Normoglycaemia in Intensive Care Evaluation

NICE STUDY

Protocol 293201

Amendment 2, dated June 3, 2005

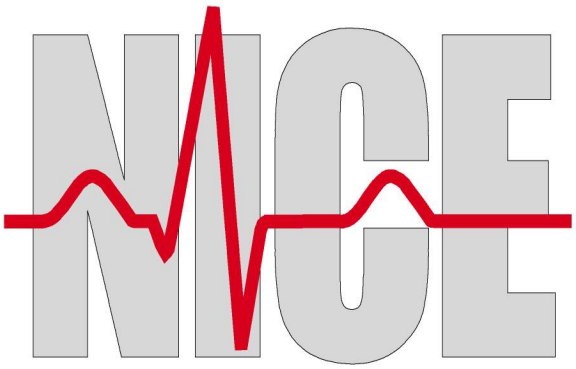
Amendment 3, dated December 8, 2006

Amendment 4, dated 14th January 2008

Survival Using Glucose Algorithm Regulation

SUGAR STUDY

A multi-centre, open label, randomised controlled trial of two target ranges for glycaemic control in Intensive Care Unit patients



THE **NICE** STUDY

THE **NICE** STUDY

Australia and New Zealand Intensive Care Society Clinical Trials Group
Canadian Critical Care Trials Group (CCCTG)
and
The George Institute for International Health

TABLE OF CONTENTS

A multi-centre, open label, randomised controlled trial of two target ranges for glycaemic control in Intensive Care Unit patients.

STUDY ORGANISATION & ADMINISTRATION

This Section provides background information on the establishment of the NICE study, the projected timelines and contact details for all participants.

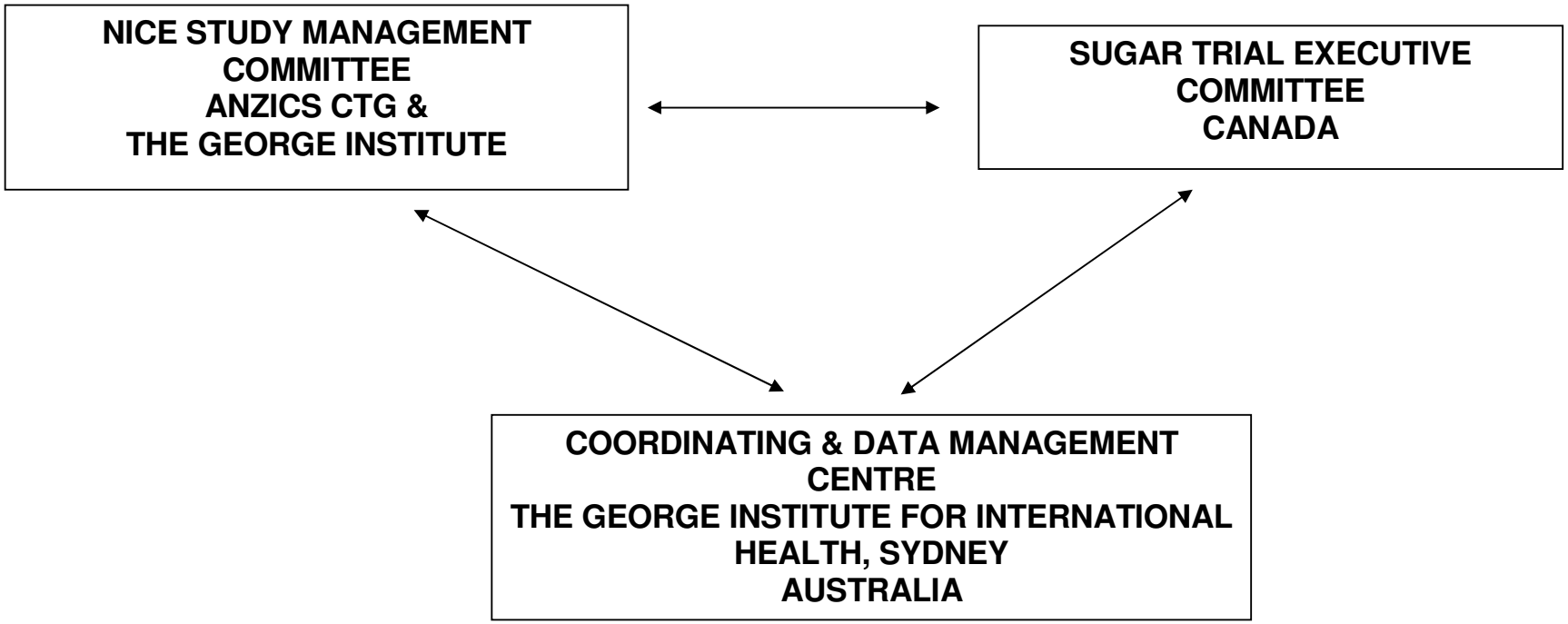
Study Timelines

Figure 1.1 A brief description of how the study has developed and is planned is summarised below:

2002, 2003 & 2004	**INITIAL DISCUSSIONS & STUDY DESIGN** ANZICS Clinical Trials Group (CTG) Canadian Critical Care Trials Group (CCCTG) Following publication of G. van den Berghe study Nov 2001
2003 & 2004	**PROTOCOL DESIGN, PRINCIPAL INVESTIGATOR, RECRUITMENT & FUNDING APPLICATIONS** ANZICS CTG; CCCTG; The George Institute for International Health, University of Sydney
March – December 2003	**PILOT STUDY n = 70 patients** **9 month pilot phase prior to main study** The Canberra Hospital, ACT
2004	**TALKS WITH DATA & SAFETY MONITORING BOARD AND INITIATION OF DATA** ANZICS CTG; CCCTG The George Institute for International Health, University of Sydney
2004 & 2005	**ETHICS COMMITTEE SUBMISSIONS AND APPROVALS** Principal Investigators The George Institute for International Health, University of Sydney
Nov 2004 to Dec 2008	**MAIN STUDY N= 6100** Investigator Meeting Initiation of study at participating centres Patient recruitment Data collection and follow up
Sept 2008 To Feb 2009	**FINAL QUERY RESOLUTION** **DATA CLEANING** **DATABASE LOCK**
Feb 2009 To June 2009	**DATA ANALYSIS AND PUBLICATIONS**

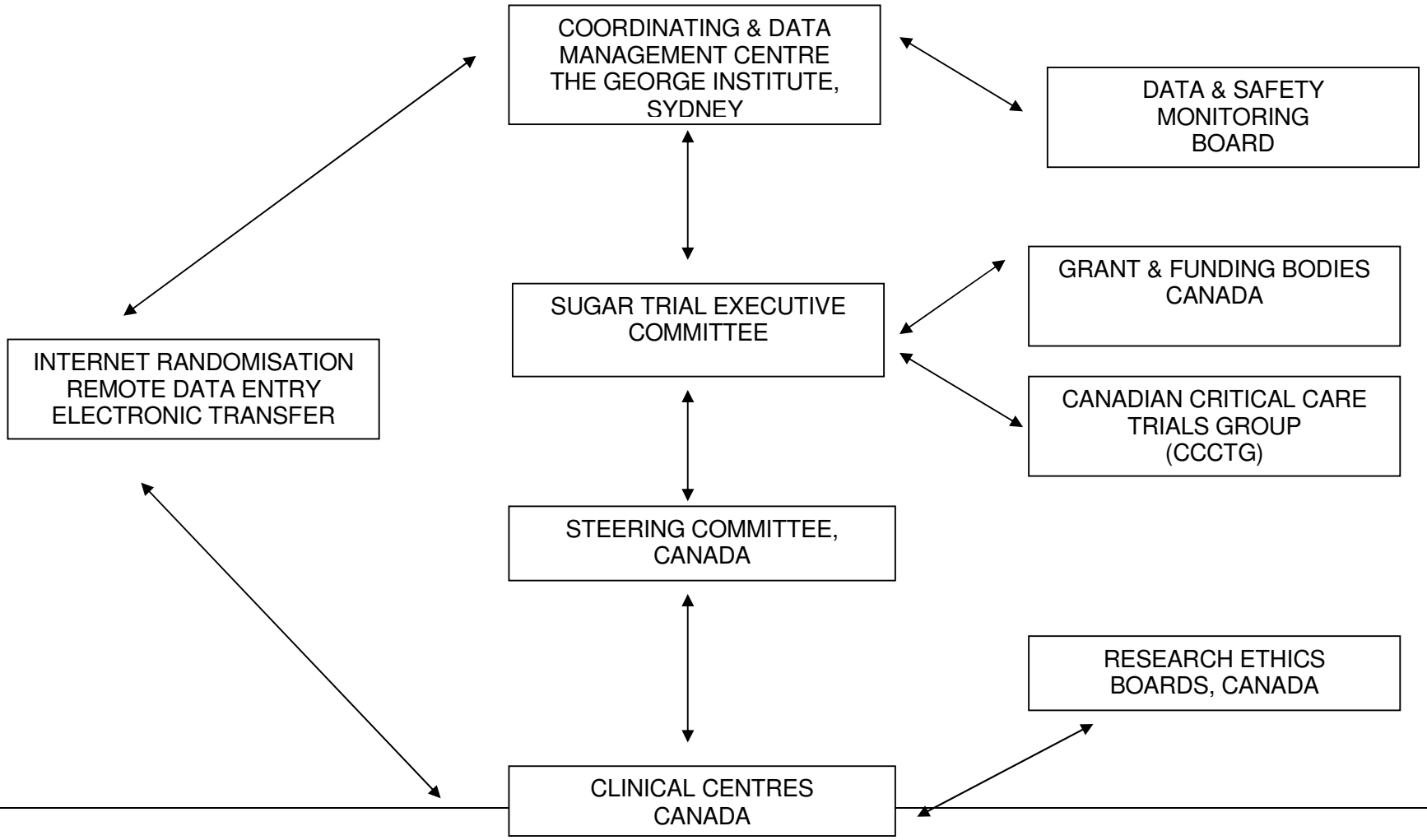
International Organisational Structure

Figure 1.1 **The overall organisational structure of NICE/SUGAR collaboration is summarised below:**



