
<td>Pre-Intervention Period (2 hours)</td>
<td>+ 489</td>
<td>- 544 - 270 - 315 + 477 - 552</td>
</tr>
<tr>
<td>Post Intervention Period (4 hours)</td>
<td>+ 489</td>
<td>- 544 - 270 - 315 + 477 - 552</td>
</tr>
<tr>
<td>Total dose of vasoactive drugs</td>
<td>Norepinephrine 167 mcg Milrinone 6000 mcg</td>
<td>Norepinephrine 576 mcg Milrinone 7000 mcg</td>
</tr>
<tr>
<td>Pre-Intervention Period (2 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Intervention Period (4 hours)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. ID = identification; -- = none; † this is total oral and crystalloid intravenous fluid intake as no participant received colloid fluid in the post-intervention period; ‡‡ this was primarily losses due to urine output. No changes to the mechanical ventilation settings were made in the pre or post intervention period for any participant.*

The analysis for the only participant in the placebo group (#1) was further limited by the loss of vital sign data (see Figure 6). For this participant, statistical description
was done with the available data. In the pre-intervention period, vital signs were recorded every 5 minutes for the first 35 minutes, then hourly. In the post-intervention period vital signs were recorded every 5 minutes for the first 40 minutes, then hourly thereafter.

There was no evident pattern in the pre- or post-intervention vital sign data in the six participants (see Figures 6 to 11). These data are presented in Table 9 to allow for a case-by-case comparison of the pre-post data. All six participants had less than 10 units of variability in the average pre-post data for heart rate. Three participants (#3, #4 and #6) in the intervention group had a greater than 10% change in SBP, MAP and DBP. Participant #3’s had a 16.3% increase in SBP (117.5 to 136.6 mmHg), 13.9% increase in MAP (66.0 to 75.2 mmHg) and a 15.4% increase in DBP (82.5 to 95.2 mmHg) after the intervention. Alternately, Participants #4 and #6 had a greater than 10% decrease in SBP, DBP and MAP. Participant #4’s had a 13.0% decrease in SBP (140.3 to 122.1 mmHg) and MAP (67.7 to 58.9 mmHg); and a 14.0% decrease in DBP (89.9 to 77.3 mmHg) after the intervention. Similarly, Participant #5 had a 14.3% decrease in SBP (155.5 to 133.3 mmHg), 11.0% decrease in MAP (82.5 to 73.5 mmHg) and 12.1% decrease in DBP (105.0 to 92.3 mmHg) after the intervention. Despite these decreases in blood pressure, neither Participants #4 nor #6 required vasoactive infusions on the day of the intervention.
Table 9

*Change in Vital Signs Pre- and Post-Intervention*

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Placebo</th>
<th>Acetaminophen Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>HR in beats/min, mean (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Period (2h)</td>
<td>95.5 (91–100)</td>
<td>88.5 (84–96)</td>
</tr>
<tr>
<td>Post Intervention Period (4h)</td>
<td>87.0 (84–90)</td>
<td>86.5 (80–94)</td>
</tr>
<tr>
<td><strong>Mean Difference</strong></td>
<td>-8.5</td>
<td>-2</td>
</tr>
<tr>
<td><strong>Percentage Change</strong></td>
<td>-8.9%</td>
<td>-2.2%</td>
</tr>
<tr>
<td><strong>SBP in mmHg, mean (range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Period (2h)</td>
<td>141.6 (102–159)</td>
<td>107.3 (99–115)</td>
</tr>
<tr>
<td>Post Intervention Period (4h)</td>
<td>141.5 (127–157)</td>
<td>109.8 (98–121)</td>
</tr>
<tr>
<td><strong>Mean Difference</strong></td>
<td>-0.1</td>
<td>+2.5</td>
</tr>
<tr>
<td><strong>Percentage Change</strong></td>
<td>-0.1%</td>
<td>+2.3%</td>
</tr>
<tr>
<td>Participant ID</td>
<td>Placebo Group</td>
<td>Acetaminophen Group</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>1 1</td>
<td>2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>DBP in mmHg, mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Period (2h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>57.4 (46–63)</td>
<td>60.1 (55–67)</td>
<td>66.0 (62–70)</td>
</tr>
<tr>
<td>Post Intervention Period (4h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51.0 (47–55)</td>
<td>58.2 (50–68)</td>
<td>75.2 (70–80)</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>-6.4</td>
<td>-1.9</td>
</tr>
<tr>
<td>Percentage Change</td>
<td>-11.1%</td>
<td>-3.2%</td>
</tr>
<tr>
<td>MAP in mmHg, mean (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Period (2h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80.8 (61–90)</td>
<td>73.5 (67–81)</td>
<td>82.5 (77–88)</td>
</tr>
<tr>
<td>Post Intervention Period (4h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75.5 (68–83)</td>
<td>71.7 (63–87)</td>
<td>95.2 (88–101)</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>-5.3</td>
<td>-1.8</td>
</tr>
<tr>
<td>Percentage Change</td>
<td>-6.6%</td>
<td>-2.4%</td>
</tr>
</tbody>
</table>

Note. ID = identification; h = hours; HR = heart rate; MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; § the low value of 63 may have been due to measurement error as it only occurred once, no treatment was implemented, and the next lowest reading was 80;  □ vital sign data lost, reduced from every 5 minutes to every 60 minutes due to a technical failure.
Figure 6. Vital signs by hour for Participant 1 (Placebo Group).

**Note.** BP = Blood pressure; MAP = mean arterial pressure; fever burden (shaded area) is defined as the area between recorded temperatures above 37.7 °C and the threshold of 37.7 °C; missing vital sign data: vital signs were only recorded every 5 minutes for the first 35 minutes in the pre intervention period and then hourly after that.
Figure 7. Vital signs by hour for Participant 2 (Acetaminophen Group).

Note. BP = Blood pressure; MAP = mean arterial pressure; fever burden (shaded area) is defined as the area between recorded temperatures above 37.7 °C and the threshold of 37.7 °C.
Figure 8. Vital signs by hour for Participant 3 (Acetaminophen Group).

Note. BP = Blood pressure; MAP = mean arterial pressure; fever burden (shaded area) is defined as the area between recorded temperatures above 37.7 °C and the threshold of 37.7 °C.
Figure 9. Vital signs by hour for Participant 4 (Acetaminophen Group).

Note. BP = Blood pressure; MAP = mean arterial pressure; fever burden (shaded area) is defined as the area between recorded temperatures above 37.7 °C and the threshold of 37.7 °C, lost temperature data in the last 40 minutes of the pre-intervention period.
Figure 10. Vital signs by hour for Participant 5 (Acetaminophen Group).

Note. BP = Blood pressure; MAP = mean arterial pressure; fever burden (shaded area) is defined as the area between recorded temperatures above 37.7 °C and the threshold of 37.7 °C.
Figure 11. Vital signs by hour for Participant 6 (Acetaminophen Group).

Note. BP = Blood pressure; MAP = mean arterial pressure; fever burden (shaded area) is defined as the area between recorded temperatures above 37.7 °C and the threshold of 37.7 °C.
**Fever burden.** During the pre-intervention period, the only participant (#1) in the placebo group also had the lowest average temperature (38.16 °C) and fever burden (AUC$_{0-2h}$ = 0.49 °C-hr) of the entire sample. During the post-intervention period, this participant continued to have the lowest average temperature (37.38 °C) and fever burden (AUC$_{0-6h}$ = 0.74 °C-hr) of all six participants. If the fever burden were unchanged, the AUC$_{0-6h}$ value would be expected to be three times larger than the AUC$_{0-2h}$ because fever burden was calculated for a greater length of time (i.e., 6 hours for AUC$_{0-6h}$ and 2 hours for AUC$_{0-2h}$). The fever burden would therefore be considered reduced in the post-intervention period (i.e., AUC$_{0-6h}$) if it is less than triple the value of the pre-intervention fever burden (AUC$_{0-2h}$).

Overall, fever patterns varied between participants in the intervention group. In the pre-intervention period, average core temperatures ranged from 38.23 °C (Participant #2) to 39.59 °C (Participant #6). Similarly Participant #2 had the lowest pre-intervention fever burden (AUC$_{0-2h}$ = 1.07 °C-hr) and Participant #6 had the highest pre-intervention fever burden (AUC$_{0-2h}$ = 1.89 °C-hr). This changed in the post-intervention period as Participant #4 had the lowest average temperature (37.69 °C) and fever burden (AUC$_{0-6h}$ = 1.60 °C-hr) while Participant #5 had the highest average temperature (39.41 °C) and fever burden (AUC$_{0-6h}$ = 10.24 °C-hr). Even the range of body temperatures varied between participants. In the post-intervention period, Participant #2 had the narrowest range of 0.6 °C while Participant #4 had the widest range of 2.6 °C in that same period (see Table 10).
Table 10

**Temperature and Fever Burden**

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Placebo</th>
<th>Acetaminophen Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participant</td>
<td>1</td>
</tr>
<tr>
<td>Temperature in °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Intervention Period (2 hours)</td>
<td>Mean</td>
<td>38.16 °C</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>38.16 °C</td>
</tr>
<tr>
<td></td>
<td>(Min-Max)</td>
<td>(37.9-38.6 °C)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.9 °C</td>
</tr>
<tr>
<td>Post-Intervention Period (6 hours)</td>
<td>Mean</td>
<td>37.38 °C</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>37.28 °C</td>
</tr>
<tr>
<td></td>
<td>(Min-Max)</td>
<td>(36.8-38.2)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1.4 °C</td>
</tr>
<tr>
<td>Net change(^1) in mean temperature</td>
<td>-0.78 °C</td>
<td>-0.03 °C</td>
</tr>
<tr>
<td>Fever Burden in °C-hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Fever Burden Pre (2 hours)*</td>
<td>0.97 °C-hr</td>
<td>1.07 °C-hr</td>
</tr>
<tr>
<td>Total Fever Burden Post (6 hours)**</td>
<td>0.74 °C-hr</td>
<td>3.01 °C-hr</td>
</tr>
<tr>
<td>Net change(^2) in Fever Burden</td>
<td>-2.17 °C-hr</td>
<td>-0.20 °C-hr</td>
</tr>
</tbody>
</table>

*Note.* *AUC\(_{0-2h}\) = area under the curve for 2 hours in the pre-intervention period; **AUC\(_{0-6h}\) = area under the curve for 6 hours in the post-intervention period; AUC was calculated by equation 3.1; hourly average AUC was determined by dividing AUC\(_{0-2h}\) by 2 or AUC\(_{0-6h}\) by 6; hourly average AUC was provided to allow for meaningful comparisons between the pre and post-intervention AUC values; net change\(^1\) refers to the net difference in measurement in the pre and post-intervention period for each participant; Net change\(^2\) in fever burden is calculated with the formula: Net change\(^2\) = AUC\(_{0-6h}\) − 3(AUC\(_{0-2h}\)) to account for the difference in time between the pre and post intervention period (i.e., 2 hours vs. 6 hours).
Table 11

*Net Changes in Temperature & Fever Burden and mean differences in HR & MAP*

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Placebo Participant</th>
<th>Acetaminophen Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Net change in mean temperature</td>
<td>-0.78 °C</td>
<td>-0.03 °C</td>
</tr>
<tr>
<td>Net change in Fever Burden (in °C-hr)</td>
<td>-2.17</td>
<td>-0.20</td>
</tr>
<tr>
<td>Mean Difference in Heart Rate (in beats per minute)</td>
<td>-8.5</td>
<td>-2.0</td>
</tr>
<tr>
<td>Mean Difference in MAP (in mmHg)</td>
<td>-5.3</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

Participants also experienced variations between the pre and post intervention period irrespective of which group they had been assigned to (see Figures 6 to 11). Net change in average temperature between the pre to post-intervention period ranged from a -1.20 °C to +0.78 °C increase. Similarly, net change in fever burden ranged from -6.10 °C-hr to +4.42 °C-hr from baseline.

One pattern emerged: when the net change in fever burden and average temperature was positive, net change in average MAP and heart rate was also positive (see Table 11). Conversely, if the net change in fever burden and average temperature is negative, so was net change in average MAP and average heart rate. This relationship was more apparent when the data are plotted on a scatter plot (see Figure 12). A simple linear regression was calculated to predict mean difference in MAP based on net change in fever burden. A statistically significant regression equation was found (F(1, 4) = 38.376, p = 0.003) with an $R^2$ of 0.906. Participants' mean difference in MAP is equal to 2.200(fever burden) mmHg when fever burden is measured in °C-hours. The
participants’ mean difference in MAP increased by 2.20 mmHg for every 1 °C-hour net change in fever burden (95% CI [1.214, 3.186]). The relationship between mean difference in heart rate based on net change mean temperature was similar. Again, a statistically significant regression equation was found (F(1, 4) = 38.179, p = 0.003) with an $R^2$ of 0.905. Participants’ mean difference in heart rate is equal to $-3.212 + 4.840$ (mean difference in temperature) in beats per minute when mean difference in temperature is measured in °C. The participants’ mean difference in heart rate increased by 4.840 beats per minute for every 1 °C increase in mean temperature (95% CI [2.665, 7.014]).
Figure 12. The relationships between fever and hemodynamic status (vital signs).

