Participants' Views of Delayed Consent for a Randomised Controlled Trial in Intensive Care

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Certificate of Authorship/Originality

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Signature of Student

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Abstract

Each year many people experience critical illness and require a stay in an intensive care unit. Critical illness has a high mortality, making evaluation of therapies a priority for research in this area. Research conducted in the critical care environment is difficult with respect to obtaining first person informed consent. Patients who are critically ill have diminished capacity for decision making and consequently they are rarely able to provide informed consent before enrolment in a clinical trial. In Australia, critically ill patients are enrolled into clinical trials using delayed consent. However, there is a paucity of research on the opinion of clinical trial participants about consent obtained following enrolment.

The aim of this study was to determine the opinion of participants enrolled in the NICE-SUGAR study, under the provision for delayed consent, of the delayed consent process. A secondary aim was to investigate their opinions of third party consent and their preferences for decision makers. Former ICU patients who were enrolled in the NICE-SUGAR study at the Royal North Shore Hospital (RNSH) with delayed consent, who were cognitively intact when screened, and were judged to have sufficient proficiency in the English language, were contacted and invited to participate in this study. Willing participants completed a questionnaire regarding their opinion of the delayed consent process. The questionnaire was developed for this study and contained fixed response and open ended questions.

There were 634 participants in the NICE-SUGAR study at the RNSH, 256 of these former ICU patients were contacted and responses were received from 210 (response rate 82%). Participants were 37.6% female with mean±SD age of 61±16 and APACHE II scores of 18±6.79. Delayed consent was obtained from participants (57/210; 27.1%) and the substitute decision maker (152/210; 72.4%). Most respondents (195/204; 95.6%) reported they would have consented to participate in NICE-SUGAR if asked before enrolment. Most respondents (163/198; 82.3%), ranked first (mean=1.49) “the person who consented on their behalf for the NICE Study” as most preferred to make decisions on their behalf. Most (177/202; 87.6%) agreed with the decision made by their relative/friend.

In conclusion, most former ICU patients who had been enrolled in the NICE-SUGAR study from the RNSH with delayed consent, would have provided consent to participate had they been capable. Furthermore, most respondents agreed with the decision made by the substitute decision maker.

Chapter One: Background and Literature Review

1.1 Introduction

Each year many people in Australia and New Zealand (ANZ) require a stay in an intensive care unit (ICU) due to critical illness. For example, in the 2005/2006 financial year over 163,000 people were admitted to an ICU (Martin, Hart & Hicks 2010). Critical illness typically includes acute medical conditions such as cardiac arrest, respiratory distress, haemorrhagic or septic shock, trauma and traumatic brain injury. Characteristics of critical illness include sudden onset, severity and high mortality rate. The hospital mortality rate from critical illness is high (16%) (Moran et al. 2008) and in some subgroups, such as those who experience severe sepsis, it is even higher (over 37%) (Finfer et al. 2004). However, the overall mortality rate from critical illness has been falling over time, due in part to research into treatments in this area. A difficulty for health care research is the unpredictability and high acuity of critical illness, which reduces the likelihood of the patient providing prospective, informed consent.

Traditionally, investigators seek consent from the patient before enrolment in health care research, but this procedure is difficult during critical illness. One difficulty is the time dependant nature of potential enrolment in a clinical study. Other difficulties are the effects of critical illness and subsequent treatments, such as sedation, on the patient's cognitive functioning. The resulting cognitive impairment coupled with a frequent inability to communicate verbally, due to the presence of artificial airways, contributes to the patient's loss of decision making capacity. The patient's lack of decision making capacity is often present when they would be typically invited to provide prospective, informed consent for participation in research. Consequently the inability of critically ill patients to provide first person consent may reduce their likelihood of enrolment in clinical studies, and deprive them of the benefits of participation in research.

In order that patients who lack decision making capacity can participate in health care research, additional methods to prospective, first person informed consent may be approved by an institutional ethics committee. Those methods include third party consent provided by the substitute decision maker, provision of a waiver of consent, that is, no consent, and delayed or deferred consent either from the participant or the substitute decision maker. In Australia, the National Statement (National Health and Medical Research Council, Australian Research Council & Australian Vice-Chancellors' Committee 2007) provides guidance for human research ethics committees (HREC)s to evaluate the appropriate consent procedure for a clinical

study. The context of the clinical study is considered and the balance of risks versus benefits is based on available evidence relating to choices, perceptions and vulnerability of the relevant population. Accordingly, research risks may be classified as negligible risk, low risk and greater than minimal risk. When a HREC approves the use of delayed consent, eligible patients may be enrolled in a clinical trial and study treatment commenced in the absence of consent. Written informed consent, either to continue participation or to use the data, is obtained subsequently. Most patients were enrolled using delayed consent in intensive care randomised controlled trials (RCTs) in fluid resuscitation (SAFE Study Investigators et al. 2004), continuous dialysis for acute kidney failure (RENAL Replacement Therapy Study Investigators et al. 2009) and targeted blood glucose management (NICE-SUGAR Study Investigators et al. 2009).

When HREC approvals of the clinical study have been obtained, some states in Australia have additional regulations in order for the substitute decision maker to be authorised to provide consent for the patient who lacks decision making capacity. In New South Wales, a clinical trial of experimental treatment involving patients unable to give consent requires approval by the Guardianship Tribunal in order to authorise the "person responsible" to provide substitute consent. When the clinical trial compares available treatments the person responsible is able to provide substitute consent, as with medical treatment. The person responsible is not necessarily the next of kin, but is defined in a hierarchy of: legal guardian(s); the most recent spouse or defacto partner who has a close, continuing relationship with the patient; an unpaid carer or a relative, such as an adult child, or friend, or another such person previously nominated by the patient (Guardianship Tribunal 2011). In this thesis the term "substitute decision maker" is given the same meaning as the "person responsible" and is interchangeable with other terminology such as surrogate, legal surrogate, surrogate decision maker, proxy decision maker and legal representative.

There are some potential difficulties associated with third party consent provided by the substitute decision maker. One potential difficulty is that family members may be unavailable when the patient is eligible to be enrolled in a clinical study. Not all jurisdictions have legislation that authorises family members or other relatives (when available), to provide consent for the critically ill patient to participate in research. Other potential problems are centred on the ability of the substitute decision maker to understand the medical information contained in a consent form. Substitute decision makers experience stress and other emotional problems that may limit their capacity to process detailed information. They may fail to accurately predict the patient's potential decision to enroll in clinical studies.

In addition to potential difficulties associated with the substitute decision maker providing informed consent, there are some problems with the delayed consent process. The validity and legality of obtaining delayed consent for research in which prior consent had not occurred has been questioned. The delayed consent process is currently not permitted by institutional ethics committees in all states, even within the same country. For example, variation exists in the method of consent approved by different hospitals' ethics committees for the same protocol, as reported by the NICE-SUGAR study Investigators (2009) in the Normoglycaemia in Intensive Care-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study. Delayed consent was permitted in New South Wales but not in all Australian states.

The NICE-SUGAR study was a RCT conducted in the ICUs of 42 hospitals in ANZ, Canada and the United States (US). Ethics approval was provided by the institutional ethics committee from the University of Sydney, the University of British Columbia and each hospital. Written informed consent was obtained either before randomisation or subsequently using delayed consent from each patient, substitute decision maker or HREC. Eligible critically ill patients were allocated to either conventional or intensive blood glucose control; 6104 patients were randomised. The study results were reported in March 2009. The findings revealed that patients whose blood sugar was allowed to be in the conventional range had higher rates of survival (NICE-SUGAR Study Investigators et al. 2009).

Despite the problems obtaining informed consent either from or on behalf of patients who lack decision making capacity, investigators in ANZ have enrolled more patients in multicentre, RCTs in absolute terms and per capita, than from other countries such as Canada and the US (Bellomo, Stow & Hart 2007). One of the reasons for this disparity in recruitment over the past decade may be HREC approval of the delayed consent process in ANZ, supporting increased participation of critically ill patients who lack decision making capacity in health care research. However, there is a paucity of published data regarding participants' views of their enrolment in a RCT using the delayed consent process. The opinions of participants who were enrolled when they lacked decision making capacity have not been sought regarding decisions made by the substitute decision maker to provide consent. This research project investigated the views of surviving former participants in the NICE-SUGAR study, who were enrolled using the process of delayed consent from the Royal North Shore Hospital, Sydney. Their opinions were sought regarding their enrolment using the delayed consent process and of decisions to consent made by the substitute decision maker.

1.2 Consent for Research in Intensive Care

Traditionally investigators seek prospective, informed consent from the patient before enrolling them in health care research. A patient may be able to consider the information over a number of days before making a decision to participate in a clinical study. Knifed et al. (2008) reported that participants in neuro-oncology clinical trials improved their understanding of the clinical trial when returning to the hospital to give informed consent, after being provided with study information earlier. Patients attributed this improvement in understanding to being allowed more time to review the study information in their home, and being able to discuss participation with whomever they wanted before providing informed consent. However, the provision of time is not typically available in the case of critical illness research. The onset of critical illness is often unpredictable so the patient has little or no warning of the need for treatment in an ICU. Once the patient fulfils the eligibility criteria for enrolment in a clinical study, it is unlikely they will regain decision making capacity in time to provide prospective, valid informed consent.

Valid informed consent for research consists of three major elements: adequate disclosure of the information, sufficient understanding of the information and voluntariness of the decision (Silverman & Lemaire 2006). Critically ill patients are rarely able to provide valid informed consent for research because they are often unconscious and unable to effectively communicate their wishes when eligible for enrolment in a clinical study. For example, rates of prior written informed consent from patients for RCTs conducted in ICU are low, 0.6% (SAFE Study Investigators et al. 2004), 2.6% (Harvey et al. 2006) and 3% (Annane et al. 2004).

When seeking consent investigators disclose standardised and complete information about the clinical study using an information sheet and consent form approved by the HREC. Study information sheets explain the clinical study purpose, methods, interventions, alternative treatments and benefits or risks that may potentially be experienced by the participant. Legal details regarding compensation and confidentiality (National Health and Medical Research Council, Australian Research Council & Australian Vice-Chancellors' Committee 2007) are also included, which may result in some documents as long as eight pages (Silverman et al. 2005). These detailed forms must be understood and signed by the patient or the substitute decision maker when providing informed consent for participation in health care research. However, there may be limited time available for the patient or the substitute decision maker to sufficiently understand both the information and the implications of participation when the patient is eligible for enrolment in a clinical study.

Critically ill patients often lack the cognitive capacity to sufficiently understand detailed information in order to make an informed decision. There are several factors that contribute to a patient's diminished cognitive capacity and difficulties communicating, such as the severity of illness and intensive care treatments including artificial airways, sedatives and analgesics. While cognitive impairment is usually temporary, it may continue for some days or weeks during the hospital stay. The patient's understanding of the documentation and the investigator's response to questions may be limited by emotional factors and stress. The loss of decision making capacity during the intensive care, and sometimes hospital stay, make critically ill patients a vulnerable population.

The voluntariness of decisions made by critically ill patients may be impaired due to their psychological and physical vulnerability. Patients are physically vulnerable because they are ostensibly captive in the ICU and dependent on the ICU team for care and therapy (Luce et al. 2004; Rischbieth, Blythe & Australian and New Zealand Intensive Care Society Clinical Trials Group 2005; Schweickert & Hall 2005). Vulnerability due to an impaired capacity for decision making, physical dependency, as well as the unpredictable and severe nature of critical illness collectively result in ICU patients rarely having the ability to provide written informed consent before enrolment in research.

Despite the difficulties in obtaining valid informed consent from the patient, evidence suggests that patients benefit from inclusion in a clinical study, regardless of the treatment arm, due to more stringent application of protocolised care or guidelines. Braunholtz, Edwards, & Lilford (2001) highlight evidence that closer observation of patients during well conducted RCTs benefit participants. A combination of factors such as closer attention to the implementation of protocolised care, which in itself is linked to improved patient outcomes, provides benefits to participants. An example is the NICE-SUGAR study; both groups in the investigation conducted by the NICE-SUGAR study Investigators et al. (2009) received protocolised care via a standardised algorithm for maintenance of blood sugar targets. The proportion of participants who experienced severe hypoglycaemia was markedly less (6.8%) in the intensive control group than that reported in large English hospitals (42%) (Mackenzie et al. 2005), which used the bedside nurse alone to manage glycaemic control per usual practice.

1.3 Alternative Methods of Consent for Research

Institutional ethics committees may approve methods of consent in addition to prospective, informed consent from the patient for intensive care research, where patients who lack decision making capacity are necessarily part of the study population. Methods include third party consent provided by the substitute decision maker, HREC provision of a waiver of consent, and delayed or deferred consent either from the participant or the substitute decision maker.

Substitute decision maker consent

The substitute decision maker is typically the first person approached to provide consent for research on behalf of the patient who lacks decision making capacity. An authorised substitute decision maker is expected to make a decision that represents the best interests of the patient who lacks decision making capacity, regarding participation in a clinical study.

The substitute decision maker may be approached to provide consent either before or subsequent to enrolment of the patient in a clinical study. For example, the majority of participants (n=393; 81.2%) had written or oral relative assent obtained before randomisation or soon afterwards in the PAC-Man study, conducted in the United Kingdom (UK) (Harvey et al. 2006). However, in Europe, the European Union Directive 2001/20/CE, enacted in 2004, required prospective informed consent from the legal representative of patients who lacked decision making capacity to participate in research (Lemaire et al. 2005).

Waiver of consent

A HREC may approve a complete waiver of consent, such that the participants or the substitute decision maker will typically be unaware of the patient's involvement in research, as with database analyses and observational studies (National Health and Medical Research Council, Australian Research Council & Australian Vice-Chancellors' Committee 2007). A HREC may also approve a waiver of consent for interventional studies on patients with emergency medical conditions. This provision is important in the conduct of critical illness research because of the often limited time available in which to locate the appropriate substitute decision maker to provide written informed consent. Provision of a waiver of consent can positively affect the timely commencement of the study treatment, particularly in clinical studies with limited eligibility windows. Monthly recruitment rates for a clinical study in critical illness are also improved by the provision of a waiver of consent.

In a RCT with a limited time framework for patient enrolment, provision of a waiver of consent assists enrolment of eligible patients. An example is the Corticosteroid Randomization After Significant Head Injury (CRASH) trial (CRASH Trial Management Group 2004), a multicentre RCT coordinated from the UK, that required adult patients with acute traumatic brain injury to be randomised within eight hours of the traumatic event. The investigators found that institutional ethics committees in 78 of 116 sites approved patient enrolment using a waiver of consent. The average time from injury to randomisation was shorter (3.2 hours), in sites using the waiver of consent than sites where prior consent was required from a relative (4.4 hours).

Investigators observed recruitment rates increased when an institutional ethics committee waived the requirement for consent. For example, the CRASH study investigators found the average monthly recruitment in sites approved to use a waiver of consent was more (2 patients per month) than sites that required prior consent from a substitute decision maker, usually a relative (1.5 patients per month) (CRASH Trial Management Group 2004). In France, Annane et al. (2004) found recruitment in a clinical trial on a treatment for sepsis increased greatly from four to 10 participants per month following approval of a waiver of consent from the French Competent Authority.

Delayed consent

Patients may be enrolled in clinical trials using the process of delayed or deferred consent. The delayed or deferred consent process permits enrolment of a patient who lacks decision making capacity when they are eligible, study procedures or interventions are commenced and data are collected in the absence of consent. The option of either withdrawing or providing written informed consent is subsequently offered to either the participant or their substitute decision maker at an appropriate time (National Health and Medical Research Council, Australian Research Council & Australian Vice-Chancellors' Committee 2007; Rischbieth, Blythe & Australian and New Zealand Intensive Care Society Clinical Trials Group 2005). In Australia, the National Statement provides guidelines for HRECs to approve delayed consent for clinical studies when it is impossible to conduct the research involving a consenting patient and the risks are in proportion to the condition treated. In addition, there must be a reasonable possibility of benefit to the participant over standard care and any potential risks must be outweighed by potential benefits to the participant. Therefore the participant may be willing to consent to continue participation in the clinical study (National Health and Medical Research Council, Australian Research Council & Australian Vice-Chancellors' Committee 2007).

Thousands of critically ill patients have been enrolled in RCTs conducted in ANZ using delayed consent. It was used in clinical trials that compared emergency treatments, for example the landmark Saline versus Albumin Fluid Evaluation (SAFE) study, conducted in 17 ANZ ICUs. Delayed consent was used to enroll most patients (6628 of 6997; 94.7%), with consent provided by 38.8 % (n=2713) of participants and the remaining two thirds from the substitute decision maker or a HREC (SAFE Study Investigators et al. 2004). Delayed consent was also approved by HRECs in RCTs that evaluated other available standard treatments such as continuous dialysis for acute kidney failure (RENAL Replacement Therapy Study Investigators et al. 2009) and targeted blood sugar control (NICE-SUGAR Study Investigators et al. 2009).