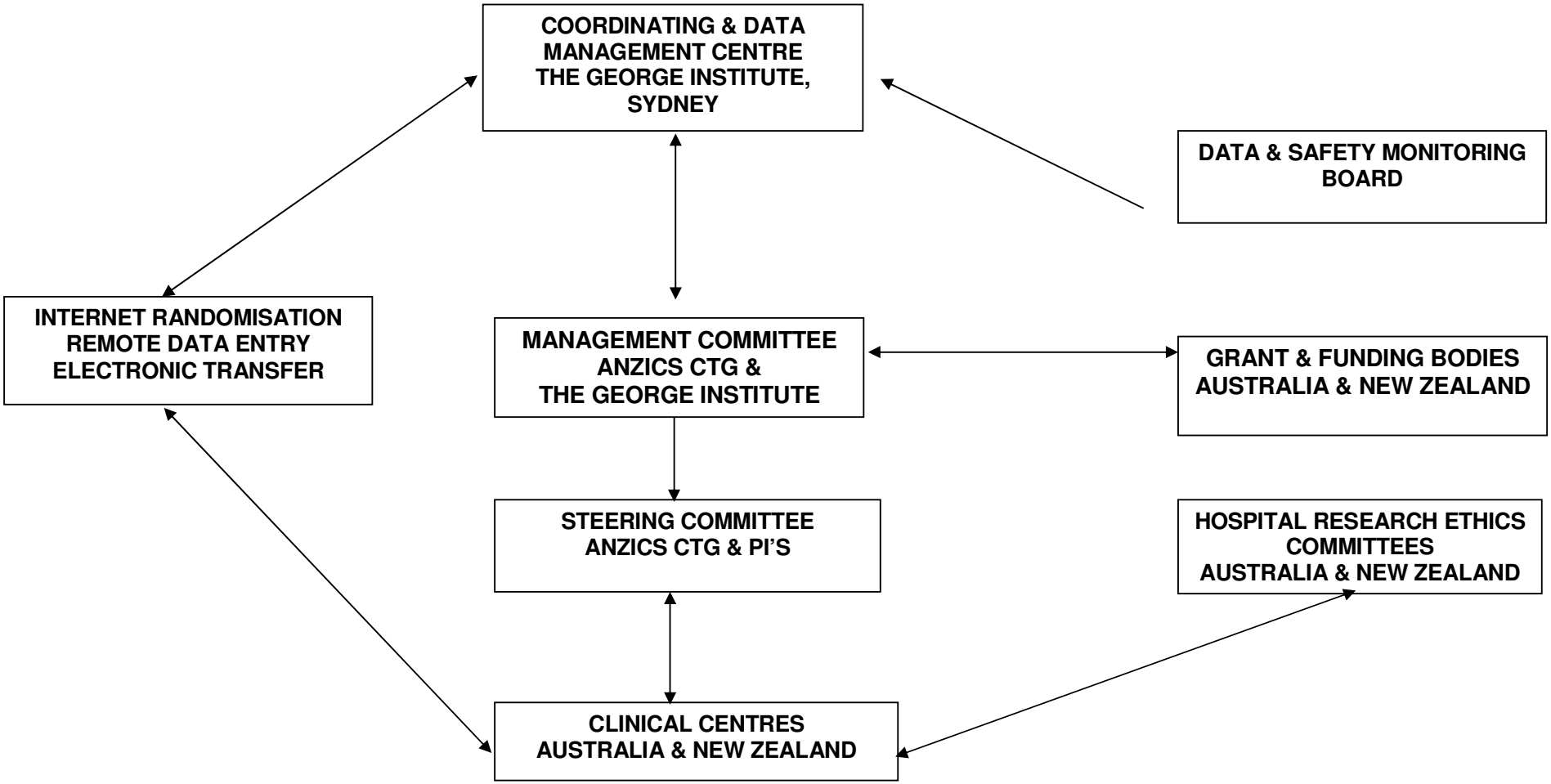
Organizational Structure (Canada)

Figure 1.2 The overall organizational structure of SUGAR is summarized below:



Organisational Structure (Australia & New Zealand)

Figure 1.3 The overall organisational structure of NICE is summarised below:



Administrative Structure

Following is a brief description of the various study committees, their role and membership.

2.1 Coordinating & Data Management Centre, The George Institute for International Health, The University of Sydney

We have created formal trial collaboration between the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and the Canadian Critical Care Trials Group (CCCTG). The spirit of international co-operation studying similar problems in a joint venture will help to answer this question in a timely and effective manner. These two highly productive research consortia will also be able to utilize the resources of The George Institute for International Health employing a web based data collection system which has been tested extensively and used successfully in the largest published trial in ICU patients (SAFE Investigators 2004). This will also facilitate the dissemination of trial results following the end of recruitment. In summary, the joint venture of the ANZICS-CTG AND CCCTG will facilitate completion of this trial and enhance the generalisability of the results.

Responsibilities:

Overall management of the study including: assistance with HREC applications; management of study budget and liaison with funding bodies; final protocol and case report form design and production; preparation and arrangement of Investigator contracts; management of regulatory affairs (TGA etc); database design and management; study set up, monitoring and close out site visits; protocol training of Research Nurse/Coordinators and Principal Investigators; study website design and maintenance; organisation of Investigator meetings; liaison with Data and Safety Monitoring Committee; data analysis and collaboration on publications.

Staff: Robyn Norton, Principal Director of The George Institute
Stephen MacMahon, Principal Director of The George Institute
Michael Fitzharris, Senior Research Fellow
Deborah Blair Project Manager
Suzanne Ryan, Data Management Coordinator
Manuela Schmidt, Clinical Data Manager
Sameer Pandey, Programmer
Beverley Mullane, Graphic Designer
George Vukas, Website Maintenance
Fotios Darcy, NICE Study Monitor
Lorraine Little, NICE Study Monitor
Ravi Shukla, Clinical Trials Assistant

Meetings: As required

2.2 Australian Management Committee

Responsibilities:

Overseeing all aspects of the study management including: Liaison with Coordinating Centre staff, Steering Committee, SUGAR Study Executive Committee, ANZICS CTG; CCCTG; funding applications, negotiations and communications; budget reporting to funding bodies and Steering committee; approval of final protocol and data collection forms; general study management issues;.

Chair: Simon Finfer, Royal North Shore Hospital, Immediate past Chair ANZICS CTG

Members: Rinaldo Bellomo, Austin Hospital, ANZICS CTG
Colin McArthur, Auckland Hospital, ANZICS CTG New Zealand
John Myburgh, St. George Hospital, Chair, ANZICS CTG
Imogen Mitchell, The Canberra Hospital, ANZICS CTG
Robyn Norton, Principal Director of The George Institute
Deborah Blair, Project Manager, The George Institute
Julie Potter, Research Coordinator, Royal North Shore Hospital

Ex-officio: Bruce Robinson

Meetings: Monthly by teleconference. Minutes distributed to Steering Committee and SUGAR Study Executive Committee.

2.3 SUGAR Study Executive Committee

Responsibilities:

Overseeing all aspects of the study management including: Liaison with Coordinating Centre staff, Steering Committee, NICE Study Management Committee and ANZICS CTG; funding applications, negotiations and communications; budget reporting to funding bodies and Steering committee; approval of final protocol and data collections forms; general study management issues in Canada.

Chair: Dean Chittock, Program in Critical Care Medicine, University of British Columbia
Members: William Henderson, Program in Critical Care Medicine, University of British Columbia
Vinay Dhingra, Program in Critical Care Medicine, University of British Columbia
Juan Ronco, University of British Columbia
Peter Dodek, Program in Critical Care Medicine, University of British Columbia
Deborah Cook, Critical Care Medicine, McMaster University, Hamilton, Ontario
Daren Heyland, Critical Care Medicine, Queens University, Kingston, Ontario
Paul Hebert, Critical Care Medicine, University of Ottawa, Ontario
Denise Foster, Project Manager, Vancouver, British Columbia, Canada
Ex- Officio: Simon Finfer, John Myburgh, Deborah Blair.

Meetings: Monthly by teleconference.
Minutes distributed to Steering Committee and NICE Study Management Committee.

2.4 Steering Committee

Responsibilities:

Initiation of study, definition of overall design, continuing input and feedback; approval of full protocol, data collection tools and methods; collaboration and approval of study publications; reporting to local Ethics Committees; data analysis and collaboration on publications

Chair: Simon Finfer, Royal North Shore Hospital, Immediate past Chair ANZICS CTG

Members: Stephen MacMahon, The George Institute for International Health

Management Committee Members and Investigators at each participating hospital:

Auckland Hospital, New Zealand, Colin McArthur
Auckland Cardiovascular Hospital, New Zealand, Shay McGuinness
The Austin Hospital, Victoria, Rinaldo Bellomo
Ballarat Base Hospital, Victoria, Robert Gazzard
Blacktown Hospital, New South Wales, Graham Reece
Box Hill Hospital, Victoria, David Ernest
The Canberra Hospital, ACT, Imogen Mitchell
Concord Repatriation Hospital, New South Wales, David Milliss
Fremantle Hospital, WA, David Blythe
John Hunter Hospital, New South Wales, Brett McFadyen & Peter Harrigan
Liverpool Hospital, New South Wales, Michael Parr
Middlemore Hospital, New Zealand, Anthony Williams
Nepean Hospital, New South Wales, Louise Cole
North Shore Hospital, Auckland, New Zealand, Janet Liang
Prince of Wales Hospital, New South Wales, Yahya Shehabi
Queen Elizabeth Hospital, SA, Sandra Peake
Royal Brisbane Hospital, QLD, Jeffrey Lipman
Royal Hobart Hospital, Tasmania, Anthony Bell and Andrew Turner
Royal North Shore Hospital, New South Wales, Simon Finfer
St. George Hospital, New South Wales, John Myburgh
St. Vincent's Hospital, Victoria, John Santamaria
Sir Charles Gairdner Hospital, Western Australia, Stuart Baker
Wellington Hospital, New Zealand, Dick Dinsdale
Western Hospital, Victoria, Craig French
Wollongong Hospital, New South Wales, Sundaram Rachakonda

Meetings: Six monthly aligned with ANZICS Annual Scientific Meetings and CTG meetings

2.5 Data & Safety Monitoring Board

Responsibilities:

The role of the independent Data and Safety Monitoring Board is to monitor response variables and serious adverse events for early dramatic benefits or potential harmful effects. This committee, which will be composed of at least one senior methodologist and two clinicians, will meet at least twice during the trial's conduct and will use the approach developed by Sir Richard Peto for safety monitoring. All safety monitoring activities will be carried out in a

blinded fashion such that any decision to stop the trial will be arrived at in an unbiased way. No key study personnel will be unblinded as a result of data and safety monitoring.

Members: Richard Peto (Chair), Clinical Trials Service Unit, Oxford, UK
Charles Sprung, Hadassah University Hospital, Jerusalem, Israel
Duncan Young, Radcliffe Infirmary, Oxford, England
Peter Sandercock, Western General Hospital, Edinburgh, Scotland

Meetings: To be determined by the DSMB members

2.6 Clinical Centres

Responsibilities:

Overall management of study at own site in accordance with the study protocol; research coordinator recruitment and orientation; protocol education of colleagues, patient recruitment, data collection and data transfer from the Intensive Care Unit (ICU), data query resolutions, liaison with local ethics committee, adherence to local ethics committee guidelines and reporting requirements, adverse event reporting to ethics committee and The George Institute for International Health, in accordance with protocol.