Note. FB = fever burden; MAP = mean arterial pressure.
Summary

In 9 months, 848 patients were screened which accounted for 83% of all ICU admissions during this time period. While the screening strategies were effective in capturing most patients admitted to the ICU, recruitment remained an ongoing challenge. The strategy to broaden the enrolment criteria in the 6th month of this study did resulted in a statistically significant increase in the eligibility rate from 10.0% to 16.3% ($p = 0.016$). In total, 100 patients were eligible for this study; however, due to challenges in connecting with the family in a timely manner, the short amount of time most patients remained eligible for this study, and somewhat limited availability of the research team due to budget constraints, the research team was only able to invite 27 patients into this study. Of those, 17 (63%) refused to participate, 10 (37%) were enrolled and 6 of those (60%) completed the study. The randomization process could not achieve balanced groups because of the small sample size. There were other challenges, yet the blinding, intervention, measurement and data collection processes, as well as the management of the study were successful in achieving their respective objectives.

In regards to the scientific factors, there were no adverse events for any participant in this study and the outcome measures were found to be reliable and accurate. The sample size was too small to verify if the criteria for a clinically significant hypotensive event were effective in discerning between usual variability in blood pressure in critically ill patients and a notable event. Fever burden was found to be a useful way to quantify fever for research purposes because there were highly variable temperature patterns both between and within participants. Fever burden, unlike peak temperature, or maximum temperature change, is a more meaningful way to measure
fever because it accounts for both the measured temperature and the duration a participant experiences that temperature, allowing researchers to make better comparisons despite the variety of fever patterns participants may experience.

Of the six participants enrolled in the study, five received acetaminophen and one received a placebo, therefore making comparisons of outcomes difficult. No participant had a clinically significant hypotensive event. There was a great deal of variability in heart rate SBP, DBP, MAP, temperature and fever burden, both between and within participants, when comparing the pre- and post-intervention periods. While the sample size is too small, acetaminophen did not appear to have any discernable hemodynamic or antipyretic effects. Despite the small sample size, there was a strong positive correlation between mean difference in pre-post temperature and mean difference in pre-post heart rate \( (R^2 = 0.905) \) as well as a strong positive correlation between net change in fever burden and mean difference in MAP \( (R^2 = 0.906) \)
Chapter 5: Discussion

This pilot, double-blinded, randomized controlled trial (RCT) had three objectives: first, to examine the feasibility of conducting a larger study; second, to examine if a single dose of acetaminophen has a hemodynamic effect in the febrile, non-brain injured intensive care unit (ICU) population and third, to determine the antipyretic efficacy of acetaminophen in this population. This chapter provides a discussion of the feasibility results, the case series report results, the limitations of this study, as well as the implications for clinical practice, health policy and clinical research. Three aspects of feasibility are discussed: the discrepancies between the anticipated versus actual recruitment rates, the challenges with the consent process, and compared with previous related research. The discussion of the case series report will focus on the both the strengths and limitations of how both hemodynamic and antipyretic effects were measured because there are too few participants to draw conclusions about these effects of acetaminophen in febrile ICU population.

Overview of Feasibility

There was a large discrepancy from the anticipated eligibility (38.2%) and recruitment rate (45.4%) and the actual eligibility (11.8%) and recruitment rates (10.0%). This study failed to achieve its target recruitment goal of 62 participants because there were several barriers to the recruitment process. Of the 950 patients who were admitted to VGH ICU during the 9-month recruitment period, 83% were screened for eligibility to this study. A total of 100 patients were found to be eligible for this study but due to their critical illness, patients could not consent for themselves. Changes to the exclusion criteria implemented on November 5, 2015, resulted in a statistically significant increase
the eligibility rate from 10.0% (61/608) to 16.3% (39/240; \( p = 0.016 \)). However, only 27 substitute decision-makers were successfully contacted to invite the patient to participate in this study. Of these, 63% refused to participate. Finally, only six of the ten participants who were recruited to this study developed a fever and completed the study.

**Discrepancy between total patients admitted and total patients screened.** The discrepancy between the estimated number of patients who could be screened and the number of patients who were actually screened was due to the erroneous assumption that it would be possible to screen every admitted patient. The *a priori* prediction of total number of admitted patients was accurate. Based on a review of the ICU database from September 2011 to March 2012 there were 653 admitted patients or 109 per month. During the 9 months this study was enrolling patients, 950 patients (i.e., 106 per month) were admitted to the ICU; however, only 83% of those were screened. The *a priori* estimation did not take into account the short length of stay of a significant proportion of ICU patients (i.e., 25% have a length of stay of less than 2.3 days) or the missed opportunities due to limitations in research staff coverage.

**Discrepancies between estimated and actual eligibility rate.** The limitation of using exclusively retrospective data extracted from the ICU database resulted in a three-fold overestimation in eligibility rate. The estimated eligibility rate was 38.2% (250/653) but the actual overall eligibility rate was 11.8%. The ICU database has a record of basic demographics, admitting diagnoses, acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores. This provided information about liver function and fever status, but only for the first few days. What the database did not account for were secondary diagnoses, medications, nutritional status
or need for dialysis, all of which could be reasons for exclusion that were not captured in the \textit{a priori} estimation.

One method to improve the eligibility estimation would have been to augment the retrospective data with prospective data. For example, the researcher could have piloted the exclusion criteria for four randomly selected days in a 2-week period. At the 34-bed unit at VGH ICU, this could have resulted in 90 to 120 patients screened which is a sufficiently sized sample to identify the degree of over-estimation that was made in the \textit{a priori} estimation of eligibility rate for this study.

There is an advantage to having broad eligibility criteria and evaluating barriers to recruitment as early as possible. The adaptive design of this pilot RCT permitted changes to the exclusion criteria, which were implemented in the 6th month of this study. While this did significantly increase the eligibility rate from 10.0\% to 16.3\%, had those changes been identified earlier, the number of eligible patients would potentially have increased from 100 to 138. Pre-testing the screening process, and conducting an interim analysis earlier could have increased the overall eligibility rate. Waiting until the midpoint of the study to examine exclusion criteria resulted in a missed opportunity to optimize recruitment earlier.

\textbf{Missed opportunities to invite patients to participate.} The fact that the research coordinator was available only during business hours was one barrier to making contact with substitute decision makers. There were a number of factors that limited the ability of the patient’s family to be present in the ICU during the times the research coordinator was available to invite participants into this study. Many family members held occupations that required them to be at work during business hours, and 44.4\% of ICU
patients did not live locally. While the research team did attempt to address this challenge with the use of telephone consent, it was found to be ineffective at overcoming this barrier.

Another barrier to recruitment was the rapidly changing nature of an ICU patient’s clinical status. Half of all admitted patients were close to discharge by the third day, and therefore no longer eligible for this study. This becomes more significant when considering that there were delays in identifying patients. For example, if the patient was admitted over the weekend, screening had been delayed for one to three days. Add to this, the time substitute decision makers needed to make a decision and the variable nature of an ICU patient’s clinical status becomes a significant barrier to recruitment.

Nearly three-quarters of eligible patients were never invited to participate in this study because of the unique challenges of conducting clinical research in the ICU setting. The barriers encountered to inviting eligible participants to this study are common to clinical research in critical care. Patient factors (i.e., unable to consent themselves, reliance on substitute decision-makers, short length of stay, unpredictable and variable clinical status) in conjunction with logistic factors (i.e., one research coordinator with no weekend, evening or vacancy coverage) and research protocol factors (i.e., exclusion criteria, short time frame for recruitment) contributed to the high number of missed opportunities. This high rate of missed opportunities to invite eligible patients to participate in this study and the factors that contributed to this rate are consistent with what has been reported with other clinical research in the ICU setting. The Consent Study was a prospective, multi-centered cross-sectional study which examined recruitment practices in the 23 Canadian critical care settings, and this study also found
the majority of eligible patients (57.3%) missed the opportunity to be invited to participate in clinical research for similar reasons, despite the fact that some sites had evening (13/23) or weekend (8/23) coverage (Burns et al., 2013).

Addressing the factors that contributed to the missed opportunities to invite eligible patients could improve recruitment efficiency in clinical research with critically ill populations. Expanding human resources to employ more than one research coordinator is often the most costly strategy but in light of the experience in this study, and the evidence from other studies (Burns et al., 2013), there is the potential to double the recruitment efficiency of a clinical site. With an additional research coordinator, it would have been possible to extend the availability of research coordinators by staggering the working hours. These strategies to expand research coordinator availability during evenings and weekends are recommended (Burns et al., 2013; Cook et al., 2008; Dechert, 2008). Making alterations in study design (i.e., cluster randomization) and/or consent models (i.e., delayed consent, waived consent or non-investigator physician consent when there is no substitute decision maker available) are other possibilities that may improve recruitment efficiency by addressing the barriers to consent (Burns et al., 2013; Cook et al., 2008).

**Addressing patient’s and family’s reasons for refusal.** The substitute decision-makers who declined participation in this study fell into three categories of refusal: overwhelming distress, not willing to consider participating in any research and a specific objection to the use of a temperature probe. While the first two responses were expected because a critical illness is a stressful experience both for patients and their loved ones (Cook et al., 2008), the specific objection to the use of a temperature probe was a surprise
to both the research team and the VGH ICU staff. A possible reason for this discrepancy is the differing experiences with the temperature probe between critical care clinicians and the general public. The ICU team have experience with this device and its risk factors and, in comparison to the many other invasive tools used in the ICU, a temperature probe is considered very safe. The general public however, and the substitute decision-makers contacted in this study, had never seen and may not have ever heard of this device before. For them, it was perceived to be a foreign measurement tool therefore it elicited a strong aversion. It is possible that as health care professionals, the research team members were biased in what was viewed as acceptable.

Recruitment may have been improved if the research team had engaged with patients and families in the development of study protocols. Patients and families who are unfamiliar with the ICU setting have a different perspective and, as a result, have much to share about the acceptability of study procedures (Domecq et al., 2014; Sacristán et al., 2016). In this study, the aversion to the temperature probe possibly could have been identified earlier, resulting in the development of proactive strategies to address these concerns in the design of the study. The research team could have altered the information or language to better introduce this device. Alternately, the research team could have selected a study site that routinely placed continuous core temperature probes in most ICU patients, thus the need to insert one and describe it as an additional research procedure might have been averted. While VGH ICU does not routinely use continuous core temperature monitoring, other regional sites do.

**Comparing recruitment achievements to related research.** Six participants completed this study after 9 months of recruitment from a single 34-bed ICU. It is not
simple to compare the recruitment achievements of this study to other similar studies because of differences in clinical settings, consenting procedures, interventions, exclusion criteria and study protocols, but there were five RCTs with similar patient populations and antipyretic interventions to which comparisons can be made. The first two studies examined the hemodynamic and antipyretic effects of acetaminophen (Cruz et al., 2002; Gozzoli et al., 2004) and were presented in chapter two. The other three studies (and the published study protocols) compared mortality between participants who were exposed to either permissive or aggressive antipyretic therapies (Niven, Léger, Kubes, Stelfox, & Laupland, 2012; Niven, Stelfox, Léger, Kubes, & Laupland, 2013; Schulman et al., 2005; Young, Saxena, Bellomo, et al., 2012; Young et al., 2015). While these three studies were identified in the literature search, they were not presented in chapter two because they did not meet the inclusion criteria for the literature searches.

The first two RCTs (Cruz et al., 2002; Gozzoli et al., 2004) recruited more participants than was achieved in this study. Both recruited from a single center, but neither reported the duration of their recruitment periods. Cruz et al. (2002) recruited 60 participants from a Spanish academic ICU. They did not discuss the consent procedures or standard clinical practice in their setting (Cruz et al., 2002). All participants in that study had pulmonary arterial catheters as a part of their routine care and it was used to monitor core temperature. Pulmonary artery catheters are more invasive and are associated with a higher risk of complications than the temperature probe used in this study. Gozzoli et al. (2004) enrolled 30 participants from a Swiss academic ICU to examine the antipyretic efficacy of three different therapies. In this case, consent was prospectively obtained but the authors provided little information about the clinical
settings. They reported that participants were sedated and many also obtained continuous temperature readings from pulmonary arterial catheters. Both the routine use of pulmonary artery catheters and keeping patients sedated are practices that were common more than a decade ago, but that are no longer considered best practice. Standard use of pulmonary arterial catheters meant that invited patients did not need additional measurement devices for core temperature monitoring and this could have had an effect on the patient and family’s willingness to consent.

The study conducted by Schulman et al. (2005) was a single centre RCT with exclusion criteria that were similar to what was planned for this study. Febrile patients were randomized to either the aggressive group (i.e., regular acetaminophen for temperature greater than 38.5 °C and external cooling for temperature greater than 39.5 °C) or permissive group (i.e., acetaminophen and external cooling for temperature greater than 40.0 °C). While Schulman et al. (2005) had also had a 9-month recruitment period and a similar eligibility rate (14.3%), they successfully enrolled 82 participants because a waiver of consent was initially granted by their research ethics board, as minimal risk was assumed. This study was stopped before they completed enrolling the target of 672 participants because they detected a trend towards a difference in mortality, thus the waiver of consent was withdrawn.

