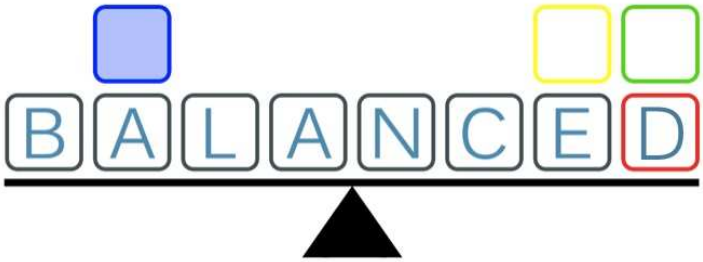


The BALANCED Anaesthesia Study

A prospective, randomised clinical trial of two levels of anaesthetic depth on patient outcome after major surgery

An international collaborative project endorsed by the Australian and New Zealand College of Anaesthetists Trials Group

Funding Sources:

New Zealand: Health Research Council Project Grant 12-308-Short

Australia: NHMRC Project Grant APP1042727

Hong Kong: Research Grants Council Project Grant

Trial registration:

Australian New Zealand Clinical Trials Registry No: ACTRN12612000632897

Website:

www.balancedstudy.org.nz

Sponsor:

Auckland District Health Board

2. PROTOCOL AGREEMENT

Sponsor: Auckland District Health Board

AGREEMENT

This document is confidential. The investigators declare that they have read the final study protocol and any amendments and the study authorship plan. The investigators will conduct the study according to the procedures specified in the study protocol and New Zealand National Ethics Advisory Committee Ethical Guidelines for Intervention Studies (latest revision July 2012) (available at www.ethics.health.govt.nz) or in accordance with ICH GCP notes for Guidance on Good Clinical Practice (CPMP/ICH/135 annotated with TGA comments) and the NHMRC National Statement on Ethical Conduct in Research Involving Humans. Any information related to this trial will be kept confidential until publication or presentation at a scientific meeting. I have read and accept this agreement.

…… …….

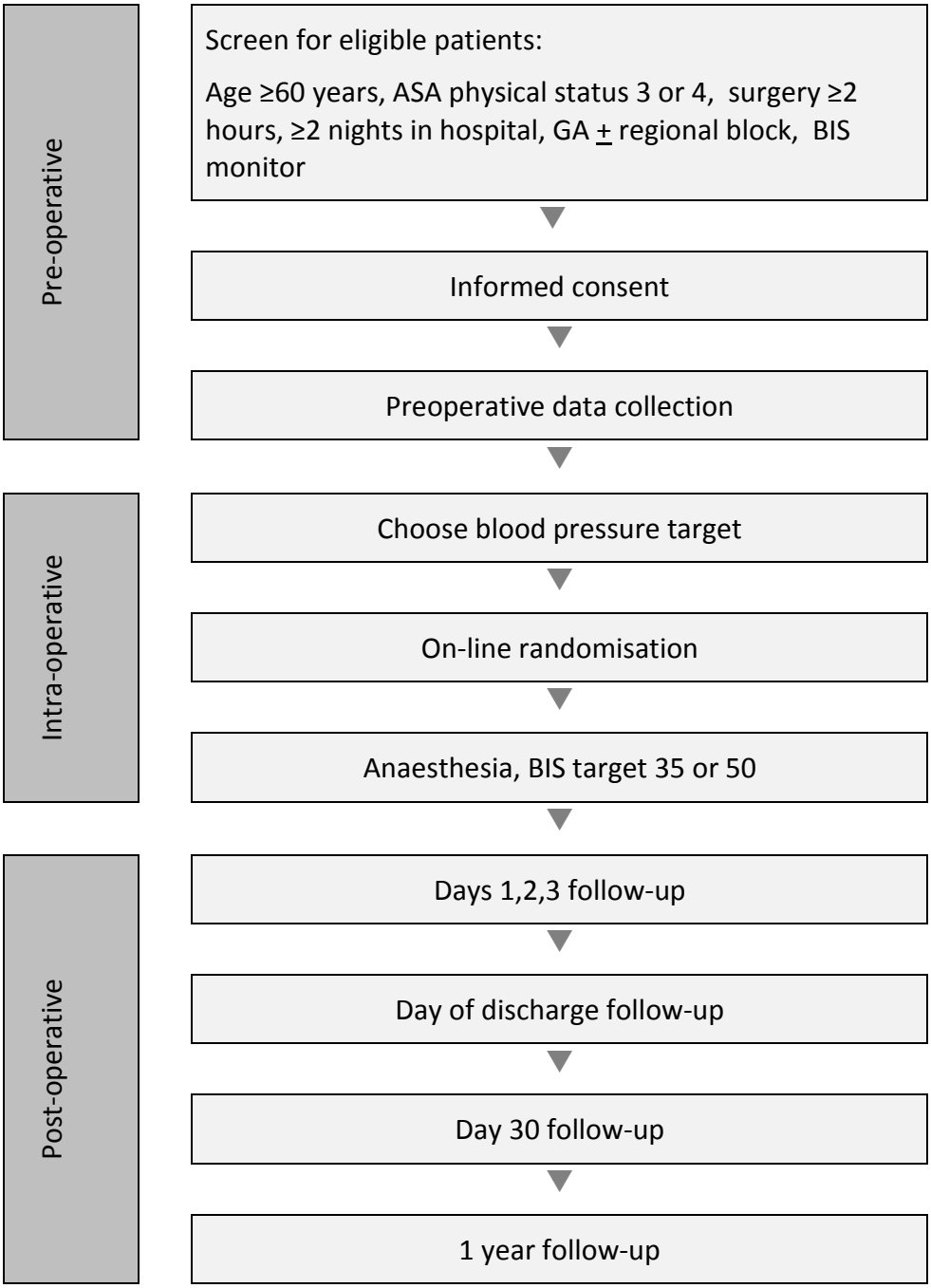
Investigator signature Date

…….. ……

Investigator name Hospital

Please photocopy this page and return to research coordinator via post or fax: +64 9 375 4378

3. TRIAL FLOW CHART



4. TRIAL SUMMARY

Title	The influence of anaesthetic depth on patient outcome after major surgery (The **BALANCED** anaesthesia study)
Project Office	Department of Anaesthesia and Peri-operative Medicine, Auckland City Hospital, 2 Park Road, Grafton, Auckland, 1023, New Zealand. Tel+64 9 3074949 extn 25725, Mobile +64 27 4891940, Fax +64 9 375 4378
Study Size	6,500 patients
Study Design	International multicentre double blind, prospective, intention to treat, safety and efficacy study
Primary Outcome	One year all-cause mortality
Secondary Outcomes	MI, cardiac arrest, pulmonary embolism, stroke, sepsis, surgical site infection, ICU stay, hospital stay, awareness, WHODAS score, persistent postoperative pain and cancer recurrence
Inclusion Criteria	≥60 years, ASA physical status 3 or 4, surgery lasting ≥2 hours, post-op hospital stay ≥2 nights, general anaesthesia with or without major regional block, able to monitor BIS
Study Protocol	
Pre-operative	Age, sex, weight, height, ASA physical status, ECG, haemoglobin, creatinine, albumin, Charlson co-morbidity score, WHODAS 12 item score
Intra-operative	Pre-defined mean arterial blood pressure target Randomised BIS target of 35 or 50 Computerised recording of BIS, SR, BP, HR, ETvol conc. Manual record of drugs administered and recovery indicators
Post-operative day 1-3	QoR-15 score, Analgesic and antiemetic requirements MI, cardiac arrest, pulmonary embolism, stroke, sepsis, surgical site infection, awareness (once)
Hospital Discharge	Length of hospital stay, unanticipated ICU admission, ICU stay, unplanned second operation
Post-operative day 30	Survival and disability free survival MI, cardiac arrest, pulmonary embolism, stroke, sepsis, surgical site infection, awareness, QoR-15 score, WHODAS 12 item score, persistent postoperative pain, staging of cancer
1 year follow-up	Survival and disability free survival MI, cardiac arrest, pulmonary embolism, stroke, sepsis, surgical site infection, WHODAS 12 item score, persistent postoperative pain, cancer recurrence