Staff: Principal Investigator, Co-Investigators, Research Coordinator and Research Associate

Contact details

2.7 Coordinating and Data Management Centre

The George Institute for International Health
PO BoxM201
(Street address: Level 10, King George V Building, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050)
Missenden Road
Sydney, NSW 2050
Australia

Robyn Norton
Tel: 02 9993 4504 Fax: 02 9993 4501 Email: rnorton@george.org.au

Simon Finfer
Tel: 02 9657 0381 Fax: 02 9657 0301 Email: sfinfer@george.org.au

John Myburgh
Tel: 02 9657 0381 Fax: 02 9657 0301 Email: jmyburghr@george.org.au

Michael Fitzharris
Tel: 02 9657 0347 Fax: 02 9657 0301 Email: mfitzharris@george.org.au

Deborah Blair
Tel: 02 9657 0345 Fax: 02 9657 0301 Email: dblair@george.org.au

2.8 NICE Study Management Committee

Robyn Norton, Simon Finfer, John Myburgh, Deborah Blair and:

Colin McArthur
Intensive Care Unit
Auckland Hospital
Corner Grafton and Park Streets
Grafton
Auckland, New Zealand
Tel: 64 9 307 2892 Fax: 64 9 307 4927 Email: colinm@adhb.govt.nz

Rinaldo Bellomo
Department of Intensive Care
Austin Hospital
Studley Road
Heidelberg, VIC 3084
Tel: 03 9496 5992 Fax: 03 9496 3932 Email: Rinaldo.bellomo@austin.org.au

Imogen Mitchell
Intensive Care Unit
The Canberra Hospital
Yamba Drive, Garran
Canberra ACT 2605
Tel: 02 6244 3423 Fax: 02 6244 3507 Email: Imogen.Mitchell@act.gov.au

Julie Potter
Intensive Care Unit
Royal North Shore Hospital
Pacific Highway
St. Leonard's NSW 2065
Tel: 02 9926 5616 Fax: 02 9439-8418 Email: jpotter@ jpotter@nsccahs.health.nsw.gov.au

2.9 Steering Committee (in hospital/institution alphabetical order)

Colin McArthur
Intensive Care Unit
Auckland Hospital
Corner Grafton and Park Streets
Grafton
Auckland, New Zealand
Tel: 64 9 307 2892 Fax: 64 9 307 4927 Email: colinm@adhb.govt.nz

Lynette Newby, Research Coordinator
Tel: 64 9 307 2892 Fax: 64 9 307 4927 Email: DCCMResearch@adhb.govt.nz

Jeanette Bell, Research Coordinator
Tel: 64 9 307 2892 Fax: 64 9 307 4927 Email: DCCMResearch@adhb.govt.nz

Shay McGuinness
Intensive Care Unit
Auckland City Hospital
Cardiovascular ICU
4th Floor, Building 32
Corner Grafton and Park Streets
Grafton
Auckland, New Zealand
Tel: 64 9 307 4949 Fax: 64 9 623 6463 E mail: ShayMc@adhb.govt.nz

Rachael Parke, Research Coordinator
Tel: 64 9 307 4949 Fax: 64 9 307 4473 Email: rparke@adhb.govt.nz

Heidi Buhr, Research Coordinator
Tel: 64 9 307 4949 Fax: 64 9 307 4473 Email: Hbuhr@adhb.govt.nz

Rinaldo Bellomo
Intensive Care Unit
Austin Hospital
145 Studley Road
Heidelberg, Victoria 3084
Tel: 03 9496 5992 Fax: 03 9496 3932 Email: rinaldo.bellomo@austin.org.au

Donna Goldsmith, Research Coordinator
Tel: 03 9496 3424 Fax: 03 9496 3932 Email: Donna.GOLDSMITH@austin.org.au

Kim O'Sullivan, Research Coordinator
Tel: 03 9496 3424 Fax: 03 9496 3932 Email: Kim.O'Sullivan@austin.org.au

Inga Mercer, Research Coordinator
Tel: 03 9496 3424 Fax 03 9496 3932 Email: Inga.Mercer@austin.org.au

Robert Gazzard
Intensive Care Unit
Ballarat Base Hospital
Drummond Street North
Ballarat, Victoria 3353
Tel: 03 5320 4000 Fax: 03 5320 4753 Email: robg@bhs.org.au

Christine Tauschke, Research Coordinator
Tel: 03 5320 4001 Fax: 03 5320 4753 Email: christinet@bhs.org.au

Graham Reece
Intensive Care Unit
Blacktown Hospital
Blacktown Road
Blacktown, NSW 2148

Tel: 02 9881 8000 Fax: 02 9881 8504 Email: Graham_Reece@wsahs.nsw.gov.au

Treena Sara, Research Coordinator
Tel: 02 9881 8000 Fax: 02 9881 8504 Email: Treena_Sara@wsahs.nsw.gov.au

Kiran Nand, Research Coordinator
Tel: 02 9881 8000 Fax: 02 9881 8504 Email: Kiran.Nand@wsahs.nsw.gov.au

David Ernest
Intensive Care Unit
Box Hill Hospital
Nelson Road
Box Hill, Victoria 3128
Tel: 03 9895 3149 Fax: 03 9895 4808 Email: david.ernest@boxhill.org.au

Suzanne Elliott, Research Coordinator
Tel: 03 9895 3419 Fax: 03 9895 3713 Email: suzanne.elliott@boxhill.org.au

Imogen Mitchell
Intensive Care Unit
The Canberra Hospital
Yamba Drive
Garran, ACT 2605
Tel: 02 6244 3423 Fax: 02 6244 3507 Email: Imogen.Mitchell@act.gov.au

Andrew Bailey, Research Coordinator
Tel: 06 6244 3303 Fax: 02 6244 3506 Email: Andrew.bailey@act.gov.au

Jamie Ranse, Research Coordinator
Tel: 06 6244 3303 Fax: 02 6244 3506 Email: Jamie.Ranse@act.gov.au

Rebecca Ashley, Research Coordinator
Tel: 02 6244 3303 Fax: 02 6244 3506 Email: Rebecca.Ashley@act.gov.au

David Milliss
Intensive Care Unit
Concord Repatriation Hospital
Hospital Road
Concord, NSW 2139
Tel: 02 9767 8313 Fax: 02 9767 6870 Email: millissd@email.cs.nsw.gov.au

Jeff Tan, Research Coordinator
Tel: 02 9767 6116 Fax: 02 9767 6870 Email: Jeff.tan@email.cs.nsw.gov.au

David Blythe
Intensive Care Unit
Fremantle Hospital
Alma Street
Fremantle, WA 6160
Tel: 08 9431 2145 Fax: 08 9431 3009 Email: david.blythe@health.wa.gov.au

AnnaMaria Palermo, Research Coordinator
Tel: 08 9431 2145 Fax: 08 9431 3009 Email: Anna.Palermo@health.wa.gov.au

Brett McFadyen & Peter Harrigan
Intensive Care Unit
John Hunter Hospital
Lookout Road
New Lambton
Newcastle, NSW 2305
Tel: 02 4921 3887 Fax: 02 4921 4799 Email: Peter.Harrigan@hunter.health.nsw.gov.au

Miranda Hardie, Research Coordinator
Tel: 02 4921 3887 Fax: 02 4921 4799 Email: miranda.hardie@hunter.health.nsw.gov.au

Michael Parr
Department of Intensive Care Unit
Liverpool Hospital
Locked Bag 7103
Liverpool BC, NSW 1871
Tel: 02 9828 3400 Fax: 02 9828 3551 Email: Michael.Parr@swsahs.nsw.gov.au

Sharon Micallef, Research Coordinator
Tel: 02 9828 3193 Fax: 02 9828 3551 E mail: sharon.micallef@sswahs.nsw.gov.au

Anthony Williams
Department of Critical Medicine
Middlemore Hospital CMDHB
Auckland, NZ
Tel: 64 9 276 0112 Fax: 64 9 276 0080 Email: twilliams@middlemore.co.nz

Judi Tai, Research Coordinator
Tel: 64 9 276 0112 Fax: 64 9 276 0080 Email: jtai@middlemore.co.nz

Louise Cole
Intensive Care Unit
Nepean Hospital
Great Western Highway
Kingswood, NSW 2340
Tel: 02 4734 1351 Fax: 02 4734 3134 Email: colel@wahs.nsw.gov.au

Leonie Weisbrodt, Research Coordinator
Tel: 02 4734 2000 Fax: 02 4734 3134 Email: weisbrl@wahs.nsw.gov.au

Sarah Whereat, Research Coordinator
Tel: 02 47342584 Fax: 02 47343134 Email: smorton@med.usyd.edu.au

Janet Liang
Intensive Care Unit
North Shore Hospital Auckland
Crn Taharoto & Shakespeare Rds
Takapuna, Auckland.
Tel: 64 9 489 0523 Email: Janet.Liang@waitematadhb.govt.nz

Annette Flanagan, Research Coordinator
Tel: 64 9 489 0523 Email: Annette.Flanagan@waitematadhb.govt.nz

Tracey Mellows, Research Coordinator
Tel: 64 9 489 0523 Email: Tracey.Mellows@waitematadhb.govt.nz

Yahya Shehabi
Intensive Care Unit
Prince of Wales Hospital
Barker Street
Randwick, NSW 2031
Tel: 02 9382 4720 Fax: 02 9382 4748 Email: yshehabi@ozemail.com.au

Frances Bass, Research Coordinator
Tel: 02 9382 4720 Fax: 02 9382 4780 Email: Frances.Bass@sesiahs.health.nsw.gov.au

Michelle Campbell, Research Coordinator
Tel: 02 9382 4720 Fax: 02 9382 4780
Email: Michelle.Campbell@sesiahs.health.nsw.gov.au

Sandra Peake
Intensive Care Unit
Queen Elizabeth Hospital
28 Woodville Road
Woodville, SA 5011
Tel: 08 8222 6463 Fax: 08 8222 6045 Email: Sandra.Peake@nwahs.sa.gov.au

Patricia Williams, Research Coordinator
Tel: 08 8222 7317 Fax: 08 8222 6045 Email: tricia.williams@nwahs.sa.gov.au

Jeffrey Lipman
Intensive Care Unit
Royal Brisbane & Women's Hospital
Butterfield Street
Herston
QLD 4029
Tel: 07 3636 8897 Fax: 07 3636 3542 Email: j.lipman@mailbox.uq.edu.au

Renae Deans, Research Coordinator
Tel: 07 3636 8894 Fax: 07 3636 3542 Email: renae_deans@health.qld.gov.au

Cheryl Fourie, Research Coordinator
Tel: 07 3636 8894 Fax: 07 3636 7589 Email: Cheryl_Fourie@qld.gov.au

Kerry McNamara, Research Coordinator
Tel: 07 3636 8894 Fax: 07 3636 3542 Email: kerry_mcnamara@health.qld.gov.au

Anthony Bell and Andrew Turner
Intensive Care Unit
Royal Hobart Hospital
Liverpool Street
Hobart, TASMANIA 7000
Tel: 03 6238 8308 Fax: 03 6222 8010 Email: anthony.bell@dchs.tas.gov.au

Kathryn Marsden, Research Coordinator
Tel: 03 6222 8212 Fax: 03 6222 8312 Email: kathryn.marsden@dhhs.tas.gov.au

Richard McAllister, Research Coordinator
Tel: 03 6222 8212 Fax: 03 6222 8312 Email: richard.mcallister@dhhs.tas.gov.au

Simon Finfer
Intensive Care Unit
Royal North Shore Hospital
Pacific Highway
St. Leonard's, NSW 2065
Tel: 02 9657 0381 Fax: 02 9657 0301 Email: sfinfer@george.org.au