1.4 Potential Problems with the Substitute Decision Maker

There are some potential problems with third party consent provided by the substitute decision maker. When a patient who lacks decision making capacity is eligible to be enrolled in a clinical study, a practical concern for investigators, particularly in clinical studies with a limited timeframe for enrolment, is the lack of availability of the substitute decision maker. For instance, in France, Annane et al. (2004) found substitute decision makers were unavailable for the 74% of participants who were enrolled using a waiver of consent, so those patients would otherwise not have been included in the study. In the US, Cooke et al. (2010) reviewed screening logs from three RCTs in acute lung injury (ALI) conducted by the Acute Respiratory Distress Syndrome Network (ARDSnet). From 17,459 patients screened only 10.6% (n=1,855) were enrolled, with 5.4% (n=936) excluded because the patient was unable to provide consent and the substitute decision maker was unavailable.

Other potential problems with the substitute decision maker include authorisation of family members or other relatives to provide consent, their capacity for decision making and their ability to accurately predict the patient's decision of whether to potentially consent to enrolment in a clinical study.

Authorisation of the substitute decision maker

The authorisation and designation of the substitute decision maker to provide third party consent for health care research varies between countries. In ANZ, the US, Canada and most Western European countries family members are authorised to provide consent for research. Other European countries such as Austria, Germany and Italy require consent for research to be provided by a legal representative who is appointed by a judge (Robinson & Andrews 2010). In the UK, Harvey et al (2006) reported that if the personal representative related to the patient is unavailable, then a professional legal representative such as the patient's treating doctor or a person

nominated by the health care provider may provide consent. However, Gong, Winkel, Rhodes, Richardson, & Silverstein (2010) reported that in the US, 6% of research ethics committees (RECs) do not approve surrogate consent under any circumstance and only 68% of RECs permit adult children to provide consent for research. The restriction on the selection of family members or other relatives may not be congruent with the wishes of critically ill patients, and may limit their participation in health care research.

Decisional capacity of the substitute decision maker

Consent on behalf of the patient who lacks decision making capacity to participate in research is often sought at a time when the substitute decision maker is experiencing stress and emotional distress, typically as a result of the sudden onset and severity of the patient's illness. These psychological factors may limit the capacity of the substitute decision maker to understand the details of medical information contained in a consent form (Eyler & Jeste 2006). The process of making medical treatment decisions in particular has been described to have substantial negative emotional effects on approximately one third of substitute decision makers, which can last for many years (Wendler & Rid 2011).

Adverse symptoms of anxiety, depression and post-traumatic stress disorder (PTSD) are described in family members of critically ill patients between the third and fifth day of a patient's stay in the ICU. In a study conducted in 43 adult and paediatric ICUs in France, Pochard et al. (2001) identified high rates of symptoms of anxiety (69%) and of depression (35%) reported by family members (n=836) of critically ill patients. In a hospital in the US, McAdam, et al. (2010) also identified high rates of anxiety (80%) and of depression (70%) in family members. Over 57% of family members in the US study had moderate to severe levels of traumatic stress symptoms. Female gender was associated with anxiety and depression symptoms in both studies (McAdam et al. 2010; Pochard et al. 2001). Those symptoms may affect the decision making capacity of substitute decision makers when required to provide consent for research on behalf of the patient.

The requirement to make decisions about medical treatment and research participation for ICU patients, who lack decision making capacity, may be related to family members experiencing moderate PTSD symptoms. Azoulay et al. (2005) reported that decisions about consenting for research were associated with PTSD symptoms in over 35% of family members following the patient's death or discharge from one of 21 ICUs in France. This proportion was substantially higher than that related to decisions about clinical care such as tracheotomy and to discussions about

the appropriate level of care, found to be related to PTSD symptoms in 6.4% and 9.6% of cases respectively. Female gender and younger age were associated with PTSD symptoms (Azoulay et al. 2005).

Another factor contributing to the difficulty of decision making for the substitute decision maker is the uncertainty regarding the patient's position on participation in research studies. This uncertainty may have contributed to relatives asked to provide surrogate consent for one study (Abramson & Safar 1990), delaying decision making until they had consulted with other family members and sometimes a private physician when deciding whether to consent for a clinical study.

Accuracy of the substitute decision maker

Lack of agreement with decisions regarding potential enrolment in hypothetical clinical studies has been described between patients and substitute decision makers. Potential decisions regarding consent for enrolment in a clinical study made by the substitute decision maker and the ICU physician were compared to the patient's decision for the same study. The patient's decision either to potentially enroll or to refuse participation in the hypothetical clinical study was considered the correct one. Investigators in two studies compared decisions from 100 surrogate-patient pairs and 100 surrogate-patient-ICU physician combinations, for potential enrolment in hypothetical ICU RCT scenarios. Coppolino & Ackerson (2001) interviewed patients and their surrogate when they attended a booking for elective cardiac surgery at a single centre in the US. Ciroldi et al. (2007) interviewed ICU patients who had stayed in one of ten adult ICUs in France for >48 hours, and their surrogate and the ICU physician on the day of ICU discharge. The surrogate was reported to potentially enroll the patient against their wishes in 16% (Coppolino & Ackerson 2001) and 11% of cases (Ciroldi et al. 2007) for the minimal risk scenarios. Furthermore, Ciroldi et al. reported the rate of discrepancy in potential enrolment decisions was reported to be greater between patients and surrogates (32%) than patients and physicians (25%). This result may indicate that physicians are marginally better able to predict a patient's potential wishes for enrolment in hypothetical research than the surrogate. However it is difficult to compare the results of these studies due to the different patient populations. A limitation of the study conducted in the US is that the sample was comprised entirely of elective cardiac surgical patients. This group is seldom included in intensive care research due to their low mortality rate and lack of eligible conditions. Another limitation for both studies was the use of hypothetical clinical study scenarios.

A problem when interpreting results from hypothetical clinical trial scenarios is that participants may view the hypothetical scenario differently compared to an actual clinical trial of equivalent risk or benefit. An example of this are the opinions about waived consent expressed by focus groups of participants (n=42), from 15 buildings of the 61 community locations from New York City, in the Public Access Defibrillation (PAD) trial. An unexpected finding was that participants gave different and sometimes opposite views about the acceptability of the actual study they were enrolled in versus an equivalent hypothetical scenario the group had previously discussed (Richardson et al. 2005). These findings indicate that participants in an actual trial perceive research risks differently than when presented with theoretical enrolment in a hypothetical trial. A possible reason for this discrepancy may be the influence of previous personal experience with the medical profession and investigators.

Decisions made by participants and their substitute decision makers to potentially enroll in hypothetical ICU clinical trials were associated with factors including education levels and age. Coppolino & Ackerson (2001) reported strong agreement between the patient and the substitute decision maker to potentially enroll in the minimal risk scenario. This was associated with patient characteristics of median age >61yrs and education level less than college attendance. A predictor of less agreement in decisions was an age difference of greater than five years between patients and substitute decision makers. In the study conducted in France, Ciroldi et al. (2007) found no association between characteristics of study participants and decisions made regarding potential enrolment in the hypothetical scenarios. However, there were some findings regarding a need for information, with many substitute decision makers reporting they would have liked further information about the prognosis, diagnosis and treatment. This finding may be indicative of the limitation of hypothetical scenarios or a perception by substitute decision makers of limited time provided to study participants to understand the scenario and complete the survey.

In summary, despite the jurisdictional variation in legislation authorising personnel to provide third party consent for health care research, it appears the designation of substitute decision maker is predominantly a family member or other relative. There appears to be some consistent evidence that many substitute decision makers experience symptoms of anxiety, depression and PTSD during and after the patient's ICU stay. Those psychological symptoms are related to decisions regarding the patient's medical management and consent for research. Female relatives and family members of younger patients report symptoms more frequently. Stress and emotional distress experienced by substitute decision makers may affect their ability to

sufficiently understand detailed medical information and consequently to make valid, informed decisions on behalf of the patient. Potentially, patients may be enrolled in ICU clinical studies against their wishes, although the conclusions that may be drawn from previous research in decision making for clinical studies in ICU are limited due to the use of hypothetical scenarios.

1.5 Potential Problems with Delayed or Deferred Consent

There are some potential problems related to the delayed consent process. Investigators in multicentre RCTs have found that not all institutional ethics committees approved enrolment of eligible patients using the delayed consent process, despite hospitals following the same research protocol. An example is the NICE-SUGAR study. The NICE-SUGAR Study Investigators et al. (2009) reported a disparity in recruitment related to the consent procedure permitted by different states and countries. A provision for delayed consent was used at some ANZ but not Canadian hospitals. A high number of patients (n=1634) were eligible but not enrolled as they were unable to provide consent before randomisation, the substitute decision maker was unavailable and local institutional ethics committee regulations did not permit delayed consent.

The validity and legality of obtaining deferred consent for research in which prior consent had not occurred has been questioned. In the US, the Office for the Protection from Research Risks at the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) banned deferred consent in 1993. Subsequently the Department of Health and Human Services Code of Federal Regulations (CFR) was amended in 1996 and the conditions were revised for the application of waived consent for research into treatments for life-threatening illness (Salzman et al. 2007). The consent procedure endorsed under the “Final Rule” permits patients to be enrolled using a waiver of consent with a proviso that community consultation and public disclosure occur before the study commences. The substitute decision maker must be informed subsequently when appropriate and offered the opportunity to withdraw the patient (Lemaire 2007), thereby reinstating a modified deferred consent process.

1.6 Preferences for Informed Consent

The preferences of members of the general public and former ICU patients, should they hypothetically lose decision making capacity, vary regarding agreement for a relative to act as their substitute decision maker to provide consent for participation in research. In Australia, Stephenson et al. (2007) described agreement with substitute decision maker consent for a hypothetical greater than minimal risk clinical study to be acceptable by one quarter of relatives surveyed in ICU and Emergency Department

(ED) waiting rooms in a metropolitan hospital. Relatives who reported they were sick, disabled or unemployed agreed to consent by a substitute decision maker more often, whereas those who reported their occupation as home or family duties were more likely to object to research. A perception of benefit to participants from the research study was associated with a willingness to participate. However, this study has limitations such as the small proportion of relatives of ICU patients, and the high number (60%) of "neutral" or "undecided" responses. In contrast to the Australian findings, many former ICU patients from Swiss (Chenaud et al. 2009) and Canadian (Scales et al. 2009) ICUs and members of the general public in Canada (Burns et al. 2011) and France (Azoulay et al. 2003), were reported to agree to potential consent by a substitute decision maker for hypothetical ICU research scenarios.

Former ICU patients and their relatives prefer potential consent for research to be provided by the relative, should the patient be hypothetically admitted to ICU in an unconscious state. In Switzerland, Chenaud et al. (2009) surveyed pairs of former surgical ICU patients and their relatives (n=52 pairs) three years after the patient was discharged from hospital. A postal self-report questionnaire was used to record patient and relative preferences for potential consent for two hypothetical ICU research studies, one in which the patient was unconscious and one in which the patient was conscious. Most patients (72%) and relatives (67%) preferred a relative to potentially provide consent if the hypothetical patient was unconscious. However, one quarter of patients (n=13) and nearly one third of relatives (n=15) were indecisive about whether to agree or to decline participation in the hypothetical research scenarios. The results of this study are difficult to generalise because of the poor response rate (52 of 400; 13%) and small sample size.

Little is known of the preferences of ICU patients for additional methods of seeking informed consent for critical illness research. Scales et al. (2009) interviewed former ICU patients (n=240) from five university-affiliated hospitals to investigate preferences for potential informed consent with a substitute decision maker available or not available. Hypothetical clinical study scenarios varied from a baseline scenario with respect to risk, low or increased risk and intervention, standard or new. The consent model participants most preferred (n=180; 76%) was consent by the substitute decision maker before enrolment regardless of the hypothetical level of risk. The delayed consent model with enrolment followed by consent from the participant or the substitute decision maker was preferred by a small number of respondents (n=21; 8.9%). However, when the substitute decision maker was unavailable the majority (n=175; 77%) preferred delayed consent to waived consent.

Opinions of enrolment using delayed consent

There is a paucity of information regarding the opinions of actual ICU patients regarding enrolment using delayed consent. There are low refusal rates of consent to continue participating in RCTs conducted to evaluate treatments for acute medical conditions and comparisons of available standard treatments, which had HREC approval to enroll patients using delayed consent. In the SAFE study, 56 of 6997 participants or substitute decision makers withheld or withdrew consent following enrolment (SAFE Study Investigators et al. 2004). The NICE-SUGAR Study Investigators et al. (2009) reported that in the NICE-SUGAR study few (74 of 6104; 1.2%) participants had consent either withheld or withdrawn, or the use of study-related data and the recording of outcome measures refused. The RENAL Replacement Study Investigators et al. (2009) reported a low rate of refusal to continue (24 of 869; 2.8%) by participants or substitute decision makers, for patients who were enrolled using delayed consent. Similarly, Harvey et al. (2006) reported that in the PAC-Man study, only six of 169 participants refused consent subsequent to regaining mental capacity. However, a limitation of the PAC-Man study is the high mortality rate in the study population. From 500 randomised patients nearly half (49.8%) were deceased before seeking participant consent following relative agreement, thus many participants' opinions were unable to be ascertained. These findings suggest that some patients enrolled in research using delayed consent may disagree with that process. Although there may be other unknown factors that contribute to the low rate of refused consent or withdrawal from treatment.

1.7 Summary of Findings Located in the Literature

Patients who require a stay in intensive care are critically ill and need treatment urgently. A difficulty in evaluating treatments for critical illness is obtaining informed consent for research from patients, because they often lack decision making capacity and are unable to communicate verbally at the time they are eligible for enrolment in a clinical trial. The traditional method of obtaining informed consent, before enrolling the patient in health care research, is rarely possible in critical illness because of the unpredictable onset and high acuity of the medical conditions commonly treated. Therefore alternative methods may be approved by HRECs to ensure that patients who lack decision making capacity are not unfairly deprived of the benefits from participation in research. Those methods include obtaining informed consent for ICU research from the substitute decision maker. Other methods include a HREC waiving the requirement for consent, and delayed or deferred consent either from the participant, substitute decision maker or the HREC.

In ANZ, many critically ill patients were enrolled in RCTs using the process of delayed consent, with consent obtained subsequently from the patient, substitute decision maker or the HREC. However, the ability of the substitute decision maker to make valid decisions and accurately predict the patient's wishes regarding enrolment in research may be affected by stress and emotional problems. Despite that difficulty, it appears that former ICU patients prefer their relatives to provide potential consent for enrolment in hypothetical clinical scenarios. A fundamental problem is a lack of published data from the Australian population regarding the opinions of patients who were enrolled in an actual RCT using delayed consent, of that process, and of decisions made on their behalf when they lacked decision making capacity.

1.8 Outline of the Thesis

Given the potential problems regarding enrolment of critically ill patients in RCTs using delayed consent, this thesis addresses the questions of whether patients enrolled in the NICE-SUGAR study from the RNSH, in Sydney, Australia, agreed with enrolment using the delayed consent process and with decisions to consent made by the substitute decision maker. This chapter has provided an overview of methods of consent for health care research in critical illness. Potential problems were identified regarding the ability of the substitute decision maker to provide informed consent on behalf of patients who lack decision making capacity. Preferences of members of the public and former ICU patients for methods of seeking consent for clinical studies in intensive care were also described. The aims of this study are outlined in the final section of the chapter.

In chapter two the research methods are outlined including the process of data collection and the analysis procedures. Chapter three presents the results of the study, describing the characteristics of the study sample and the results with respect to the research questions. Chapter four discusses the interpretation of the results, identifies the strengths and limitations of the study and explores the implications of the results on future ICU research with respect to research participants, substitute decision makers and institutional ethics committees and concludes in relationship to the study questions.

1.9 Study Aims

The broad aim of the study described in this thesis was to investigate the opinions of former ICU patients who were enrolled in the NICE-SUGAR study from the RNSH, in Sydney, Australia, using the process of delayed consent.

The following questions were addressed in the research:

1. What are adult intensive care participants' opinions of delayed consent when it was used to enroll them in the NICE-SUGAR study?
2. When the substitute decision maker provided consent, or was approached for consent, was there congruence between the decision of the participant and the decision of their substitute decision maker, to consent or decline continued participation the NICE-SUGAR study?

Chapter Two: Methods

2.1 Introduction

This chapter describes the research design, the setting, the sample and the recruitment procedures. Methods of data collection, data management, ethical considerations and an overview of the methods of data analysis are described. The development and testing of the study questionnaire are detailed.

This study is a substudy of the NICE-SUGAR study. The sample population was former ICU patients who were enrolled in the NICE-SUGAR study from the ICU at the RNSH, Sydney using delayed consent. To summarise the eligibility criteria for the NICE-SUGAR study, included patients were adults (aged ≥ 18 years) who had an arterial catheter in situ and the opinion of the treating doctor was that treatment would be required beyond the following calendar day. Patients were excluded if they were expected to be having oral nutrition in that time, were thought to be at risk of hypoglycaemia or were admitted for treatment of diabetic ketoacidosis. All eligible patients were required to be enrolled in the NICE-SUGAR study within 24 hours of admission to the ICU (NICE-SUGAR Study Investigators 2005).

2.2 Research Design

This project is an observational study that combined quantitative and qualitative methods. Quantitative and qualitative data were collected concurrently within the same survey instrument, a printed self-report questionnaire that was designed specifically for this study. Additional quantitative data were collected from electronic databases, paper medical records and case report forms.