5. TRIAL PERSONNEL

PRINCIPAL INVESTIGATOR

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Hong Kong Principal Investigator

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Chinese University Hong Kong

TRIAL STEERING COMMITTEE

A/Prof Timothy Short (Chair), Prof Kate Leslie, Prof Matthew Chan, Prof Paul Myles, A/Prof Chris Frampton, Dr Douglas Campbell

In attendance: Ms Davina McAllister, Ms Sofia Sidiropoulos

OPERATIONS COMMITTEE

Prof Kate Leslie (Chair), A/Prof Timothy Short, Dr Douglas Campbell, Ms Davina McAllister, Ms Sofia Sidiropoulos

WRITING COMMITTEE (main paper)

A/Prof Timothy Short (Chair), Prof Kate Leslie, Prof Matthew Chan, Prof Paul Myles, A/Prof Chris Frampton

DATA MONITORING COMMITTEE

NZ HRC Data Monitoring Core Committee

A/Prof Katrina Sharples (Chair), Dr Mark Jeffery, Prof Ngaire Kerse, Prof John McCall, A/Prof Andrew Moore, Prof Thomas Lumley, Dr Mark Webster

Anaesthetic experts: Prof Jamie Sleigh, Prof Guy Ludbrook

In attendance: A/Prof Chris Frampton

ENDPOINT ADJUDICATION COMMITTEE

Dr Johann van Schalkwyk (Chair), Dr Andrew MacCormick, Dr Gordon Choi, Dr Paul Gardiner

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6. TABLE OF CONTENTS

7. ABBREVIATIONS

ANZCA	Australian and New Zealand College of Anaesthetists
ASA	American Society of Anesthesiologists
BIS	Bispectral index
CRF	Case report form
DMC	Data monitoring committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EEG	Electroencephalogram
GA	General anaesthesia
GCRP	Good clinical research practice
ICU	Intensive care unit
MAC	Minimum alveolar concentration (of a volatile anaesthetic)
MAP	Mean arterial pressure
mBPI	Modified brief pain inventory
MI	Myocardial infarction
MIBI	Technetium-99m with the ligand methoxyisobutylisonitrile scan
PE	Pulmonary embolus
QoR-15	Quality of recovery -15 item questionnaire
RCT	Randomised controlled trial
SD	Standard deviation
SR	Suppression Ratio (of EEG)
WHODAS	World Health Organisation disability assessment schedule 2.0, 12 item.

8. AIM OF TRIAL

Recent observational studies have found an association between deep anaesthesia and increased post-operative mortality in elderly and infirm patients undergoing major surgery. It is unknown whether there is a causal relationship in this observation, which occurs at levels of anaesthetic depth that are within the normal range of practice. We are performing a large randomised trial of 'deep' versus 'light' anaesthesia to definitively answer the question of whether anaesthetic depth alters perioperative outcome. Elderly patients undergoing major surgery will be randomised to an anaesthetic targeting either BIS=35 or BIS=50 for the deep and light groups respectively. The primary outcome variable will be all-cause mortality at one year and secondary outcomes will be MI, cardiac arrest, PE, stroke, sepsis, surgical site infection, ICU stay, hospital stay, awareness, WHODAS score, persistent postoperative pain and cancer recurrence.

Primary hypothesis

Light general anaesthesia (BIS = 50) is associated with decreased all cause mortality compared with deep general anaesthesia (BIS = 35) one year after major surgery in elderly patients.

Secondary hypotheses

Light general anaesthesia (BIS = 50) is associated with decreased incidences of MI, cardiac arrest, PE, stroke, sepsis and surgical site infection compared with deep general anaesthesia (BIS = 35) at 30 days and one year after major surgery in elderly patients.

Light general anaesthesia (BIS = 50) is associated with decreased incidences of a composite endpoint of MI, cardiac arrest, PE and stroke compared with deep general anaesthesia (BIS = 35) at 30 days and one year after major surgery in elderly patients.

Light general anaesthesia (BIS = 50) is associated with decreased cancer recurrence compared with deep general anaesthesia (BIS = 35) one year after major surgery in elderly patients.

Light general anaesthesia (BIS=50) is associated with an increased incidence of persistent postoperative pain compared with deep anaesthesia (BIS=35) at 30 days and one year after surgery in elderly patients.

Light anaesthesia (BIS = 50) is associated with increased disability-free survival compared with deep general anaesthesia (BIS = 35) one year after major surgery in elderly patients.

Safety and quality hypotheses

Light general anaesthesia (BIS = 50) is associated with improved early quality of recovery compared with deep general anaesthesia (BIS = 35) after major surgery in elderly patients.

Light general anaesthesia (BIS = 50) does not increase the incidence of awareness compared with deep general anaesthesia (BIS = 35) after major surgery in elderly patients.

9. BACKGROUND

Anaesthetic depth monitoring in current anaesthetic practice

General anaesthesia uses a combination of intravenous hypnotics, anaesthetic vapours and gases, analgesics and muscle relaxants to create the anaesthetised state. This is known as *balanced* anaesthesia, a term first used by Lundy in 1926 [1]. It provides unconsciousness for patients, lack of movement to facilitate surgery and suppression of sympathetic reflexes sufficient to maintain reasonable body homeostasis. Current practice centres on ensuring adequate anaesthetic dosage to prevent awareness and movement, and titration of additional anaesthetic to prevent excessive sympathetic reflexes. Light anaesthesia speeds early recovery, decreases early post-operative nausea and vomiting and may reduce intra-operative hypotension [2-3]. However light anaesthesia also increases the risk of awareness, increases central sympathetic responses to the noxious stimulus of surgery, increasing bleeding, stress hormone release and inflammatory response and may increase post-operative pain [4-7]. For the past ten years, the technology to continuously monitor anaesthetic depth in individual patients using the EEG has been available. These devices, such as the bispectral index (BIS) monitor (Covidien, Dublin, Ireland) enable titration of anaesthetic depth to individual needs, rather than using population based dosing guidelines that ensure unconsciousness in almost everyone [8]. However, the optimal depth at which anaesthesia should be maintained is unknown, and indeed anaesthetic depth has not been the subject of patient outcome research, largely because until recently it could not be measured [9].

The BIS monitor measures the frontal lobe EEG using electrodes applied to the forehead. It presents the anaesthetic depth of the patient as an ordinal number between 98 (wide awake) and 0 (EEG electrically silent). The index represents mainly depression of the spectral edge frequency and power of the EEG between 100 and ~35 and the increasing level of burst suppression between ~35 and 0. Recommendations for routine general anaesthesia are to target values between 40 and 60. However there have been case reports of awareness at the upper end of this range, and patients are more commonly anaesthetised at levels of 30 – 50 [10]. When anaesthesia has been conducted with the BIS value hidden from the anaesthetist, this lower range has typically been where most anaesthetics were administered [10,11].