Two other multi-centered RCTs were found that compared mortality rates between febrile ICU patients who received aggressive versus permissive antipyretic protocols. Both had similar exclusion criteria and both tested acetaminophen as the antipyretic therapy. Niven, Stelfox, Léger, et al. (2013) recruited 26 participants from two ICUs in Canada over 18 months (completed on January 2012). While there were
differences in the recruitment and participant flow processes, the completion rate (i.e., 26 participants recruited over 18 months from two sites) was comparable to the completion rate reported in this study (i.e., six participants completed in 9 months recruited from a single center). A higher completion rate was achieved by Young et al. (2015) who recruited 19.2% (690/3,601) of all eligible participants from 23 ICUs in New Zealand and Australia over 18 months (approximately 30 per site). This study had a key advantage; depending on the site and local research ethic board requirements, consent was obtained prospectively, deferred or waived. While it not a straightforward process to make comparisons in the recruitment achievements because of differences in clinical context, the eligibility and completion rates achieved in this study were comparable with similar studies.

**Overview of the Hemodynamics Effects of Acetaminophen**

While no participant experienced a clinically significant hypotensive event, there was variability in hemodynamic measurements, use of vasoactive infusions and fluid balance between participants. There was variability in heart rate (i.e., 75 to 133 beats per minute), SBP (i.e., 80 to 170 mmHg) and MAP (i.e., 56 to 114 mmHg) during the study period between participants. Only participants #1 and #2 had vasoactive infusions running intermittently during the study period. Participants #1 and #5 had a positive fluid balance in the post-intervention period. This variability created complexity in the measurement of hemodynamic changes.

**Utility of clinically significant hypotension for hemodynamic measurement.**

There are inherent challenges in quantifying the hemodynamic effects of any therapy in the critically ill population. A research protocol cannot mandate the avoidance of
treatment of hypotension in order to determine the total hemodynamic effects of an intervention, because that would compromise participants’ safety. ICU clinicians must act to reverse any hypotensive event, but those treatments confound the measurement of hemodynamic effects. Relying only on changes in SBP or MAP is insufficient because researchers must also account for the variety of therapies available to reverse hypotension.

Previous research into AAH has not fully addressed this limitation in measuring hypotension in the critically ill populations. None of the papers reporting the 13 studies that examined the hemodynamic effects of acetaminophen provided an operational definition for a clinically significant hypotensive event. In addition, three reports did not discuss whether participants received either fluid bolus or changes to vasoactive infusions to reverse hypotension (Avellaneda et al., 2000; Gozzoli et al., 2004; Mrozek et al., 2009). The other 10 papers all reported that a proportion of participants received either a fluid bolus and/or a change in vasoactive infusions to reverse hypotension, although the details of the doses received were not consistently presented (Boyle et al., 1997; Boyle et al., 2010; Cruz et al., 2002; de Maat et al., 2010; Forouzanfard et al., 2012; Hersch et al., 2008; Krajčová et al., 2013; Mackenzie et al., 2000; Picetti et al., 2014; Vera et al., 2012).

Unlike previous research, there was an attempt to standardize the variety of therapies available to clinicians. In this clinical setting, the two common strategies used to reverse hypotension are administration of a fluid bolus, or a change in vasoactive infusion (Myburgh & Mythen, 2013). The additional challenge is that even within these two strategies, there are a variety of types of fluid (crystalloid or colloid) or vasoactive
infusions available to choose from, and the best therapy is dependent on the ICU patient’s underlying condition (Myburgh & Mythen, 2013). In the current study, the definition of a clinically significant hypotensive event (i.e., fluid bolus equal to or greater than 500 mL, or increase in vasoactive infusions by equal to greater than 5 mcg/min of norepinephrine) attempted to account for the variety of anti-hypotensive therapies by calculating the equi-volume of fluid to standardize a crystalloid versus colloid fluid bolus, and equi-dose of vasoactive infusions to calculate the norepinephrine-equivalent dose.

Determining and using a standardized definition of clinically significant hypotensive event would aid researchers in making valid comparisons between studies that examine hemodynamic effects of therapies in critically ill populations. The operational definition of a clinically significant hypotensive event was based on clinical judgement. While theoretically, it appears though these criteria could differentiate between usual variability in blood pressure in ICU patients and a notable event, by accounting for treatments administered, there were too few participants enrolled in this study to assess if these parameters were reasonable and clinically relevant.

The degree to which any intervention increases the likelihood of an ICU patient to experience a clinically significant hypotensive event is more meaningful information than changes in blood pressure to the ICU clinicians who are responsible for caring for critically ill patients. In this study, no participant had a clinically significant hypotensive event. Therefore it was not possible to detect whether the defined parameters were able to discern between expected variability and a hemodynamic effect of the therapy. Further
research to better evaluate this outcome measure would have both academic and clinical value.

**Overview of the Antipyretic Effects of Acetaminophen**

There was variability in fever patterns between participants as well as the degree of temperature change between the pre- and post-intervention period. Between participants, fever burden ranged from 0.97 to 3.78 °C-hours in the pre intervention period and 0.74 to 10.24 °C-hours in the post intervention period. While there were too few participants enrolled to assess antipyretic efficacy, acetaminophen did not appear to have any antipyretic action. In fact, two of the five participants who received acetaminophen (i.e., #3 and #5) had a net increase in fever burden and average temperature post intervention.

**Utility of fever burden for measurement of antipyretic efficacy.** Previous antipyretic efficacy studies in the critically ill population use a variety of methods to quantify the antipyretic efficacy of acetaminophen measure fever. Poblete et al. (1997), I. M. Mackenzie et al. (2000), and Gozzoli et al. (2004) quantified antipyretic efficacy by measuring absolute or percentage change in core temperature from baseline at predetermined time points (i.e., 1, 3, or 4 hours post-intervention). Greenberg et al. (2010) measured absolute reduction in temperature. A limitation of these methods of measurement is that they do not account for the variety of fever patterns that can occur. Participants in the study reported in this thesis demonstrated a variety of fever patterns. Both Sulter et al. (2004) and Vera et al. (2012) measured antipyretic efficacy as proportion of participants who achieved a targeted decrease in temperature. While their method highlights that a proportion of critically ill patients do not experience a clinically
significant decrease in core temperature after receiving acetaminophen, it does not measure smaller decreases in core temperature. Dippel et al. (2003), Dippel et al. (2001), and Kasner et al. (2002) all attempted to measure how effective acetaminophen was at supressing fever in brain injured participants by comparing mean core temperature readings over a day or more. While mean core temperature is comparable to fever burden, the frequency of temperature measurement can affect the accuracy of the estimation. Kasner et al. (2002) recorded temperature every 30 minutes and temperature was recorded every 2 hours for the first 24 hours then every 6 hours afterwards in the studies by Dippel et al. (2003) and Dippel et al. (2001). All of these methods of measurement create limitations, both with statistical analysis and in the ability to make comparisons between studies.

Using fever burden to measure antipyretic efficacy in the study reported in this thesis offers a method to quantify fever that overcomes many of the limitations seen in previous pharmacological antipyretic efficacy studies. Like most biophysiologic variables, core body temperature varies over time. Even in an afebrile state, core body temperature fluctuates within a narrow range (Drewry et al., 2013; Kurz, 2008). Fever also creates changes in core temperature that may evoke a wide variety of fever patterns (Cunha, 1996), which were also demonstrated in this study (see Figures 6 to 11). The challenge lies in determining an effective way to measure overall fever burden that also accounts for minute-to-minute variability. While fever burden has been used to determine the antipyretic efficacy of non-pharmacological therapies in the critically ill population (Hammond & Boyle, 2011), the study presented in this thesis was the first, to
our knowledge, to use fever burden to examine the antipyretic efficacy of a pharmacological therapy.

Matthews et al. (1990) outlined three key goals in creating biophysiological variables in research: (a) a variable that can take into account the variations in serial biophysiological measurements, (b) a variable that is amenable to statistically valid analysis, and (c) a variable that can be meaningful and relevant in clinical practice. Matthews et al. (1990) proposed that converting serial measurements into an area under a curve (AUC) meets all three goals of measurement.

Fever burden has yet to be used in the clinical setting however, it is a measure that may have clinical relevance. For example, a patient who spikes a high temperature that quickly falls will have a lower fever burden and metabolic demand than a patient who has a consistent moderate fever for a long duration, even though that patient has a lower peak temperature. Because fever burden accounts for both the core temperature and the duration a patient remains at any temperature reading, it offers a more accurate way to estimate the metabolic demand or immunological response of fever, regardless of the fever pattern. This could this allow not only more accurate measures of antipyretic efficacy, but also better comparisons between a patient’s fever burden and other physiologic or outcome measures.

Further research is needed to examine if fever burden, rather than fever, is associated with other important outcomes like morbidity, mortality or length of stay. The question of how fever and antipyretic interventions impact patient outcomes continues to be explored. In the Fever and Antipyretic in Critically ill patients Evaluation (FACE) study, researchers compared the highest recorded temperature of the participants’ ICU
stay (i.e., MAXICU) and antipyretic use with 28-day mortality (Lee et al., 2012). In this observational study, antipyretic use in septic febrile ICU participants was associated with a higher mortality rate, while MAXICU, not antipyretic use, was associated with a higher mortality in non-septic febrile ICU participants (Lee et al., 2012). Using the MAXICU simplified the analysis, but using fever burden, which accounts for both temperature and duration, for future studies may reveal additional relationships.

Using fever burden instead of, or in conjunction with, traditional methods to quantify fever, such as peak daily temperature, could lead to a better understanding of how fever is associated with morbidity and mortality in addition to improved measurement of the efficacy of antipyretic therapies. To date, studies that have asked if it is better to treat or not treat fever during a critical illness had as an underlying assumption that acetaminophen is effective at reducing fever. Despite the completion of two systematic reviews (Hammond et al., 2013; Jefferies et al., 2011) and a large double-blinded RCT (Young et al., 2015) there still are no definitive recommendations of whether fever should be routinely treated. There are two limitations of how previous research measured fever that the use of fever burden could address. First, previous researchers have presumed that acetaminophen is effective and consistent at reducing fever. Comparisons were made on whether or not participants received acetaminophen and other outcome measures of morbidity and mortality. Second, if temperature was measured, it was limited to point measures of temperature like peak daily readings. Fever burden would have offered a more accurate method to quantify fever because it accounts for both temperature and the duration for which the fever persisted. Not only would fever burden allow researchers to better measure the antipyretic efficacy of treatments
like acetaminophen, but if fever is measured more accurately, then perhaps different relationships between fever and other outcome measures can be uncovered.

The largest RCT to date \( (n = 700) \) examined the relationship between fever and acetaminophen use with morbidity and mortality (Young et al., 2015). They recorded axilla temperatures every 6 hours and made comparisons with both peak and mean temperatures (Young et al., 2015). They found a small (-0.29 °C) but statistically significant \( (p < 0.001) \) difference in daily mean temperatures between the acetaminophen and placebo groups but no difference in length of ventilation-free days, length of stay or mortality (Young et al., 2015). Using more frequent temperature measures \textit{and} fever burden would have resulted in a more accurate measure of fever and again, potentially led to uncovering additional relationships. It is uncertain if the 0.29 °C difference in mean daily temperature is clinically significant because of the limitations of how fever was measured. The lack of a relationship between acetaminophen use and mortality could also be due to the fact that acetaminophen was ineffective at reducing fever. Future studies examining the effects of acetaminophen in febrile ICU populations should not presume its antipyretic efficacy; this is still certain.

**Limitations**

There are several limitations to this study. First, feasibility did not become the primary focus until after the interim analysis when it was apparent that the targeted sample size was unachievable. Had feasibility been the primary focus at the beginning of this study, the examination of the four components of feasibility (i.e., research processes, resources, management and scientific factors) would have been able to be more thorough. Additionally, recruitment barriers would have been monitored on an ongoing basis, and
adaptive changes to improve recruitment may have been implemented earlier, thus increasing the sample size. It is also possible that the problems related to obtaining data from the bedside monitors would have been identified if feasibility had been the primary focus.

The small sample size was a limitation to both the examination of feasibility and the hemodynamic and antipyretic effects of acetaminophen. The evidence presented in this and previous studies suggests that the targeted sample size of 62 was unrealistic, given the resources available; however, even a small improvement in recruitment might have allowed for better evaluation of the participant safety, data management, effectiveness and clinical relevance of measurement outcomes. No participant experienced a clinically significant hypotensive event, received any type of fluid bolus, and only two participants were on vasoactive infusions; therefore, none of these measurements could be evaluated for scientific merit or clinical relevance. The calculations to determine equi-volume and equi-dose equivalents are at best, an approximation. While more research is needed to test these calculations, there will always be limitations in the accuracy of such calculations because the best treatment to reverse hypotension is dependent on the clinical context: the best therapy is the one that most effectively addresses what caused the hypotension. In this study, it was difficult to discern any consistent antipyretic effect of acetaminophen because this sample size was too small to draw conclusions.

Implications for Nursing/Clinician Practice in Critical Care

Acetaminophen is a drug with over sixty years of clinical use, which is currently still is reported as a safe and effective antipyretic effect. Like most drugs used in the
critically ill populations these assumptions are based upon research conducted in non-critically ill populations, yet critically ill patients demonstrate that they have a unique physiology to consider. As treating fever is a foundational role for nursing, including critical care nursing, the decision to administer acetaminophen is almost always in the nurses’ hands. Therefore, awareness of the possible deleterious effects of acetaminophen is essential for safe care; definitive results from studies in this area will be of importance to critical care nurses. Moreover, critical care nurses are in a unique position to monitor for, identify and intervene for these unexpected effects because of the constant one-on-one care that critical care nurses provide.