Data regarding respondent characteristics, self-reported attitudes, opinions and, or, beliefs were sourced directly from respondents in the survey questionnaire. Measurable items were used such as forced choice questions and a Likert scale to produce quantitative data. Qualitative data were produced from responses to two open ended questions in the survey questionnaire, where respondents could write their thoughts and additional comments. Quantitative demographic data and details about participation in the NICE-SUGAR study were obtained from existing data sources such as the NICE-SUGAR study case report forms and the ICU database at the RNSH.

2.3 Setting

Patients were enrolled in the NICE-SUGAR study from the ICU at the RNSH from December 2004 to November 2008. This unit admits medical and surgical patients and consists of a 14-bed general ICU, a nine-bed cardiothoracic ICU and an eight-bed neurosurgical ICU. RNSH is a metropolitan 600-bed hospital in Sydney, Australia. It is a tertiary referral centre for several specialties, including spinal cord injury, burn injury, trauma, renal disease and cardiology. The ICUs are classified as 'closed units' with intensive care staff specialists overseeing treatment in each unit.

2.4 Sample

All of the NICE-SUGAR study participants who were enrolled at the RNSH (n=634) were assessed for eligibility to participate in this study. Participants were eligible to be approached if they met all inclusion and no exclusion criteria. Those criteria are detailed below:

Inclusion criteria

1. Enrolled in the NICE-SUGAR study under the provision of delayed consent, including those for whom consent was obtained from the substitute decision maker.
2. Enrolled under the provision of delayed consent and later withdrawn from the NICE-SUGAR study treatment by their substitute decision maker, with consent provided for use of study-related data.

Exclusion criteria

1. Enrolled with written informed consent obtained from themselves or the substitute decision maker before randomisation in the NICE-SUGAR study.
2. Insufficient proficiency in the English language to complete the questionnaire.
3. Limited cognitive capacity when screened for this study. This criterion included participants who had preexisting impaired mental capacity, for example dementia, or had a Public Guardian or Power of Attorney appointed. Impaired cognitive capacity could be assessed by their carers, general practitioners or by the investigator (below).

2.5 Cognitive Assessment

In order to assess the cognitive capacity of former ICU patients with suspected cognitive impairment, the second question from the orientation section of the Mini-Mental State Exam (MMSE) (Folstein, Folstein & McHugh 1975), was used as a screening tool to assess cognitive capacity. This question was administered in the form of a request to former ICU patients to confirm their best postal address, ostensibly so that the survey package would reach them. This contact also enabled evaluation of the appropriateness of the person's conversation (Fan et al. 2008). When the responses

were dubious, key informants such as spouses and adult children were contacted, because they are considered to be highly reliable observers of a person's cognitive functioning (Gordon et al. 2004). Information about the former ICU patient's cognitive status was also sought from general practitioners.

Screening of former ICU patients, who had fulfilled the diagnostic criteria for a traumatic brain injury (TBI) at enrolment in the NICE-SUGAR study, was undertaken in consultation with an independent assessor. At approximately two years following enrolment in the NICE-SUGAR study the assessor had scored participant's functional neurological outcomes during a structured interview conducted using the Extended Glasgow Outcome Scale (GOSE) (Wilson, Pettigrew & Teasdale 1998). The GOSE is an eight-point hierarchical scale containing lower and upper ranges for three major outcome categories which are: severe disability (3-4), moderate disability (5-6) and good recovery (7-8). For this study, the allocated GOSE score, in combination with the independent assessor's judgement of the cognitive capacity of the individual, was used for evaluation of those who were categorised with a moderate disability. Individuals who were categorised with a good recovery were deemed to have cognitive capacity.

2.6 Questionnaire

Items in the questionnaire consisted of forced choice and open ended questions. Initially, the questionnaire contained 11 items consisting of two open ended questions and nine forced choice items including two rating scales. A five-point Likert scale item (strongly agree to strongly disagree), was used to measure the direction and intensity of self-reported opinions to statements about decisions made on the person's behalf. Participants also ranked their relative preferences for eight alternative people and organisations to give consent on their behalf when they were unable to decide for themselves. Demographic questions were positioned at the end of the questionnaire. Following pilot testing, the questionnaire was sent by mail (or email) to eligible previous NICE-SUGAR study participants

Pilot testing

Assessment of the questionnaire by one or more experts is a minimum prerequisite when judging whether it appeared appropriate for the intended purpose (Streiner & Norman 2008). Accordingly, a panel of volunteers comprised of intensive care staff specialists, social workers, senior nurses, a chaplain, a research coordinator, a nurse researcher, a ward clerk, a secretary and laypersons, reviewed the face validity and content validity of the questionnaire. Members of the panel reviewed the questionnaire twice before its distribution to study participants to assist in item generation, to ensure that questions had sufficient responses to choose from and to

identify any that were poorly worded, difficult to answer or understand and required revision.

The panel were given the questionnaire and feedback sheet with three questions to answer:

Are the questions written clearly?

Do the questions make sense?

Are there any other questions or issues you think we should ask about (Heyland, Tranmer & Kingston General Hospital I. C. U. Research Working Group 2001)?

The first round of pilot testing took place following approval of the questionnaire and cover letter by the Northern Sydney Central Coast Health (NSCCH) Hawkesbury HREC in January 2009. On this occasion there were 17 panel members made up of 16 health care personnel and one layperson. Responses were received from 10 health care personnel and the layperson. Their suggested revisions were incorporated into the questionnaire by replacing one item, addition of four Semantic Differential Rating Scales to indirectly measure subjective feelings and rewording of other items and the covering letter.

The revised questionnaire was sent for the second round of testing to six health care personnel and one layperson in April 2009. Responses were received from five health care workers and one layperson. An additional covering letter and telephone transcript was developed for participants who were withdrawn from the NICE-SUGAR study by their substitute decision maker. The feedback from the panel assisted in confirming the wording, layout, clarity and meaning of the items and was conducted with the aim of ensuring the questions were interpreted the same way by all respondents. A copy of the final participant questionnaire is enclosed (Appendix A).

2.7 Recruitment Procedures

Recruitment commenced following approval of the study and associated documents by the NSCCH HREC and subsequent ratification by the University of Technology Sydney (UTS) HREC. The hospital database was reviewed before contacting eligible former ICU patients to ascertain whether it contained a record of death. Current contact details were also confirmed for those who had subsequent admissions to hospitals in NSCCH.

Follow up procedure

A three stage follow up procedure was developed to maximise the return rate. The first stage involved initial contact via telephone to briefly introduce this study. The second stage was a reminder telephone call approximately one week later, using a technique described by Aitken, Gallagher & Madronio (2003) that was effective in maximising retention . Participants were also offered the opportunity to complete the survey by telephone with an independent research nurse at this point or to return it via fax or email. The third stage and final follow up was three weeks later when non-responders were reposted the information that was sent initially. If this final contact was unsuccessful, further attempts at follow up ceased and people were categorised as non-responders.

When the person could not be contacted, the next of kin, the local hospital or the general practitioner were contacted to ascertain the person's current address or their cognitive or survival status. A maximum of three telephone messages at different times of day and days of the week were left on their answering machine (when available), with the researcher's return telephone number. When these methods were unsuccessful in contacting the person, the information package was posted to the last known address.

The information package was addressed to the individual and included:

- A comprehensive cover letter on University and Area Health Service letterhead, signed by hand in blue ink to personalise the letter (Appendix C),
- A copy of the signed NICE-SUGAR study consent form as it was anticipated that former ICU patients may not recall they had been in the clinical trial, or remember (or be aware of) the identity of the person who provided consent on their behalf,
- Participant questionnaire,
- A copy of the one page NICE-SUGAR study results, also signed by hand in blue ink (Appendix D). The full publication was also provided when requested during the initial phone call or if notification was made subsequently,
- A postage paid envelope for return of the questionnaire.

The information package was also scanned and emailed when requested, in preference to mailing. Hard copies were posted if a postal address was known and if follow up proceeded to stage three.

2.8 Data Collection

The demographic and clinical characteristics of all NICE-SUGAR study participants enrolled at the RNSH were sourced mainly from the NICE-SUGAR case report forms and original copies of the signed consent forms. Demographic data included details of the patient's date of birth, gender and location before admission to the ICU. Patients who were admitted directly from the operating or recovery room were classified as operative admissions.

Severity of illness during the first 24 hours in the ICU was measured with the Acute Physiology and Chronic Health Evaluation (APACHE) II (Knaus et al. 1985) score that was collected routinely and obtained from the RNSH ICU database. This score can range from 0 to 71, with higher scores indicating a higher severity of illness, and was calculated from the worst physiological values in the first 24 hours of admission to ICU, plus points for chronic health and age. Total days spent in ICU and in hospital for that admission were also recorded. "Form 1 Demographic data" is provided (Appendix E).

Characteristics of randomisation in the NICE-SUGAR study and details about the type of consent obtained were sourced from the NICE-SUGAR study clinical trial records at the RNSH. Data collected included the date of randomisation in the NICE-SUGAR study and the allocated treatment group. Details recorded about written informed consent were the date it was obtained, who provided it and their relationship to the patient (for substitute decision maker consent). Also recorded was the geographical location of the patient when consent was obtained either in the ICU, the general ward or discharged from the RNSH. The classification of the known personnel who were involved in obtaining consent was recorded and the number of days from randomisation to the date that written informed consent was obtained. "Form 2 Characteristics of NICE study enrolment and consent" is provided (Appendix E).

Quality of secondary data sources

Demographic and NICE-SUGAR enrolment and consent data were predominantly obtained from the clinical trial records at RNSH. These data were collected by Research Coordinators during the course of the NICE-SUGAR study, and a selection had been source verified by study monitors from the coordinating centre at The George Institute (NICE-SUGAR Study Investigators et al. 2009). The details of who had provided the written consent and the date it was signed were verified by the investigator by checking the original NICE study Information Sheet and Consent Forms.

The classification of personnel involved in obtaining written informed consent was sourced from the original signed consent form, the case report forms and a database completed during the NICE-SUGAR study by the Research Coordinators at the RNSH.

2.9 Data Entry

Data were entered into a Microsoft Office Excel® (Microsoft Corporation, 1997) spreadsheet by the investigator and subsequently imported to PASW® Statistics GradPack 18 (SPSS, 2009). The quantitative data from the questionnaire were added to the database by two research nurses. The free text responses to the open ended questions were transcribed verbatim into Microsoft Office Word® (Microsoft Corporation, 2007) by a research nurse.

A random check to verify data accuracy was performed on 10% of the responder case report forms (n=21). A random number generator (Network) was used to select cases for 100% source data verification of the demographic data (Form 1), NICE-SUGAR enrolment/consent data (Form 2) and the questionnaire data. A data entry error of omission was found for only one question in the 21 sets of forms checked.

2.10 Data Analysis

The quantitative and qualitative datasets were analysed separately. The qualitative findings were used to complement the quantitative data findings and to give a greater depth of understanding of the quantitative results.

All quantitative data analysis was performed using PASW®. The semantic differential scales required an ‘X’ to be marked on a continuous line. The distance from the left edge of the line to the “X” was measured in millimetres (mm). The line measured 105mm in the questionnaire completed by respondents. A conversion factor was applied in the analysis to convert the line to 100mm.

Categorical data were summarised by frequencies and percentages. No assumptions were made regarding missing data when reporting proportions, the total responses for an item in the questionnaire are reported. Categorical variables were compared using Pearson Chi-Square test or Fisher’s exact test as appropriate.

Continuous data were assessed for normality using histograms. The data were summarised using means and standard deviation for normally distributed data and median and interquartile range for non-normally distributed data. Normally distributed data were compared using the 2-tailed Student t-test. Non-normally distributed data was compared using non-parametric tests such as Mann-Whitney U. For all comparisons a p-value of < 0.05 was considered statistically significant.

Content analysis was used to systematically interpret the free text responses to the open ended questions. The responses were read through a number of times to obtain a sense of the data. Exact words from the text that seemed to capture key ideas were highlighted and their frequencies counted. Text was tabulated and grouped into units of meaning, arising from text containing the key words. These units were further reduced by condensing the text and then allocating a code that was derived from the data and based on their representativeness of the ideas. Similar or related codes were confirmed in a thesaurus and grouped to form categories.

The investigator performed data analysis, under the supervision of the Principal and Cosupervisor. Selections of the codes developed for the content analysis were independently checked by the Principal Supervisor. Agreement was reached following discussion when there were differences in judgement.

2.11 Minimisation of Personal Bias

Duties of the investigator's previous position as an ICU Research Coordinator at the RNSH included obtaining consent and collecting data for the NICE-SUGAR study. Potentially, this previous relationship with former ICU patients and their families could introduce personal bias if the investigator completed the study questionnaire with participants via the telephone. To minimise this potential bias an independent research nurse, who was experienced in contacting former ICU patients, conducted all telephone interviews when completion of the questionnaire was needed. Verbal assent for this contact from the research nurse was obtained by the investigator when discussing telephone completion of the questionnaire with potential participants.

Another strategy to reduce personal bias was the development of an objective telephone transcript that was followed by the investigator when initial contact was made with former ICU patients (Appendix B). Therefore the invitation to participate in this study was presented in a similar manner for all people who were invited to participate. Subsequent telephone contact from the investigator was to follow up non-responders and to invite them to complete the questionnaire with the research nurse when necessary.

Using a combination of postal and telephone survey is a potential weakness of this study, resulting in different methods of data collection, and potentially the introduction of interviewer bias. However, by use of a single independent interviewer who did not previously have contact with former ICU patients regarding the NICE-SUGAR study, it was planned to minimise that potential.

2.12 Ethical Considerations

The study commenced following approval of the study procedures and documents including the questionnaire, data collection forms, telephone transcripts, cover letter and NICE-SUGAR results summary by the HREC (Appendix F). Consent was implied by completion and return of the questionnaire to the investigator. Consenting participants had the option of withdrawing at any time, either when contacted via the telephone or by non-return of the questionnaire.

The questionnaire contained items that could not be obtained from existing records, hospital records or the NICE-SUGAR study records. Inconvenience to participants was further minimised by ensuring the questionnaire included only questions to answer the study questions.

Emotional wellbeing of study participants

Contacting former ICU patients was undertaken using experienced researchers, in order to minimise possible distress from the contact. A referral mechanism to an intensive care Social Worker from RNSH was instituted and three referrals were made. Participants who disclosed medical issues to the investigator were advised to contact their general practitioner (GP) or specialist as appropriate.

Chapter Three: Results

3.1 Introduction

This chapter describes the demographic and clinical characteristics of the sample and of the population who were enrolled in the NICE-SUGAR study from the RNSH. The characteristics of enrolment in the NICE-SUGAR study and of delayed consent are described for respondents. Responses to the questionnaire are reported in a box plot and bar graphs. Preferences for decision makers are presented as frequencies and percentages. The results of the association of respondent characteristics to preferences for the person to consent on their behalf for the NICE-SUGAR study, using Pearson's Chi-Square and Fisher's exact tests, are presented. The results of the association of respondent characteristics to willingness to participate in NICE-SUGAR study, using Pearson's Chi-Square and Fisher's exact tests, are also presented. Content analysis was used to explore the comments provided by respondents in the questionnaire. The word frequency, which emerged from these comments are presented.

3.2 Participants

There were 634 ICU patients enrolled in the NICE-SUGAR study from RNSH. Nearly 60% of those participants were ineligible for this study. The main reason for ineligibility was that up until May 2010, over one third was deceased. A small number (n=33, 5.2%) were lost to follow up and a similar proportion (n=33, 5.2%) were excluded due to written informed consent obtained before enrolment. Over 40% of remaining participants were eligible to be approached to complete this study. Questionnaires were completed by 210 former participants in the NICE-SUGAR study, yielding a response rate of 82% (Figure 1).

Recruitment took place for this study from September 2009 until June 2010. The average time from enrolment in the NICE-SUGAR study to the date the questionnaire was completed was 153.73 weeks (SD ± 43.53), ranging from a minimum of 85 weeks to a maximum of 250 weeks.