Studies of the role of anaesthetic depth on perioperative outcome

Recently seven observational studies of the relationship between anaesthetic depth and patient outcome have been published (Table 1) [12-18]. Six of these studies have shown an association between relatively deep anaesthesia and increased subsequent mortality. However, various definitions of 'deep' anaesthesia have been used, centred on the duration the BIS value was either <45 or <40. The first study, by Monk, was a prospective observational study of 1064 patients undergoing major non-cardiac surgery [12]. All patients had BIS monitoring in addition to standard monitoring. Overall mortality was 5.5%, mortality in those over 65 years was 10.3%; 50% of deaths were due to cancer, there was a 24% increase in the risk of death per hour of deep hypnotic time and also a small increase in mortality if systolic blood pressure was less than 80 mmHg. The study implied that the anaesthetic itself may influence mortality. The study has been criticized for industry influence and the medical illness score (Charlson) being arbitrarily treated as bivariate [19,20]. Six subsequent studies have

been published using available databases. Five of these have found similar increases in mortality. In Lindholm et al.'s study, deep hypnotic time was not a predictor when pre-existing malignancy was included in the model. If deep hypnotic time was >2 hours subsequent mortality was much higher. Searleman et al.'s study found that non-surviving patients received slightly less volatile anaesthetic than the survivors, implying that patients who died may have been sensitive to the anaesthetic drugs. Saager et al.'s study used a very large database with 24,000 patients, and found three independent predictors of increased one year mortality, which were minimum alveolar concentration (MAC) <0.4, mean arterial pressure (MAP) <80 mmHg and BIS<40. (MAC is a normalised measure of anaesthetic potency). The risk to those who received deep anaesthesia was again a 20% increase in one-year mortality. Patients with a low MAP during the procedure faired even worse, and the combination of all three factors was associated with a RR=1.6 for one year mortality. They also found that patients who had an instance of low MAP, which was treated within 5 minutes had improved outcomes, indicating that although patients who were sensitive to anesthesia did poorly, early intervention was effective. Leslie *et al* analysed long-term outcomes in the B-Aware Trial, a 2,500 patient trial conducted principally in New Zealand, Australia and Hong Kong. This study also found an increased risk of myocardial infarction and cerebrovascular accident in the deep anaesthesia group. There were a large number of cardiac patients in the study and the same relationship of depth with poor outcome was confirmed, a finding repeated by Kertai et al. [17].

TABLE 1 Observational studies of the relationship between depth of anaesthesia and subsequent mortality

Author	**N**	**ASA 3&4 ***	**1 y mortality**	**Increased risk of death if 'deep' #**
Monk 2005 [12]	1064	35%	5.5	RR = 1.24
Lindholm 2009 [13]	4087	6%	4.3	HR = 1.18
Saager 2009 [14]	23,999	~30%	4.8	RR = 1.63
Searleman 2010 [15]	1791	71%	10.7	OR = 1.25/h
Leslie 2010 [16]	2463	74%	10.8	PS = 1.42 (at 4y)
Kertai 2010 (cardiac) [17]	460	100%	17.8	HR = 1.29 (at 3y)
Kertai 2011 (non-cardiac) [18]	1473	60%	24.3	HR = 1.03 (at 3y)

*ASA=American Society of Anaesthesiologists physical status scale, 1=normal health, 2=mild to moderate systemic disturbance, 3=severe systemic disturbance which limits activity, 4=incapacitating life threatening disease, 5=moribund.

#RR=relative risk, HR=hazard ratio, OR=odds ratio, PS=propensity score

These studies imply a greater role for anaesthesia in determining surgical outcome than previously suspected, but have been greeted with disbelief by the anaesthetic fraternity, rather than the design of robust studies investigating causality [19-21]. The question of the best depth at which to give general anaesthesia has not been addressed in large randomised trials. The marketing and use of processed EEG monitors such as BIS has been largely based on their use to prevent awareness under anaesthesia. All six study groups have recommended that prospective randomised studies are required to determine whether causality exists in the excess mortality rate, as have three accompanying editorials [10,19,21], however none of the investigators has commenced such a study (personal communications). The fact that multiple observational studies have been positive reduces the risk that the phenomenon is a simple case of publication bias [22].

An audit of 6,984 BIS monitored anaesthetics performed at Auckland City Hospital found the median BIS to be 38 (SD 8) [23]. Over 50% of patients had a BIS <40 for >1 hour. This is in line with the typical anaesthetic depths found in the studies mentioned above, but indicates our current work practices may put patients at similar risk. Past studies from Australia and New Zealand have shown that the elderly and the sick, defined as aged over 70 years and ASA physical status 3 or 4, have an expected mortality at one year of ~10% and are therefore most at risk of mortality as a result of sensitivity to anaesthesia [24].

Possible advantageous and deleterious effects of overly deep anaesthesia

There have been two small clinical studies looking at the influence of anaesthetic depth on postoperative pain. A study on 71 morbidly obese patients undergoing gastric banding found a decrease in visual analogue scores (VAS) for pain and decreased morphine requirements in patients who had consistently deep anaesthesia, as assessed by a spectral edge frequency target of 8-12 Hz [25]. These patients had average end tidal isoflurane concentrations of 0.81% vs 0.7% in the light group. Hennenberg et al. found a similar result in 43 patients undergoing gynaecological procedures using propofol and remifentanil, and guided by middle latency auditory evoked potentials [26]. It was, however, possible that the results were due to increased residual sedation in the 'deep' anaesthesia group. Indeed a randomised prospective study of 20 patients undergoing elective hysterectomy reported no difference in VAS-pain or morphine consumption and also no difference in plasma cortisol, glucose or lactate concentrations [27]. This study used desflurane anaesthesia with a target BIS of 50 or 25. Desflurane concentrations were 4% and 9% in the light and deep groups respectively.

The possible deleterious effects of anaesthesia are protean [28-34]. In animal models, anaesthesia can provoke the inflammatory response, increase deposition of Alzheimer's proteins, induce neuronal apoptosis and cause prolonged post-anaesthetic cognitive dysfunction. Neuronal apoptosis in particular is also induced by burst suppression of the EEG. These effects occur with both volatile anaesthetic agents such as isoflurane and intravenous agents such as propofol. Opioids also induce tissue angiogenesis by a peripheral effect and may decrease cancer survival times [35]. Other pharmacological effects of anaesthetic agents include immune depression and direct tissue toxicity. There may also be indirect physiological effects due to cardiovascular or neuronal depression causing tissue hypoperfusion and hypoxia [21,36,37].

The relationship between deep sedation and adverse outcomes including mortality has also been demonstrated in intensive care medicine [37,38]. Burst suppression is a common consequence of surgical anaesthesia that is unlikely to occur at the higher BIS targets which equate to light anaesthesia [39].

If any of these possible causes are confirmed to be increasing mortality, then a study such as the one that we propose, looking at outcome at two different levels of anaesthetic depth becomes a question of dose-response effects and whether a lower dose of anaesthetic is safer.

Could organ hypoperfusion be the problem?

We recently proposed a model to explain the complex interplay among the various perioperative factors that may lead to a poor outcome – relative anaesthetic overdose, organ dysfunction and organ hypoperfusion (each of which may lead to a low BIS value and result in an apparent association between low BIS values and death) (Figure 1) [9]. We observed that the apparent association between low BIS values (low MAC and low MAP) and death is likely to be due to anaesthetic intolerance (a marker of illness?) rather than inherent anaesthetic toxicity. The tantalising question is whether preventing relative anaesthetic overdose and/or low BIS values, whilst maintaining adequate organ perfusion, will make any difference. The simple answer to this complex question is a well-controlled randomised trial of a large group of patients at high risk of postoperative morbidity and mortality, such as the one we propose.