Julie Potter, Research Coordinator
Tel: 02 9926 5616 Fax: 02 9439 8418 Email: jpotter@nsccahs.health.nsw.gov.au

Anne O'Connor, Research Coordinator
Tel: 02 9926 7851 Fax: 02 9439 8418 Email: AOConnor@nsccahs.health.nsw.gov.au

Simon Bird, Research Coordinator
Tel: 02 9926 5616 Fax: 02 9439 8418 Email: SBird@nsccahs.health.nsw.gov.au

Susan Ankers, Research Coordinator
Tel: 02 99265965 Fax 02 9439 8418 Email: SAnkers@nsccahs.health.nsw.gov.au

John Myburgh
Intensive Care Unit
St. George Hospital
Belgrave Street
Kogarah, NSW 2217
Tel: 02 9350 3265 Fax: 02 9350 3971 Email: j.myburgh@unsw.edu.au

John Santamaria
Intensive Care Unit
St. Vincent's Hospital
PO Box 2900
Fitzroy, Victoria 3065
Tel: 03 9288 4488 Fax: 03 9288 4487 Email: john.santamaria@svhm.org.au

Jenny Holmes, Research Coordinator
Tel: 03 9288 3972 Fax: 03 9288 4487 Email: Jennifer.Holmes@svhm.org.au

Roger Smith, Research Coordinator
Tel: 03 9288 3972 Fax: 03 9288 4487 Email: Roger.Smith@svhm.org.au

Dick Dinsdale
Intensive Care Unit
Wellington Hospital
Private Bag 7902
Wellington South, New Zealand
Tel: 64 4 385 5999 Fax: 64 4 385 5333 Email: Dick.Dinsdale@ccdhb.org.nz

Diane Mackle, Research Coordinator
Tel: 64 4 385 5999 (x6248) Fax: 64 4 385 5333 Email: Diane.Mackle@ccdhb.org.nz

Lynne Andrews, Research Coordinator
Tel: 64 4 385 5999 (x6248) Fax: 64 4 385 5333 Email: Lynne.Andrews@ccdhb.org.nz

Craig French
Intensive Care Unit
Western Hospital
Gordon Street
Footscray, Victoria 3011
Tel: 03 8345 6639 Fax: 03 8345 6572 Email: craig.french@wh.org.au

Heike Raunow, Research Coordinator
Tel: 03 8345 6569 Fax: 03 8345 6572 Email: Heike.Raunow@wh.org.au

Sundaram Rachakonda
Intensive Care Unit
Wollongong Hospital
Loftus Street
Wollongong, NSW 2500
Tel: 02 4222 5316 Fax: 02 4222 5123 Email: RachakondaS@iahs.nsw.gov.au

Francisco Hill, Research Coordinator
Tel: (02) 4222 5106 Fax: 02 4222 5123 Email: HillF@iahs.nsw.gov.au

2.10 Funding

The NICE-SUGAR study is currently funded by a grant from:

- The National Health and Medical Research Council (NHMRC; Australia), 3 year Project Grant
- The Health Research Council of New Zealand (HRC): a 3 year Project Grant
- The Canadian Institute of Health Research (CIHR), a 3 year Project Grant

The NICE-SUGAR study was initiated and designed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and The Canadian Critical Trials Group. The study design, protocol and procedures have been finalised in collaboration with The George Institute for International Health, independently of the aforementioned funding bodies. The data will be collected, analysed and published independent of the funding bodies and a copy of the final report will be distributed to the funding bodies on completion of the study.

3. BACKGROUND AND RATIONALE

3.1 Hyperglycaemia in Intensive Care Unit patients

Hyperglycaemia is a common finding in patients who are acutely ill even in the absence of a prior diagnosis of diabetes mellitus.[1] In these patients, hyperglycaemia is associated with adverse outcome.[1, 2, 3] For example, patients suffering an acute myocardial infarction who have a blood glucose concentration above 8 mmol/L have a three-fold increase in mortality and a greater risk of developing cardiac failure.[2] This association has been recognised for some time: hyperglycaemia was included in the predictive Acute Physiology and Chronic Health Evaluation (APACHE) III severity of illness scoring system in 1991.[4]

There are a number of mechanisms by which hyperglycaemia may adversely affect the outcome of the critically ill. In particular, hyperglycaemia impairs white cell function with abnormal granulocyte adhesion, phagocytosis, respiratory burst and superoxide formation, and intracellular killing.[5, 6, 7] If infection results, the risk of developing multiple organ failure increases and the likelihood of the patient surviving to discharge from the intensive care unit (ICU) decreases.[8]

The causes of hyperglycaemia in Intensive Care patients are multifactorial. In normal healthy adults blood glucose is tightly regulated by homeostatic mechanisms. This includes the release of insulin from the ß cells of the pancreas once blood glucose concentration is above 3.9 mmol/L with resulting decrease in glucagon release. This leads not only to increased cellular glucose uptake but also increased glycogen synthesis that prevents the peak blood glucose exceeding 8.3 mmol/L. In Intensive Care patients, insulin resistance develops and patients with protracted critical illness exhibit increased serum concentration of insulin-like growth factor binding-protein 1, reflecting an impaired response of hepatocytes to insulin. Increased concentration of the insulin-like growth factor binding-protein have been associated with an increase in the risk of hospital death.[9, 10] Peripheral insulin resistance probably develops as a result of increased concentrations of stress hormones (adrenaline, growth hormone, glucocorticoid and glucagon), all of which counteract the action of insulin. It is also likely that cytokines released as part of the stress response play a similar role.[11]

Control of blood glucose concentration to normal levels by exogenous insulin infusions may improve neutrophil function.[12] Control of blood glucose may also reduce the risk of critical illness polyneuropathy, either by a direct effect or indirectly by reducing the incidence of infection and sepsis. [13,14,15,16]

3.2 Evidence in favour of treating hyperglycaemia

As hyperglycaemia is associated with worse outcome in patients treated in ICUs, the question of whether maintaining normoglycaemia may improve outcome in this cohort of patients arises. Previous studies have demonstrated that targeting normoglycaemia improves outcome in diabetic patients with an acute myocardial infarction.[17, 18, 19] Two recent studies performed in a Belgian Intensive Care Unit used high does of insulin (intensive insulin therapy) to lower blood sugar levels to normal. The first study, a single centre randomised tria, studied the effects of normoglycaemia in surgical Intensive Care patients [20]. In this study by Van den Berghe and colleagues, 1548 surgical Intensive Care patients were randomised to receive either an insulin sliding-scale maintaining the blood glucose between 4.4-6.1 mmol/L (intensive insulin group) or an insulin sliding-scale maintaining blood glucose between 10-11.1 mmol/L (conventional insulin group). The study reported an absolute reduction in hospital mortality of 3.7% (Relative risk reduction, RRR 33.0%) with IIT (NEJM 2001; 345: 1359-67). The study patients received high doses of intravenous (IV) glucose and the control group mortality was unexpectedly high. Other positive findings for those in the intensive insulin group included a reduction in hospital stay, blood stream infections, acute renal failure requiring dialysis, incidence of critical illness polyneuropathy and blood transfusions. The effect was limited to patients who stayed in the ICU more than 5 days. The incidence of hypoglycaemia was significantly increased in the intensive insulin group (39 patients) compared to those in the conventional glucose group (6 patients). However there were no detectable long-term sequelae from these episodes of hypoglycaemia. In February 2006 Van den Berghe published a second single centre RCT of IIT in 1200 critically ill medical patients expected to be treated in the ICU for 3 days or more (NEJM 2006; 354: 449-61). That study did not find a significant reduction in mortality in the intention-to-treat population, although in 767 patients who were in the ICU on three or more calendar days, 90-day mortality was reduced from 49.1% to 42.2% (RRR 14.1%, P=0.06). The doctors were not able to predict accurately how long each patient was likely to stay in the ICU. The publication of this second study has increased clinicians uncertainty over the role of IIT in Australasian ICU's. Van den Berghe called for additional large scale RCT's of at least 5000 participants to answer the key question – does intensive insulin therapy reduce mortality in ICU patients?

Given the prevalence of hyperglycaemia in the ICU, its serious health consequences, and the results of a recent trial, the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS) has jointly developed a major multinational randomised controlled trial (RCT)

with the Canadian Critical Care Trials Group (CCCTG) called the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE/SUGAR) Study to test the hypothesis that intensive glycaemic control will decrease morbidity and mortality in critically ill patients.

3.3 Current practice in Australian and New Zealand Intensive Care Units

Despite the positive results of the trial, the practice of intensive insulin therapy has not been widely adopted in Australasian ICUs. A survey of units active in the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG) found a minority of units had adopted the intensive insulin regimen. Thirty three ICU directors were surveyed on their current glycaemic management and 939 consecutive ICU admissions were studied in 29 ICUs. Only four (12%) ICU directors reported using an intensive insulin regimen in all their patients. Ninety two percent of the patient population studied had a blood glucose concentration greater than 6.1 mmol/L during their ICU stay. Two hundred and eighty seven patients (31.1%) were administered insulin and the median (IQR) blood glucose concentration that triggered insulin administration was 11.9 (9.4, 14) mmol/L. (I Mitchell, S Finfer, R Bellomo, T Higlett. Intensive Care Med. 2004 In press (Abstract)

3.4 Why has Australian Practice not changed?

We found 100% awareness of the Van den Berghe study, however, only 4 out of 33 units have adopted the intensive insulin therapy (IIT) and none of the NICE study ICUs have implemented IIT. Overall, there is concern about the applicability of the results from the Van den Berghe study to a wider, heterogeneous Intensive Care patient population in Australasia. The reasons for not adopting IIT were:

a) High mortality in the Van den Berghe study control group despite low median APACHE II score.
b) Outcomes in Australasian ICUs are considered to be as good as the IIT group of the Van den Berghe study despite 30% higher APACHE II scores.
c) Concern about the routine use of TPN and its potential toxicity in the Van den Berghe study.
d) Concern that potentially harmful hypoglycaemia would occur frequently for little gain.
e) Reluctance to change practice on the basis of a single centre unblinded study.
f) Different case mix in Australasian ICUs compared with that in the Van den Berghe study.

A positive multicentre study in medical and surgical Australasian ICUs using a feeding regimen reflecting current practice would overcome these concerns. In addition, the safety of applying an intensive insulin regimen in Intensive Care patients outside a controlled clinical trial, or in the absence of high-dose intravenous glucose administration, has not been established. This is of particular concern as many patients in ICUs are sedated or neurologically impaired and so at risk of unrecognised hypoglycaemia.

3.5 Patient selection and outcome

The patient population in Van den Berghe's first trial was limited to surgical Intensive Care patients who were ventilated on admission to the ICU, whereas the majority of Australasian ICUs have a mixed population of medical and surgical patients. As stated by Van den Berghe and co-authors, whether the result applies to medical patients is unknown.
The mortality rate in the conventional treatment group of Van den Berghe's study is higher than expected in Australasian Intensive Care practice. For example, the patients in the conventional

group who had undergone cardiac surgery had a mortality rate of 5.1%, compared to 0.98% for cardiac surgical patients admitted to Australasian ICUs.