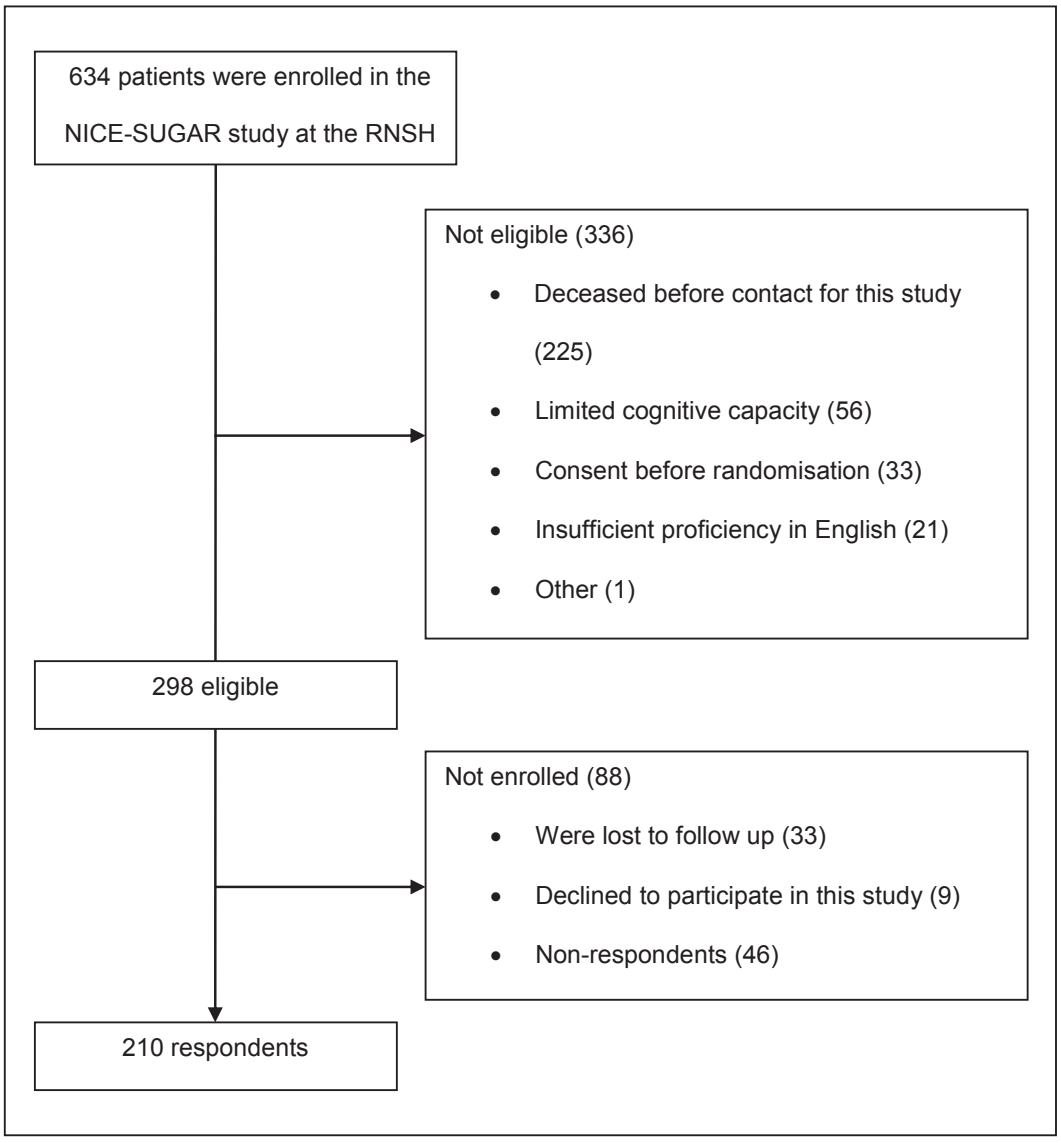

Figure 1 *Screening and enrolment*

3.3 Characteristics of Participants in the NICE-SUGAR study at the RNSH

Demographic, clinical and group allocation data were collected for all former ICU patients who were enrolled in the NICE-SUGAR study from the RNSH (Table 1). Respondents were on average 61 (SD ± 16) years of age with an APACHE II score of 18 (SD ± 6.8), and 38% were female. In contrast to responders, the non-responder group was younger, male, a higher proportion had a trauma classification when enrolled in the NICE-SUGAR study, and were allocated the intensive glucose control group.

Table 1

Characteristics of participants enrolled in the NICE-SUGAR study at the RNSH

Characteristic	Responder n=210	Non-responder & declined n=55	Total RNSH n=634
Age in years, mean (SD)*	61 (16.2)	60 (19.4)	64 (16)
Female (%)	79 (37.6)	17 (30.9)	226 (35.6)
APACHE II score, mean (SD)	18 (6.8)	18 (7.9)	20 (7.8)
APACHE II score ≥ 25 (%)	33 (15.7)	10 (18.2)	177 (27.9)
Reason for ICU admission *(%)*			
Operative	95 (45.2)	25 (45.5)	280 (44.2)
ICU Admitting Diagnostic Category *(%)*			
Cardiovascular	79 (37.6)	16 (29.1)	234 (36.9)
Trauma	41 (19.5)	13 (23.6)	97 (15.3)
Respiratory	30 (14.3)	7 (12.7)	93 (14.7)
Gastrointestinal	22 (10.5)	10 (18.2)	74 (11.7)
Neurological	21 (10.0)	5 (9.1)	86 (13.6)
Other	17 (8.1)	4 (7.3)	50 (7.9)
ICU length of stay in days, median (IQR)†	8 (4-12)	7 (4-13)	7 (4-13)
Hospital length of stay in days, median (IQR)	21 (13-36)	22 (14-37)	21 (12-36)
Group Assignment for the NICE-SUGAR study *(%)*			
Intensive glucose control	111 (52.9)	32 (58.2)	311 (49.1)
Conventional glucose control	99 (47.1)	23 (41.8)	323 (50.9)

Note. NICE-SUGAR=Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm, RNSH=Royal North Shore Hospital, APACHE=Acute Physiology and Chronic Health Evaluation, ICU=intensive care unit.

*SD Standard deviation.

†IQR Interquartile range.

3.4 Characteristics of Respondents

When completing the questionnaire over two thirds of respondents reported their general health was excellent (13/210; 6.2%), good (68/210; 32.4%) or very good (59/210; 28.1%) with approximately one third indicating fair (54/210; 25.7%) or poor (16/210; 7.6%) health. Half of respondents reported their highest education level as further study (including technical qualifications). Just over one third of respondents reported they were employed full time before the ICU admission (Table 2). Delayed consent for the NICE-SUGAR study was provided by the substitute decision maker for over 70% of respondents. The substitute decision maker was the respondent's spouse or partner in over half of cases. Approximately one quarter of the respondents who had written informed consent provided by their substitute decision maker, reported that previous discussions had been held regarding participation in research (Table 3).

Table 2

Demographic characteristics of respondents

Characteristics	*n*	Responses
Main language spoken at home *(%)*	208	
English only		188 (90.4)
European		15 (7.2)
Asian		4 (1.9)
Other		1 (0.5)
Highest education level attained *(%)*	209	
College/university (some or completed)		61 (29.2)
Technical school (some or completed)		44 (21.1)
High school (some or completed)		90 (43.1)
Other education		14 (6.7)
Main activity before ICU admission *(%)*	209	
Paid employment (full time)		80 (38.3)
Retired		55 (26.3)
Paid employment (part time/casual)		28 (13.4)
Domestic duties looking after home or family		21 (10.0)
Permanent long-term sickness or disability		18 (8.6)
Unpaid employment		4 (1.9)
Student		3 (1.4)

Note. Total % for some categories will deviate from 100% by ± 0.1% due to rounding.

Table 3

Characteristics of delayed consent for respondents

Characteristic	*n*	Total
Who provided written consent *(%)*	210	
Substitute decision maker (SDM)		152 (72.4)
Patient		57 (27.1)
HREC approval for data usage		1 (0.5)
Days from enrolment to written consent, median (IQR)*	209 †	4 (2-8)
Days to written consent from the SDM, median (IQR)		3 (1-5)
Days to written consent from the patient, median (IQR)		8 (5-27.5)
Relationship with the substitute decision maker *(%)*	152	
Spouse or partner		82 (53.9)
Adult child		36 (23.7)
Sibling		17 (11.2)
Parent		14 (9.2)
Other		3 (2.0)
Duration of relationship with the SDM in years, mean (SD) ‡	140	38 (15.8)
Previously discussed participation in research with the SDM *(%)*	142	
No		109 (76.8)
Yes		33 (23.2)
Classification of staff who obtained consent *(%)*	210	
Research Coordinator		145 (69)
Staff Specialist in Intensive Care		36 (17.1)
Registrar or Resident (medical trainee)		29 (13.8)
Location of the patient when written consent was obtained *(%)*	210	
Inpatient in ICU		158 (75.2)
Inpatient in the general ward		36 (17.1)
Following discharge from the hospital		16 (7.6)

Note. Total % for some categories will deviate from 100% by ± 0.1% due to rounding.

*Interquartile range.

†The value was not included for the respondent who had written consent provided by the HREC.

‡Standard deviation.

3.5 Opinion of Delayed Consent

The majority of respondents reported favourably regarding enrolment in the NICE-SUGAR study when they were eligible, and unable to make a decision themselves. The distribution of responses was positively skewed towards delighted, pleased, content and fair (Figure 2). A small proportion of respondents rated their feeling as “don’t know” regarding delighted-angry (16/153, 10.5%), pleased-displeased (14/170, 8.2%), content-discontented (10/167, 6.0%) and fair-unfair (15/170, 8.8%). A few respondents reported negative responses, for example angry (n=4/153), displeased (n=1/170) and discontented (n=1/167), with the same person selecting displeased and discontented.

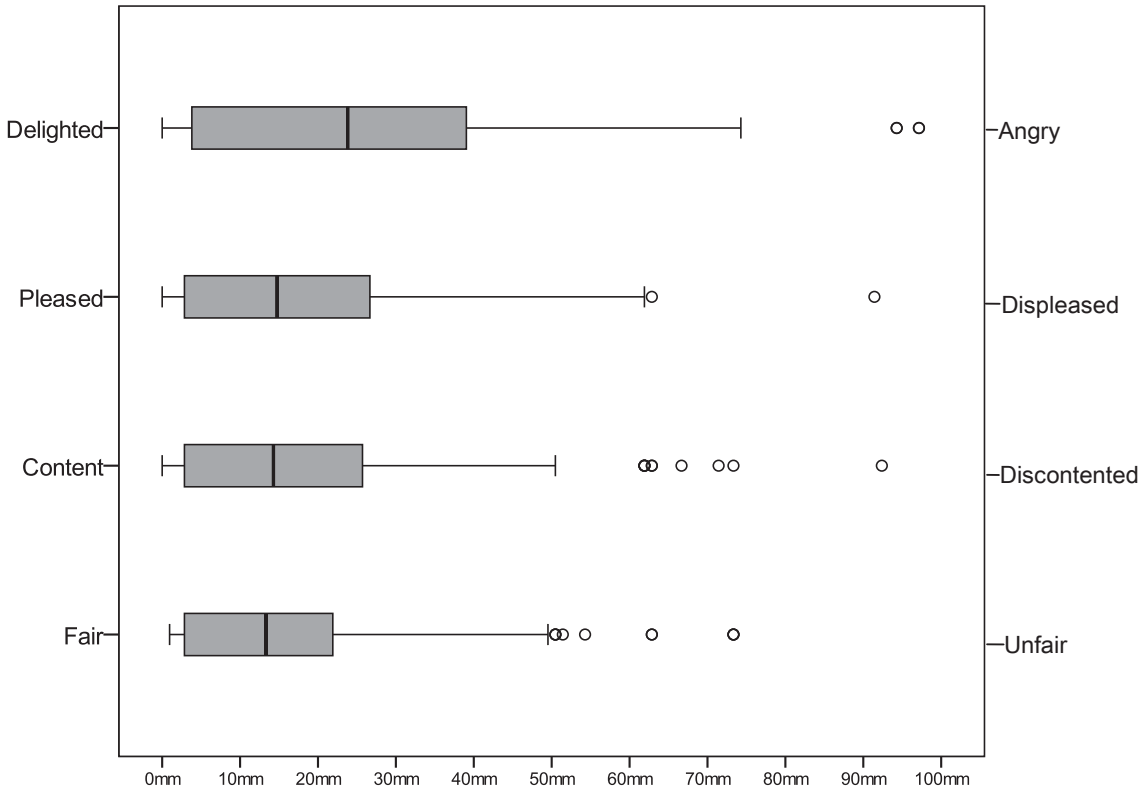

Figure 2 *Box plot summarising respondents' feelings about enrolment using delayed consent*

When the open ended responses were reviewed it was found that four from five respondents who commented negatively had recorded their thoughts when discovering they had been enrolled in the NICE study. Rather than displeasure, surprise was the predominant thought, for example:

Surprised, I had no idea about the arrangement made on my behalf.

Surprised, happy to help.

Surprised, all this time I had not been informed by my son who gave consent. I trust him … I agree with him.

3.6 Thoughts about Enrolment in the NICE-SUGAR Study

Most respondents (202/210; 96.1%) answered the question "What were your thoughts when you found out that you had been enrolled in the blood sugar (NICE) study?" Responses were coded using content analysis and are expressed as a percentage of respondents. In summary, over half of respondents reported they were not worried about the process, were neutral or reported positive thoughts such as happy and good. Some respondents (11.9%) reported surprise and a similar proportion (11.4%) reported no recollection (Table 4).

Table 4

Content analysis for the open ended question, "What were your thoughts about enrolment in NICE?"

Content	Total (%) n=202
Okay/fine, Not worried, Not a problem	47 (23.3)
Happy (& synonyms pleased, delighted), Happy to help, Happy to participate, Happy for self, Happy to help self and others, Happy to be alive	37 (18.3)
Surprise (& synonyms shock, taken aback)	24 (11.9)
Cannot remember	23 (11.4)
Help research, Help diabetes research	20 (9.9)
(Positive) Help others	18 (8.9)
No thoughts, neutral	13 (6.4)
Good	7 (3.5)
Other things to think about	5 (2.5)
Trust of person who made the decisions	3 (1.5)
Interested	2 (0.9)
In the hands of the doctors and nurses	2 (0.9)
Angry about non-medical events when unconscious	1 (0.5)

Statements included thoughts such as:

Not concerned, being unable to decide for myself.

I was fine with it. Didn't really think much about it.

No problem. These things needed to be studied.

As the aim of the study is to assist in the recovery of future patients, I was delighted.

I was happy to perhaps help someone else in similar circumstances to mine.

At first I asked why. Once it was explained to me I was okay with the process. There is some initial shock, but I was happy to help.

I thought that it will be among the very few good things that resulted from my accident. I had no concerns whatsoever and was indeed glad that I could participate in a test that in future may result in even more exceptionally good care of seriously ill people.

3.7 Participation will Help Others

Most respondents (197/207; 95.2%) agreed with a statement regarding their participation in the NICE-SUGAR study helping future patients (Figure 3). The options "disagree" and "strongly disagree" were not selected.

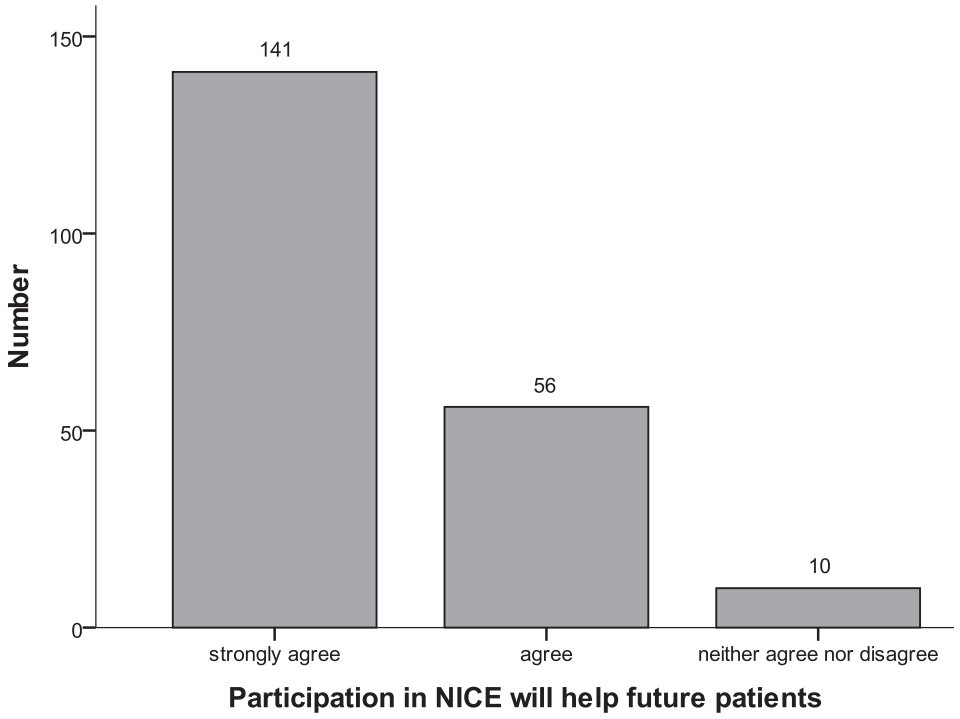

Figure 3 *Bar graph showing opinions of participation in the NICE-SUGAR Study helping future patients.*

3.8 Preferences for Decision Makers

Respondents were asked to rank a selection of persons and organisations in the order they would have most preferred to make decisions on their behalf to participate in the NICE–SUGAR study. A rank of "1" equated to their first preference. Most respondents (163/198; 82.3%) preferred "the person who consented on their behalf for the NICE Study" to make decisions on their behalf (Table 5).

Respondents who had provided consent to the NICE-SUGAR study themselves, were less likely to rank "the person who consented on my behalf" as "1" (Fisher's exact test p <.001). Fewer patients ranked themselves "1" that is, "the person who consented on my behalf for the NICE study" (Table 6).

Table 5

First preference for a person or organisation for decision making

Variables	*n*	Responses
The person who consented on my behalf for the NICE study (%)	198	163 (82.3)
The intensive care doctor looking after me (%)	173	29 (16.8)
Another relative or friend (%)	174	12 (6.9)
My General Practitioner (%)	168	9 (5.4)
An independent doctor not looking after me (%)	165	2 (1.2)
An ethics committee (%)	162	1 (0.6)
A Government Regulatory Authority/Guardianship Tribunal (%)	0	Not ranked 1
Other ranked "1" Free text: solicitor (n=1), adult child (n=1), medical or nursing staff (n=2), spouse or partner (n=2) (%)	138	6 (4.3)

Table 6

Characteristics of respondents who preferred "The person who consented on my behalf for the NICE study."