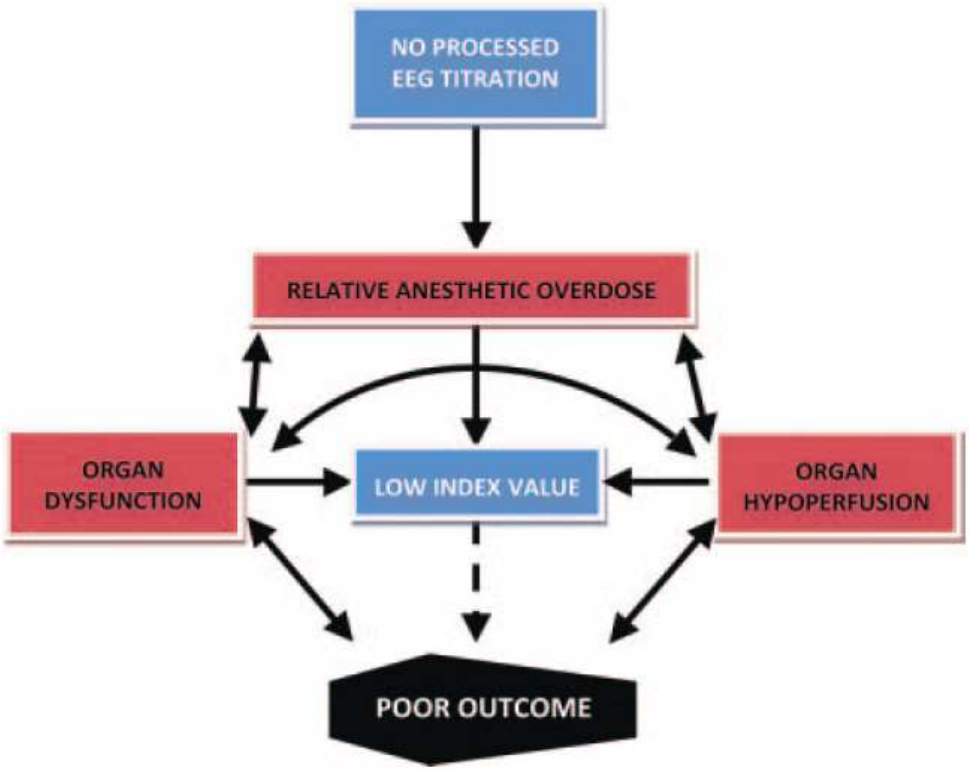


Figure 1. Model of low processed electroencephalographic (EEG) index values and their relationship to perioperative morbidity and mortality. Organ dysfunction = organ disease, genetic malfunction, or toxicity.

Recent Literature

The Saager study which was published as conference proceedings has now been published using one-month mortality as the primary outcome variable by Sessler et al., with an accompanying editorial [40,41]. The study included 24,170 adult patients, mean MAP, BIS and MAC were determined and patients divided into three groups for each variable –high, medium or low. The medium group served as a reference for relative risk of lengthened hospital stay and 30 day mortality in the other groups. Reference means were MAP=87 $\pm$5 mmHg, BIS = 46 $\pm$4 and MAC = 0.56 $\pm$0.11. 30-day mortality was doubled in double low combinations and quadrupled in the triple low group (Table 2). Unfortunately demographic data for each of these groups are not available so it is difficult to directly compare this study with the earlier ones. It is of note that a recent abstract from another large tertiary hospital has found a similar association in a retrospective study of 20,146 patients [42]. This finding strengthens the possibility that organ hypoperfusion may be part of the problem, and that this is detected by the BIS as a low reading.

A recent prospective study of 73 patients has found decreased cerebral oxygenation using non-invasive cerebral oximetry (SICO-Somanetics Invos Cerebral Oximeter, Covidien Inc, Co, USA) in patients with low BIS and subsequent post-operative cognitive dysfunction persisting out to 52 weeks, indicating hypoperfusion of the brain may be part of the problem, that is reflected by overly deep anaesthesia and anaesthetic sensitivity [43]. The same study also found an association with raised S100B plasma concentrations in those that had prolonged anaesthesia, or anaesthesia outside of the target range. The S100B protein is a marker of brain injury.

TABLE 2 Adapted from Sessler 2012 [40]. Relationship between blood pressure, anaesthetic depth, volatile anaesthetic use and 30-day mortality in 24,000 patients. The paired combinations of lows were all associated with worse outcome.

MAP/BIS/MAC state	N	MAP	BIS	MAC	30 day Mortality	Hazard Ratio	P
REF (med/med/med)	8034	87	46	0.56	0.5	1.0	<0.001
High/high/low	1653	96	56	0.38	1.1	1.11	0.19
Low/high/high	2070	78	54	0.72	0.4	0.97	0.63
High/low/high	2985	97	39	0.72	0.2	0.95	0.37
Low/high/low	2332	77	56	0.38	1.6	1.14	0.05
High/low/low	1782	97	38	0.39	1.0	1.21	0.01
Low/low/high	1798	79	39	0.72	1.0	1.08	0.28
High/high/high	1971	96	53	0.73	0.5	0.90	0.13
Low/low/low	1459	78	38	0.37	2.9	1.47	<0.001

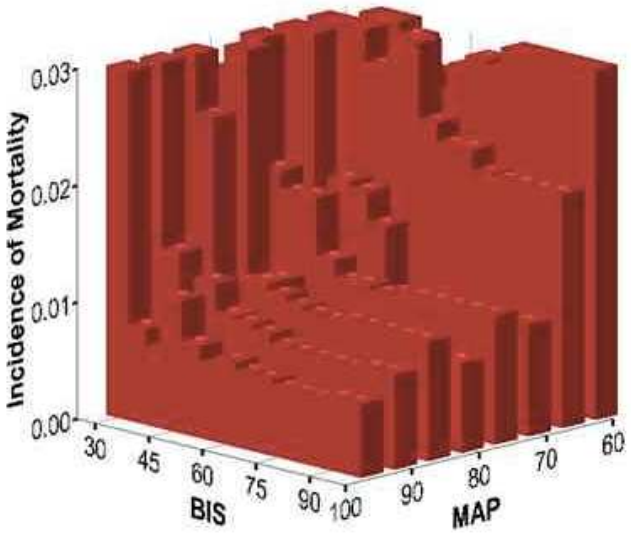


Figure 2

30-day mortality in patients who had a mean MAC=0.6 during their anaesthetic (the low group). The figure demonstrates the marked effect of either low BIS or low MAP and mortality [40].

A much larger study of postoperative delirium and cognitive decline in 921 patients aged over 60 years and undergoing major non-cardiac surgery has compared BIS guidance between 40 and 60 with standard of care and BIS concealment [44]. Patients in the control group had lower BIS values (mean 36) compared to the treatment group (mean 53). There was a 30% reduction in volatile anaesthetic use, significantly less delirium in the BIS guided group (16% vs 24% incidence) and significantly less postoperative cognitive dysfunction at three months (10% vs 15% incidence). Most patients were ASA physical status 1 and 2. The study was not powered to detect a difference in mortality, but interestingly found evidence of predominantly deep anaesthesia in the control group, when anaesthesia was not BIS guided.

A pilot study of the proposed trial methodology

A pilot study of 125 patients has been completed at six hospitals in New Zealand, Australia and Hong Kong [45]. The study was approved as meeting current ethical committee requirements in all three jurisdictions, and was also approved by the Māori research review committee at Auckland District Health Board. The study protocol was found to be acceptable to our patients and anaesthetists and no ethical concerns were raised. The results reassured us that BIS targets could be met, that a lower blood pressure in the 'deep' group was not a confounding factor and demonstrated a 50% higher anaesthetic dose in the deep group (Table 3). The pilot study also allowed us to refine details of the protocol and perform an accurate costing.

A summary of one-month and one year outcomes is presented in Table 4. It must be noted that although there are differences in the two groups in one of these outcomes, the study is under powered to attach any significance to this difference.