**Implications for Health Policy**

Health policy makers not only must recognize, but also address gaps in knowledge; many clinical decisions about therapies for critically ill patients are based on extrapolations from studies conducted in non-critically ill populations. Policies and practice guidelines should not only strive to identify gaps, but also build in a systematic process to close the knowledge gaps. If it is justifiable to expose patients to a therapy despite the limitations of current evidence, then it should also be imperative to mandate that new knowledge be generated to close that gap. Good clinical practice guidelines that are generated today routinely appraise the evidence, identify knowledge gaps and make therapeutic recommendations. These documents are often reviewed and updated on a regular basis. However, recommendations for ongoing measurement, data collection and analysis plans to address those gaps are not always carried out. While ongoing monitoring for unexpected effects are required for new therapies, and therapies administered in new populations, in the case of drugs like acetaminophen that were
approved for use when regulations were less stringent, this has not been done. Also, for most therapies used in the critically ill patients, have not been fully studied in this population despite the fact that ICU patients demonstrate a unique physiology. Yet we could address both of these gaps. Clinical guidelines already identify the gaps in evidence, they could also outline specific outcome measures and mandate routine data collection for post-marketing analysis of safety outcomes.

Modern technological advances in patient monitoring, data capture and computer analysis can help scientist address those challenges by facilitating data capture during routine clinical care processes. This is possible only when information systems are designed to capture meaningful data and allow for easy extraction of that data. Detailed, thorough and accurate vital sign data are captured easily in patients that are monitored. Acetaminophen is the most common antipyretic used today, yet it is a laborious process to collect and extract the data needed to determine the hemodynamic effects of acetaminophen. This holds true for many of the therapies offered to critically ill patients that still require further study. Implementing information systems may be challenging and costly, yet has the potential to springboard our understanding of the physiology of critical illness, which ultimately may improve care. If closing the knowledge gap becomes a routine mandate of clinical practice policies, then investing in creating information systems that help fulfill this mandate should be a strategic priority of health organizations.

**Implications for Clinical Research**

There are inherent challenges in recruiting critically ill patients to clinical research, the most significant being the consent process, that need to be addressed. While
there is great need for clinical research with the ICU population, being critically ill prevents patients from participating in the consent process. As a result, conducting clinical research in the ICU is expensive, slow, and prone to selection bias because of the added time required to complete the consent process, and only patients with available substitute decision makers can be invited to participate in clinical research. Critical care clinical research teams, research ethics boards and patient and family partners need to collaborate to develop consent processes that both meet ethical standards, but also address the clinical context of research in the ICU setting with critically ill patients.

This study could not determine the hemodynamic or antipyretic effects of acetaminophen but such research is still needed. In the ICU, clinicians continue to administer acetaminophen to treat fever with the assumption that it is hemodynamically inert and effective at reducing fever. What limited research is available does challenge these assumptions, but those studies are not rigorous enough to refute the assumptions entirely. A double-blinded RCT is still needed.

Any research that examines the hemodynamic effect of therapies in the ICU population could benefit from a valid measure of clinically significant hypotensive events in conjunction with standard measures of blood pressure. The operational definition of a clinically significant hypotensive event used in this study attempted to capture a variety of treatments that participants may receive. Although these treatments are necessary to prevent or reverse hypotension, the treatments themselves confound the measurement of blood pressure. Future research should consider further testing and refining the definition of a clinically significant hypotensive event as a measurement strategy in conjunction
with blood pressure when they examine for the hemodynamic effects of therapies in the ICU population.

**Summary**

In this study not enough participants were enrolled to answer the question of whether acetaminophen has any hemodynamic or antipyretic effects. However, this study did explore the feasibility of conducting an RCT that could address this question. In particular, this thesis outlined the barriers to recruitment and offered strategies to address them. While using retrospective data to estimate eligibility rates may be a beginning, this can be improved by pilot testing screening procedures. This thesis discusses implications for nurses, health policy, and future research. Critical care nurses have a unique vantage point and therefore have a role to play in the generation of research. Guidelines that include an evaluation of evidence and make recommendations about therapies should not only include the limitations of the evidence but also mandate a systematic plan to ensure those knowledge gaps are closed. While resources will be required to address this, the strategic use of information systems could make this work possible. This thesis also offers novel ways to measure hemodynamic changes and fever to critical care researchers. Augmenting traditional measurements of blood pressure with the measurement of clinically significant hypotensive events could address how treatments to reverse hypotension confound the measurement of hemodynamic changes. Fever burden offers a better strategy to measure fever, which could uncover differently relationships between fever, antipyretic therapies and patient outcomes.
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Appendix A: Original Statistical Analysis Plan

A Priori Power Analysis
An effect size of a 25% incidence of AAH was utilized for the power analysis (Boyle et al., 1997; Boyle et al., 2010; de Maat et al., 2010; Mackenzie, Forest, Thompson, & Marsh, 1999; Vera et al., 2012). The sample size was calculated based on the second research question to detect a difference in the number of clinically significant hypotensive events; this resulted a required sample size of 62 (31 in each arm), for a Fisher’s Exact test (Faul, Erdfelder, Lang, & Buchner, 2007) with an effect size of 0.25, a power of 0.80 and \( \alpha = 0.05 \). For the third research question regarding antipyretic efficacy, a two-sample t-test with an effect size of one degree per 4 hour AUC, power of 0.80 and \( \alpha = 0.05 \) (two-tailed), a total sample size of 34 would be sufficient.

A Priori Estimation of Recruitment Period
The ICU database admission record was reviewed between the dates September 2011 to March 2012. This revealed that 653 patients were admitted to the VGH ICU over 6 months. Of those, 280 met this study’s inclusion criteria. The presence of fever was not noted in the ICU database; therefore, it was estimated that fever occurred for 25% of the cases (based on previously reported research (Laupland et al., 2008; Niven, Stelfox, Shahpori, et al., 2013). Considering that the annual admission rate had increased by 5% per annum since 2011, it was estimated that up to 250 participants could be eligible in 6 months, with an anticipated 75 to 81 patients proceeding to completion of the study.

Statistical Analysis
The Fisher’s Exact test (or \( \chi^2 \) if possible; Pallant, 2013) would have been used to determine if there was a statistically significant difference in the incidence of clinically significant hypotensive events between the treatment and control groups in the 4 hours after the intervention (Hypothesis 1). Also, the one-way repeated measures of the analysis of variance (rm-ANOVA), or the non-parametric equivalent (Friedman test; Pallant, 2013) if assumptions were not met, would have been used to determine if there was a statistically significant difference in either the MAP or SBP between the treatment and control groups (Hypothesis 2). For Hypothesis 3, once all fluid volume had been converted to the crystalloid equivalent volume, the independent sample t-test or Mann-Whitney U test, if a non-parametric test was required (Pallant, 2013) would have been used to test for a difference in total fluid volume administered in the 4 hours after the intervention. For Hypothesis 4, once all vasoactive infusion doses had been converted to the norepinephrine equivalent dose, the independent sample t-test (or Mann-Whitney U; Pallant, 2013) would have been used to test for a difference in total dose of vasoactive drugs administered in the 4 hours post intervention. For Hypothesis 5, the independent sample t-test (or Mann-Whitney U) would have been used to compare the difference in fever burden (in °C-hr for the 6-hour period post intervention) between the treatment and control groups.
Appendix B: SEA-ICU Laminated Cards

- randomized control study looking at temperature, heart rate, and blood pressure after Tylenol/placebo is given
- data is collected for 6 hours after the participant gets the study drug
- Please call Vini ([telephone number]) 24/7 if core temp is >38.3 °C

The Onsite SEA-ICU research team:
Vini, Allana, Jen W., Greg (PharmD), Dr. Henderson

Version 1 – April 27, 2015
Appendix C: SEA-ICU Recruitment Sheet

SEA-ICU Recruitment Sheet
SEA-ICU: Safety and Efficacy of Acetaminophen in the ICU

Acetaminophen is commonly given to ICU patients to critically ill patients to treat fever. Acetaminophen has been shown to be safe and effective at reducing fever in studies conducted in non-critically ill patients but ICU patients may respond differently. Some observational studies suggest acetaminophen may not work as well at reducing fever for critically ill patients and some critically ill patients have been reported to experience a drop in blood pressure after being given acetaminophen to treat fever. The purpose of the SEA-ICU study will examine how effective acetaminophen is at reducing fever and explore if acetaminophen increases the chances of a hypotensive event in the ICU patient.

This ICU patient has been pre-screened and is potentially eligible for the SEA-ICU study. To facilitate participant recruitment and communication with the research team, when possible please offer the family/next of kin a copy of the SEA-ICU Information Pamphlet and update this recruitment sheet as needed.

| Has the family/next of kin received a copy of the SEA-ICU Information Pamphlet? | YES | NO |
| Who was given the SEA-ICU Information Pamphlet? |
| Date/Time given? |

| Has the family/next of kin stated they WOULD be interested in being contacted by telephone about participating in this study? | YES | NO |

| Has the family/next of kin requested NOT to be contacted about this study at all? | YES | NO |

If you have any questions please contact Vininder Bains at [telephone number]. Thank you from the SEA-ICU Research Team.

Principal Investigator: Dr. Leanne Currie, RN, PhD., Associate Professor
UBC School of Nursing
Office: [telephone number]
Fax: [fax number]
Email: [email address]

Co-Investigator(s): Dr. William Henderson, MD FRCPC;
Dr. Martha Mackay, PhD, RN CCN(C)
Vininder K Bains, RN, BSN, CNCC(C)
Allana LeBlanc RN, BSN, CNCC(C)
Jennifer Wong RN MSN
Dr. Greg Mah, B.Sc. (Pharm.), Pharm. D., ACPR

UBC School of Nursing
T201-2211 Wesbrook Mall
Vancouver, BC, V6T 2B5
Currently we are enrolling intensive care unit (ICU) patients in the SEA-ICU study. All patients who are admitted to the ICU are screened to see if they can participate in this study. If you or your family member is an ICU patient at Vancouver Hospital you may be contacted to be invited to participate.

If you are interested in learning more about this study and are okay with receiving a telephone call, please let your (or your family member’s) nurse know. If you have told the nurse telephone contact is okay, then your contact information can be gathered from the ICU patient’s chart.

If your family member is eligible for this study, then the Research Coordinators at Vancouver Hospital’s ICU will contact you. This will occur when you are in the ICU, (or by phone if you have told the nurse so) Monday to Friday during business hours.

Participation is Voluntary
It is important to note that, you, or your family member’s participation in this study is voluntary. If you choose not to participate, in no way will this affect the quality of care you, or your family member will receive as an ICU patient.

For more information please contact:

The SEA-ICU Research Team

Principal Investigator:
Dr. Leanne Currie RN, PhD
Associate Professor
UBC School of Nursing
T201-2211 Westbrook Mall
Vancouver BC, V6T 2B5

Co-Investigators:
Dr. William Henderson MD FRCP
Dr. Martha Mackay RN, PhD, CCN(C)
Vini Bains RN, BSN, CN(C)(C)
Allana LeBlanc RN, BSN, CCN(C)(C)
Jennifer Wong RN, BSN, CCN(C)
Dr. Greg Mah BSc, Pharmacy, Pharm D, ACPR

Version 2; Dec. 12, 2014

Appendix D: SEA-ICU Information Pamphlet
SCRENNING
All ICU patients are screened to see if they are eligible for this study.

ICU patients who consent will get a final safety screening before moving to the next step.

WHAT IS THE PURPOSE?
This research project has 2 purposes:
- To see if acetaminophen (also known as Tylenol®) increases the risk of a drop in blood pressure in the ICU patient with a fever.
- To measure how effective acetaminophen is at bringing down a fever.

WHO IS ELIGIBLE?
In order to be considered for this study a patient must be admitted to the ICU at Vancouver Hospital and may have a fever. Also an ICU patient must be able to:
- Safely take acetaminophen
- Safely tolerate a fever for short time.

ARE THERE ANY BENEFITS?
No one knows whether or not you will benefit from this study. There may or may not be direct benefits to you or your family member from taking part in this study. We hope that information learned from this study can be used in the future to benefit other ICU patients with a fever.

WHAT HAPPENS IN THE STUDY?
If you consent to participate in this study then the ICU patient will be randomly assigned into one of 2 groups:

ACETAMINOPHEN GROUP
Participants selected for this group will get a single dose of acetaminophen 650mg.

PLACEBO GROUP
Participants selected for this group will get a single dose of placebo. A placebo is a pill that looks exactly like the study drug but have no medicine in it.

WHAT INFORMATION IS COLLECTED?
Information will be collected for a total of 4 hours after the participant gets the study drug. The information which will be collected are:
- Heart rate
- Blood pressure
- Temperature

This information will be collected from the ICU monitor.

Other information will also be collected from the patient chart. This data will only include information about the current ICU admission.

CONFIDENTIALITY
Your privacy will be respected. If you, or your family member agree to participate in this study, the ICU patient will be assigned a unique study number.