Characteristic	*n*	Total Yes	Statistical Test	*p*
Gender *(%)*	198			
Male		102 (82.9)		
Female		61 (81.3)	0.081*	.776
Group assignment for the NICE-SUGAR study *(%)*	198			
Conventional glucose control		82 (87.2)		
Intensive glucose control		81 (77.9)	2.966*	.085
Provision of written consent for the NICE-SUGAR study *(%)*	197[†]			
Substitute decision maker		129 (88.4)		
Patient		33 (64.7)	Fisher's exact test	<.001

Note. *Pearson's Chi-Square.

[†]The HREC provided consent for data usage for one respondent in this group.

3.9 Decisions Regarding Consent

Most (191/206; 92.7%) respondents agreed the research or medical staff had asked the right person to consent on their behalf (Figure 4).

Most respondents (177/202; 87.6%) agreed their relative or friend had made the same decision they would have made (Figure 5).

Most respondents (187/201; 93%) were content with the decision made by their relative or friend (Figure 6).

A total of eight respondents disagreed with the statements above. For those people, delayed consent was provided by the patient (n=3), a sibling (n=2), a partner (n=2) and an adult child.

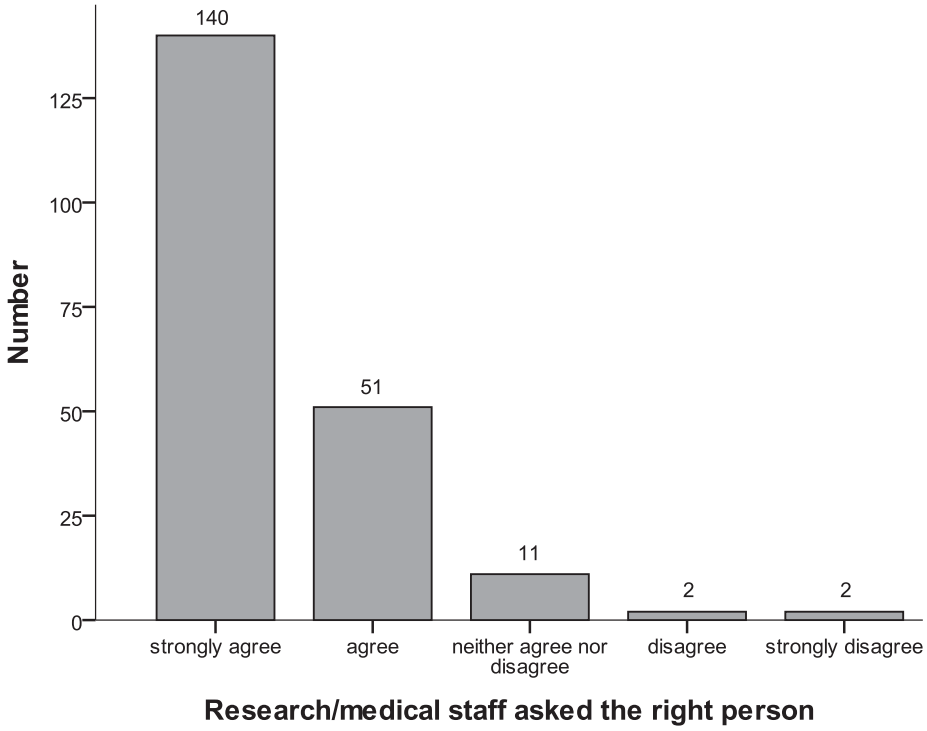

Figure 4 *Bar graph showing opinions about the selection of substitute decision maker.*

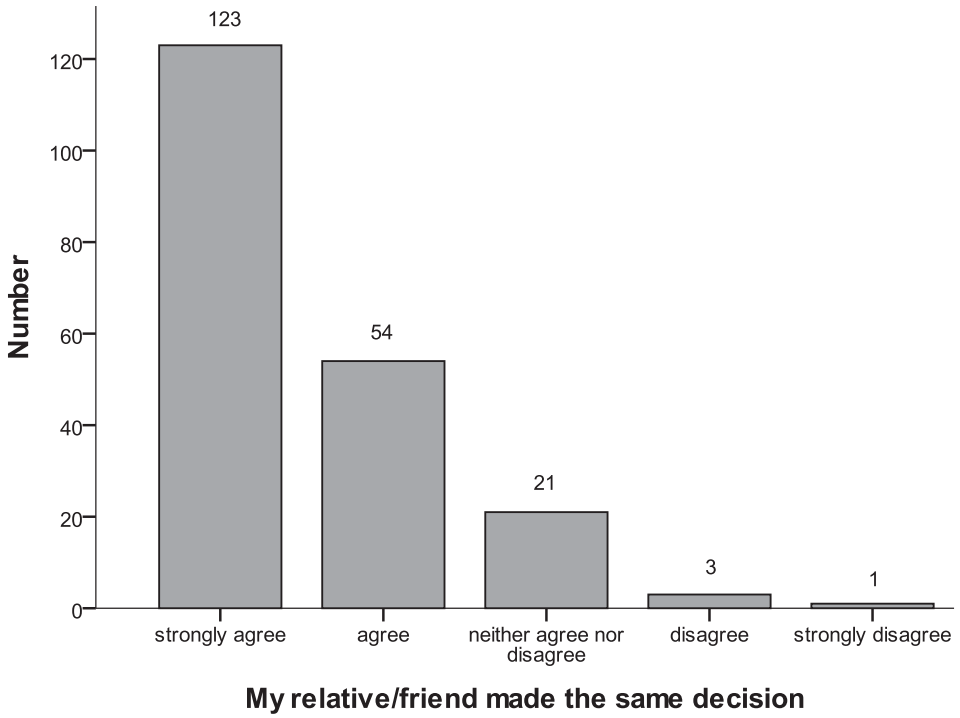

Figure 5 *Bar graph showing agreement with the decision made by the substitute decision maker.*

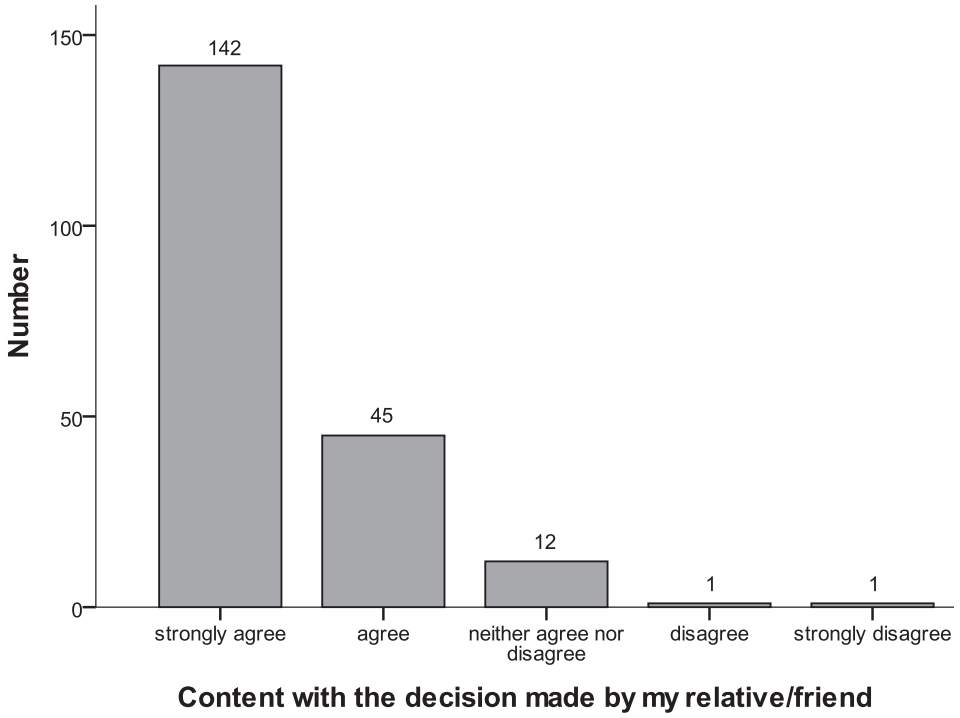

Figure 6 *Bar graph showing contentment with the decision made by the substitute decision maker.*

3.10 Would have Provided Consent Before Enrolment?

Most respondents (195/204; 95.6%) answered “Yes” they would have consented to participate in the NICE-SUGAR study before enrolment, if they could have. A small proportion (9/204; 4.4%) indicated “No”.

Participant characteristics were examined in relation to the answers about their willingness to participate in the NICE-SUGAR study, if we could have asked them (Table 7). Responses to questions were examined for relationships with demographic or other factors such as the respondent’s age, gender, level of education, prior employment and allocated treatment group in the NICE-SUGAR study. Significantly more women (9.3%) than men (1.6%) responded “No” to this question (Fisher’s exact test p= .013). No other relationships were found.

Table 7

Association of respondent characteristics with willingness to participate in the NICE-SUGAR study

Variable	*n*	Yes	Statistical Test	*p*
Age in years *(%)*	204			
≥ 61		113 (97.4)		
≤ 60		82 (93.2)	Fisher's exact test	.178
Gender (%)	204			
Male		127 (98.4)		
Female		68 (90.7)	Fisher's exact test	.013
No chronic health conditions *(%)*	204	179 (95.7)		
Chronic health conditions		16 (94.1)	Fisher's exact test	.551
Education (%)	203			
College/university (some or completed)		61 (100.0)		
High school (some or completed)		83 (95.4)		
Technical school (some or completed)		38 (92.7)		
Other education		12 (85.7)	6.487*	.077
Group Assignment for the NICE–SUGAR study *(%)*	204			
Intensive glucose control		106 (97.2)		
Conventional glucose control		89 (93.7)	Fisher's exact test	.309
Who provided written consent for the NICE–SUGAR study *(%)*	203 †			
Substitute decision maker		142 (95.3)		
Patient		52 (96.3)	Fisher's exact test	1.000

Note. *Pearson's Chi-Square.

† The HREC provided consent for data usage for one respondent in this group.

3.11 Further Comments

More than 60% (131/210; 62.4%) of former ICU patients responded to the question “Is there anything else regarding your participation in the blood sugar (NICE) study, you wanted to raise?” Responses were coded using content analysis and are expressed as a percentage of respondents. In summary, some commented on their willingness to participate in future research in order to help others. Some commented on the content of the NICE-SUGAR results, as it related to them and others on receiving the outcome of the NICE-SUGAR study (Table 8).

Table 8

Content analysis for the open ended question, “Is there anything else regarding your participation in the NICE study you wanted to raise?”

Content	Frequency (No. %) n=131
No, Nothing, Not really, No thanks	84 (64.1)
Help others in the future through research	11 (8.4)
Interpretation of the NICE study results	8 (6.1)
Thank you	6 (4.6)
Management of blood sugars and diabetes	4 (3.0)
Comments about when to be informed of the NICE study	4 (3.0)
Selection of substitute decision maker*	4 (3.0)
Appreciation for hospital staff (includes one patient who commented about the lack of availability of a particular therapy in Australia)	4 (3.0)
Requirement for consent for routine treatment, timing of consent	3 (2.3)
Don’t remember, don’t know	3 (2.3)

* Comments included positive and negative comments about the substitute decision maker and recommendations for alternative substitute decision makers, should the nominated relative have diminished decisional capacity due to mental or other health problems.

3.13 Conclusion

Most former ICU patients, who had been enrolled in the NICE-SUGAR study at the RNSH, would have agreed to enrolment in that study had they been asked beforehand. Furthermore, they agreed with the decision to consent made by the substitute decision maker, and the selection of substitute decision maker by the research or medical personnel. Most preferred the person who had provided consent, a relative, to make decisions on their behalf.

Chapter Four: Discussion and Conclusion

4.1 Introduction and Summary of Major Findings

This project was an observational study of the views of former ICU patients, who had been enrolled in the NICE-SUGAR study using delayed consent, of the delayed consent process and of decisions to consent made by the substitute decision maker. Former ICU patients, who were enrolled in the NICE-SUGAR study using delayed consent from the ICU at the RNSH from 2004 to 2008, were invited to participate in this study. Willing participants completed a self-report questionnaire, developed for this study, which was mailed to them. The response rate was good.

The main findings were that an overwhelming majority of respondents were positive regarding their enrolment in the NICE-SUGAR study using delayed consent. Most respondents agreed that they would have participated in the NICE-SUGAR study, had they been asked beforehand. They agreed the research or medical staff had asked the right person to provide consent and most preferred that person to make decisions on their behalf, should they lack decision making capacity. They agreed the substitute decision maker made the same decision as they would have and were content with that decision. Free text comments were positive with nearly half of respondents reporting they were “not worried” or were “happy” regarding enrolment using delayed consent.

A small minority of respondents indicated they would not have provided consent beforehand if able, and commented negatively regarding their feelings of enrolment using delayed consent. They disagreed with the decision made regarding consent by the substitute decision maker, and that the right person had been chosen to provide consent. A few of them reported “surprise” when discovering they had been enrolled in the NICE-SUGAR study. Unwillingness to participate in the NICE-SUGAR study was associated with female gender. There were no other clinical or demographic factors found to be associated with responses. These results support the use of delayed consent in RCTs that evaluate available standard intensive care treatments in critically ill patients.

4.2 Interpretation of the Results

The potential problem of including patients who lack decisional capacity in low risk critical care research in the absence of consent is generally addressed by institutional ethics committees. Approval by institutional ethics committees to include patients who lack decision making capacity in interventional research using deferred consent is not authorised in all European countries for example, Greece, Italy, Ireland and Portugal (Lemaire et al. 2005), or in Canada (NICE-SUGAR Study Investigators et

al. 2009). Institutional ethics committees in some US states (Gong et al. 2010) restrict the inclusion of patients who lack decision making capacity in interventional research to those whom prior consent from a legally authorised substitute decision maker has been provided. However, consent provided by the substitute decision maker for interventional research is not supported by institutional ethics committees in other US states (Gong et al. 2010).

There are some data on community and patient preferences for research conducted with a waiver of consent, subsequent to a period of community consultation, but information is lacking on opinions of the delayed consent process. In Canada, surveys were conducted to ascertain community (Burns et al. 2011) and former ICU patients' (Scales et al. 2009) attitudes to consent, including models of delayed consent, for research in critically ill patients who lacked decision making capacity. In a survey of the general public in Toronto, Burns et al. reported that most citizens expressed comfort with waived and deferred consent for a hypothetical low risk scenario and would potentially wish to be enrolled. Similarly, Scales et al. described most former ICU patients to be agreeable or neutral regarding potential enrolment in hypothetical research using delayed consent. That theoretical work is extended in this study through description of the self-reported opinions of former ICU patients who had been enrolled using delayed consent in an actual RCT. The results showed that most respondents agreed with enrolment in a clinical trial of available standard treatments, the NICE-SUGAR study, and would have provided consent before enrolment, had they been able.

There are also regulations specifying who may provide third party written consent in order that a patient who lacks decision making capacity can participate in research. The identity of the substitute decision maker can range from a professional legal representative to a relative (Robinson & Andrews 2010). However, not all relatives are authorised to act as the substitute decision maker with some institutional ethics committees in the US failing to permit adult children to provide consent (Gong et al. 2010). At the RNSH, the selection of the substitute decision maker reflected the predefined hierarchy of "person responsible" from the NSW Guardianship Tribunal (Guardianship Tribunal 2011). The identity of that person was predominantly the participant's relative, frequently a spouse or partner, followed by an adult child then sibling. Similarly in Canada, Heyland et al. (2003) found that substitute decision makers involved in decisions regarding the patient's medical treatment were relatives, with nearly half being partners, followed by adult children then siblings. Findings from this study indicate that most respondents' first preference for a decision maker when they

lacked decision making capacity was the person who had provided consent, a relative. Furthermore, most respondents agreed the research or medical personnel had selected the correct person to provide informed consent on their behalf.

Research personnel who obtain consent in the ICU in ANZ are often research coordinators. The research coordinator typically functions in tandem with the clinical team and is able to allocate time to interact with relatives and address concerns that may arise during the process of obtaining informed consent. Rickard, Roberts, Foote, & McGrail (2006) described intensive care research coordinators in ANZ to be predominantly experienced nurses with nearly half holding a postgraduate degree. Requesting consent for research was reported by research coordinators to comprise 78% of their time. At the RNSH, research coordinators obtained the majority (69%) of written consents to continue in the NICE-SUGAR study, for respondents to this study.

The style of decision making preferred by the substitute decision maker may affect discussions between the doctor and the substitute decision maker regarding medical and end-of-life treatment decisions for the patient. A shared role in decision making with the patient's doctor was preferred by most relatives (28 of 50; 58%) of ICU patients in the US (Anderson et al. 2009) and substitute decision makers (n=296; 39.1%) in Canada (Heyland et al. 2003). Fewer relatives (8 of 50; 17%) in the US and substitute decision makers in Canada (n=112; 14.8%) preferred a passive decision making role, wherein the patient's doctor had final responsibility. Moreover Heyland et al. found substitute decision makers reported higher satisfaction with a passive decision making role compared to those who preferred more active roles. These results may relate to the preferred style of decision making of former ICU patients in the Australian population. In this study, over 16% of respondents preferred the intensive care doctor looking after them to make decisions on their behalf, if they lacked decision making capacity. This result may indicate trust in the medical profession and preference of a passive decision making role when critically ill.