TABLE 3: Pilot study, depth, volatile anaesthetic dosing and mean arterial pressures

	BIS 35	**BIS 50**
N	61	64
Duration (min), mean (sd)	198 (79)	196 (105)
BIS (mean (sd) of means)	39 (5)	48 (6)
MAC (mean (sd) of means) *	0.95 (.23)	0.63 (.19)
MAP (mean (sd) of means) #	86 (11)	89 (10)

*MAC is minimum alveolar concentration of anaesthetic vapour.
#MAP is mean arterial pressure

TABLE 4: One month and one year outcomes in the pilot study

Outcome	**BIS 35**	**BIS 50**
Primary		
N	61	62
Mortality	7 (11%)	6 (9%)
Secondary		
Time to discharge from recovery (min)	61	62
Discharge from hospital (days)	10.1	8.2
Surgical site infection	8 (13%)	2 (3%)#
Composite complications score*		
At one month	19 (31%)	11 (17%)
At one year	9 (15%)	3 (5%)
Cancer		
Pre-op.	27 (44%)	30 (48%)
At one year	20 (33%)	13 (21%)

*Composite complications score = 'yes' to any of myocardial infarction, congestive cardiac failure, pulmonary embolus, deep vein thrombosis, pneumonia or stroke in first month after surgery
#P=0.029 (Chi Square)

Rationale for Research

Over 234 million people worldwide undergo surgery each year for both acute and chronic conditions [46]. Most of these people receive general anaesthesia. Over 10% are having moderate or major operations and are in the higher risk categories that are the target study group. These are the patients most likely to benefit should the study show that light anaesthesia is preferable.

Current public perceptions are that anaesthesia is very safe and indeed in healthy patients mortality purely attributable to the anaesthesia used is ~1:200,000 anaesthetics. However the influence of anaesthetic technique on perioperative outcome has barely been explored. Where such trials have been performed, they have also not shown the expected results. The MASTER trial, conducted in Australia and New Zealand in the 1990's comparing major regional anaesthesia for post-operative pain relief with intravenous analgesics showed no difference in mortality in spite of strong evidence from meta-analysis [47,48]. The POISE trial, a major international trial with strong Australian and New Zealand input on the role of beta-blockade in preventing myocardial infarction and death in patients with ischaemic heart disease also showed increased mortality. This was due to an unexpected increase in strokes counterbalancing the expected decrease in myocardial infarctions [49]. These results have led to a call for more such outcome studies to be performed to answer important public health questions about how we conduct anaesthesia.

The ANZCA Trials Group

The ANZCA Trials Group arose from the informal group of interested anaesthetists and hospitals that have participated large scale outcome studies in Australasia.

These studies include:

Master	Multicentre Australian study of epidural anaesthesia [47]
B-Aware	Bispectral index monitoring to prevent awareness during general anaesthesia [50]
ENIGMA	Evaluation of nitrous oxide in the gas mixture for anaesthesia [51]
POISE	Perioperative ischaemia evaluation of metoprolol in at-risk individuals–Australasian component [49]

Current Trials Group coordinated studies are:

ATACAS	Aspirin and tranexamic acid for coronary artery surgery Registration: (ACTRN No. ACTRN012605000557639)
ENIGMA2	Evaluation of nitrous oxide in the gas mixture for anaesthesia in patients at risk of perioperative ischaemia (clinicaltrials.gov ID: NCT00430989)
POISE2	Perioperative ischaemia evaluation of aspirin and/or clonidine in at-risk individuals–Australasian component (clinicaltrials.gov ID: NCT00860925).

The current study proposal has been presented to the Australian and New Zealand College of Anaesthetists (ANZCA) Trials Group and received its endorsement. The results will have global implications and we believe the protocol avoids the obvious pitfalls of this type of trial when they use techniques that are not easily translated into everyday practice [52].

10. STUDY DESIGN

Study Type

Interventional

Study Design

International multicentre, prospective, randomised, double blind (subjects, investigators and outcomes assessors), active control, parallel assessment, intention to treat, safety and efficacy study.

Primary endpoint

One-year all-cause mortality

Secondary endpoints

1. **MI:** Defined by any of

   a) A typical rise of troponin OR a typical fall of an elevated troponin OR a rapid rise and fall of CK-MB, PLUS one of the following: i) ischaemic symptoms, ii) pathological Q waves, iii) ECG changes indicative of ischaemia, iv) coronary artery intervention, and/or v) new or presumed new wall motion abnormality on echo or mibi scan; OR b) Autopsy findings of MI.

2. **Cardiac arrest:** Defined as a successful resuscitation from either documented or presumed ventricular fibrillation or sustained ventricular tachycardia or asystole.

3. **Pulmonary embolism:** high probability VQ scan or documented on pulmonary angiogram or spiral CT, or at autopsy.

4. **Stroke:** cerebral infarction or haemorrhage on CT or MRI scan, or new neurological signs (paralysis, weakness or speech difficulties) lasting more than 24 hours or leading to earlier death.

5. **Sepsis:** Surviving Sepsis Campaign definitions with backdating of data. [62] (Previously Centers for Disease Control and Prevention with National Healthcare Safety Network criteria [53]: - SIRS plus infection (positive blood culture or purulence from any site). This change means a clearer distinction between systemic inflammatory response syndrome and sepsis.

6. **Surgical site infection:** if associated with purulent discharge and/or a positive microbial culture.

7. **ICU stay:** including initial ICU admission and readmission time.

8. **Hospital stay:** from the start (date, time) of surgery until actual hospital discharge.

9. **Awareness:** Questioning for evidence of awareness under anaesthetic using the modified Brice questionnaire administered once, preferably on the day following surgery and again on day 30 [50,54,55]. This consists of four questions:

    1. What is the last thing you remember happening before you went to sleep?

2. What is the first thing you remember happening on waking?
3. Do you remember anything in between?
4. Did you have any dreams while you were asleep?

Affirmative responses will trigger a more detailed interview and counselling as required for the patient should there have been frank awareness.

10. **WHODAS score:** pre-operative, day 30 and 1 year
11. **Disability free survival**: disability-free survival up to 1 year: survival and freedom from new-onset disability, the latter defined as a 4-point reduction in the WHODAS score [56]. Disability in the WHODAS score is self reported by the participant, if the participant is unable to complete the score, then we will use a proxy's report as per WHODAS standard procedures. The date of onset of new disability will be recorded.
12. **Persistent post-operative pain**: pain over the surgical site, for at least three months after surgery, that cannot be explained by other causes, such as disease recurrence or a pre-existing pain syndrome.
13. **Cancer recurrence:** defined as clinical radiological or pathological evidence for recurrence of the tumour either at the local or a distant site.

Inclusion criteria

Age ≥60 years, ASA physical status 3 or 4, surgery expected to last ≥2 hours, post-operative hospital stay expected to be ≥2 nights, general anaesthesia with or without major regional block, able to monitor BIS throughout anaesthesia.

Exclusion criteria

Unable to monitor BIS (e.g. cranial or intracranial surgery), unable to consent , surgery with 'wake-up' test, propofol infusion for part or all of maintenance of anaesthesia ('total intravenous anaesthesia'), previous enrolment in Balanced study.

Intervention

General anaesthesia monitored with BIS. BIS targets will be either 50 or 35. We expect 90% of anaesthesia time to be within 5 units of the target BIS value and no deviations for >5 minutes.

Consent

Patients who are eligible for the trial will be given the patient information sheet by a member of the research team and encouraged to discuss the study with their family (or family/whanau in New Zealand) before written informed consent is sought, in accordance with local practice.

Treatment allocation

Once all entry details are recorded and eligibility confirmed, randomisation will be performed by contacting the automated on-line randomisation service with back-up phone service. Assignment to one of the two groups will be stratified by collaborating centre and a unique study number assigned. Investigators and research staff involved in patient followup are blinded to treatment allocation.

Perioperative Care

Anaesthesia will consist of standard anaesthetic hypnotics, volatiles, opioids and relaxants, intravenous or inhalational induction, volatile maintenance, opioids and muscle relaxants, with continuous BIS monitoring. No use of nitrous oxide will be allowed due to its interference with accurate BIS readings and similarly no infusions of ketamine above 25 mg/h will be allowed.

An individualised mean arterial blood pressure target range appropriate for the patient being studied will be set by the anaesthetist before BIS target randomisation. Anaesthetists will be encouraged to maintain patient normothermia and to give DVT prophylaxis and antibiotic prophylaxis as per local institutional practice. Other aspects of anaesthesia and perioperative care will be at the discretion of the anaesthetist. All complications (including those defined as secondary outcomes) will be managed according to routine institutional practice.