Details on the outcome of surgical patients aged 18 or over ventilated in private or tertiary Australian ICUs have been extracted from the ANZICS database and are given in Tables 1 and 2, and comparison is made with the intensive insulin and conventional groups in Van den Berghe et al. and Anderson T & Hart G (2002) Review of Intensive Care Activity 2000/2001. ANZICS, Melbourne.

Table 1. Surgical patients aged 18 or over ventilated in Private or Tertiary Australian and New Zealand ICUs. Number of patients, age (Mean and SD), number and % for male, type of surgery by number and %, APACHE II score median and interquartile range, number and % with APACHE II score greater than 9. Comparison of ANZICS database patients and intensive insulin and conventional groups reported in Van den Berghe et al.

	Van den Berghe et al		
	Conventional	**Intensive**	**ANZICS**
Number	783	765	8184
Male	557 (71)	544 (71)	5512 (67.4)
Age	62.2 (13.9)	63.4 (13.6)	62.7 (14.9)
BMI	25.8 (4.7)	26.2 (4.4)	Unknown
Type of surgery			
Cardiac	493 (63)	477 (62)	4168 (50.9)
Neurological	30 (4)	33 (4)	735 (8.98)
Thoracic	56(7)	66 (9)	553 (6.76)
Abdominal	58 (7)	45 (6)	1189 (14.53)
Vascular	32 (4)	30 (4)	827 (10.11)
Trauma	35 (4)	33 (4)	226 (2.76)
Transplant	44 (6)	46 (6)	
Other	35 (4)	35 (5)	486 (5.94)
APACHE II Score	9 (7-13)	9 (7-13)	12 (9-16)
APACHE II >9	458 (58)	429 (56)	5797 (71)

Table 2. Surgical patients aged 18 or over ventilated in private or tertiary Australian and New Zealand ICUs: Mortality rates, comparison of ANZICS database patients and intensive insulin and conventional groups reported in Van den Berghe et al. Absolute numbers (%)

	Van den Berghe et al		
	Conventional	**Intensive**	**ANZICS**
Death During ICU	63/783 (8.0)	35/765 (4.6)	345/8184 (4.22)
Death in 5 days	14/783 (1.8) *14/540 (2.59)*	13/765 (1.7) *13/457 (2.84)*	244/8184 (2.98) *244/7506 (3.25)*
Death > 5 days	49/243 (20.2)	22/208 (10.6)	101/678 (14.9)
Type of surgery			
Cardiac	25/493 (5.1)	10/477 (2.1)	41/4127 (0.98)
Neurological	7/30 (23.3)	6/33 (18.2)	44/691 (5.99)
Thoracic	10/56 (17.9)	5/66 (7.6)	30/533 (3.62)
Abdominal	9/58 (15.5)	6/45 (13.3)	104/1085 (8.75)
Vascular	2/32 (6.2)	2/30 (6.7)	74/753 (8.95)
Trauma	3/35 (8.6)	4/33 (12.1)	39/187 (17.26)
Transplant	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	23/463 (4.73)
In Hospital Death	85/783 (10.9)	55/765 (7.2)	586/8184 (7.2)

Death >5days	64/243 (26.3)	35/208 (16.8)	163/678 (24.04)

Table one demonstrates that surgical patients ventilated in Australian and New Zealand (ANZ) private and tertiary hospital ICUs are similar in terms of age, sex distribution and type of surgery to the patients reported by Van den Berghe. The median APACHE II {Knaus, Draper, et al. 1985} score of the ANZ patients was higher and the ANZ group contained a greater percentage of patients with an APACHE II score of greater than 9, suggesting that the ANZ patients were "sicker" than those studied by Van den Berghe. Table two demonstrates that despite the suggestion the ANZ patients were sicker, the overall hospital mortality rate was the same as the Van den Berghe's patients treated with the intensive insulin regimen (7.2% both groups). Despite the limitations of these comparisons, these data have caused ICU practitioners to doubt the external validity of Van den Berghe's study, particularly in relation to ANZ ICU practice.

3.6 Management of Nutrition

Another significant difference between the study protocol and standard management in Australasian ICU practice is in the management of nutrition. At the time of ICU admission, patients in Van den Berghe's trial received 200-300 g of intravenous glucose per day, followed by combined total parenteral and enteral nutrition with the aim of administering 20-30 non-protein kilocalories per kilogram of body weight per 24 hours. Total enteral nutrition was attempted as early as possible. Neither the use of high dose intravenous glucose nor the early institution of parenteral nutrition are common in Australasian Intensive Care practice, [21] or supported by current evidence.[22] It is possible that the management of nutrition in Van den Berghe's study resulted in an iatrogenic increase in the incidence of hyperglycaemia, thereby magnifying the treatment effect.

3.7 Safety concerns

In addition to concerns about the external validity of Van den Berghe's study, the hazards of employing strict glycaemic control in a population of Intensive Care patients not administered large amounts of intravenous glucose are not known and could result in an unacceptable incidence of hypoglycaemia.

3.8 Is another study needed?

Previous experience has demonstrated that single centre studies may produce results that can not be replicated in larger multi-centre studies, examples in the ICU literature include hypothermia for the treatment of traumatic brain injury [23,24] and targeting supranormal oxygen delivery.[25,26,27] As a result, intensive care specialists may be reluctant to adopt treatments tested in single centre studies, particularly unblinded studies, unless the results are validated in larger multi-centre studies.

4 STUDY DESIGN

4.1 Aim

The primary aim of the study is to compare the effects of the two blood glucose targets on 90 day all-cause mortality in Intensive Care patients who are predicted on admission to stay in the ICU for at least one full calendar day. The hypothesis is that there is no difference in the relative risk of death between patients assigned a glucose range of 4.5 - 6.0 mmol/L (81 – 108 mg/dl) and those assigned a glucose range of less than 10.0 mmol/L with insulin being infused if blood glucose exceeds 10.0 mmol/L (180 mg/dl), and adjusted when needed to maintain blood glucose of 8.0 – 10.0 mmol/L (144 – 180 mg/dl).

4.2 Design

The NICE-SUGAR study is a multi-centre, open label, randomised controlled trial of blood glucose management with an intensive insulin regimen to maintain blood glucose between 4.5 - 6.0 mmol/L (81 – 108 mg/dl) versus an insulin regimen maintaining blood glucose less than 10.0 mmol/L (180 mg/dl) with insulin being infused if blood glucose exceeds 10.0 mmol/L (180 mg/dl), and adjusted when needed to maintain blood glucose between 8.0 – 10.0 mmol/L (144 – 180 mg/dl).

To ensure patient safety, the target blood glucose concentration must be closely monitored and the results known to the clinical staff treating the patients. As patient safety is paramount, it is not possible to blind the clinical staff to treatment allocation. In this open-label trial, bias will be minimised by ensuring concealment of treatment allocation prior to randomisation. The unblinded design risks introducing a systematic difference in some other treatment between the two groups, this is unlikely in the ICU setting where many other interventions will be administered simultaneously. The primary outcome measure is mortality and therefore not subject to ascertainment bias.

5. STUDY POPULATION

5.1 Patient recruitment

The treatment effect in Van den Berghe's study was limited to patients who stayed in Intensive Care for five days or longer, but all ventilated patients were admitted to the study at the time of ICU admission. Identifying patients who will stay in the ICU for five days or longer is problematic whereas it is relatively easy to identify patients, particularly patients admitted for routine post-operative monitoring, who will be discharged alive from the ICU after the day following admission. For that reason we propose to consider all patients but exclude those expected to be discharged alive or dead before the end of the day following admission.

The attending Intensive Care physician will make this assessment. In addition it is essential that patients who will stay in the ICU for greater than the eligible criteria time frame but who have a very low risk of death are excluded. For this reason we will exclude patients who are able to eat (or who are tube fed due to pre-existing bulbar or laryngeal dysfunction) and patients who do not merit an arterial line as part of their normal management.

Patients who are moribund and at imminent risk of death (brain death or cardiac standstill) will be excluded. This exclusion is on the basis that treatment allocation can not alter the patient's outcome.

5.2 Patient Inclusion Criteria

Patients are eligible for **INCLUSION** in the study if **ALL** the following criteria are met:

1. At time of the patient's admission to the ICU the treating ICU specialist expects the patient will require treatment in the ICU that extends beyond the calendar day following the day of admission.
2. Patient has an arterial line in situ or placement of an arterial line is imminent (within the next hour) as part of routine ICU management.

5.3 Patient Exclusion Criteria

Patients will be **EXCLUDED** from the study if ONE or MORE of the following criteria are present:

1. Age < 18 years.
2. Imminent death (cardiac standstill or brain death anticipated in less than 24 hours) and the treating clinicians are not committed to full supportive care. This should be confirmed by a documented treatment-limitation order that exceeds a "not-for-resuscitation" order.
3. Patients admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state.
4. Patient is expected to be eating before the end of the day following admission
5. Patients who have suffered hypoglycaemia without documented full neurological recovery.
6. Patient thought to be at abnormally high risk of suffering hypoglycaemia (e.g. known insulin secreting tumour or history of unexplained or recurrent hypoglycaemia or fulminant hepatic failure)
7. If a patient has previously been enrolled in the NICE-SUGAR Study (patients cannot be enrolled in the NICE-SUGAR Study more than once).
8. If the patient can not provide prior informed consent, there is documented evidence that the patient has no legal surrogate decision maker and it appears unlikely that the patient will regain consciousness or sufficient ability to provide delayed informed consent
9. The patient has been in the study ICU or another ICU for longer than 24 hours for this admission.

There is no upper age limit for inclusion into the study unless any of the specific exclusion criteria are present.

5.4 Sample size and power calculations

The ANZICS adult patient database contains information on mortality of patients staying more than 48 hours in ICUs. In the financial years 2000, 2001 and 2002, of 43,760 patients treated in intensive care for greater than 48 hours for whom complete data were available, 9476 died prior to hospital discharge. The hospital mortality rate was 22%. As we will exclude less sick patients who stay greater than 48 hours and 90-day mortality is the primary outcome measure, the study had assumed a 90-day mortality rate of 26% in the control group.

We initially planned to enrol 4000 patients thus providing a 90% power of detecting a 4.5% reduction in absolute mortality from a baseline of 26% (α <0.05). Van den Berghe's first study demonstrated a relative reduction in risk of in-hospital death of 33.9%, our study was powered to detect a relative risk reduction of 17.3%, 52% of the treatment effect seen in Van den

Berghe's first study. Following addition of the North American centres and using data from Canadian sources, we have revised the estimated mortality rate for the control group to 30%.

The data from Van den Berghe's second (MICU) study suggests that in a combined medical and surgical population a RRR of 14% is a more appropriate target and 6100 patients are needed to provide a 90% power to detect a 12.7% RRR from an estimated baseline mortality of 30%, (α <0.05).