It is possible that the Australian community views participation in research favourably because there are few reports of serious research misconduct in Australia (Australian Government et al. 2007). Although previous findings in an Australian study of the attitudes of Emergency Department and ICU visitors (Stephenson, Baker & Zeps 2007) revealed that only one quarter of respondents found substitute consent for potential participation in a clinical trial to be acceptable, should they lack decisional capacity. Findings from this study revealed that respondents who had provided delayed consent to the NICE-SUGAR study themselves were less likely to rank "the person who consented on my behalf" as their first preference for a decision maker when they

lacked decision making capacity. This result may indicate that some former ICU patients preferred written consent to be obtained from a substitute decision maker to providing delayed consent themselves. Although it is possible that one quarter of respondents who had provided delayed consent themselves may have misinterpreted the wording of this question. A reason for the difference in opinions may be the respondents, Emergency Department and ICU visitors versus former ICU patients. The visitors may have been experiencing emotional distress or anxiety about the patient's condition when completing the questionnaire, shown by the high proportion of "neutral or "undecided" responses. Another reason could be the different scenarios that of a hypothetical RCT of an experimental treatment versus an actual trial of available treatments.

The substitute decision maker does not always make the same decision as the patient when providing potential consent for hypothetical clinical studies (Ciroldi et al. 2007; Coppolino & Ackerson 2001). One reason for the disparity may be the difference between hypothetical and actual scenarios with respect to the time permitted for the substitute decision maker to make a decision. Ciroldi et al. reported that surrogates wanted more information regarding the patient's prognosis, diagnosis and treatment, when participating in a survey containing hypothetical clinical study scenarios. When consent is delayed, the substitute decision maker has time to gather facts about the patient's medical condition and consult with others as required. At the RNSH written consent was provided for respondents to this study, who had consent provided by the substitute decision maker, a median of three days following enrolment in the NICE-SUGAR study. This duration may reflect the substitute decision maker taking the time to consult with others in order to make the decision that represented the patient's best interests. However, patients who had provided consent took a median of eight days, possibly representative of the increased time required for them to regain decision making capacity. In contrast to the literature, respondents to this study overwhelmingly agreed the substitute decision maker made the same decision they would have, regarding consent for an actual clinical study of available standard treatments.

Stress is another important factor that may affect the capacity of the substitute decision maker to make the same decision as the patient. Relatives are often distressed or emotionally overwhelmed during the patient's ICU stay and have been reported to experience high rates of psychological symptoms including anxiety, depression and PTSD (Azoulay et al. 2005; McAdam et al. 2010; Pochard et al. 2001). Azoulay et al. found PTSD symptoms were associated with the requirement to make medical treatment and research decisions on the patient's behalf. These factors may

affect the substitute decision makers' ability to process medical information and impair their decisional capacity (Saks & Jeste 2006). Responses to this study indicate that most former ICU patients were content with the decision made by their relative or friend. Therefore relatives may be reassured that the majority of former ICU patients agree with decisions made regarding ongoing participation in research when the patient was enrolled using the process of delayed consent.

A small proportion of patients were presumably enrolled in the NICE-SUGAR study against their will, as several respondents indicated they would not have provided consent if they were able, before enrolment in the study. Factors shown to be associated with congruence of decisions made by patient-surrogate pairs in previous research, such as education level or age, were not confirmed in this study. Negative responses were reported by significantly more females than males. These results may be indicative of a gender disparity in the Australian population regarding decisions to consent for inclusion in a RCT of available standard treatments. However, due to the small number of females, the possibility of a Type I error cannot be excluded.

The number of patients enrolled in clinical trials in cancer and cardiovascular disease varies with respect to gender. When compared to disease prevalence in the general population, females are underrepresented compared to males in US government funded clinical trials in cancer (Murthy, Krumholz & Gross 2004) and chronic heart failure (Harris & Douglas 2000; Heiat, Gross & Krumholz 2002), with the disparity increasing in the older age (>65 years) group. Possible reasons for the underrepresentation of women may be trial eligibility criteria or simply that more women, especially older women (>65 years), either decline to participate, or later withdraw, than do men. However, Sen Biswas, Newby, Bastian, Peterson, & Sugarman (2007) reported that reasons patients gave for declining to enroll in one of 25 RCTs in treatments for cardiovascular disease in an acute hospital setting, were related to inconvenience and preferring not to be experimented upon. Gender was not associated with a refusal to enroll. Patients refused participation more frequently when they had a higher acuity of illness.

4.3 Strengths and Limitations of the Study

There are a number of strengths in this study. These include the study design, population, large sample size, and the methods, inclusive of the follow up strategy and minimisation of personal bias from the investigator.

The study design combined quantitative and qualitative methods in the study instrument, a self-report questionnaire. The questionnaire underwent rigorous development. Following approval by the NSCCH HREC the questionnaire underwent

two rounds of pilot testing with a panel of volunteers, including expert health care personnel. The panel evaluated face and content validity to ensure the questionnaire was appropriate to be completed by the population of former participants in the NICE-SUGAR study. The provision of open ended questions permitted respondents to add further information to the options provided in the forced choice items. This design addressed some of the weaknesses of forced choice responses, for example patients were able to expand their responses beyond the limits provided. This consideration was important in the study design because the purpose of the study was exploratory.

Sampling former ICU patients who had participated in an actual RCT correctly identified members of the community who were eligible to participate in studies of available standard treatments during an ICU stay. Previous research in this area was limited by inclusion of participants who are often excluded from critical illness research due to a low mortality rate and a lack of eligible conditions, for example cardiac surgical patients (Chenaud et al. 2009; Coppolino & Ackerson 2001). The scenario of an actual instead of a hypothetical RCT is a key strength of this study because former ICU patients' perception of potential risks, benefits and personal meaning from participation may differ in reality compared to theoretical situations. Respondents may have a greater interest in the actual scenario due to a stronger sense of personal relevance.

The large sample size obtained from the high response rate may have been assisted by respondents' self-motivation and the study methods, specifically the follow up strategy. Aitken et al. (2003) suggested motivation to help others or to give something back to the hospital where they were treated, positively influenced peoples' agreement to participate in clinical trials. The method of follow up in this study was designed as a three step process with initial contact by telephone, when possible, then posting the research material. The second and third steps were for non-responders and involved a subsequent telephone reminder followed by a final reposting of the questionnaire package. Non-responders were also offered the opportunity to complete the questionnaire by telephone. To maximise opportunities of contacting people who were not at home during office hours, telephone calls were made at different times and days of the week, that included after hours and weekends. Provision of alternative methods of returning the questionnaire such as email and completion over the telephone, subsequent to confirmation of receipt of the questionnaire, also positively assisted the response rate. An important consideration was speaking to people, when possible, before mailing the questionnaire package because it was anticipated that many former ICU patients would have no recollection of participation in the NICE-SUGAR study.

The methods utilised to contact the former ICU patients and to facilitate completion of the questionnaire, were designed to minimise potential personal bias from the researcher in two ways. The first was by using a standardised transcript that was approved by the NSCCH HREC for the initial telephone call. The second was by an independent ICU research nurse conducting the interviews when patients requested completion of the questionnaire by telephone.

There are some limitations to this study that include recruitment from a single centre that may have patient clinical and demographic characteristics that differ to other metropolitan, tertiary referral hospitals in the NICE-SUGAR study. Other limitations are; the length of time elapsed from enrolment in the NICE-SUGAR study to screening former ICU patients for this study, the high proportion of deceased patients, the opinions of non-responders were unavailable and the selection of a RCT of available standard treatments.

The length of time elapsed from enrolment in the NICE-SUGAR study to screening for this study may be a limitation, and could be related to the high proportion of deceased patients. While over one third of former participants in the NICE-SUGAR study were deceased when screened for this study, this proportion is expected after three years in critically ill survivors. In a review of the literature on long term outcomes in the population of medical and surgical patients from general ICUs, Williams, Dobb, Finn & Webb (2005) found that mortality ranged from 26% to 63% at 12 months, from 20% to 72% at two years and from 40% to 72% at three years. From those ranges, it would appear that evidence is weak that a substantial increase in recruitment could have been gained by contacting former ICU patients earlier, for example, an average of 12 months after enrolment in the NICE-SUGAR study.

Another difficulty in finding the best time to seek the opinions of former ICU patients is the presence of potential cognitive impairment. Ongoing cognitive impairment is experienced by a high proportion of former ICU patients. In a review of the evidence, Gordon et al. (2004) suggest that while cognitive functioning improves over 12 months following hospital discharge, as many as 46% of former ICU patients continue to experience cognitive impairment at one year. While the prevalence of cognitive impairment is higher in patients who had experienced acute respiratory distress syndrome (ARDS), one third of general ICU patients also experienced cognitive impairment that was comparable to mild or moderate dementia, at 12 months after discharge from hospital. The relatively low number of former ICU patients who fulfilled the exclusion criterion of cognitive impairment for this study may reflect the benefit of time for patients to regain cognitive functioning.

Those patients who had a good outcome may have reflected positively on research undertaken during their stay in ICU due to emotional factors from the ICU experience and subsequent recovery. Their survival may have positively influenced responses such that issues of consent and research were of secondary importance. Another potential source of "yea-saying" bias is the relationship between respondents and study investigators. Respondents may have thought an investigator on this study had looked after them and wished to please them by answering positively. However, the possibility that the small number of non-responders (18%) had different views to responders cannot be excluded. The selection of a RCT of available standard treatments limits conclusions regarding former ICU patients' opinions of decisions made by substitute decision makers to clinical studies of similar risk, but that is the type of study that HRECs may approve the use of delayed consent.

A limitation of the study tool, the self-report questionnaire, was that it did not allow interactive exploration of responses or investigation of incongruity in answers. Another limitation was the option of "self" was not further investigated in regard to the best time to provide delayed consent. The high level of agreement with the substitute decision makers' decision regarding consent was possibly related to the postal format, because the respondent may have been residing with the substitute decision maker and was unwilling to comment negatively. Respondents were not asked to recall details of the NICE-SUGAR study as they would be expected to have little knowledge or memory of the research. However, the purpose of this study was exploratory and obtained a representative sample of eligible participants in the NICE-SUGAR study from the RNSH.

4.4 Implications for Practice

The findings of this research may be used to contribute to the understanding of complex issues in the area of consent for research in intensive care. Institutional ethics committees, regulatory bodies and clinical trialists may be informed that former ICU patients overwhelmingly agreed with enrolment in a clinical trial of available standard treatments using the process of delayed consent. Importantly, it would follow from the participants' perspective that the process of delayed consent may continue for similar research in patients who lack decision making capacity.

The findings of this study may also be used to reassure families when they are worried about decisions they make regarding continued participation of their relative in research. The majority of former ICU patients will agree with the decision to consent to continued participation in a clinical trial of available standard treatments.

4.5 Future Recommendations

Several areas have emerged from this study that require further investigation. Those areas are related to the information needs of women and patients' preferences for decision makers. Further investigations could inquire into gender differences in the group who found delayed consent unacceptable, in order to explore barriers to participation in critical illness research for women. Information gained could be used to inform the approaches to the consent process for female substitute decision makers or patients. A study design that allows interaction to explore anomalous responses and reasons for refusal or acceptance, such as interviews, could be utilised.

Further exploration is needed on the preferences of ICU patients for the optimum time to provide consent to participate in research conducted when they are experiencing or recovering from critical illness. A broader sample could be obtained by surveying former ICU patients recruited from additional centres or countries to evaluate possible cultural differences and treatment variation. RCTs that compare other aspects of intensive care treatment, such as intravenous fluid administration, and have HREC approval to enrol patients using delayed consent could be included.

4.6 Conclusion

This thesis reported the results of an observational study of former ICU patients who had been enrolled in the NICE-SUGAR study from the RNSH using delayed consent. The purpose of the research was to investigate their opinion of enrolment in the NICE-SUGAR study using the process of delayed consent. The literature on the provision of informed consent for participation in critical illness research for patients who lacked decision making capacity showed that critically ill patients are rarely able to provide first person informed consent when they are eligible to be enrolled in a RCT. When a RCT compares available standard treatments, some HRECs approve enrolment of eligible patients who lack decision making capacity using the process of delayed consent. However there was some evidence that patients and substitute decision makers did not make the same decision to potentially consent to enrolment in hypothetical RCTs. Furthermore, the capacity of the substitute decision maker to understand detailed medical information and make informed decisions can be diminished due to factors such as emotional distress and anxiety.

Many ICU patients have been enrolled in RCTs conducted in ANZ using the process of delayed consent. Yet the opinion of ICU patients of enrolment in an actual RCT when they had impaired decisional capacity, using the process of delayed consent, was lacking from the Australian population. The research questions addressed by this thesis were firstly to ascertain the opinion of the former ICU patient

who was enrolled in the NICE-SUGAR study at the RNSH using the provision of delayed consent, of that consent process. The second question related to those who had consent provided by the substitute decision maker, and investigated the participant's opinion of the decision by the substitute decision maker to either consent or decline continued participation in the NICE-SUGAR study.

Most respondents in this study would have agreed to participate in the NICE-SUGAR study had they been able to be asked. Most respondents also agreed that delayed consent had been sought from the right person and that they were content with the substitute decision maker's decision to consent. Importantly, the results from this study support the continued use of delayed consent in low risk RCTs that evaluate standard intensive care treatments in critically ill patients.

Research is important in order to continue the process of evaluating and improving treatments for the critically ill. Patients who cannot consent for themselves deserve to benefit from research. There is evidence that patients benefit in research regardless of the treatment arm (Braunholtz, Edwards & Lilford 2001) from consistent application of protocols that have been shown to improve patient outcomes, within a well conducted RCT. The findings from this study show overwhelming support from former ICU patients for enrolment using the delayed consent process in a well conducted RCT.

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Study No:

Appendix A Questionnaire

The following questions will help us to understand your opinion of the type of consent used for the blood sugar study (NICE). Your responses will be coded, so you will not be able to be identified personally.

When you were admitted to intensive care, your treating doctor enrolled you in the blood sugar (NICE) study. You were enrolled because your blood sugar levels were increased above normal or were thought likely to be. At that time you were unable to make a decision yourself.

1) How do you feel about being enrolled in the blood sugar (NICE) study in that circumstance?

   Please indicate how you feel about this using the following pairs of descriptions below.

   For each description place an 'X' on the line that comes closest to your first impression. There are no right or wrong answers.

Fair								**Unfair**	**Don't know**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Content								**Discontented**	**Don't know**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Pleased								**Displeased**	**Don't know**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Angry								**Delighted**	**Don't know**
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

2) What were your thoughts when you found out that you had been enrolled in the blood sugar (NICE) study?

_____

_____

_____

_____

_____

_____

_____

_____

Please continue to the next page.

Your participation in the blood sugar (NICE) study was discussed with you and/or your relative/friend as soon as possible after enrolment.

3) This question is about the person or organisation that you would have most preferred to make the decision on your behalf to participate in the blood sugar (NICE) study, given that you were unable to make the decision yourself.

   Please rank your preferences 1 to 8, with 1 being the person/organisation you would have most preferred and 8 being the one you would have least preferred. Please use each number only once.

_____ The person who consented on my behalf for the NICE study

_____ Another relative or friend

_____ A Government Regulatory Authority/Guardianship Tribunal

_____ An Ethics Committee

_____ The intensive care doctor looking after me

_____ An independent doctor not looking after me

_____ My General Practitioner (GP)

_____ Someone else (please specify)_____

4) Please indicate with a tick (✔) the response that best describes the extent you agree with the following statements below**:**

Statements	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
The research/medical staff asked the right person to consent on my behalf.	( )	( )	( )	( )	( )
My relative/friend made the same decision that I would have made, had I been able to decide.	( )	( )	( )	( )	( )
I am content with the decision made by my relative/friend on my behalf.	( )	( )	( )	( )	( )
Participation in the blood sugar (NICE) study will help intensive care patients in the future.	( )	( )	( )	( )	( )

Please continue to the next page.

5) If we could have asked you, would you have consented to participate in the blood sugar (NICE) study before we enrolled you?

- ❑ Yes
- ❑ No

6) Is there anything else regarding your participation in the blood sugar (NICE) study, you wanted to raise?

_____
_____
_____
_____
_____
_____
_____
_____

7) In general, would you say your health is: (Circle One)

Excellent	Very good	Good	Fair	Poor
1	2	3	4	5

Please continue to the next page.

Appendix A

Study No:

The following questions are about a little background information from everyone. Your responses will be coded, so you will not be able to be identified personally.

If you provided consent yourself, please start at question (10) and skip questions (8) and (9).

8) How long have you known the relative/friend who provided consent on your behalf for the NICE study, in years? ☐

9) Have you talked with the relative/friend (above), about participation in research before your participation in the NICE study?

- ❑ Yes
- ❑ No

10) Do you speak any languages other than English *at home*?

Remember to tick all boxes that apply

- ❑ No, English only
- ❑ Yes, Italian
- ❑ Yes, Greek
- ❑ Yes, Cantonese
- ❑ Yes, Arabic
- ❑ Yes, Vietnamese
- ❑ Yes, Mandarin
- ❑ Yes, other (please specify) _____

11) What is the *highest* educational level you attained?