Only this number will be used on any research related information collected about you or your family member during the course of this study.

AFTER THIS STUDY IS COMPLETE
If you are interesting in the results, please let the research team know and we will forward you a summary of the findings.

ADDITIONAL DATA
Information will also be gathered from the ICU patient chart.

4 HOURS OF DATA COLLECTION
Temperature
Heart Rate & Blood Pressure
Any Treatments that Affect Blood Pressure
Appendix E: SEA-ICU Clinician Information about Enrolled Participants

<table>
<thead>
<tr>
<th>SEA-ICU: Safety and Efficacy of Acetaminophen in the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen is commonly given to ICU patients to critically ill patients to treat fever. Acetaminophen has been shown to be safe and effective at reducing fever in studies conducted in non-critically ill patients but ICU patients may respond differently. Some observational studies suggest acetaminophen may not work as well at reducing fever for critically ill patients and some critically ill patients have been reported to experience a drop in blood pressure after being given acetaminophen to treat fever. The purpose of the SEA-ICU study will examine how effective acetaminophen is at reducing fever and explore if acetaminophen increases the chances of a hypotensive event in the ICU patient.</td>
</tr>
</tbody>
</table>

What is involved when your patient is a SEA-ICU participant?
When your patient is enrolled in the SEA-ICU we will be continuously monitoring the participant’s core temperature. When the participant has a new fever (core temperature greater than 38.3 °C for less than 48 hours since onset) we will proceed to the intervention stage. At this time participants will be randomly allocated to either the treatment or control group. Participants in the treatment group will receive 650 mg acetaminophen, and participants in the control group will receive a placebo. Researchers, participants, and ICU clinicians caring for this patient will be blinded to which group the participant is in until the end of this study. After receiving the study drug, 4 hours of data collection will commence. The participant’s heart rate, rhythm, blood pressure and any treatments to reverse blood pressure will be collected. At the end of these 4 hours the study is complete.

What are my responsibilities as the ICU Physician?
The ICU physician responsible for caring for this participant was consulted before consent was pursued. As the ICU physician responsible for caring for this patient, you will be consulted once again immediately before proceeding to the intervention phase to ensure you do not have any objection for this patient to participate in this study. If you feel at any time and for any reason that this patient should NOT continue to participate in this study, please let the research team know so we can stop the study for this participant.

What are my responsibilities as the ICU Nurse?
The research team has ensured that a method for core temperature monitoring is in place. Please monitor the participant’s core temperature continuously. If the participant’s core temperature rises above 38.3 °C please contact the research team (Vini Bains: [telephone number]). The research team will then complete a final safety check and organize delivery of the study drug (placebo or 650 mg acetaminophen) to your patient’s bedside. A sealed envelope with information indicating whether the participant is to receive a placebo or 650 mg acetaminophen will also be delivered with the study drug. Please keep this envelope sealed and place it in the participant’s chart until the end of the study. The research team will arrange returning envelope to the pharmacy department. Once the
safety check is complete, please administer the study drug (via the nasogastric tube or orally as appropriate) and document the exact time it was given on the patient’s medication administration record (MAR). Use the time indicated on the CARESCAPE Patient Monitor if possible. The study will complete 4 hours after the study drug administered.

**What do I do if the participant’s temperature rises above 40.0 °C?**
If the participant’s core temperature rises above 40.0 °C please contact the SEA-ICU research team immediately. If the participant has already received the study drug, you may open the envelope and find out if the participant received acetaminophen or placebo, and treat the participant as per your clinical judgement. Please let the research team if, when and why the envelope was opened.

**What do I do if the participant becomes hypotensive?**
If the participant becomes hypotensive, please continue to treat the participant in accordance with your clinical judgement. If the hypotensive event occurred within 4 hours after receiving the study drug we ask that you try to be as accurate as possible in documenting how the hypotension was treated.

**What if I need to know whether my patient received acetaminophen or placebo?**
If at any time you as the clinician responsible for caring for this participant decide it necessary for the delivery of safe care to be unblinded (i.e., know if the participant is in the control group or treatment group) you may open the envelope and find out if the participant has received the placebo or 650 mg acetaminophen. We ask you also contact the ICU research team. (Vini Bains at [telephone number] or Dr. Leanne Currie at [telephone number]). This envelope will remain on the participant’s chart from the time the study drug is dispensed until data collection is completed. If data collection completes after 10 pm, please keep the envelope on the chart until the following day. The research team will arrange having the envelope returned to the pharmacy department.

**Who do I contact if I have any questions or concerns?**
If you have any questions or concerns, please feel free to contact any of the SEA-ICU research team. For immediate assistance you may call Vini Bains ([telephone number]) or Dr. Leanne Currie ([telephone number]).

Thank you from the SEA-ICU Research Team.

**Principal Investigator:** Dr. Leanne Currie, RN, PhD.
Associate Professor
UBC School of Nursing
Office: [telephone number]
Fax: [fax number]
Email: Leanne.Currie@nursing.ubc.ca

**Co-Investigator(s):**
Dr. William Henderson, MD, FRCP C
Associate Director, VGH ICU 2
Dr. Martha Mackay PhD. (Nursing) CCN(C)
St. Paul’s Hospital Heart Centre
Mrs. Vininder K Bains, RN, BSN, CNCC(C)
Ms. Allana LeBlanc, RN, BSN, CNCC(C)
Mrs. Jennifer Wong, RN, MSN
Staff Nurses, Intensive Care Unit 2
Dr. Greg Mah, B.Sc. (Pharm.), Pharm. D., ACPR
Clinical Pharmacist, VGH ICU 2
To be placed at in the Participant’s Room,
(at the Head of the Bed)

This Participant is Enrolled in the
SEA-ICU Study

Temperature

> 38.3 °C?

Call Vini Bains (24-7) if the core
temperature is greater than 38.3 °C
(cell: [telephone number])

Thank you from the SEA-ICU Research Team.

Principal Investigator:
Dr. Leanne Currie, RN, PhD.

Co-Investigator(s):
Dr. William Henderson, MD, FRCPC
Dr. Martha Mackay PhD, (Nursing) CCN(C)
Mrs. Vininder K Bains, RN, BSN, CNCC(C)
Ms. Allana LeBlanc, RN, BSN, CNCC(C)
Mrs. Jennifer Wong, RN, MSN
Dr. Greg Mah, B.Sc. (Pharm.), Pharm. D., ACPR
Appendix F: SEA-ICU Consent Form

Participant/Substitute Decision Maker Information and Consent Form
SEA-ICU: Safety and Efficacy of Acetaminophen in the Intensive Care Unit

Principal Investigator: Dr. Leanne Currie, RN, PhD.
Associate Professor, School of Nursing
Office: [telephone number]
Fax: [fax number]
Email: [email address]

Co-Investigator: Mrs. Vininder K Bains, RN, BSN, CNCC(C)
UBC Student – Masters of Nursing Program
Staff Nurse, Intensive Care Unit 2, Vancouver General Hospital
Phone: [telephone number]
Email: [email address]

Co-Investigator: Dr. William Henderson, MD, FRCPC
Associate Director, Intensive Care Unit 2
Critical Care Medicine, Vancouver General Hospital
Office: [telephone number]
Email: [email address]

Co-Investigators: Ms. Allana LeBlanc (VGH ICU RN), BSN, CNCC(C)
Mrs. Jennifer Wong (VGH ICU RN), MSN
Dr. Greg Mah (VGH ICU Clinical Pharmacist), Pharm. D., ACPR
Dr. Martha Mackay, PhD. (Nursing), CCN(C)
Clinical Assistant Professor, UBC School of Nursing
Clinical Nurse Specialist – Cardiology, St. Paul’s Hospital

Sponsors: Vancouver Coastal Health Research Institute

Emergency Telephone Number: [telephone number] (Vininder K Bains RN) and/or [telephone number] (Dr. Leanne Currie) are available 24-hours, and 7 days a week.

If you are the substitute decision maker for someone who may take part in this study, permission from you and the agreement and the assent (agreement) of the potential research participant may be required. When we say “you” or “your” in this consent form, we mean the research participant; “we” means the doctors and other research staff.
Invitation

You are invited to take part in a research study that is being done in the Intensive Care Unit (ICU) at Vancouver General Hospital (VGH). You are eligible to take part in this research study because you have been admitted to the ICU with a critical illness and you have a fever.

Your participation is voluntary

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences to the medical care, education, or other services to which you are entitled or are presently receiving.

Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study and the possible benefits, risks and discomforts. Your involvement in the study is in addition to the care you would otherwise receive from the staff doctors and nurses in the ICU. The information acquired during the study is meant to provide new information that will help other patients in the future but will not benefit you directly during your hospitalization. The researchers have a duty of care to all participants and will inform you of any information that may affect your willingness to remain in the study.

If you wish to participate in this study, you will be asked to sign this form. Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

Who is conducting this study?

This study conducted in the Vancouver Hospital ICU and is being sponsored by the Vancouver Coastal Health Research Institute.

Background

Fever is a common symptom in intensive care unit (ICU) patients. Fever has some important benefits, such as improved immune function. When you have a fever, your need for oxygen, heart rate, and metabolic rate goes up. Health care workers often treat fever with a standard dose of 650 mg acetaminophen (also known as Tylenol) every 4 hours to reduce a patient’s fever. Research done in people who are not critically ill tells us acetaminophen is good at bringing down a fever without affecting blood pressure. ICU patients are complex and may not respond to common drugs in the same way.

One purpose of this study is to see what effect acetaminophen has on blood pressure. It is important to note that if you do experience a drop in blood pressure, your health care team will act promptly to reverse it as a standard of care.

The second purpose of this study is to see how well acetaminophen (Tylenol) is at bringing down a fever in the ICU patient. Most studies that measure exactly how good acetaminophen (Tylenol) is at reducing a fever were done in healthy people. We don’t know how well acetaminophen (Tylenol) is at bringing down a fever in the ICU patient.
We ask for your participation in this study in order to improve the medical care of critically ill patients with a fever in the future and thus help others suffering the same problem. If you agree to participate in this study you will be one of 250 study participants at the ICU at VGH.

**What is the purpose of the study?**

The two main purposes of this study is to first, see if acetaminophen (Tylenol) will affect the blood pressure when it is given to treat fever in the ICU patient, and second to see how good acetaminophen (Tylenol) is at bringing down a fever in the ICU patient.

**Who can participate in this study?**

You may be able to participate in this study if you are in the ICU at VGH and have or may develop a new fever during your ICU stay.

**Who should not participate in this study?**

The doctors and the study team will review your medical history in order to determine if there are any conditions that would exclude you from participating. In general you will be excluded if you cannot safely take acetaminophen to treat your fever. Also, you will be excluded if you have any conditions or treatments that change your natural fever response.

**What does the study involve?**

Participants who consent to enrolment in this study will be randomly assigned to either receive a single dose of 650 mg acetaminophen (Tylenol) or a single dose of a placebo. (A placebo is an inactive substance that looks identical to the acetaminophen capsules but it contains no medication. It is used so researchers and participants won’t know if they are in the treatment or control group until all the data is collected) We will then monitor heart rate, blood pressure, and temperature continuously for 4 hours. It is standard practice for ICU patients to have continuous monitoring of heart rate, heart rhythm, and blood pressure.

**If You Decide to Join this Study:**

If you do not already have a continuous measure of core temperature in place, we will place a temperature probe (a small soft plastic covered wire) into your throat beside your breathing or feeding tubes.

**Random Assignment:** You will then be randomly assigned to either the treatment group or the placebo group. Randomization is like flipping a coin, in that you have an equal chance of being placed in either group, but we cannot predict which group that will be. The randomization procedure will be done by the hospital pharmacy department.

**Double Blinded Study:** This is also a double blinded study, meaning both you and the research team will not know which group you have been assigned to until after the study is completed. In case of an emergency, we will break the code and find out which group you were assigned to. This can be done in less than 5 minutes.

**Treatment Group:** If you have been enrolled in the treatment group, you will receive 650 mg of acetaminophen either by mouth or the nurse will give it to you through your feeding tube.
**Placebo Group:** If you have been enrolled in the placebo group, you will receive a placebo, either by mouth or through your feeding tube that is in place as a part of usual care.

A placebo is an inactive substance that looks identical to the acetaminophen capsules but it contains no medication. We are using a placebo so both the researchers and the participants will not know if they received acetaminophen or not until after the study. This allows us to find out the true effect of the drug because we can compare the results from the treatment group to a group who went through the exact same procedures but did not receive the drug.

**Follow-up:** No additional blood tests or other tests will be conducted for this study.

**Use of Data from Secondary Data Sources**

The research personnel will review your chart and record other vital signs, measurements, and blood test results. This information will only be gathered from your current ICU visit. No additional data will be gathered from your chart prior to this ICU admission, or from any subsequent hospital admissions.

**What are my responsibilities?**

If you chose to participate in this study, you do not have any additional responsibilities.

**What are the possible harms and discomforts?**

**Temperature Probe Insertion:** If one is not already in place, a temperature probe will be inserted in your throat beside your breathing or feeding tube. Inserting a temperature probe will not cause any pain, although you may feel the probe going in when it is placed. There is very little risk of injury from this temperature probe, and it is commonly used in the ICU at VGH. Reported risks include injury to the throat, lung infection and blockage of the airway.