We plan to enrol 6100 patients providing 90% power to detect an absolute decrease in mortality of 3.8% from a baseline of 30% (two-sided alpha <0.05). The study is powered to detect a relative risk reduction of 12.7%, which is 37.5% of the treatment effect documented in Van den Berghe's first study. Thus, our proposed relative risk reduction is more plausible than that observed in Van den Berghe's first study; this difference is still clinically important and if detected would likely lead to widespread change in the practice of glycemic control in ICUs in Australia, New Zealand, North America and beyond.

A total of 6100 patients will be recruited, 4100 of these patients will be recruited from the ANZICS CTG centres and 2000 patients will be recruited in Canada and United States of America.

5.5 Screening Log

A screening log will be maintained at each participating centre by the Research Coordinator to document patients who enter the pre-trial screening. This will document patients that are considered for eligibility, either randomised into the study or considered not eligible to be enrolled into the study. Also, the purpose of the screening log is to monitor patient recruitment and ensure that any issues are quickly resolved by the Coordinating and Data Management Centre. The screening log will be maintained and sent to the Coordinating and Data Management Centre monthly.

A record of the number of admissions to the ICU for each month will also be maintained to assess if patient recruitment is as projected for each unit.

6. METHODS

6.1 Human Research Ethics Committee Approvals

An application requesting approval to conduct this study will be submitted to the Human Research Ethics Committee (HREC) at each of the participating hospitals. Each application will be submitted according to the requirements of each hospital committee, all of which have been formed and are conducted in accordance with the guidelines of the National Health and Medical Research Council of Australia or the Health Research Council of New Zealand as appropriate. The content and format of the patient and next of kin or legal surrogate Information Statements and Consent Forms will be approved by each ethics committee and formatted in accordance with their own guidelines and requirements. Each participating hospital will therefore use their own consent documents as approved by their local HREC.

Each Principal Investigator will be responsible for producing regular status reports, serious adverse event reports, and any other required documentation to the local HREC in accordance with their guidelines. Any amendments or additions to the study protocol and material must be notified to the HREC by the Principal Investigator.

It is the responsibility of the Principal Investigator at each participating hospital to maintain up to date records of all correspondence and applicable documentation with the local HREC and the regulatory authorities. The Template of the Informed Consent Form and Patient Information Statements that are to be used at each hospital, together with a copy of all signed Informed Consent Forms and any other consent related correspondence must also be kept in a separate file for audit purposes. All study records and documents must be stored for a minimum of 2 years from the end of the study or for a period as required by the individual HREC for each participating centre or as required by regulatory authorities (TGA).

6.2 INFORMED CONSENT

Gaining written and informed consent from patients in high dependency situations such as the ICU is difficult because Intensive Care patients are often unconscious, sedated, intubated or too ill to understand information relating to clinical trial participation (NHMRC 1999). The Declaration of Helsinki recognises that some clinical research will involve patients who are physically incapable of giving informed consent (Principle 26, World Medical Association Declaration of Helsinki, 2000). It states "*Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical or mental condition that prevents obtaining informed consent is a necessary characteristic of the research population".* Patients in the ICU are such a population. The standard for obtaining informed consent for participation in the NICE Study will be in the form of written informed consent from the conscious and comprehending patient, prior to enrolment in the study.

However, it is expected that the majority of patients eligible for NICE will be severely ill and/or receiving sedative medications as part of their treatment. For critically ill patients who are not able to provide consent an explanatory statement will be provided to their legal surrogate at the earliest opportunity. The patient information will also be provided to the patient, when and if they regain consciousness and are able to make an informed decision concerning continued participation in the study. The randomised treatment may be withdrawn at any time at the discretion of the patient, their legal surrogate or by their treating physician. If the patient or their legal surrogate request that study treatment is withdrawn the site investigator or delegate will request specific consent to continue study data collection and use, particularly in respect of the primary outcome measure. Unless specifically prohibited by the patient or their legal surrogate, follow up data will be collected to Day 90 and to 2 years if the patient was admitted to the ICU with a traumatic brain injury as defined by CT evidence of traumatic brain injury and a Glasgow Coma Score of <14 at last non-sedated pre-randomisation assessment..

The use of delayed consent is in keeping with NHMRC Guidelines and precedent has been established in previous studies in Intensive Care patients conducted by the ANZICS Clinical Trials Group (for example, the NHMRC-funded SAFE study). In compliance with the NHMRC Guidelines, local hospital ethics committees have agreed to allow delayed consent in this patient group.

6.2.1 Prior Informed Consent from the patient, prior to ICU admission

Whenever possible, prior written informed consent will be obtained from the patient. One such group will include those patients awaiting elective surgery that will require a scheduled post-operative intensive care admission. For these patients, whenever possible prior written informed consent should be obtained prior to surgery, in case the patient requires glycaemic control postoperatively in the ICU and is unable to give informed consent because of sedative treatment, endotracheal intubation or other incapacity. The patient should be aware that he or she may not actually be required to participate in the study due to eligibility and that the informed consent is being gained as a "reserve measure". An informed consent and patient information sheet (approved by the Ethics Committee) must be signed and dated by patient

and Principal Investigator or Research Coordinator or other approved delegate following an explanation of the study purpose and the patient's requirements for participation. The patient is given a copy of the signed Informed Consent and Patient information sheet. Where applicable by the hospitals ethics committee, an independent witness will be available to witness the informed consent procedure. As patients staying in the ICU less than 24 hours will be excluded from the study, the majority of patients admitted to the ICU following routine surgery will be excluded. If written informed consent has not been obtained from a patient prior to planned ICU admission because they are not expected to meet the study entry criteria, and the patient subsequently does meet entry criteria due to a complication occurring during surgery then they may be enrolled in the study using the provision for delayed consent.

6.2.2 Prior Informed Consent from the patient, during ICU admission

Prior written informed consent can also be requested from conscious and alert patients in the ICU. The patient may be approached "in anticipation" of a later requirement for glycaemic control or at a time the treatment is required, depending on the individual situation. The same procedures as outlined above should be used.

6.2.3 Delayed surrogate informed consent from the patient's next of kin or responsible person

For critically ill patients that are not able to give written informed consent (and these are expected to be the majority) enrolment in the study may take place without consent except where there is documented evidence that the patient has no legal surrogate decision maker, and where it appears unlikely the patient will regain consciousness or sufficient ability to provide delayed informed consent. The 'next of kin or legal surrogate' in the context of obtaining informed consent for this study may be a relative or a friend nominated or identified by the patient or the referring doctor or by themselves as the patient's representative at the time of the patient's admission to care. An explanatory statement, approved by the participating centre's ethics committee, will be provided to the next of kin or legal surrogate at the earliest suitable opportunity after the patient has been enrolled into the study, to enable them to make an informed decision about their next of kin's continuing participation in the study. An informed consent form, approved by the ethics committee, may also be available for the next of kin or legal surrogate to sign and date. A copy of the signed informed consent and patient information form will be given to the next of kin or legal surrogate. The conscious patient, next of kin or legal surrogate, will have the opportunity to request withdrawal of the study treatment at any time. They may also request that collection of study data and use be discontinued.

"Next of Kin" is the actual next of kin or any other person with legal right to assent to treatment in the jurisdiction in which the patient is enrolled in the study. The rules and definitions for the terms 'next of kin' and 'legal surrogate' in the context of a clinical trial and medical care may differ between States and Territories in Australia and in New Zealand. The specific legislation or wording covering each region in which the study is being conducted should be checked before enrolling patients in the study.

Every reasonable effort will be made to contact a next of kin or legal surrogate in the course of the patient's routine ICU care. Patients who are conscious and alert at the time of the admission to hospital will normally be able to supply the contact details of a next of kin or legal surrogate at the time of the admission. If any situation arises where the legality or appropriateness of the consent process is unclear investigators are advised to contact their Human Research Ethics Committee for clarification or guidance and to notify the Coordinating and Data Management Centre.

6.2.4 Prior surrogate informed consent from the patient's next of kin

A next of kin or legal surrogate may also provide prior surrogate informed consent if time allows prior to enrolment into the study. Prior surrogate consent may also be requested in anticipation of the unconscious, sedated or intubated patient requiring glucose control at a later period of time during the patient's admission to the ICU. A copy of the signed informed consent and patient information sheet will be given to the next of kin or legal surrogate.

6.2.5 Delayed informed consent from the patient

This informed consent should also be obtained in addition to the next of kin or legal surrogate informed consent. If a patient regains consciousness and the ability to give informed consent for continuation in the study, this consent should be obtained as the preferred method. A copy of the informed consent and patient information sheet will be given to the patient, next of kin or legal surrogate.

A copy of the signed informed consent form and/or any documents relating to the consent procedure (such as a record of the date and time and from whom verbal consent from a next of kin or legal surrogate is obtained) must be documented in the hospital records and original consent forms must be filed in the patient's paper research records. All informed consents and related documentation must be stored at the participating ICU for a period of two years and will be requested for viewing at monitoring visits or other audits associated with of the study. These records are stored at the ICU and a memo to file, detailing the type of consent procedure conducted, is also stored in the Coordinating and Data Management Centre Database.

6.2.6 Documentation of Consent

A copy of the signed informed consent and patient information sheet will be given to the person who has provided the informed consent. The copy of the signed informed consent will be filed in the patient's medical records. The original copy of the signed informed consent will be filed with the patient trial records within the office of the research coordinator. Information regarding the acquisition of the informed consent and other relevant information (if consent obtained by telephone, which relative of next of kin was contacted and when; any difficulties experienced in contacting someone who could provide consent etc) should be recorded in the patient's hospital records with a copy or memo filed in the Patient trial record.

6.2.7 Withdrawal of Consent

At any time during the study, the patient or next of kin or legal surrogate may withdraw consent to participate in the study. This is documented in the informed consent form and patient information sheet. If a patient or next of kin or legal surrogate withdraws consent the study treatment will cease and the patient will receive glycaemic control as prescribed by their treating clinicians. In this situation specific consent will be sought to continue study follow-up procedures and to use study data.

Where prior informed consent was not gained, and the patient has been commenced in the study and delayed consent is sought from either the patient or next of kin or legal surrogate, the right to refuse consent for *continuing* participation in the study (as opposed to withdrawing an existing consent) is an available option. Should continuing participation be refused, the patient will no longer receive the randomly allocated treatment, the study treatment will cease and the patient will receive glycaemic control as prescribed by their treating clinicians. In this situation specific consent will be sought to continue study follow-up procedures and to use study data.

If there are several relatives or legal surrogates who may be able to provide delayed consent, the Investigator and his/her staff will need to make a judgement about the most appropriate person and time to discuss the study and this may be done with several members of the patient's representatives. There may be a situation where one person wishes to give consent and another in the family or patient's close associates wishes to withdraw consent. Each situation will need to be assessed individually and should involve the relevant individuals to ensure that a decision is made that can be agreed on by all concerned.

6.2.8 Australian State and Territory Legislation – The Guardianship and Administration Act

Where it has been requested by the local Ethics Committees in Australia, contact has been made with the State or Territory Guardianship Tribunal to enable assessment of the purpose of the study, the suggested consent procedures, the risks to the patient who participates and any alternatives available to conducting the study.