Remember to tick one box

- ❑ Some high school
- ❑ Completed high school
- ❑ Some college/university
- ❑ Completed college/university
- ❑ Some technical school (e.g TAFE)
- ❑ Completed technical qualification
- ❑ Other education

12) What was your main activity before the illness that led to your intensive care admission?

Remember to tick one box

- ❑ Paid employment (full-time)
- ❑ Paid employment (part-time/casual work)
- ❑ Unpaid employment
- ❑ Domestic duties looking after home or family
- ❑ Permanent long-term sickness or disability
- ❑ Retired
- ❑ Student
- ❑ Other (please specify) _____

What is the date today? ☐

Thank you for your time in completing this survey.

Appendix B Telephone Transcript

Transcript for introducing the delayed consent survey to verify patient contact details.

Good morning/afternoon. My name is Julie Potter_____
(or name of another authorised ICU Research Coordinator conducting the interview)

I am a student at the University of Technology, Sydney. I am also an Investigator on the NICE-SUGAR study at Royal North Shore Hospital. [**insert as necessary am a Research Coordinator in Intensive Care at the Royal North Shore Hospital and am assisting with research into…'**] I am conducting research into patients' opinions of consent for intensive care research when they were too sick to decide for themselves, and consent was provided by someone else on their behalf.

I would welcome the assistance of _____if he/she is available.
(participant name)

The research would involve completing a questionnaire that I would like to post to you. Completing the questionnaire should take no more than 10-15 minutes of your time.

I have contacted you because when you were a patient in intensive care at Royal North Shore Hospital in [**insert year**], you were enrolled in a research study called the NICE study (or the blood sugar study). The purpose of the NICE study was to compare two target ranges of blood sugar concentration in intensive care patients. The doctors treating you considered both ranges of blood sugar concentration appropriate for you.

The blood sugar study has finished now and you don't need to do anything more regarding that research.

Today I am seeking permission to record your current mailing address so that I can send you more detailed information and the short questionnaire for you to complete. With your permission, I'd like to ring you again about a week or so after I've posted the questionnaire. This will be to see whether you have any questions after reading it. Could you let me know what is the best day of the week and time of day to ring?

You are under no obligation to participate in this research.
Do you have any questions so far?

If the patient refuses contact details, thank them for their time today.

If the patient says yes, record their address and phone number below.

(If yes) Thank you very much. I will post the questionnaire to you. Thank you for your time today.

Appendix B

Transcript for introducing the delayed consent survey to verify patient contact details (consent to continue declined).

Good morning/afternoon. My name is Julie Potter_____
(or name of another authorised ICU Research Coordinator conducting the interview)

I am a student at the University of Technology, Sydney. I am also an Investigator on the NICE-SUGAR study at Royal North Shore Hospital. [**insert as necessary am a Research Coordinator in Intensive Care at the Royal North Shore Hospital and am assisting with research into…'**] I am conducting research into patients' opinions of consent for intensive care research when they were too sick to decide for themselves, and consent was provided by someone else on their behalf.

I would welcome the assistance of _____if he/she is available.
(participant name)

The research would involve completing a questionnaire that I would like to post to you. Completing the questionnaire should take no more than 10-15 minutes of your time.

I have contacted you because when you were a patient in intensive care at Royal North Shore Hospital in [**insert year**]**,** you were enrolled in a research study called the NICE study (or the blood sugar study). The purpose of the NICE study was to compare two target ranges of blood sugar concentration in intensive care patients. The doctors treating you considered both ranges of blood sugar concentration appropriate for you.

At that time your relative/friend declined permission for you to continue in the study. The blood sugar study has also finished now and you don't need to do anything more regarding that research.

Today I am seeking permission to record your current mailing address so that I can send you more detailed information and the short questionnaire for you to complete. With your permission, I'd like to ring you again about a week or so after I've posted the questionnaire. This will be to see whether you have any questions after reading it. Could you let me know what is the best day of the week and time of day to ring?

You are under no obligation to participate in this research.
Do you have any questions so far?

If the patient refuses contact details, thank them for their time today.

If the patient says yes, record their address and phone number below.

(If yes) Thank you very much. I will post the questionnaire to you. Thank you for your time today.

Appendix C
Cover Letters

Insert date

Insert patient's address

Dear ***insert name of the patient***

Re: The Delayed Consent Survey

NSCCH Protocol No: 0812-254M (Other). AU RED Ref:08/HAWKE/161/162
and University of Technology Sydney (UTS) Approval No: 2009-142R

My name is Julie Potter and I am a student at the University of Technology, Sydney. My supervisors are Professor Sharon McKinley and Dr Anthony Delaney. I am also an Investigator on the NICE-SUGAR study at Royal North Shore Hospital.

I am conducting research into patients' opinions of consent for intensive care research when they were too sick to make decisions for themselves and consent was provided by someone else on their behalf. I am writing to ask your assistance with my project.

The research will involve completing the questionnaire enclosed with this letter. Completion of the questionnaire should take no more than 10-15 minutes of your time. When you have completed the questionnaire, we would like you to post it back in the pre-paid envelope provided. I will telephone you in a week or so to see if you have any questions.

You may not remember the research project in which you were involved when you were a patient in intensive care at Royal North Shore Hospital, as it was some time ago. When you were admitted to intensive care you were enrolled in a research study called the NICE study (or the blood sugar study). The NICE study was the Australian and New Zealand part of the NICE-SUGAR study. The purpose of the study was to compare two target ranges of blood sugar concentration in intensive care patients. The doctors treating you considered both ranges of target blood sugar concentration in the study appropriate for you.

The concentration of sugar in the blood is increased above normal in virtually all intensive care patients due to their critical illness, so the nurses monitor blood sugar levels routinely in intensive care. If your blood sugar levels became raised you were treated with insulin given through a drip into your vein. Likewise, if your blood sugar concentration became too low you would have been treated with sugar given via your drip. You would have received these treatments if necessary, regardless of whether you were in the NICE study. Both treatments are standard intensive care treatment for maintaining target blood sugar concentration in intensive care patients.

The NICE study was therefore considered by the Human Research Ethics Committee and the NSW Guardianship Tribunal to be of minimal risk to patients because it involved only standard

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intensive care treatments. The Ethics Committee gave the NICE study investigators permission to enroll patients into the study when they arrived in the intensive care unit.

You were enrolled in the study when you were admitted to intensive care because your blood sugar levels were increased above normal or were thought likely to be by your treating doctor. We attempted to discuss the study with you and/or your relative/friend as soon as possible after that and to obtain informed consent. At the time we gave you or your relative/friend a copy of the information sheet and consent form to keep. Another copy of the information sheet and consent form is included with this letter.

The NICE-SUGAR study has finished now and you don't need to do anything more regarding that research.

The purpose of my project, the Delayed Consent Survey**,** is to learn your opinion about the consent process we used when we enrolled you in the NICE-SUGAR study.

Privacy

Any information about you that is collected as a result of you completing this survey, that can identify you, will remain confidential. It will only be used for the purpose of this research survey. Your information will only be disclosed beyond the study as required by law.

The results of this study may be published in medical journals or presented at scientific meetings. In any information which is presented, you will not be identified.

You will not receive any payment or other benefits for answering this survey. Your responses, however, will be useful to patients, researchers, Ethics Committees and Regulatory Authorities in the future.

If you have questions concerning this request, I would be glad if you would contact me on 02 9926 7769.

Concerns about the conduct of this survey?

This survey has been approved by the Hawkesbury Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Health (NSCCH). Any person with concerns or complaints about the conduct of this survey should contact the Research Office Secretary, who is nominated to receive complaints from research participants. You should contact them on 02 9926 8106 and quote Protocol No: 0812-254M (Other), AU RED Ref: 08/HAWKE/161/162.

If you would like to talk to someone who is not connected with the research, you may contact the UTS Research Ethics Officer on 02 9514 9615, and quote this number 2009-142R.

You are under no obligation to participate in this research but I thank you for considering this request and hope you will complete the questionnaire.

Yours sincerely,

Julie Potter
Nurse Researcher
Department of Intensive Care Office
Level 6, Main Building
Royal North Shore Hospital
Pacific Highway
St Leonards 2065

Ph: 02 9926 7769
Fax: 02 9439 8418
Email: jpotter@nsccahs.health.nsw.gov.au

Appendix C

UNIVERSITY OF TECHNOLOGY SYDNEY

NORTHERN SYDNEY CENTRAL COAST NSW HEALTH

ROYAL NORTH SHORE HOSPITAL
THE UNIVERSITY OF SYDNEY

INTENSIVE CARE UNIT

Insert date

Insert patient's address

Dear ***insert name of the patient***

Re: The Delayed Consent Survey

NSCCH Protocol No: 0812-254M (Other). AU RED Ref:08/HAWKE/161/162
and University of Technology Sydney (UTS) Approval No: 2009-142R

My name is Julie Potter and I am a student at the University of Technology, Sydney. My supervisors are Professor Sharon McKinley and Dr Anthony Delaney. I am also an Investigator on the NICE-SUGAR study at Royal North Shore Hospital.

I am conducting research into patients' opinions of consent for intensive care research when they were too sick to make decisions for themselves and consent was provided by someone else on their behalf. I am writing to ask your assistance with my project.

The research will involve completing the questionnaire enclosed with this letter. Completion of the questionnaire should take no more than 10-15 minutes of your time. When you have completed the questionnaire, we would like you to post it back in the pre-paid envelope provided. I will telephone you in a week or so to see if you have any questions.

You may not remember the research project in which you were involved when you were a patient in intensive care at Royal North Shore Hospital, as it was some time ago. When you were admitted to intensive care you were enrolled in a research study called the NICE study (or the blood sugar study). The NICE study was the Australian and New Zealand part of the NICE-SUGAR study. The purpose of the study was to compare two target ranges of blood sugar concentration in intensive care patients. The doctors treating you considered both ranges of target blood sugar concentration in the study appropriate for you.

The concentration of sugar in the blood is increased above normal in virtually all intensive care patients due to their critical illness, so the nurses monitor blood sugar levels routinely in intensive care. If your blood sugar levels became raised you were treated with insulin given through a drip into your vein. Likewise, if your blood sugar concentration became too low you would have been treated with sugar given via your drip. You would have received these treatments if necessary, regardless of whether you were in the NICE study. Both treatments are standard intensive care treatment for maintaining target blood sugar concentration in intensive care patients.

The NICE study was therefore considered by the Human Research Ethics Committee and the NSW Guardianship Tribunal to be of minimal risk to patients because it involved only standard

Intensive Care Unit
Royal North Shore Hospital, Level 6, Main Building, St Leonards NSW 2065
Telephone (+61) 2 9926 8656 Facsimile (+61) 2 9439 8418

Northern Sydney Central Coast Area Health Service
ABN 48 344 669 728

intensive care treatments. The Ethics Committee gave the NICE study investigators permission to enroll patients into the study when they arrived in the intensive care unit.

You were enrolled in the study when you were admitted to intensive care because your blood sugar levels were increased above normal or were thought likely to be by your treating doctor. We attempted to discuss the study with you and/or your relative/friend as soon as possible after that and to obtain informed consent. At that time, your relative/friend declined permission for you to continue in the NICE study. Their decision did not affect other aspects of your treatment in intensive care. A copy of the information sheet and consent form for the study is included with this letter.

The NICE-SUGAR study has finished now and you don't need to do anything more regarding that research.

The purpose of my project, the Delayed Consent Survey**,** is to learn your opinion about the consent process we used when we enrolled you in the NICE-SUGAR study.

Privacy

Any information about you that is collected as a result of you completing this survey, that can identify you, will remain confidential. It will only be used for the purpose of this research survey. Your information will only be disclosed beyond the study as required by law.

The results of this study may be published in medical journals or presented at scientific meetings. In any information which is presented, you will not be identified.

You will not receive any payment or other benefits for answering this survey. Your responses, however, will be useful to patients, researchers, Ethics Committees and Regulatory Authorities in the future.

If you have questions concerning this request, I would be glad if you would contact me on 02 9926 7769.

Concerns about the conduct of this survey?

This survey has been approved by the Hawkesbury Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Health (NSCCH). Any person with concerns or complaints about the conduct of this survey should contact the Research Office Secretary, who is nominated to receive complaints from research participants. You should contact them on 02 9926 8106 and quote Protocol No: 0812-254M (Other), AU RED Ref: 08/HAWKE/161/162.

If you would like to talk to someone who is not connected with the research, you may contact the UTS Research Ethics Officer on 02 9514 9615, and quote this number 2009-142R.

You are under no obligation to participate in this research but I thank you for considering this request and hope you will complete the questionnaire.

Yours sincerely,

Julie Potter
Nurse Researcher
Department of Intensive Care Office
Level 6, Main Building
Royal North Shore Hospital
Pacific Highway
St Leonards 2065

Ph: 02 9926 7769
Fax: 02 9439 8418
Email: jpotter@nsccahs.health.nsw.gov.au

Appendix D Summary of the NICE-SUGAR Study Results

Dear ***insert name of the patient***

Results of the Normoglycaemia in Intensive Care-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study: a study of two target ranges of blood sugar in patients in intensive care

Critical illness often causes a patient's blood sugar levels to be increased even if they are not diabetic. Worldwide, doctors had traditionally treated intensive care patients with insulin if the blood sugar levels increased above 10-12 mmol/L, which is moderately higher than the upper limit of normal. Recent research had made doctors uncertain whether patients did better when their blood sugar was kept lower than this level. Because of this uncertainty, the Australian & New Zealand Intensive Care Society and the Canadian Critical Care Trials Groups undertook the NICE-SUGAR study to determine the best blood sugar level for intensive care patients.

Each participant in the NICE-SUGAR study was randomly allocated to keep his or her blood sugar either in a lower range (4.5–6.0 mmol/L) or in a higher range allowing blood sugar to go up to 10 mmol/L while in intensive care. We then found out how patients were doing 3 months later.

6104 patients from 4 countries were involved in the study. The results were published earlier this year. The results found that the number of patients surviving critical illness was higher than expected in both groups and that patients whose blood sugar was allowed to be in the higher range did the better of the two groups.

You were randomly allocated to the <<lower /higher >> range. Whilst you were in the study we noted no significant complications or side effects related to your participation.

Thank you again for participating in this important study that has improved care for future patients in intensive care. If you would like further information or a copy of the full publication, please do not hesitate to contact me or Professor Simon Finfer (Principal Investigator), on 02 9926 8656.

Sincerely,

Julie Potter
Nurse Researcher
Department of Intensive Care Office
Level 6, Main Building
Royal North Shore Hospital
Pacific Highway
St Leonards 2065

Ph: 02 9926 7769
Fax: 02 9439 8418
Email: jpotter@nsccahs.health.nsw.gov.au

Version 2 date Jan 15, 2010

Appendix E Data Collection Forms
Form 1: Demographic data

1. **Date of birth (dd/mm/yyyy):** _____/_____/19____

2. **Gender:**
   - Male ❑
   - Female ❑

3. **Date of hospital admission (dd/mm/yyyy):** _____/_____/20____

4. **Date of ICU admission (dd/mm/yyyy):** _____/_____/20____

5. **Location prior to ICU admission:**
   - Readmission to this ICU ❑
   - Emergency Department ❑
   - Hospital ward ❑
   - Transfer from another hospital ICU ❑
   - Transfer from another hospital (except from another ICU) ❑
   - Operating theatre/recovery following emergency surgery ❑
   - Operating theatre/recovery following elective surgery ❑

   Select one

6. **APACHE III admission diagnostic category:**_____

7. **APACHE II score (first 24 hrs in ICU):**_____

8. **APACHE II chronic health evaluation**:
   - No chronic health ❑
   - Liver ❑
   - Renal ❑
   - Cardiovascular ❑
   - Respiratory ❑
   - Immunocompromised ❑

   Select all applicable

9. **Date of ICU discharge (dd/mm/yyyy) *(index admission)*:** _____/_____/20____
   (*If readmitted to ICU within 24 hrs of index ICU discharge enter discharge date of second admission*)

10. **Alive:**
    - Yes ❑
    - No ❑

    (*If deceased at ICU discharge – data collection for Form 1 is completed*)

11. Readmission to study ICU within same hospitalisation?

Yes ❑

No ❑

(*if No go to Q 12*)

11.1 ICU readmission #1 date (dd/mm/yyyy): _____/_____/20___

11.2 ICU discharge date # 1(dd/mm/yyyy): ____/_____/20____

11.3 ICU readmission #2 date (dd/mm/yyyy): _____/_____/20___

11.4 ICU discharge date # 2 (dd/mm/yyyy): ____/_____/20____

11.5 ICU readmission # 3 date (dd/mm/yyyy): _____/_____/20___

11.6 ICU discharge date # 3 (dd/mm/yyyy): ____/_____/20____

11.7 ICU readmission # 4 date (dd/mm/yyyy): _____/_____/20___

11.8 ICU discharge date # 4 (dd/mm/yyyy): ____/_____/20____

12. Date of hospital discharge (dd/mm/yyyy): _____/_____/20____

13. Alive:

Yes ❑

No ❑

Appendix E

Form 2: Characteristics of NICE study enrolment and consent

1. **Date of randomisation to NICE (dd/mm/yyyy):** _____/____/20____

2. **What was the allocated treatment group?**

   Lower ❑
   Higher ❑

3. **Was the patient withdrawn from NICE study treatment by the person responsible?**

   Yes ❑
   No ❑

4. **When response to Q 3 is 'yes', please record the date of withdrawal from NICE study treatment (dd/mm/yyyy):**