**Risks and Discomforts for Participants in the Acetaminophen Group**

- **Acetaminophen-associated hypotension:** A few studies have revealed that ICU patients may have a temporary drop in blood pressure after receiving acetaminophen to lower fever. The exact percentage is not known but it is estimated to be a rare (1%-2%) to less common (2%-20%) occurrence. If this were to occur, your health care team, as standard practice would quickly act by giving you fluid or drugs to maintain your blood pressure at a safe level.

**Risks and Discomforts for Participants in the Placebo Group**

- **Fever:** If you are selected to the placebo group, your fever will continue along its natural course. Fever is associated with increased heart rate and oxygen needs. For most people, even ICU patients, fever below 40 °C (or 104 °F) is considered safe, and is not known to cause damage to the body. Fever above 40 °C (or 104 °F) is a rare occurrence (5% or less). If at any time your temperature increases above 40 °C (or 104 °F) we would stop the study, find out if you received placebo or acetaminophen act to reduce your temperature as per usual care.
What are the potential benefits of participating?

No one knows whether or not you will benefit from this study. There may or may not be direct benefits to you from taking part in this study. We hope that the information learned from this study can be used in the future to benefit other people with a fever.

What are the alternatives to the study treatment?

If you choose not to participate in this study or to withdraw at a later date, you will continue to receive the best current management that is given to all patients with a fever. All care will be given as deemed necessary by treating physicians according to the current standard practice. Your decision will in no way affect the quality of care that is provided.

What if new information becomes available that may affect my decision to participate?

If you choose to enter this study and at a later date a more effective treatment becomes available, it will be discussed with you. You will also be advised of any new information that becomes available that may affect your willingness to remain in this study.

What happens if I decide to withdraw my consent to participate?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data will not be able to be withdrawn for example where the data is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data, please let your study doctor know. If your participation in this study includes enrolling in any optional studies, or long term follow-up, you will be asked whether you wish to withdraw from these as well.

How will my taking part in this study be kept confidential?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Vancouver Coastal Health Research Institute sponsoring the study and University of British Columbia Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g., it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your
name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

Your personal information or information that could identify you will not be revealed without your express consent unless required by law. If facts become known to the researchers which must be reported by law to public health authorities or legal authorities, then your personal information will be provided to the appropriate agency or authority.

**What happens if something goes wrong?**

By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your Provincial medical plan.

**What will the study cost me?**

You will not incur any personal expenses as a result of participation in this study, nor will you be paid for participation.

**Who do I contact if I have questions about the study during my participation?**

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Dr. Leanne Currie at [telephone number].

**Who do I contact if I have any questions or concerns about my rights as a participant?**

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at [email address] or by phone at [telephone number] (Toll Free: [telephone number]).
SEA-ICU Safety and Efficacy of Acetaminophen in the Intensive Care Unit

Participant’s Consent Signature

My signature on this consent form means:

- I have read and understood the information in this consent form.
  - I have had enough time to think about the information provided.
  - I have been able to ask for advice if needed.
  - I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that my participation in this study is voluntary.
- I understand that I am completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that I will receive.
- I authorize access to my health records as described in this consent.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefit to me.

I will receive a signed copy of this consent form for my own records.

I consent to participate in this study.

Participant’s Signature  Printed name  Date

Signature of Person Obtaining Consent  Printed name  Study Role  Date
SEA-ICU Safety and Efficacy of Acetaminophen in the Intensive Care Unit

Substitute Decision Maker Consent Signature

My signature on this consent form means:

- I have read and understood the information in this consent form.
  - I have had enough time to think about the information provided.
  - I have been able to ask for advice if needed
  - I have been able to ask questions and have had satisfactory responses to my questions.
- I understand that the participation of person for whom I am acting as substitute decision maker for is voluntary.
- I understand that I am completely free at any time to refuse to participate or to withdraw from this study at any time, and that this will not change the quality of care that the person for whom I am acting as substitute decision maker will receive.
- I authorize access to the health records of the person for whom I am acting as substitute decision maker as described in this consent.
- I understand that I am not waiving any of the legal rights of the person for whom I am acting as substitute decision maker as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefit to me or the person for whom I am acting as substitute decision maker for.

The substitute decision maker and the investigator are satisfied that the information contained in this consent form was explained to the participant to the extent that he/she is able to understand it, that all questions have been answered, and that the participant assents to participating in the research.

I will receive a signed copy of this consent form for my own records.

I consent to my family member’s participation in this study.

Name of the Participant (Print)

Substitute Decision Maker’s Signature  Printed name  Date

Signature of Person Obtaining Consent  Printed name  Study Role  Date

Signature of Person Witnessing Consent  Printed name  Role  Date

(for telephone consent only)
SEA-ICU Safety and Efficacy of Acetaminophen in the Intensive Care Unit

Consent by Participant to Continue Participation

I understand that I have been critically ill and have been participating in a research study. The decision to include me in this study was made by the doctor caring for me or consent was obtained from my substitute decision maker at a time when I was unable to consent for myself. I have now recovered sufficiently to make my own decisions and I am being asked if I wish to continue in this study.

My signature on this consent form means:
- I have read and understood the participant information and consent form.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
- I authorize access to my health record and samples as described in this consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I will receive a signed copy of this consent form for my own records.

If you do not wish to continue participation in this study you may request that your study data be withdrawn.

I consent to participate in this study.

Participant’s Signature  Printed name  Date

Signature of Person Obtaining Consent  Printed name  Study Role  Date
Appendix G: SEA-ICU Data Collection Form

SEA-ICU: Safety and Efficacy of Acetaminophen in the ICU
To be completed by SEA-ICU Research Team

PARTICIPANT ID NUMBER: ________________________________

<table>
<thead>
<tr>
<th>Data Collection Subsections</th>
<th>Completed by (Research Team member name)</th>
<th>Date Completed MM/DD/YYYY</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Consenting Details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Participant Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. Participant Demographics (to be extracted from the ICU Database)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV. Pre-Intervention Safety Check</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. Pre-Intervention Verification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI. Pre-Intervention Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII. Post-Intervention Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII. Safety Review &amp; Study Completion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I. Consenting Details

1. Date Consent Obtained (MM/DD/YYYY) ______________________ ICU Day: ________________________

2. Consent Obtained from:
   [ ] Participant
   [ ] Substitute Decision Maker (SDM)

   1. If from SDM, renewal of consent from Participant is:
      [ ] Pending (participant unable yet)
      [ ] Unlikely (participant has persistent neurologic impairment at ICU discharge)
      [ ] Participant Approached for consent renewal (date) _____________
      [ ] Consent Renewed
      [ ] Consent Withdrawn
II. Participant Demographics

Data gathered for the “day of ICU admission” is to be gathered from the first 24 hours in the unit, (beginning from the date/hour the participant arrived in the ICU).

1. Gender:  
   - [ ] Male  
   - [ ] Female  
   - [ ] Transgendered  
   - [ ] Not Reported

2. Age at time of enrolment (in Years): YEARS________

3. Height (in cm)_____________  
   - [ ] Measured  
   - [ ] Estimated

4. Weight (in kg) ____________  
   - [ ] Measured  
   - [ ] Estimated  
   - [ ] Reported/Pre-Hospital

5. ICU Admitting Diagnosis: _______________________________

6. ICU Admission Classification:  
   - [ ] Medical  
   - [ ] Surgical  
   - [ ] Trauma (+/- Surgical)  
   - [ ] Mixed (Med/Surg)  
   - [ ] Unknown

7. Admitted from:  
   - [ ] ER  
   - [ ] OR  
   - [ ] PACU  
   - [ ] WARD ____________

8. HIGHEST recorded temperature on DAY OF ICU admission: __________

9. LOWEST recorded temperature on DAY OF ICU admission: __________

10. Acetaminophen received on DAY OF ICU admission:  
    - [ ] NONE  
    - [ ] 325 mg x _________  
    - [ ] 650 mg x _________  
    - [ ] 975/1000 mg x _________  
    - [ ] Unknown

11. If Acetaminophen given, for what purpose?  
    - [ ] Pain control  
    - [ ] Fever control  
    - [ ] Both  
    - [ ] Unknown

12. Any other NSAIDS given on DAY OF ICU admission?  
    - [ ] YES  
    - [ ] NO  
    - [ ] Unknown
14. Presence of Infection on the DAY OF ICU Admission:

Please tick if cultures were drawn. Also if samples were taken, tick results as they are completed.

- Blood Cultures
  - Negative
  - Positive
  - Microbe

- Sputum Cultures
  - Negative
  - Positive
  - Microbe

- Urine Cultures
  - Negative
  - Positive
  - Microbe

- Wound Cultures
  - Negative
  - Positive
  - Microbe

15. Antibiotics Ordered on the DAY of ICU Admission

<table>
<thead>
<tr>
<th>Drug</th>
<th>YES</th>
<th>NO</th>
<th>UNKNOWN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td></td>
<td>Route</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16. CORE TEMPERATURE MONITORING

Please ensure some form of core temperature monitoring has been established.

- Esophageal temp. probe
  - Pre-existing
  - Inserted by RN
  - Research Team

- Foley cath. temp. probe
  - Pre-existing
  - Inserted by RN
  - Research Team

- Other
  - Pre-existing
  - Inserted by RN
  - Research Team

17. For Esophageal probes only

  Insertion depth (in cm) Confirmed on next X-ray

18. FOR MEASUREMENT VERIFICATION (compare 2 measures simultaneously)

  Initial Core Temp Reading (°C)
  Initial Oral Temp Reading (°C) Time (24hr format)
III. Participant Demographics (obtained from ICU Database)

For data extracted from the ICU database, the “DAY OF ICU Admission” is as per standard practice of the ICU database (Questions 3 to 5 are also obtained from ICU database).

1. Acute Physiology and Chronic Health Evaluation II (APACHE II) Recorded as the WORST physiologic values on the DAY OF ICU ADMISSION (Knaus, Draper, Wagner, & Zimmerman, 1985).

<table>
<thead>
<tr>
<th>Physiologic Variables</th>
<th>Abnormally High Range</th>
<th>Abnormally Low Range</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>≥41°C</td>
<td>39-40.9°C</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>38.5-38.9°C</td>
<td>36-38.4°C</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>34-35.9°C</td>
<td>32-33.9°C</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>30-31.9°C</td>
<td>≤29.9°C</td>
<td>+1</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>≥160</td>
<td>130-159</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>110-129</td>
<td>70-109</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>50-69</td>
<td>≤49</td>
<td>+2</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≥180</td>
<td>140-179</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>110-139</td>
<td>70-109</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>55-69</td>
<td>40-54</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>≤39</td>
<td></td>
<td>+1</td>
</tr>
<tr>
<td>Respiratory Rate (vent or non-vent)</td>
<td>≥50</td>
<td>35-49</td>
<td>+5</td>
</tr>
<tr>
<td></td>
<td>25-34</td>
<td>12-24</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>10-11</td>
<td>6-9</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>≤5</td>
<td></td>
<td>+2</td>
</tr>
</tbody>
</table>

Oxygenation A-aDO₂ or PaO₂ (mmHg)

If FIO₂ ≥0.50 then record A-aDO₂:

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
</tr>
<tr>
<td>350-499</td>
</tr>
<tr>
<td>200-349</td>
</tr>
<tr>
<td>&lt;200</td>
</tr>
</tbody>
</table>

If FIO₂ <0.50 then record PaO₂:

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70</td>
</tr>
<tr>
<td>61-70</td>
</tr>
<tr>
<td>55-60</td>
</tr>
<tr>
<td>&lt;55</td>
</tr>
</tbody>
</table>

Arterial pH (preferred)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7.7</td>
</tr>
<tr>
<td>7.6-7.69</td>
</tr>
<tr>
<td>7.5-7.59</td>
</tr>
<tr>
<td>7.33-7.49</td>
</tr>
<tr>
<td>7.25-7.32</td>
</tr>
<tr>
<td>7.15-7.24</td>
</tr>
<tr>
<td>&lt;7.15</td>
</tr>
</tbody>
</table>

Or Serum HCO₃ (mEq/L)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥52</td>
</tr>
<tr>
<td>41-51.9</td>
</tr>
<tr>
<td>32-40.9</td>
</tr>
<tr>
<td>22-31.9</td>
</tr>
<tr>
<td>18-21.9</td>
</tr>
<tr>
<td>15-17.9</td>
</tr>
<tr>
<td>&lt;15</td>
</tr>
</tbody>
</table>

Serum Sodium (mEq/L)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥180</td>
</tr>
<tr>
<td>160-179</td>
</tr>
<tr>
<td>150-159</td>
</tr>
<tr>
<td>130-149</td>
</tr>
<tr>
<td>120-129</td>
</tr>
<tr>
<td>111-119</td>
</tr>
<tr>
<td>≤110</td>
</tr>
</tbody>
</table>

Serum Potassium (mEq/L)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥7</td>
</tr>
<tr>
<td>6-6.9</td>
</tr>
<tr>
<td>5.5-5.9</td>
</tr>
<tr>
<td>3.5-5.4</td>
</tr>
<tr>
<td>3-3.4</td>
</tr>
<tr>
<td>2.5-2.9</td>
</tr>
<tr>
<td>&lt;2.5</td>
</tr>
</tbody>
</table>

Serum Creatinine (double points for acute renal failure)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35</td>
</tr>
<tr>
<td>200-349</td>
</tr>
<tr>
<td>150-199</td>
</tr>
<tr>
<td>60-140</td>
</tr>
<tr>
<td>&lt;60</td>
</tr>
</tbody>
</table>

Hematocrit

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.6</td>
</tr>
<tr>
<td>0.50-0.599</td>
</tr>
<tr>
<td>0.46-0.499</td>
</tr>
<tr>
<td>0.30-0.459</td>
</tr>
<tr>
<td>0.20-0.299</td>
</tr>
<tr>
<td>&lt;0.20</td>
</tr>
</tbody>
</table>

White Blood Cell Count (total/mm³)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥40</td>
</tr>
<tr>
<td>20-39.9</td>
</tr>
<tr>
<td>15-19.9</td>
</tr>
<tr>
<td>3-14.9</td>
</tr>
<tr>
<td>1-2.9</td>
</tr>
<tr>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Glasgow Coma Score

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCIRE = (GCS) - 15</td>
</tr>
</tbody>
</table>

TOTAL ACUTE PHYSIOLOGY SCORE (from above 12 items)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age points (in years): If</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>&lt;44 yrs</td>
</tr>
<tr>
<td>45-54 yrs</td>
</tr>
<tr>
<td>55-64 yrs</td>
</tr>
<tr>
<td>Chronic Health Points (See Next Page)</td>
</tr>
<tr>
<td>Non-operative or Emergency post-operative patients</td>
</tr>
<tr>
<td>Elective post-operative patients</td>
</tr>
</tbody>
</table>

TOTAL = Total Acute Physiology Score + Age Points + Chronic Health Points
Participant ID # _________    SEA-ICU Data Collection Form

CHRONIC HEALTH POINTS
Must have organ insufficiency or immuno-compromise that is evident PRIOR to this hospital admission. (If any are present then +2 for elective post-op, and +5 for non-op/emergency op.)