7. Randomisation and Allocation of Treatment

The George Institute for International Health will take responsibility for the web-based randomisation. This will be available 24 hours a day. A minimisation program will stratify treatment allocation by type of critical illness (medical vs. surgical) and by country. Randomisation will be achieved via a password protected fully secure study website.

A complete guide to the procedures for randomising a patient is provided in the Procedures Manual and Website Users Guide.

8. Study treatments

8.1 Glycaemic control

Each participant will be randomised to receive an insulin sliding scale regimen to control blood glucose concentration between either:

> 4.5 - 6.0 mmol/L (81-108 mg/dl) (lower range group) ***or*** less than 10.0 mmol/L (180 mg/dl) with insulin being infused if blood glucose exceeds 10.0 mmol/L (180 mg/dl), and titrated when needed to maintain the blood glucose concentration between 8 and 10 mmol/L (144 – 180 mg/dl) (higher range group).

In the lower range group, a continuous infusion of insulin administered by syringe pump will be commenced if the blood glucose concentration exceeds 6.0 mmol/L (108 mg/dl) and the infusion rate will be adjusted to maintain the blood glucose concentration between 4.5 - 6.0 mmol/L (81 – 108mg/dl).

In the higher range group, a continuous infusion of insulin administered by syringe pump will be started if the blood glucose concentration exceeds 10.0 mmol/L (180 mg/dl) and the infusion rate adjusted to keep the blood glucose concentration to less than 10.0 mmol/L (180 mg/dl) and titrated when needed to maintain the blood glucose concentration between 8 - 10 mmol/L (144 – 180 mg/dl).

Adjustments to the insulin dose will be made based initially on the measurement of whole blood glucose in undiluted arterial blood performed initially at hourly intervals. Sampling of arterial blood will require the presence of an intra-arterial catheter in situ for routine clinical management at the time of enrolment. The frequency of blood glucose measurement may be

reduced to two-hourly and then four hourly once the insulin regimen, blood glucose concentration and calorie intake are sufficiently stable.

Clinical staff (both doctors and nurses) in the study ICUs will undergo formal training and familiarisation with the insulin regimens by local study coordinators assisted by staff from the appropriate national study coordinating centre. Subsequently the administration of insulin will be adjusted by the intensive care doctors and nurses using the study algorithm accessed via the secure, password protected, encrypted study website. The study algorithm recommends insulin infusion rates whilst allowing clinician discretion, ultimate responsibility for the safe and effective use of insulin infusions remains with the treating clinicians

Patients being discharged from the ICU will receive conventional blood glucose management subsequent to discharge.

The glycaemic ranges of this study are within the range of current practice as reflected by recent surveys of critical care practitioners in Australia, New Zealand and Canada.

8.2 Nutrition

All patients will receive nutrition according to the study guideline. The guideline that will be used is the recent ANZICS CTG-endorsed cluster randomised trial of nutrition guidelines. This reflects current ANZ practice and current evidence in emphasising the early (within 24 hours) use of enteral feeding. Where enteral nutrition can not be started within 24 hours parenteral nutrition is recommended with continued efforts to institute enteral nutrition as soon as possible. In Canada, the accepted Canadian guideline will be used.

8.3 Risk of Hypoglycaemia

Data from Van den Berghe's study demonstrates an increased incidence of biochemical hypoglycaemia (blood glucose concentration less than or equal to 2.2 mmol/L) in patients administered the intensive insulin regimen compared to those patients receiving the conventional insulin regimen (39/765 [5.1%] vs. 6/783 [0.77%] respectively). This increased incidence was mirrored in the small pilot study (70 patients) conducted in Canberra. Comparing the intensive insulin regimen with the conventional insulin regimen 5/35 [14.3%] vs. 0/35 [0%] patients suffered biochemical hypoglycaemia respectively. The daily use of intravenous glucose in the Van den Berghe study was markedly different to that used in the Canberra study (300 g vs. 17 g). Importantly, in both studies there were no clinically significant sequelae from the episodes of biochemical hypoglycaemia. In the Canberra study, the incidence of hypoglycaemia in the intensive insulin group per blood sample taken was 8/3441 [0.23%] or 1 hypoglycaemic episode per 636 hours of treatment, this is comparable to the incidence in other Australasian ICUs routinely practising intensive insulin therapy (I Mitchell – unpublished data, J Myburgh – personal communication).

8.4 Timing and Cause of Hypoglycaemia

In Van den Berghe's study the episodes of hypoglycaemia frequently occurred in relation to cessation of enteral feeds, there was not such a clear relationship in the Canberra pilot study where only 3/8 episodes were associated with cessation of enteral feeds. The timing of hypoglycaemia in relation to the initiation of the intensive insulin regimen was variable and frequently late in the Canberra study ranging from 2 hours to 409 hours with a median duration from onset of treatment to hypoglycaemia of 172 hours.

8.5 Reducing the Incidence of Hypoglycaemia

A major focus of the research coordinators and principal investigators will be to educate staff on the safe use of both insulin regimens in the study. All episodes of biochemical hypoglycaemia will be considered serious adverse events and be reported to the coordinating centre within 24 hours. These data will also be reported to the independent data and safety monitoring committee. If it apparent that there is an unacceptable incidence of hypoglycaemia, either in the study overall or in any particular centre or centres, then the study committees will take appropriate steps to reduce the incidence. Depending on the timing and cause of the episodes, this may include any or all of altering the blood glucose control algorithm, altering the nutrition guidelines, instituting routine IV glucose supplementation, increased education at one or more centres or suspending the study at one or more centres.

8.6 Discontinuation of randomised treatment

Study treatment will continue until the patient is eating and not requiring supplementary enteral or parenteral nutrition, or until the earlier of ICU discharge or death or 90 days after randomisation. If during the 90-day follow up period the study treatment is ceased and the patient subsequently deteriorates so that they again satisfy the study entry criteria, the study treatment will be recommenced.

If at any time during the trial the treating ICU physician deems it in the patient's best interest (for example if the patient suffers significant or repeated episodes of hypoglycaemia) then, at the discretion of the treating physician, the study treatment can be withdrawn. Patients withdrawn from the randomised treatment will be followed up according to the study follow up schedule and analysed according to the intention to treat principle unless they or their legal surrogate specifically requests such follow up be ceased.

8.7 Ancillary Treatments

Other aspects of patient management are unaffected by study procedures and the treating clinicians will be free to provide whatever care is deemed appropriate and necessary.

9. Data collection and follow up

Every randomised patient will be followed up until first either death or 90 days post-randomisation as recommended by the UK Medical Research Council International Working Party for Clinical Trials in Patients with Sepsis and Septic Shock.[30] The appropriate outcome for ICU trials, especially sepsis trials, has recently been the subject of great debate. This resulted in part from the PROWESS study which demonstrated that patients treated with activated Protein C for sepsis had reduced all-cause 28-day mortality (N Engl J Med 2001;344:699-709). However, the clinical validity of this finding was questioned, as close to 40% of the patients were still in hospital at day 28 making it possible that the treatment prolonged hospital stay rather than increasing the number of patients who survived to return home. Data from the ANZICS sepsis study (S Finfer – Intensive Care Medicine 2004, 30:589-596) demonstrated that 25% of patients who suffer severe sepsis in Australasian ICUs will still be in hospital at day 28. Consequently, given concerns about the use of a 28-day outcome period, we have chosen to use a 90-day outcome (Crit Care Med 2001; 29:880-886). We will however, also collect data on 28-day outcome. Patients with traumatic brain injury will be followed to 2 years.

Streamlined data collection instruments and procedures will be developed to minimise the work in collaborating centres. The George Institute for International Health will take responsibility for the web-based randomisation and data management of the study, comparable to their involvement in the SAFE study. This includes programming and data management support associated with the establishment of the randomisation system and the overall database during the first 6 months of the study. Programming and data management support associated with ongoing management of the databases, will continue for the duration of the study. The particular advantage of this system compared with a paper-based system, is that it has been tested extensively and will facilitate the production of study findings within 6 months following the end of recruitment (recruitment for the SAFE study finished in June 2003, results were presented to study investigators at the end of October 2003 and published in May 2004).

Data collection will be restricted primarily to those variables necessary to define patient characteristics at baseline, the incidence and severity of hyperglycaemia and hypoglycaemia, and documentation of deaths and other serious adverse events during follow up. For patients being discharged alive from the ICU, follow up will be restricted to determining vital status at 28 days, hospital discharge and 90 days. This will be achieved either by direct contact with the patient or through contact with the patient's carers. Subjects admitted to the ICU with the diagnosis of traumatic brain injury will be contacted at 6 months and at 2 years for documentation of Extended Glasgow Outcome Score.

In summary, the information that will be sought from all the patients will include:

At baseline and before randomisation

- Patient identifiers
- Key clinical characteristics
- Inclusion and exclusion criteria
- APACHE II score (intensive care severity of illness score)
- Previous history of Diabetes Mellitus and type (Type I or type II)
- Previous history of steroid administration
- Initial blood glucose concentration

During follow up in the intensive care unit

- Half hourly to two hourly blood glucose concentration until ICU discharge
- Daily organ failure score (Sequential Organ Failure Score)
- Daily amount of insulin given
- Daily amount of steroids given
- Daily nutritional intake, route of administration (enteral or parenteral) and percentage administered as protein, carbohydrate and fat
- Results of blood cultures taken as part of routine care
- The need for organ support (inotropic agents, renal replacement therapy and positive pressure ventilation)
- Deaths and non-fatal serious adverse events

After live discharge from the intensive care unit

- Vital status at hospital discharge, 28 days and 90 days (for all patients who die during follow up, information about the cause of death will be sought from collaborating centres)
- For patients with traumatic brain injury, Extended Glasgow Outcome Score (GOSE) at 6 months and at 2 years by a trained blinded outcome assessor.

10. Outcomes

The principal study outcome will be whether the patient is alive or dead at 90 days. This will be determined by the research coordinator at each participating centre. The study monitor will verify the source documentation at each monitoring visit. As death is such a robust outcome, unintended bias in outcome assessment is unlikely. Intentional bias would require collusion between the study monitor and research nurses and is considered most unlikely. Given the robustness of the outcome measure, it is unnecessary to establish a blinded outcome committee.

Secondary outcomes, also determined over the same period include:

- Death in the ICU, by 28 days and by 90 days
- Length of ICU stay
- Length of hospital stay
- The need for organ support (inotropes, renal replacement therapy and positive pressure ventilation)
- Incidence of blood stream infections
- Incidence and severity of hypoglycaemia
- In the subgroup of patients admitted with diagnosis of traumatic brain injury, a follow up to determine long term functional status as determined by Extended Glasgow Outcome Scores (GOSE) will be collected at six months and at 2 years by a trained blinded outcome assessor

11. Analysis of results

The George Institute will conduct the statistical analyses. All analyses will be performed on an intention-to-treat basis. Baseline and outcome variables will be compared using Students t test, Chi squared and the Mann-Whitney U test as appropriate. Odds ratios will be estimated using multiple logistic regression analysis. Survival analysis will be performed using Kaplan Meier and Cox's proportional hazards regression analysis.