   ____/_____/20____

5. **Date written informed consent was initially obtained for NICE (dd/mm/yyyy):**

   ____/_____/20____

(*When the patient was withdrawn from study treatment by their person responsible-record the date written informed consent was obtained for data usage and follow up)*

6. **Who initially provided written informed consent?**

   Patient ❑
   Person responsible ❑
   Research ethics committee ❑

7. **When the person responsible either provided written informed consent or withdrew the patient from study treatment, what was their relationship to the patient?**

   Husband/wife ❑
   Partner ❑
   Parent ❑
   Child ❑
   Stepchild ❑
   Sibling ❑
   Aunt/Uncle ❑
   Nephew/Niece ❑
   Someone else (please specify): _____
   Not recorded ❑

Appendix E

8. Where was the patient located when written informed consent was obtained?

- Inpatient in ICU ❑
- Inpatient in the ward ❑
- Home or elsewhere following discharge from the study hospital ❑

9. What was the classification of all known personnel who were involved in obtaining consent?

- Research Coordinator (RC) ❑
- Registrar ❑
- Resident ❑
- Intensivist ❑
- Family too distressed to be approached ❑
- RC & Intensivist ❑
- RC & Registrar ❑
- RC & Resident ❑
- RC, Resident & Intensivist ❑
- Intensivist & Registrar ❑
- RC, Resident & Registrar ❑
- RC, Intensivist & Registrar ❑

Appendix F HREC Approval Letters

NORTHERN SYDNEY CENTRAL COAST NSW HEALTH

15 January 2009

Ms J Potter
c/- Intensive Care Unit Office, Level 6, Main Building
Royal North Shore Hospital
St Leonards NSW 2065

Dear Ms J Potter,

Re: LEAD HREC APPLICATION APPROVAL
NSW HEALTH ACCREDITED HREC: HARBOUR/HAWKESBURY
NORTHERN SYDNEY CENTRAL COAST (HEALTH)
LOCAL REFERENCE: Protocol 0812-254M(Other) **- J Potter**
The Participant's View of Delayed Consent for a Randomised Controlled Trial in Intensive Care: a Mixed Methods Study at one site. AU RED Ref: 08/HAWKE/161/162

Thank you for providing additional information as requested at the meeting on the **3 December 2008** by the **HAWKESBURY** Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Health (NSCCH). Please be advised that your study has now been approved. The documentation included in the approval is as follows:

- Delayed consent survey cover letter to participants, Version 2, dated 9th January 2009
- Delayed consent survey telephone transcript for patient contact details (consent obtained following enrolment), Version 2, dated 9th January 2009
- Delayed consent survey cover letter to participants PR declined consent, Version 1, dated 9 January 2009
- Delayed consent survey telephone transcript for patient contact details (consent declined prior to enrolment), Version 1, dated 9th January 2009
- Research Proposal, Amendment 1, dated 4 November 2008
- Delayed consent survey questionnaire, Version 1, dated 28 October 2008
- Form 1: Patient Demographic Data, Version 1, dated 28 October 2008
- Form 2: Characteristics of NICE study enrolment and consent, Version 1, dated 28 October 2008

It is noted that the approval covers the following NSW Health sites:

- Royal North Shore Hospital

It is noted that the study has been assessed by the HREC for *ethical* and *scientific review* ONLY and that clearance on the Site Specific aspects of the trial (local sign-off's, legal documentation etc) MUST be obtained from the above listed sites prior to commencement of research. Each site has different requirements, NSW Area Health Service sites require submission and approval of a Site Specific Assessment (SSA), which can be completed at: **www.ethicsform.org/au**. Please contact the local site for advice on what will be required.

*If you wish to add an additional site to the project within the area you will be required to complete a *'Site Specific Assessment Form'*, downloadable from the Research Office Web Page.

The Research Office
Level 2 Building 51, Royal North Shore Hospital
St Leonards NSW 2065 * PH: (02) 9926 8106 * Fax: (02) 9926 6179

Appendix F

NORTHERN SYDNEY
CENTRAL COAST
NSW HEALTH

At this time, we also remind you that, in order to comply with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia*, and in line with NSH HREC policy, the Chief Investigator is responsible to ensure that:

1. You notify the HREC at the completion of the study at this site and submit a final report (including final results) when available.
2. The HREC is notified as soon as possible of any changes to the protocol. All changes must be approved by the HREC before continuation of the research project. This includes notifying the HREC of any changes to the staff involved with the protocol.
3. All serious and unexpected adverse events are reported to the HREC within 15 working days.
4. The HREC is notified of the outcome of all submissions of this protocol to other Ethics Committees.

As at 18 May 2004, HREC approval is now valid for four (4) years from the date of the approval letter. **Your approval will therefore expire on 15 January 2013.** Investigators are requested to submit a progress report annually on 31 October. **Your first progress report is due on 31st October 2009.** The forms for progress/final reports can be down loaded from the Research Office web page.

Yours sincerely,

Production Note:
Signature removed prior to publication.

Professor Stewart Dunn
Chairperson
HAWKESBURY HREC
NORTHERN SYDNEY
CENTRAL COAST HEALTH

The Research Office
Level 2 Building 51, Royal North Shore Hospital
St Leonards NSW 2065 * PH: (02) 9926 8106 * Fax: (02) 9926 6179

CATALOGUE NO. 08692

Appendix F

NORTHERN SYDNEY CENTRAL COAST
NSW HEALTH

Monday, January 19, 2009

Ms J Potter
c/- Intensive Care Unit Office, Level 6, Main Building
Royal North Shore Hospital
St Leonards NSW 2065

Dear **Ms J Potter,**

Re: ***SITE SPECIFIC ASSESSMENT (SSA)***

Protocol 0812-254M(Other) **- J Potter**
The Participant's View of Delayed Consent for a Randomised Controlled Trial in Intensive Care: a Mixed Methods Study at one site AU RED Ref: 08/HAWKE/161/162

I am pleased to inform you that on the **15 January 2009**, the delegate of the Chief Executive authorised the Site Specific Assessment for the above study on behalf of Northern Sydney Central Coast Health (NSCCH).

It is noted that the approval covers the following site:

- Royal North Shore Hospital

The documentation included in the approval is as follows:

- Delayed consent survey cover letter to participants, Version 2, dated 9th January 2009
- Delayed consent survey telephone transcript for patient contact details (consent obtained following enrolment), Version 2, dated 9th January 2009
- Delayed consent survey cover letter to participants PR declined consent, Version 1, dated 9 January 2009
- Delayed consent survey telephone transcript for patient contact details (consent declined prior to enrolment), Version 1, dated 9th January 2009
- Research Proposal, Amendment 1, dated 4 November 2008
- Delayed consent survey questionnaire, Version 1, dated 28 October 2008
- Form 1: Patient Demographic Data, Version 1, dated 28 October 2008
- Form 2: Characteristics of NICE study enrolment and consent, Version 1, dated 28 October 2008

It is noted that Ethics & Scientific Approval for this project was granted by the **HAWKESBURY** Human Research Ethics Committee (HREC) of Northern Sydney Central Coast Area Health.

It is further noted that this committee is a LEAD HREC under the NSW Health model for single ethical review of multi-centre research.

The HREC recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purpose of conducting this clinical trial.

At this time, we also remind you that, in order to comply with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia*, and in line with NSH HREC policy, the Chief Investigator is responsible to ensure that:

The Research Office
Level 2 Building 51, Royal North Shore Hospital
St Leonards NSW 2065 * PH: (02) 9926 8106 * Fax: (02) 9926 6179

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NORTHERN SYDNEY CENTRAL COAST NSW HEALTH

1. You notify the HREC at the completion of the study at this site and submit a final report (including final results) when available.
2. The HREC is notified as soon as possible of any changes to the protocol. All changes must be approved by the HREC before continuation of the research project. This includes notifying the HREC of any changes to the staff involved with the protocol.
3. All serious and unexpected adverse events are reported to the HREC within 15 working days.
4. The HREC is notified of the outcome of all submissions of this protocol to other Ethics Committees.

As at 18 May 2004, HREC approval is now valid for four (4) years from the date of the approval letter. **Your approval will therefore expire on 15 January 2013.** Investigators are requested to submit a final report on completion of the study.

Yours sincerely,

Production Note:
Signature removed prior to publication.

Mrs Leonne Thompson
Research Governance Officer
HAWKESBURY HREC
NORTHERN SYDNEY
CENTRAL COAST HEALTH

The Research Office
Level 2 Building 51, Royal North Shore Hospital
St Leonards NSW 2065 * PH: (02) 9926 8106 * Fax: (02) 9926 6179

CATALOGUE NO. 08692

Appendix F

16 June 2009

Professor Sharon McKinley
Nursing, Midwifery and Health
CB10.07.207
UNIVERSITY OF TECHNOLOGY, SYDNEY

Dear Sharon,

UTS HREC 2009-142 – MCKINLEY, Professor Sharon, DELANEY, Dr Anthony, (for POTTER, Ms Julie, Masters student) - "The Participant's View of Delayed Consent for a Randomised Controlled Trial In Intensive Care: A Mixed Methods Study"
[*External Ratification: Hawkesbury Human Research Ethics Committee, Northern Sydney Central Coast Health HREC approval – Ref:08/HAWKE/161/162 15/01/2009 to 15/01/2013].*

At its meeting held on 09/06/2009, the UTS Human Research Ethics Committee considered the above application, and I am pleased to inform you that your external ethics clearance has been ratified.

Your UTS clearance number is UTS HREC REF NO. 2009-142R

Please note that the ethical conduct of research is an on-going process. The *National Statement on Ethical Conduct in Research Involving Humans* requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

If you have any queries about your ethics clearance, or require any amendments to your research in the future, please do not hesitate to contact the Ethics Secretariat at the Research and Innovation Office, on 02 9514 9772.

Yours sincerely,

Professor Jane Stein-Parbury
Chairperson
UTS Human Research Ethics Committee

Appendix G The NICE-SUGAR Study Investigators

NICE (ANZ) Management Committee: Simon Finfer, (Chair), Deborah Blair, (Project Manager), Rinaldo Bellomo, Colin McArthur (Lead Investigator, New Zealand), Imogen Mitchell, John Myburgh, Robyn Norton, Julie Potter.

SUGAR (North American) Management Committee: Dean Chittock (Chair), Vinay Dhingra (Past Chair), Denise Foster (Senior Project Manager), Deborah Cook, Peter Dodek, Paul Hébert, William Henderson, Daren Heyland, Ellen McDonald, Juan Ronco. (Ex officio Member: Irwin Schweitzer, Canadian Institutes for Health Research).

Independent Data Monitoring Committee: Richard Peto (Chair), Peter Sandercock, Charles Sprung, J. Duncan Young

Statistical Analysis (The George Institute for International Health, University of Sydney, NSW, Australia) Steve Su, Stephane Heritier, Qiang Li, Severine Bompoint, Laurent Billot.

Study Coordinating Centre (The George Institute for International Health, University of Sydney, NSW, Australia): Leonie Crampton, Fotios Darcy, Kathy Jayne, Viraji Kumarasinghe, Lorraine Little, Suzanne McEvoy, Stephen MacMahon, Sameer Pandey, Suzanne Ryan, Ravi Shukla, Bala Vijayan

University of Sydney (Faculty of Medicine), Kolling Institute and Department of Endocrinology, Royal North Shore Hospital: Bruce Robinson (Dean)

ANZ site investigators: (Alphabetically by institution, Australia unless stated, NZ = New Zealand. NSW = New South Wales, WA = Western Australia)

Auckland City Hospital (DCCM), Auckland, NZ: Susan Atherton, Jeanette Bell, Louise Hadfield, Craig Hourigan, Colin McArthur, Lynette Newby, Catherine Simmonds. Auckland City Hospital (CVICU), Auckland, NZ: Heidi Buhr, Michelle Eccleston, Shay McGuinness, Rachael Parke. The Austin Hospital, Melbourne, Victoria: Rinaldo Bellomo, Samantha Bates, Donna Goldsmith, Inga Mercer, Kim O'Sullivan. Ballarat Base Hospital, Ballarat, Victoria: Robert Gazzard, Dianne Hill, Christine Tauschke. Blacktown Hospital, Blacktown, NSW: Dhawal Ghelani, Kiran Nand, Graham Reece, Treena Sara. Box Hill Hospital, Box Hill, Victoria: Suzanne Elliott, David Ernest, Angela Hamilton. The Canberra Hospital, Canberra, Australian Capital Territory: Rebecca Ashley, Andrew Bailey, Elise Crowfoot, Jelena Gissane, Imogen Mitchell, Jamie Ranse, Joy Whiting. Concord Repatriation Hospital, Concord, NSW: Kristina Douglas, David Milliss, Jeff Tan, Helen Wong. Fremantle Hospital,

Appendix G

Fremantle , WA: David Blythe, Annemarie Palermo. John Hunter Hospital, Newcastle, NSW: Miranda Hardie, Peter Harrigan, Brett McFadyen. Liverpool Hospital, Liverpool, NSW: Sharon Micallef, Michael Parr. Middlemore Hospital, Auckland, NZ: Anna Boase, Judi Tai, Anthony Williams. Nepean Hospital, Nepean, NSW: Louise Cole, Ian Seppelt, Leonie Weisbrodt, Sarah Whereat. North Shore Hospital, Auckland, NZ: Annette Flanagan, Janet Liang. Prince of Wales Hospital, Sydney, NSW: Frances Bass, Michelle Campbell, Naomi Hammond, Lisa Nicholson, Yahya Shehabi. Queen Elizabeth Hospital, Adelaide, South Australia: Jonathan Foote, Sandra Peake, Patricia Williams. Royal Brisbane Hospital, Brisbane, Queensland: Renae Deans, Cheryl Fourie, Melissa Lassig-Smith, Jeffrey Lipman, Janine Stuart. Royal Hobart Hospital, Hobart, Tasmania: Anthony Bell, Tanya Field, Richard McAllister, Kathryn Marsden, Andrew Turner. Royal North Shore Hospital, Sydney, NSW: Susan Ankers, Caroline Barnett, Simon Bird, Simon Finfer, Richard Lee, Anne O'Connor, Julie Potter, Naresh Ramakrishnan. St. George Hospital, Sydney, NSW: Vanessa Dhiacou, Kathryn Girling, Alina Jovanovska, John Myburgh. St. Vincent's Hospital, Melbourne, Victoria: Nicole Groves, Jenny Holmes, John Santamaria, Roger Smith. Sir Charles Gairdner Hospital, Perth, WA: Stuart Baker, Brigit Roberts. Wellington Hospital, Wellington, NZ: Lynne Andrews, Richard Dinsdale, Rosemary Fenton, Diane Mackle, Sarah Mortimer. Western Hospital, Melbourne, Victoria: Craig French, Lorraine Little, Heike Raunow. Wollongong Hospital, Wollongong, NSW: Michelle Gales, Francisco Hill, Sundaram Rachakonda, Darren Rogan. NSW Institute of Trauma and Injury Management, Sydney, NSW, Australia: Christine Allsop. Australian and New Zealand Intensive Care Research Centre, Melbourne Victoria, Australia: Alisa Higgins

North American site investigators (Canada unless stated)

Calgary Health Region, Calgary, Alberta: Kevin Champagne, Christopher Doig, Linda Knox, Pauline Taylor, Crystal Wilson. Kingston General Hospital, Kingston, Ontario: John Drover, Sharlene Hammond, Elizabeth Mann, Monica Myers, Amber Robinson. Maisonneuve Rosemont Hospital, Montreal, Quebec: Johanne Harvey, Yoanna Skrobik. Mayo Clinic, Rochester, Minnesota, USA: Anita Baumgartner, Laurie Meade, Nicholas Vlahakis. Mount Sinai Hospital, Toronto, Ontario: Cheryl Ethier, Marnie Kramer-Kile, Sangeeta Mehta. Ottawa General Hospital, Ottawa, Ontario: Claude Gaudert, Salmaan Kanji, Tracy McArdle, Irene Watpool. St Joseph's Healthcare, Hamilton, Ontario: France Clark, Deborah Cook, Ellen McDonald, Andrea Tkaczyk. St Michael's Hospital, Toronto, Ontario: John Marshall, Jeanna Morrissey, Orla Smith, Kerri Porretta, Victoria Wen. St Paul's Hospital, Vancouver, British Columbia: Betty Jean Ashley, Peter Dodek, Sheilagh Mans. Sunnybrook Health Sciences Centre, Toronto, Ontario: Boris Bojilov, Karen Code, Robert Fowler, Nicole

Appendix G

Marinoff. Toronto General Hospital, Toronto, Ontario: Leslie Chu, John Granton, Margaret McGrath-Chong, Marilyn Steinberg. Toronto Western Hospital, Toronto, Ontario: Niall Ferguson, Stephanie Go, Andrea Matte, Jonathan Rosenberg, James Stevenson. University of Alberta Hospital, Edmonton, Alberta: Michael Jacka, Leeca Sonnema. Vancouver General Hospital, Vancouver, British Columbia: Roger Autio, Dean Chittock, Dara Davies, Pia Ganz, Maureen Gardner, Susan Logie, Laurie Smith. Vancouver Island Health Authority, Victoria, British Columbia: Leslie Atkins, Fiona Auld, Marni Stewart, Gordon Wood.