- **LIVER**
  - Biopsy proven cirrhosis & documented portal hypertension
  - Episodes of past upper GI bleeding attributed to portal hypertension
  - Or prior episodes of hepatic failure/encephalopathy/coma

- **CARDIOVASCULAR**
  - New York Heart Association Class IV (Cardiac dysfunction such that patient experiences shortness of breath and/or angina pain even at rest (bedbound patients)

- **RESPIRATORY**
  - Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or household duties)
  - Or documented chronic hypoxia, hypercapnia, secondary polycythemia
  - Or severe pulmonary hypertension (>40 mmHg)
  - Or respiratory dependency

- **RENAAL**
  - Chronic renal dialysis

- **IMMUNO-COMPROMISED**
  - Receiving therapy that suppresses resistance to infection such as:
    - immune-suppression, chemotherapy, radiation, long term or recent high does steroids
  - Or has a disease that is sufficiently advanced to suppress resistance to infection
    - Leukemia, Lymphoma, AIDS

2. Sequential Organ Failure Assessment (SOFA) SCORE on DAY OF ICU Admission (Most abnormal score of the day) (Ceriani et al., 2003; Ferreira, Bota, Bross, Mélot, & Vincent, 2001) If intervention day is between ICU day 1 to day 5, then SOFA scores obtained from ICU database:

<table>
<thead>
<tr>
<th>Variables</th>
<th>SOFA SCORES – ICU Day 1 (Admission)</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory PaO₂/FiO₂ mmHg</td>
<td>0 1 2 3 4</td>
<td></td>
</tr>
<tr>
<td>&gt;400</td>
<td>≤400  ≤300  ≤200 §  ≤100 §</td>
<td></td>
</tr>
<tr>
<td>Coagulation Platelets x10³/L</td>
<td>&gt;150  ≤150  ≤100  ≤50  ≤20</td>
<td></td>
</tr>
<tr>
<td>Liver Bilirubin, umol/L</td>
<td>&lt;20  21-33  34-100  101=204  &gt;204</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension  MAP &lt;70mmHg  Dop ≤5 or Dob at any dose†</td>
<td></td>
</tr>
<tr>
<td>Central nervous system:</td>
<td>15  13-14  10-12  6-9  &lt;6</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal: Creatinine, μmol/L or urine output mL/24hrs</td>
<td>109 110-172 173-304 305-436 or u/o &lt;500mL &gt;436 or u/o &lt;200mL</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SOFA SCORE:

§ Values are with respiratory support; † in mcg/kg/min; max infusion rate for at least 1 hour (including Norepi 0.1mcg/kg/min ≈ 7mcg/min).
### Participant ID # _________    SEA-ICU Data Collection Form

#### Variables

<table>
<thead>
<tr>
<th>Score</th>
<th>SOFA SCORES – ICU Day 2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory PaO₂/FiO₂ mmHg</td>
<td>&gt;400</td>
<td></td>
</tr>
<tr>
<td>Coagulation Platelets x10⁹/μL</td>
<td>&gt;150</td>
<td></td>
</tr>
<tr>
<td>Liver Bilirubin, umol/L</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypertension</td>
<td>MAP ≤5 or Dob at any dose†</td>
</tr>
<tr>
<td>Central nervous system: Glasgow Coma Scale</td>
<td>15</td>
<td>13-14</td>
</tr>
<tr>
<td>Renal: Creatinine, umol/L or urine output mL/24hrs</td>
<td>&lt;109</td>
<td>110-172</td>
</tr>
</tbody>
</table>

**TOTAL SOFA SCORE:**

§ Values are with respiratory support; † in mcg/kg/min; max infusion rate for at least 1 hour (including Norepi 0.1mcg/kg/min ≈ 7mcg/min)

### Variables

<table>
<thead>
<tr>
<th>Score</th>
<th>SOFA SCORES – ICU Day 3</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory PaO₂/FiO₂ mmHg</td>
<td>&gt;400</td>
<td></td>
</tr>
<tr>
<td>Coagulation Platelets x10⁹/μL</td>
<td>&gt;150</td>
<td></td>
</tr>
<tr>
<td>Liver Bilirubin, umol/L</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypertension</td>
<td>MAP ≤5 or Dob at any dose†</td>
</tr>
<tr>
<td>Central nervous system: Glasgow Coma Scale</td>
<td>15</td>
<td>13-14</td>
</tr>
<tr>
<td>Renal: Creatinine, umol/L or urine output mL/24hrs</td>
<td>&lt;109</td>
<td>110-172</td>
</tr>
</tbody>
</table>

**TOTAL SOFA SCORE:**

§ Values are with respiratory support; † in mcg/kg/min; max infusion rate for at least 1 hour (including Norepi 0.1mcg/kg/min ≈ 7mcg/min)
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>SOFA SCORES – ICU Day 4</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂ mmHg</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;400</td>
<td>≤400</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
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<tr>
<td>Platelets x10^3/μL</td>
<td>&gt;150</td>
<td>≤150</td>
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<tr>
<td>Liver Bilirubin, umol/L</td>
<td>&lt;20</td>
<td>21-33</td>
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<td><strong>Liver</strong></td>
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<td>Bilirubin, umol/L</td>
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<td><strong>Cardiovascular Hypotension</strong></td>
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<tr>
<td>Central nervous system:</td>
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<tr>
<td>Glasgow Coma Scale</td>
<td>15</td>
<td>13-14</td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td>Creatinine, μmol/L or urine</td>
<td>&lt;109</td>
<td>110-172</td>
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<tr>
<td>output mL/24hrs</td>
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</tbody>
</table>

**TOTAL SOFA SCORE:**

§ Values are with respiratory support; † in mcg/kg/min; max infusion rate for at least 1 hour (including Norepi 0.1mcg/kg/min ≈ 7mcg/min)

### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>SOFA SCORES – ICU Day 5</th>
<th>SCORE</th>
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</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
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<tr>
<td>PaO₂/FiO₂ mmHg</td>
<td>0</td>
<td>1</td>
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<td></td>
<td>&gt;400</td>
<td>≤400</td>
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<tr>
<td><strong>Coagulation</strong></td>
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<tr>
<td>Platelets x10^3/μL</td>
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<td></td>
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<tr>
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<td>110-172</td>
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<tr>
<td>output mL/24hrs</td>
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<td></td>
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</tbody>
</table>

**TOTAL SOFA SCORE:**

§ Values are with respiratory support; † in mcg/kg/min; max infusion rate for at least 1 hour (including Norepi 0.1mcg/kg/min ≈ 7mcg/min)
IV. Pre-Intervention Safety Check

ICU patient’s status can change notably from day to day, and a participant may be waiting until a fever is detected before proceeding to the intervention phase, which could be days later. For this reason, please complete a pre-intervention safety check on the proposed day of intervention, PRIOR to administering the study drug. This safety check includes:

- reconfirming the eligibility criteria,
- reconfirming the ICU physician is not opposed,
- obtaining baseline data, and organ function/illness severity data,
- and calibrating measurement equipment.

If for any reason, this participant no longer meets the eligibility criteria, then DO NOT PROCEED with the intervention phase. Continue to monitor, until such time it is determined either, the participant should be withdrawn from the study, or meets eligibility criteria at a later time.

### Eligibility Criteria

1. **INCLUSION CRITERIA – Meets ALL Inclusion Criteria**
   - Adult patients (> 18 years) admitted to ICU at Vancouver Hospital
   - Have a New fever as defined by either
     - Core temperature ≥ 38.3 °C for 2 or more consecutive hours,
     - or a core temperature ≥ 39.0 °C for 15 consecutive minutes,
     - AND not longer than 48 hours.
   - Continuous arterial pressure monitor in place at the time of intervention and data collection.
   - Participant has NOT participated in this study before.
   - To remain in the ICU for the entire study period (i.e., 2 hours prior to drug administration to 4 hours post drug administration).

2. **EXCLUSION CRITERIA – Must NOT have any of the Exclusion Criteria on the day of intervention (check if evidence of):**
   - Significant liver dysfunction (as evident by elevated liver enzymes)
   - Acute neurological injury (i.e. diagnosed during this current hospital admission)
   - Seizure disorder
   - Cardiomyopathy, as evidenced by:
     - Elevated cardiac enzymes indicative of an acute cardiac injury,
     - ECG changes indicative of cardiac ischemia (i.e., ST elevation/depression)
   - Hemodynamic instability as evident by
     - Requiring fluid boluses in past 2 hours, or greater than 5 mcg/min of vasopressors in past 2 hours. Patients receiving steady doses of vasopressor support may be included)
   - Any documented positive Pregnancy Test during this hospital admission
Participant ID # ___________ SEA-ICU Data Collection Form

☐ Severe hypoxemia,
   FiO2 requirements of more than 60% to maintain an SaO2 > 90%
   And/or PaO2 > 70)
☐ Temperature > 40.0 °C for ≥ 15 minutes in previous 2 hours
☐ Receiving external cooling
☐ Any treatment where blood is taken out of the body for processing such as
   Haemodialysis,
   Plasma exchange, etc.
☐ Acute thermal injury to skin (i.e., burn)
☐ Gut malabsorption (i.e., receiving < 40% required calories enterally)
☐ Receiving medications that have known antipyretic effects
   (Acetaminophen, ibuprofen, steroids, etc.)

If any of the exclusion criteria were checked, please provide details as to why.
_______________________________________________________________________
_______________________________________________________________________
_______________________________________________________________________
_______________________________________________________________________

Reconfirming with ICU Physician

3. Please confirm with the responsible ICU physician (ICU Staff, Fellow or assigned Resident) that is still okay to proceed with the intervention phase of this study.
   Physician consulted
   ☐ ICU Staff MD
   ☐ ICU Fellow
   ☐ ICU Resident

☐ Physician OK to proceed
☐ Physician OPPOSES proceeding to the Intervention
   ☐ At this time (do not proceed until Physician is OK at a later time)
   ☐ At all (Withdraw participant from this study)
Baseline Organ Function

4. SOFA SCORE on the DAY OF INTERVENTION (use the most abnormal values from the day of intervention) Complete if Day of ICU admission ≠ Day of Intervention.