An independent statistician will conduct two blinded interim analyses when we have primary outcome data for 2000 and 4000 patients and these will be submitted to the Data & Safety Monitoring Board.

12. Data & Safety Monitoring Board

An independent Data and Safety Monitoring Board chaired by Professor Sir Richard Peto at Oxford University, comprising experts in clinical trials, biostatistics, and intensive care has been established. The committee will review unblinded data on patient characteristics, treatment compliance and study outcomes at two interim analyses (availability of primary outcome for 2,000 and 4,000 patients), at any other time point the committee may deem necessary to protect study participants, and at the final analysis. The committee will be charged with informing the study management committee if at any time there emerges:

a. Evidence beyond reasonable doubt of a difference between randomised groups in all cause mortality
b. Evidence likely to change the practice of many clinicians already familiar with the available evidence about the comparative effects of the two blood glucose regimens

While the definition of beyond reasonable doubt will be left to the judgement of the Safety and Data Monitoring Committee, other committees have considered that a difference in total mortality between randomised groups of three standard deviations would normally constitute such evidence. While a major focus of the Committee's brief will be to monitor total mortality, they would also be provided data on serious adverse events and would not be precluded from making recommendations based on other outcomes such as cause-specific death or serious non-fatal adverse events.

13. Organisation and collaboration

The study will be conducted under the auspices of the ANZICS CTG and overseen by a study management committee. The co-ordinating centre for the project will be located at The George Institute for International Health.

The ANZICS CTG has substantial experience in the conduct of collaborative studies in the intensive care setting. Completed and ongoing studies include a randomised comparison of fluid resuscitation with human albumin solution or normal saline among critically ill patients (SAFE Study),[31, 32] and the cluster randomised controlled trial examining the impact of the medical emergency team system in 23 Australian Hospitals (MERIT Study). Other collaborative studies include the descriptive epidemiology of acute brain injury (ATBIS), acute respiratory distress syndrome (ALIVE),[33] systemic inflammatory response syndrome with organ dysfunction, blood transfusion practice in Australian ICUs (ANAEMIC),[34] antecedents to cardiac arrest, death and unanticipated ICU admission (ACADEMIA) and a randomised controlled trial of low dose dopamine versus placebo in the evolution of acute renal failure in critically ill patients with evidence of early renal dysfunction.[35]

The SAFE and MERIT study models will be replicated with weekly management committee teleconferences and face to face meetings as required. The study leaders have worked together for more than five years and have successfully overcome geographic dispersion in the conduct of multi-centre studies.

14. Publications and presentations

By early 2008, the main analyses should be completed and a paper submitted for publication. The main reports from the study will be published in the name of "The NICE-SUGAR Study Investigators" with credit assigned to the collaborating investigators. Presentations of the study findings will be made at national and international meetings concerned with the management of patients in intensive care.

15. Expected outcomes

This study will provide reliable evidence about the comparative effects of different targets for blood glucose concentration in patients treated in the Australasian and Canadian intensive care setting. This evidence will have direct relevance to decisions about the care of critically ill patients admitted to ICUs in Australia and New Zealand, Canada and the rest of the world. If the study confirms the treatment effect reported in Van den Berghe's study, maintaining normoglycaemia would likely become a treatment standard worldwide.

In summary, the data collection over the course of the 90 day follow-up period (and 6 month and 2 years if applicable) covers:

Form No.	Period of study	Data collection
	Randomisation	Patient demographics and inclusion/exclusion criteria
1	Baseline	Source and date of admission to ICU, ICU admission diagnosis, sub-group categories into 'sepsis', 'trauma', and NIDDM/IDDM patients, APACHE II score, SOFA scores for each organ system, use of renal replacement therapy or artificial ventilation, blood glucose concentration (last measurement before randomisation), weight and height, insulin and history of treatment with corticosteroids.
2	Hourly, Days 1 - 90	Blood Glucose Assessment whilst in ICU for maximum of 90 days. All blood glucose concentrations measured.
3	Daily, Days 1 - 90	Whilst in ICU: Daily SOFA scores for each organ system (excluding GCS), use of dialysis or artificial ventilation, nutrition administered and volume (calories, protein and route of administration), all iv glucose administered, all positive blood culture results that are judged clinically significant. Total amount of insulin administered. Total amount of steroids given. Volume of RBCs transfused, reasons for treatment discontinuation
4	28 Day Summary	Vital status at day 28. Place, date and cause of death, date of discharge from ICU, date of discharge from hospital, number of days in ICU, type of consent obtained
5	90 Day Summary	Vital status at day 90, length of stay in ICU, length of stay in hospital, place, date and cause of death
6	Serious Adverse Event of Hypoglycaemia	Description, date and time, cause and resolution of any serious adverse events thought to be study treatment related, hypoglycaemia (no. of episodes $\leq$ 2.2 mmol/L, signs & symptoms, treatment given), BSL
7	Extended Glasgow Outcome Score	Outcome score for category of TBI patients with GCS <14 at 6 month follow up and 2 year follow-up.

TIMETABLE FOR DATA COLLECTION for RANDOMISED PATIENTS

Study Period	Randomisation	Baseline	Daily	Days 1 - 90	Day 28	Day 90	SAE	6 month and 2 years.
Form Number		***1***	***2***	***3***	***4***	***5***	***6***	***7***
Patient Identifiers	✓							
Study Eligibility	✓							
Admission data		✓						
Clinical diagnosis		✓						
Sepsis criteria		✓						
Trauma criteria		✓						
APACHE worksheets		✓						
APACHE Score		✓						
SOFA worksheets		✓		✓				
SOFA scores		✓		✓				
B G Concentration			✓					
Insulin (total units)				✓				
Dialysis		✓		✓				
IPPV		✓		✓				
Steroids		✓	✓					
Packed RBC input				✓				
EN Data				✓				
TPN Data				✓				
GOSE***								✓
SAE [1]			✓				✓	
Treatment Discontinuation				✓				
Death [2]					✓	✓		
Consent [3]	✓				✓			

[1] Serious adverse event occurs any time after randomisation but is recorded on Form
[2] Death that occurs any time after randomisation is recorded on Forms 4 & 5 as applicable
[3] Consent is collected at any time before or after randomisation but is recorded on Form 4

***Only for patients with TBI

References:

1. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycaemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab. 2002; 87: 978-982
2. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increases risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000: 355: 773-778
3. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycaemia and prognosis of stroke in non diabetic and diabetic patients: a systematic overview. Stroke. 2001: 32; 2426-2432
4. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, Harrell FE. The APACHE III Prognostic System. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619-36
5. McMahon MM, Bistrian BR. Host defences and susceptibility to infection inpatients with diabetes mellitus. Infect Dis Clin North Am 1995; 9: 1-9
6. McCowen KC, Malhotra A, Bistrian BR. Stress induced hyperglycaemia. Crit Care Clin 2001; 17: 107-124
7. Bistrian BR. Hyperglycaemia and infection: which is chicken and which is the egg? J Parenteral Enteral Nutr. 2001; 25: 180-181
8. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995; 274:639-644.
9. Van den Berghe G, Wouters P, Weekers F et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone releasing peptide and thyrotropin releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab 1999; 84: 1311-23
10. Van den Berghe G, Baxter RC, Weekers F, Wouters P, Bowers CY, Veldhuis JD. A paradoxical gender dissociation within the growth hormone/insulin like growth factor 1 axis during protracted illness. J Clin Endocrinol Metab 2000; 85: 183-92
11. Hongsmisligil GS, Spiegelman BM. Tumour necrosis factor alpha. A key component of the obesity diabetes link. Diabetes 1994; 43: 2238-48
12. Rassias AJ, Marrin CAS, Arruda J, Whalen PK, Beach M, Yeager MP. Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Anal 1999; 88: 1011-6
13. Zochodne DW, Bolton CF, Wells GAea. Critical illness polyneuropathy: a complication of sepsis and multi-organ failure. Brain 1987; 110:819-842.
14. Webb AR, Shapiro MJ, Singer M, Suter PM eds. Oxford textbook of critical care. Oxford: Oxford University Press, 1999:490-495
15. Bolton CF. Sepsis and the inflammatory response syndrome: neuromuscular manifestations. Crit Care Med 1996;24:1408-16
16. Said G, Goulon-Goeau C, Slama G, Tchobroutsky G. Severe early-onset polyneuropathy in insulin dependent diabetes mellitus: a clinical and pathological study. N Engl J Med 1992; 326: 1257-63
17. Malmberg K, Norhammar A, Wedel H, and Ryden L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long term results from the Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction (DIAGIMI) study. Circulation 1999; 99: 2626-32
18. Malmberg K. Prospective randomised study of intensive insulin treatment in long term survival after myocardial infarction in patients with diabetes mellitus. BMJ 1997; 314: 1512-5

19. Malmberg K, Ryden L, Efendic S, et al. A randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIAGIMI) study: effects of mortality at 1 year. J Am Coll Cardiol 1995;26:57-65
20. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345: 1359-67
21. De Beaux I, Chapman M, Fraser R, Finnis M, De Keulenaer B, Liberall D, Satanek M. Enteral nutrition in the critically ill: A prospective survey in an Australasian intensive care unit. Anaes Intensive Care 2001; 29: 619-22
22. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. [comment]. JAMA 1998; 280(23):2013-2019.
23. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. New Engl J Med 1997; 336:540-6
24. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. New Engl J Med 2001; 344:556-563
25. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T-S. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94: 1176-86
26. Hayes MA, Timmins AC, Yau EH et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994; 330: 1717-22
27. Gattinoni L, Brazzi L, Pelosi P et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995; 333: 1025-32
28. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. ISIS-2. Lancet 1988; ii: 349-60
29. International Stroke Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet 1997; 349: 1569-81
30. Cohen J, Guyatt G, Bernard GR, Calandra T, Cook D, Elbourne D et al. New strategies for clinical trials in patients with sepsis and septic shock. Crit Care Med 2001; 29:880-886.
31. The Saline vs. Albumin Fluid Evaluation (SAFE) Study (ISRCTN76588266): Design and conduct of a multi-centre, blinded randomised controlled trial of intravenous fluid resuscitation in critically ill patients. ANZICS Clinical Trials Group and Institute for International Health SAFE Study Investigators BMJ.com 2003: In press
32. Finfer S, Bellomo R, Myburgh J, Norton R. Efficacy of albumin in critically ill patients. Large trial in Australia and New Zealand may provide an answer**.** BMJ 2003;326(7389):559-60
33. Bersten AD, Edibam C, Hunt T, Moran J, The Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respiratory & Crit Care Med 2002; 165:443-448.
34. French CJ, Bellomo R, Finfer SR, Lipman J, Chapman M, Boyce NW and the ANZICS Clinical Trials Group. Appropriateness of red blood cell transfusion in Australasian intensive care practice. MJA 2002;177:548-551
35. ANZICS Multicentre Trials Group. A randomised, double blind, placebo-controlled, multi-centre study of low-dose dopamine in critically ill patients at risk of renal failure. Lancet 2000; 356: 2139-2143