Recordings

Data will be collected by interviewing patients, relatives and doctors, and by review of hospital medical records and national databases (if applicable). Source documentation may be requested for any or all data recorded. Any or all data recorded may be subject to assessment by the Endpoint Adjudication Committee (on the direction of the Steering Committee).

Pre-operative

Age, sex, height, weight, ASA physical status, electrocardiogram (ECG), haemoglobin, creatinine, albumin, updated Charlson co-morbidity score [57,63], WHODAS-12 score

Intra-operative

Electronic *or* printed record with minimum of 5 minutely recording of BIS, burst suppression ratio (SR), end-tidal volatile anaesthetic concentration, mean arterial blood pressure and heart rate.

Manual record of all drugs used, including total dose of opioids used and regional or local anaesthetic blocks used.

Recovery

Analgesic and antiemetic requirements, time of arrival and eligibility for discharge.

Post-operative days 1, 2, 3

Routine laboratory testing.

Incidence of MI, cardiac arrest, PE, stroke, sepsis, surgical site infection and other adverse events.

Questioning for evidence of awareness under anaesthesia using the modified Brice questionnaire administered once, preferably on the day following surgery.

Analgesic and antiemetic requirements.

Quality of recovery: A validated post-operative quality of recovery score, the QoR-15 score will be recorded [58].

Post-operative day of discharge Length of hospital stay, unanticipated ICU admission, ICU stay, unplanned second operation

Post-operative day 30

Survival, ongoing analgesic or antiemetic requirements. Incidence of MI, cardiac arrest, PE, stroke, sepsis, surgical site infection, awareness, QoR-15, WHODAS score, persistent post-operative pain and other adverse events, staging of cancer (in cancer patients).

Post-operative one year

Survival. Disability free survival.

Incidence of MI, cardiac arrest, PE, stroke, sepsis, surgical site infection, WHODAS score, persistent post-operative pain (using modified pain inventory and neuropathic pain questionnaire if there is pain present [59,60])

In cancer patients, definitive Tumour-Node-Metastasis staging of cancer and evidence of any recurrence

All these measures are in frequent use and have been validated in past studies both of anaesthetic outcome as already discussed and in the general medical literature. Definitions of outcomes will be those used in the current ENIGMA-II Trial (a study of the influence of nitrous oxide on long term outcome from anaesthesia) and RELIEF trial [61] (see appendix).

11. EXPERIMENTAL CONTROL

Ethics committee approval for the pilot study was obtained from the Northern X Regional Ethics Committee in New Zealand and also ethics committees in Victoria, Western Australia and Hong Kong.

This trial will require approval from each site's ethics committee. Written informed consent will be required from all participants. The Data Monitoring Committee will review the safety of the trial as well as the interim analysis as soon as it becomes available.

12. BIAS CONTROL

a) *Bias Control.* The study is a comparison of two levels of depth of anaesthesia. The alternative of comparing deep and light groups with standard of care was considered. Knowing that the trial is a comparison with a BIS targeted group would also introduce a source of bias to the study. We would still need to collect BIS and volatile usage data to know at what depth the control anaesthetics were maintained, to detect this. The option of concealing the BIS data from the anaesthetist would be difficult to achieve in the large pragmatic study as proposed and would introduce another source of bias, namely that the anaesthetist may be deprived of this information which they may have otherwise used.

b) *Blood pressure management.* There is a potential confounding effect of blood pressure. Low blood pressure during anaesthesia is also associated with poor outcomes and more likely to occur in the "deep" anaesthesia group. We do not have audit data available on "usual" blood pressures during anaesthesia, for example, but the lack of standardisation of blood pressure in an open control group would further increase the variability in the sample, and therefore the numbers needed to detect a difference, if one exists.

c) Volatile anaesthetic use. Past observational studies have found an association with low BIS and low volatile anaesthetic requirement (low MAC). This may be a spurious association, and our trial design is capable of detecting these individuals and determining whether this observation is causal.

d) *Is this standard practice?* There is a possibility that neither group may be relevant as standard practice; this fear is probably unfounded. Currently, there is no standard for optimum anaesthetic depth, and so it is not surprising that a wide large range of depths, below the level associated with awareness, are employed by anaesthetists. Because no other variables or anaesthetic techniques are prescribed in the trial, the anaesthetics given should be relevant. We confirm that we are asking for blood pressure targets to be prescribed, but not stating what they should be, to allow clinicians to make their own judgement as to the optimum blood pressure for each patient. Consequently, this will prevent blood pressure differences between the groups becoming a source of bias.

e) Accurately tracking the two BIS targets Accurately tracking BIS at either 35 or 50 requires more attention to detail with drug dosage than is usual during general anaesthesia. We plan to monitor BIS tracking at all sites using de-identified BIS traces. We expect the average BIS value during the maintenance phase of anaesthesia to be within 5 units of target for 95% of patients. During the maintenance phase of the anaesthetic, we expect deviations more than 10 units from target to persist for no longer than 5 minutes 95% of the time. Sites unable to maintain this degree of accuracy may be closed down.

13. SAMPLE SIZE AND STATISTICAL ANALYSIS

Primary outcome

One year all-cause mortality will be compared between randomised groups using a Mantel-Haenszel Chi-square test, stratified by study centre. A two-tailed p-value <0.049 will be taken to indicate statistical significance.

Power analysis

One year all-cause mortality is expected to be ~10% based on the findings of Leslie et al's study and Australasian studies [9,25]. The reduction in mortality in the light anaesthesia group is expected to be 20%. A power analysis using p1=0.10 and p2=0.08 indicates that N=3250 patients are required in each group, β=0.8, α=0.049. The alpha level is reduced to allow for the single interim analysis.

The primary and secondary outcomes will initially be analysed using the full analysis set population i.e. using those individuals who have confirmed outcomes. Sensitivity analyses will also be undertaken, as appropriate, for which those missing outcome data will be assigned a poor outcome. Complete listings, according to randomised group, will be compiled of those lost to follow-up, and include relevant explanations.

Secondary outcomes

The presence of MI, cardiac arrest, stroke, PE, sepsis, surgical site infection, awareness and persistent post-operative pain at 30 days and one year as appropriate will be compared between randomised groups using Mantel-Haenszel chi-square tests or Fisher's exact test depending on the expected cell frequencies. Additionally a composite score including the presence of any of MI, cardiac arrest, stroke and PE, will be compared between randomised groups also using a chi-square test.

Additional analyses will also explore the role of MI, cardiac arrest, stroke, PE, sepsis, surgical site infection and cancer recurrence on one year mortality using Cox's proportional hazards regression to develop a model of independent predictors of one year mortality. The randomised group will be added to this model to assist explanation of any observed differences in outcome between the randomised groups.

Secondary analyses will be undertaken on an intention to treat basis. The vast majority of participants will have assessments of the primary outcome (one-year mortality) and the 30-day secondary outcomes. Permission will be sought as necessary to extract these from national databases and local hospital records.

Adverse events

The adverse event rates for non-outcome variables will be summarised for each randomised group as percentage of patients and as frequencies (number of occurrences) and compared between groups using Chi-square, Fisher's exact and Poisson regression depending on incidence rates.

Interim Analysis

The interim analysis of the primary outcome for efficacy and futility will be undertaken when 2000 participants have completed the one-year follow-up, which is likely to be after two years' recruitment. The p-value for this analysis is set at $p<0.001$ and the primary analysis p-value is adjusted accordingly to 0.049, to preserve the type I error rate. The analysis will be undertaken on the intention-to-treat (ITT) population, with all randomised participants included and analysed according to randomised treatment, irrespective of actual treatment.