<table>
<thead>
<tr>
<th>Variables</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory PaO₂/FiO₂ mmHg</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤300</td>
<td>≤200 §</td>
<td>≤100 §</td>
<td></td>
</tr>
<tr>
<td>Coagulation Platelets x10³/μL</td>
<td>&gt;150</td>
<td>≤150</td>
<td>≤100</td>
<td>≤50</td>
<td>≤20</td>
<td></td>
</tr>
<tr>
<td>Liver Bilirubin, umol/L</td>
<td>&lt;20</td>
<td>21-33</td>
<td>34-100</td>
<td>101-204</td>
<td>&gt;204</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>MAP &lt;70mmHg</td>
<td>Dop ≤5 or Dob at any dose†</td>
<td>Dop &gt;5, Epi ≤0.1, or Norepi ≤0.1†</td>
<td>Dop &gt;15, Epi &gt;0.1, or Norepi &gt;0.1†</td>
<td></td>
</tr>
<tr>
<td>Central nervous system:</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal: Creatinine, μmol/L or urine output mL/24hrs</td>
<td>&lt;109</td>
<td>110-172</td>
<td>173-304</td>
<td>305-436 or u/o &lt;500mL</td>
<td>&gt;436 or u/o &lt;200mL</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SOFA SCORE:

§ Values are with respiratory support; † in mcg/kg/min; max infusion rate for at least 1 hour (including Norepi 0.1mcg/kg/min ≈ 7mcg/min)

**DO NOT PROCEED IF PARTICIPANT SCORES 3 OR 4 ON THE LIVER FUNCTION VARIABLE OF THE SOFA SCORE.**

If participant scores 2 on liver function variable, review with ICU physician before proceeding with intervention.
V. Pre-Intervention Verification

1. Date of Intervention (MM/DD/YYYY) _______________ ICU Day: _______________
2. LAST ACETAMINOPHEN Prior to Intervention
   DOSE _________ ROUTE _________ TIME _________ DATE ____________

(If ICU Admission date is the SAME as the Intervention Date, then skip questions 3 to 14 in this section)

3. HIGHEST recorded temperature on DAY OF INTERVENTION: __________
4. LOWEST recorded temperature on DAY OF INTERVENTION: __________
5. Acetaminophen received on DAY OF INTERVENTION: □NONE
   □325 mg x _________
   □650 mg x _________
   □975/1000 mg x _____
   □Unknown

6. If Acetaminophen given, for what purpose: □Pain control
   □Fever control
   □Both
   □Unknown

7. Any other NSAIDS given on DAY OF INTERVENTION □YES
   □NO
   □Unknown

8. If yes to other NSAIDS, Name(s):_________ Dose(s)_________ Purpose __________
   Name(s):_________ Dose(s)_________ Purpose __________
   Name(s):_________ Dose(s)_________ Purpose __________
   Name(s):_________ Dose(s)_________ Purpose __________

Measurement Calibration – Core Temperature Monitoring

9. CORE TEMPERATURE MONITORING
   □Esophageal temperature probe
   □Foley catheter temperature probe
   □Other _______________

10. For Esophageal probes only
    Insertion depth (in cm) ______________ Confirmed on next X-ray □YES □NO
Participant ID # ___________  SEA-ICU Data Collection Form

11. FOR MEASUREMENT VERIFICATION
   Initial Core Temp Reading (°C) _______________
   Initial Oral Temp Reading (°C) _______________ Time (in 24hr format)
   □ Not Documented

**Measurement Calibration – Arterial Monitoring**

12. Arterial Line Site:  □ Radial  □ Left □ Right
    □ Femoral  □ Left □ Right
    □ Other _______________  □ Left □ Right

13. Zero Arterial Line Now, & record Time
    Time (24hr format) _______________

14. Confirm Transducer levelled at Mid-Axillary line:  □ Confirmed.

15. Perform Square test  □ Satisfactory (good square with flushing, minimal swing)
    □ Overshooting (good square with flushing, with swing)
    □ Dampened (does not form complete square with flushing)

16. Overall Function:  □ Very Good Function (waveform consistent)
    □ Good Function (waveform mostly consistent, occasionally dampens with participant Movement)
    □ Okay Function (waveform dampens with participant movement)
    □ Poor Function (waveform frequently dampened)

17. FOR MEASUREMENT VERIFICATION (compare 2 measures simultaneously) in mmHg
    Initial Arterial BP Systolic/Diastolic (MAP) _______________
    Initial NiBP ____________________ Time (in 24hr format) _______________

   NiBP Cuff Size  □ L (35.5-46.0 cm)
   □ M (27.5-36.5 cm)
   □ S (20.5-28.5 cm)
   □ Other ________________________________

   NiBP Location  □ Arm  □ Left □ Right
   □ Thigh  □ Left □ Right

*After you have completed the art line verification, please print out the waveforms from network printer.*

- *Include ECG, Art line tracing (set scale at 200 mmHg) and respiratory waveform.*
- *Include ECG & CVP tracing (scale set at 30 mmHg)*
VI. Pre-Intervention Data Collection

Fluid Status (day before intervention if available)

1. Data available for day BEFORE Intervention
   ☐ YES (complete questions 2-4 in this section)
   ☐ NO – Comment

   ______________________________________________________________
   ______________________________________________________________
   (If no, then skip to question 5)

2. Previous (Day before intervention) 24 hour fluid Balance:

   24 hour INTAKE: ______________ 24 hour OUTPUT ______________

3. Previous day INTAKE SUMMARY
   24 hour IV intake Total ________ Crystalloid ____________
   Colloid ____________
   24 hour Enteral Intake Total (all sources) __________
   Feed Type ____________ 24 hour Feed volume _________
   Actual total caloric intake __________ (from dietician notes)

4. Previous day OUTPUT SUMMARY
   24 hour TOTAL output (all sources) ________________
   24 hour URINE TOTAL output ________________

Fluid Status (day of intervention)

5. Day of intervention 24 hour fluid Balance: ______________________
   24 hour INTAKE: ______________ 24 hour OUTPUT ______________

6. Intervention day INTAKE SUMMARY
   24 hour IV intake Total ________ Crystalloid ____________
   Colloid ____________
   24 hour Enteral Intake Total (all sources) __________
   Feed Type ____________ 24 hour Feed volume _________
   Actual total caloric intake __________ (from dietician notes)

7. Intervention day OUTPUT SUMMARY
   24 hour TOTAL output (all sources) ________________
   24 hour URINE TOTAL output ________________
### Infections and Antibiotic Status (day of intervention)

8. Presence of Infection on the DAY OF ICU Admission:
   *Please tick if cultures were drawn. Also if samples were taken, tick results as they are completed.*

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
<th>Microbe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Cultures</td>
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<tr>
<td>Sputum Cultures</td>
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<td>Urine Cultures</td>
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<td>Wound Cultures</td>
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9. Antibiotics Ordered on the DAY of ICU Admission

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
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<tbody>
<tr>
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<td>Drug</td>
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<td>Drug</td>
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</table>
10. Pre-Intervention start time (24 hr format) ______________________________

11. VENTILATION SETTINGS
   a. BEGINNING BASELINE SETTINGS (at start of pre-intervention period)
      Mechanical Ventilation: □ YES □ NO
      MODE _________________ SETTINGS ________________________
      FiO2 ___________________ PEEP (cm H₂O) ___________________
      Actual Resp Rate (breaths/min) ______________
      Tidal Volumes (mL) ______________
      Minute Ventilation L/min) ______________
      Peak Pressure (cm H₂O) ______________

   b. RECORDED VENTILATION CHANGES
      Time _______________ Change ________________________________
      Time _______________ Change ________________________________
      Time _______________ Change ________________________________
      Time _______________ Change ________________________________

12. IV INTAKE
   c. BASELINE (at start of pre-intervention period) TIME (HH:MM):

<table>
<thead>
<tr>
<th>Infusion/Drug</th>
<th>Concentration</th>
<th>Fluid Rate</th>
<th>Pump Total</th>
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<tr>
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</table>
16. Either digital recording or hard copy print out of vital sign data must be inputted into this case file. For the Pre-Intervention 2 hour period, these include:
   Q 5 minute core temperature
   Q 5 minute heart rate
   Q 5 minute blood pressure (SBP/DBP & MAP)
   Q 5 minute oxygen saturation
   If digitally recorded, will also include ECG and arterial waveform recording (for data verification purposes)
VII. Post-Intervention Data Collection (i.e. 4 hours Post Intervention)

1. TIME intervention was administered (As per the time indicated on the CARESCAPE Patient Monitor) (24 hour clock HH:MM) HH_______MM ______

2. Method of Study Drug Administration:
   - ☐ Nasogastric Tube
   - ☐ Orally (participant able to swallow medication)

4. VENTILATION SETTINGS
   a. BEGINNING BASELINE SETTINGS (at START of POST-intervention period)
      - Mechanical Ventilation: ☐ YES ☐ NO
      - MODE _______________ SETTINGS _____________________
      - FiO2 ___________________ PEEP (cm H2O) _____________
      - Actual Resp Rate (breaths/min) _________________
      - Tidal Volumes (mL) _______________
      - Minute Ventilation (L/min) __________
      - Peak Pressure (cm H2O) ___________

   b. RECORDED VENTILATION CHANGES
      - Time _______________ Change _________________________________
      - Time _______________ Change _________________________________
      - Time _______________ Change _________________________________
      - Time _______________ Change _________________________________
      - Time _______________ Change _________________________________
      - Time _______________ Change _________________________________

   c. END OF STUDY SETTINGS (at END of POST-intervention period)
      - Mechanical Ventilation: ☐ YES ☐ NO
      - MODE _______________ SETTINGS _____________________
      - FiO2 ___________________ PEEP (cm H2O) _____________
      - Actual Resp Rate (breaths/min) _________________
      - Tidal Volumes (mL) _______________
      - Minute Ventilation (L/min) __________
      - Peak Pressure (cm H2O) ___________


5. IV INTAKE

f. BASELINE (at START of POST-intervention period) TIME (HH:MM): ______

<table>
<thead>
<tr>
<th>Infusion/Drug</th>
<th>Concentration</th>
<th>Fluid Rate Start of Intervention</th>
<th>Fluid Rate at 4 hours POST Intervention</th>
<th>Pump Total Start of Intervention</th>
<th>Pump Total at 4 hours POST Intervention</th>
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</table>

a. RECORDED IV CHANGES: Please review nurses notes, and medication administration record and document any changes to IV intake that occur in the pre-intervention period. Include volume of intermittent medications. Specifically record any fluid boluses (crystalloid or colloid) and changes in inotrope rates.

TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________
TIME: ______ CHANGE: _____________________________________

b. Did the participant experience a clinically significant episode of hypotension as (defined by a required a fluid bolus of ≥ 500 cc and/or an acute increase in inotropes of > 5 mcg/min norepinephrine) in the 2 hour pre-intervention period?

☐ YES  ☐ NO
Participant ID # _________    SEA-ICU Data Collection Form

6. BASELINE ORAL INTAKE
   a. Beginning BASELINE FEED INTAKE (rate in cc/hr) _____________________
   b. RECORDED CHANGES
      TIME:_________ CHANGE: _______________________________________
      TIME:_________ CHANGE: _______________________________________
      TIME:_________ CHANGE: _______________________________________
      TIME:_________ CHANGE: _______________________________________
      TIME:_________ CHANGE: _______________________________________
      TIME:_________ CHANGE: _______________________________________

7. HOURLY URINE OUTPUT (in cc/hr)
   HOUR ______ OUTPUT _________
   HOUR ______ OUTPUT _________
   HOUR ______ OUTPUT _________
   HOUR ______ OUTPUT _________
   HOUR ______ OUTPUT _________

8. ALL OTHER OUTPUT (please comment)
  ____________________________________________________________________
  ____________________________________________________________________
  ____________________________________________________________________
  ____________________________________________________________________
  ____________________________________________________________________

17. Either digital recording or hard copy print out of vital sign data must be inputted into this case file. For the POST-Intervention 6 hour period, these include:
   Q 5 minute core temperature
   Q 5 minute heart rate
   Q 5 minute blood pressure (SBP/DBP & MAP)
   Q 5 minute oxygen saturation
   If digitally recorded, will also include ECG and arterial waveform recording (for data verification purposes)
VIII. Completion & Safety Log

1. AT THE POINT OF STUDY COMPLETION:

Please consult with the ICU team (RN/MD) to determine if the ICU team deem it medically beneficial to continue monitoring core temperature.

☐ YES, medically valuable, temperature probe left in place
☐ NO, temperature probe removed

2. RISKS & ADVERSE EVENTS

a. TEMPERATURE PROBE: Where there any concerns, difficulties adverse events associated with:
   At Insertion   ☐ YES   ☐ NO
   During Monitoring ☐ YES   ☐ NO
   Upon Removal   ☐ YES   ☐ NO   ☐ N/A

   If YES to any of the above, please comment. __________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________

b. HIGH FEVER: Did the participant experience a high fever (greater than 40.0 °C)
   For any length of time?   ☐ YES   ☐ NO

   If YES, what was the duration (in minutes) of temp greater than 40.0 °C?  ____________

   If duration is > 15 minutes, was un-blinding procedure completed?
   ☐ YES   ☐ N O

   If YES, please report on un-blinding process.
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
c. HEMODYNAMIC INSTABILITY: Did the participant have a clinically significant hypotensive event?
   ☐ YES ☐ NO

   Did the participant have a MAP below 55 mmHg at any time?
   ☐ YES ☐ NO

   If YES, what was the TOTAL duration of time (in minutes) the participant had a MAP below 55 mmHg during the post intervention period?
   __________________________

   Did the participant have a MAP below 45 mmHg at any time?
   ☐ YES ☐ NO

   If YES, what was the TOTAL duration of time (in minutes) the participant had a MAP below 45 mmHg during the post intervention period?
   __________________________

   Were there any concerns, comments or adverse events associated with this episode of hypotension?
   ______________________________________________________________
   ______________________________________________________________
   ______________________________________________________________
   ______________________________________________________________
   ______________________________________________________________
   ______________________________________________________________
   ______________________________________________________________
   ______________________________________________________________

 d. REQUESTS FOR UN-BLINDING: AT ANY POINT, did the ICU team request the participant to be un-blinded for any reason?
   ☐ YES ☐ NO

   If YES, please describe why request was made, how the un-blinding process proceeded, and any other outcomes as a result.
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 e. Are there any other safety concerns? Please explain.
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