14. TIMELINE

The study will take about one year to get 20 centres up and running, three years to complete enrollment and a further year to wait for the one-year outcome results. This time-line is based on current recruitment rates for the ENIGMA-2 trial being performed via the ANZCA Trials Group in Australasia. The ENIGMA-2 study will be completed early in 2013. The POISE-2 evaluation will finish mid 2013. Hopefully a number of centres will then join Balanced as the patient pool from which volunteers will be recruited overlaps with these studies. An interim analysis for efficacy and futility will be performed after 2000 patients have completed 1-year follow-up. The statistical criterion will be set at $p<0.001$ (two-tailed) for the primary outcome at this interim analysis.

15. FEASIBILITY

The study has been discussed at ANZCA Trials Group meetings and has received its full endorsement. Endorsement by the group means that there is direct access to an established network of hospitals with existing clinical research programs that are capable of taking part in large-scale pragmatic outcome studies such as this one in anaesthesia.

A pilot study has already been conducted with key results presented above. It has demonstrated the feasibility and acceptability of the protocol to patients and their anaesthetists. A search of the Auckland City Hospital anaesthetic data-base showed that there are approximately 1300 eligible patients per year. We believe this can be extrapolated to other major hospitals in Australia and Hong Kong based on experience from other ANZCA studies. On past experience we would expect recruitment to be 20 - 25% of patients, which is over 200 per year.

Alternative primary outcome variables have been considered. Mean survival time rather than one year mortality would reduce the number of patients required in the study by more than a third, as would use of disability free survival. The use of a composite index of complications, such as is proposed for one of the secondary outcomes would be possible. Based on studies in other specialties the number of patients needed for adequate study power would be considerably reduced. We have rejected these alternatives primarily because the existing audits have been performed using mortality, usually at one year, as the primary outcome. We also have no data on which to base a robust power analysis for these alternatives. It would also be possible to choose two doses of anaesthetic rather than two levels of BIS monitored depth. However, again, none of the audits have chosen this approach, and differences in mortality have strongly correlated with anaesthetic depth, not dose *per se.*

16. SECONDARY STUDIES

There has already been interest expressed in doing additional studies.

To date, these include:

1. Depth and post-operative cognitive dysfunction
2. Tropinins and cardiac outcomes
3. Analysis of BIS tracking and burst suppression in relation to the anaesthetic drugs used outcome.
4. Cerebral oximetry with Invos and measurement of S100B protein
5. An economic analysis
6. Assessment of the health impact of major surgery on the elderly
7. Incorporation as a substudy of the Neurovision study, as assessment of the incidence of perioperative stroke using MRI

They would use a subset of patients from the main study at selected centres. Some would require additional funding.

17. PERSONNEL RESPONSIBILITIES

The terms of references and role descriptions of Balanced Study committees and personnel will be detailed in study documentation.

Investigators

Principal investigator: A/Prof Tim Short provides overall leadership of the study. His roles include chairing the Steering Committee, leading the design of the study protocol, data management and analysis and authorship of the main paper.

Australian and Hong Kong Principal Investigators: Prof Kate Leslie and Prof Matthew Chan oversee the use of grant funds in these countries and lead the recruitment, initiation and ongoing performance of study sites.

Site investigators: The responsibilities of site investigators will include –

- submitting the study protocol to the local ethics committee and obtaining approval and locality before commencing the study
- ensuring that all staff conducting the trial are qualified to do so
- ensuring that all staff involved in the study are fully instructed on the study procedures and are given access to the study protocol and other information relating to the study
- ensuring the study is conducted in accordance with this protocol and ICH guidelines on GCRP
- ensuring that written informed consent is obtained from each patient prior to entering the study
- ensuring that the web-based CRFs are complete and accurate on completion of the study
- ensuring that the quality control procedures are performed on both the CRF's and the data base

Steering Committee

The membership of the Steering Committee will be A/Prof Tim Short (chair), Prof Kate Leslie, Prof Matthew Chan, Prof Paul Myles, A/Prof Chris Frampton, Dr Doug Campbell. Davina McAllister (Auckland City Hospital), Sofia Sidiropoulos (Monash Health, Melbourne) will be in attendance. The Steering Committee will be responsible for all aspects of the trial.

Operations Committee

The membership will be Prof Kate Leslie (chair), A/Prof Tim Short, Dr Doug Campbell, Davina McAllister and Sofia Sidiropoulos. The Operations Committee will be responsible for the day-to-day running of the trial.

Endpoint Adjudication Committee

The membership of the Endpoint Adjudication Committee will be Dr Johan van Scalkwyk, (chair), Auckland City Hospital, New Zealand; Dr Andrew MacCormick, Royal Melbourne Hospital, Australia; Dr Gordon Choi, The Prince of Wales Hospital, Hong Kong, China; Dr Paul Gardiner, Auckland City Hospital New Zealand.

The Steering Committee will decide on the definitions of outcomes. The Endpoint Adjudication Committee will evaluate individual patient events and determine outcomes primary and secondary outcomes at the direction of the Steering Committee. The committee will receive deidentified data and be blinded as to treatment allocation.

They will also assess a random sample of 10% of outcome events. If the rate of disagreements between the site CRF and the adjudicator exceeds 10% then the Steering Committee may consider an independent process for adjudication of all trial events.

Writing Committee

The writing committee, chaired by the principal investigator A/Prof Tim Short, will write the main paper.

Data Monitoring Committee

The details of this committee are outlined in the next section.

Data Quality Committee

The Data Quality Committee roles are:

1. To ensure that the trial data is of high quality
2. To ensure the integrity of the trial data

The roles of the Data Quality Committee do NOT include:

1. Endpoint adjudication (which is the role of the Endpoint Adjudication Committee)
2. Data analysis (which is the role of the trial statistician and Steering Committee)
3. Data safety and monitoring (which is the role of the Data Monitoring Committee)
4. Trial management (which is the role of the Steering Committee and its Operations Committee)

18. DATA MONITORING COMMITTEE

The responsibilities of the DMC are outlined in the DMC Charter. They include:

- Safeguarding the interests of the study participants
- Responsibility for monitoring the conduct of the trial and assessing the safety of the trial
- Meeting every six months to assess the safety and conduct of the trial.
- Conducting an interim analysis after 2000 patients have completed their 1 year follow-up. This is expected to be at the half-way point in study recruitment.

The project will be monitored by the NZ HRC Data Monitoring Core Committee.

DMC Members

Assoc Prof Katrina Sharples (Chair), Biostatistician
Dept of Preventive and Social Medicine, University of Otago, Dunedin.
Dr Mark Jeffery, Clinical Trials
Dept of Oncology, Christchurch Hospital, Christchurch.
Prof Ngaire Kerse, Clinical
General Practice and Primary Health Care, The University of Auckland, Auckland.
Prof John McCall, Clinical Trials
Department of Surgery, Dunedin School of Medicine, Dunedin.
Assoc Prof Andrew Moore, Ethicist
Department of Philosophy, University of Otago, Dunedin.
Prof Thomas Lumley, Biostatistician
Department of Statistics, the University of Auckland, Auckland.
Dr Mark Webster, Clinical
Department of Cardiology, Auckland City Hospital
Prof Jamie Sleigh, Anaesthetist
Department of Anaesthesia, Waikato Clinical School of Medicine, Hamilton.
Prof Guy Ludbrook, Anaesthetist
Professor of Anaesthesia, University of Adelaide, School of Medicine.

DMC reports will be prepared by the trial statistician, who will attend their meetings.

Assoc Prof Chris Frampton
Department of Statistics, University of Canterbury, Christchurch.

Stopping Criteria

Interim Analyses
An interim analysis of the primary outcome will be undertaken when 2000 participants have completed the one-year follow-up, which is likely to be after two years' recruitment. The p-value for this analysis is set at $p<0.001$ and the primary analysis p-value is adjusted accordingly to 0.049, to preserve the type I error rate. The analysis will be undertaken on the

intention-to-treat (ITT) population, with all randomised participants included and analysed according to randomised treatment, irrespective of actual treatment.

Before the meeting, DMC members will be provided with summary statistics of the recruitment, eligibility violations, completeness of follow-up and compliance with the protocol and intention to treat summaries of adverse events in the two arms of the study.
The Chair of the DMC will make a recommendation to continue, modify or terminate the trial based on safety and ethical considerations. They will prepare a brief report of their findings, without unblinding the safety data.

19 ADMINISTRATIVE PROCEDURES

19.1 Amendments to the protocol

Amendments to the protocol will only be made by Steering Committee and with the approval of the Ethics Committee when applicable. All modifications will be written and filed as amendments, maintaining the original section identification. Any modifications will be applied to all subsequent patients.

19.2 Early termination or extension of the study

The Steering Committee, with Ethics Committee approval may discontinue or extend the study at any time.

19.3 Confidentiality and publication of study results

Interim and preliminary results will not be discussed or presented outside the trial group unless authorised by the Steering Committee. The investigators plan to publish the results in a peer-reviewed journal.

19.4 Retention of records

All CRFs and all other documents associated with the study must be archived for at least 15 years following the completion of the trial, in accordance with local ethics committee requirements for storage.

19.5 Audits

This study is performed in accordance with Good Clinical Research Practice. The Steering Committee reserves the right to audit a sample of patients at all sites at any time. We will audit as many sites as is feasible.

20 ETHICS

20.1 Guidelines for Good Clinical Practice

The study is to be performed in accordance with ICH GCP notes for guidance on good clinical research practice and in New Zealand, National Ethics Advisory Committee Ethical Guidelines for Intervention Studies (latest revision July 2012) (available at www.ethics.health.govt.nz)

20.2 Participant Information Sheet and Consent Form

Suitable patients who may be interested in taking part in the study may be informed of the study in advance in writing or by telephone. The investigator or delegate will explain the study verbally to the patient. The patient will also be given a copy of the patient information sheet and consent form and given the opportunity to read it and ask any questions of the investigator. The patient will be urged to obtain additional information about the study from an independent source. When the patient is satisfied with the information they have received and had an opportunity to ask questions and the investigator is satisfied that the patient understands the nature of the study, the patient will be asked to sign the consent form.

Each patient's consent form will be retained by the investigator.

20.3 Research Ethics Committee

This protocol will be submitted to the Ethics Committee or relevant regulatory body at each site and their approval obtained. In New Zealand, locality will be obtained from all hospitals or institutions where the study is carried out.

21. AUTHORSHIP PLAN

Target Journal New England Medical Journal or Lancet

Planned Authorship Short TG, Leslie K, Chan MTV, Myles PS, Paech M, Corcoran T, Campbell D, Hill J, McAllister D, Frampton C and The ANZCA Trials Group.

The planned authorship may be extended or altered according to a majority vote of the Trial Steering Committee.

Committee members and site investigators at centres recruiting more than 400 patients will be offered co-authorship on at least one of the secondary publications. A more extensive participation and higher rate of patient enrolment may support a claim for authorship on the main publication, subject to a majority vote by the Trial Steering Committee.

Following acceptance for publication, all co-investigators and site investigators at each centre may plan secondary analyses for follow-up publication or presentation. A separate protocol should be developed and will require approval by the Steering committee before the presentation or submission for publication.

Appendix to be published with the final manuscript

Members of the committees, statisticians, all participating centres and site investigators and research nurses will be named in an appendix to the main paper. The centres will be listed alphabetically (country, hospital). All investigators listed in the authorship appendix will be considered an author and should list the manuscript on their CVs.

Agreement to authorship plan

Investigators must sign the trial agreement at the beginning of this protocol and return it to the trial office.

22. REFERENCES

1. Lundy JS. Balanced anesthesia. Minnesota Medical. 1926; 9:399-404.
2. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, Mangerg P. Bispectral Index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology 1997; 87:808-15.
3. Bijker J, Kalkman C. The role of intraoperative blood pressure in the association between low bispectral index values and mortality within two years after surgery. Anesth Analg 2010; 110:639.
4. Kurata J. Deep hypnosis as a sign of "imbalance" in balanced anesthesia. Anesth Analg 2010; 110:663-4.
5. Baldini G, Bagry H, Carli F. Depth of anesthesia with desflurane does not influence the endocrine-metabolic response to pelvic surgery. *Acta Anaesthesiol Scand*. 2008; 52:99-105.
6. Soumpasis I, Kanadoudis F, Vretzakis G, Arnaoutoglou E, Stamatiou G, Iatrou C. Deep anaesthesia reduces postoperative analgesic requirements after major urological procedures. *Eur J Anaesthesiol.* 2010; 27:801-6.
7. Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, Verhagen HJ, Khan NA, Dunkelgrun M, Bax JJ, Poldermans D; Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med.* 2009; 361:980-9.
8. Glass PS, Bloom M, Kearse L, Rosow C, Sebel PS, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. Anesthesiology 1997; 86:836-47.
9. Leslie K, Short TG. Low bispectral index values and death: the unresolved causality dilemma. *Anesth Analg* 2011; 113:660-3.
10. Sleigh JW. Depth of anesthesia: perhaps the patient isn't a submarine. (Editorial) Anesthesiology 2011; 115:1149-50.
11. Bennett C, Voss LJ, Barnard JP, Sleigh JW. Practical use of the electroencephalogram waveform during general anaesthesia: the art and science. Anesth Analg, 2007; 99:532-7.
12. Monk TG, Saini V, Weldon C, Sigl JC. Anesthetic management and one-year mortality after non-cardiac surgery. *Anesth Analg.* 2005; 100:4-11.
13. Lindholm M, Traff S, Granath F, Greenwald SD, Ekbom A, Lennmarken C, Sandin RH. Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. *Anesth Analg.* 2009; 108:508-12.
14. Saager L, Greenwald SC, Kelley SD, Schubert A, Sessler DI. Hospital stay and mortality are increased by a triple low of blood pressure, BIS and anesthetic depth. *International Society of Anesthetic Pharmacology Abstracts*, New Orleans 2009; 3-9.
15. Searleman AC, Leitner A, Ridley C, Zhang L, Avidan MS. Deep hypnotic time and one-year mortality in non-cardiac and cardiac surgical patients. Anesthesiology 2008; 109 A1.
16. Leslie K, Myles PS, Andrew Forbes, Chan MTV. The effect of BIS Monitoring on long-term survival in the B-Aware trial . *Anesth Analg.* 2010; 110:816-22.
17. Kertai MD, Pal N, Palanca BJA, Lin N, Searleman SA, Zhang L, Burnside BA, Finkel KJ, Avidan MS; B-Unaware Study Group. Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the B-unaware trial. *Anesthesiology*. 2010; 112:1116-27.
18. Kertai MD, Palanca BJA, Pal N, Burnside BA, Zhang L, Sadiq F, Finkel KJ, Avidan MS; B-Unaware Study Group. Bispectral index monitoring, duration of bispectral index below 45,

patient risk factors, and intermediate-term mortality after noncardiac surgery in the B-unaware trial. *Anesthesiology.* 2011; 114:545-56.

19. Cohen N. Anesthetic depth is not (yet) a predictor of mortality! (Editorial) *Anesth Analg.* 2005; 100:1-3.
20. Levy WJ Is anesthetic-related mortality a statistical illness? Berry AJ. Observational studies identify associations not causality. Drummond PC, Patel JC. Editorial board reproached for publication for BIS-mortality correlation. In reply, Monk T et al. Response Cohen N. *Anesth Analg.* 2005; 101:1241.
21. Monk TG, Weldon BC. Anesthetic depth is a predictor of mortality. It is time to take the next step (Editorial). *Anesthesiology.* 2010; 112:1070-2.
22. Lehrer J. The truth wears off. Is there something wrong with the scientific method. The New Yorker, 2010.
23. Short TG, van Schalkwyk J. Death by BIS: does deep anaesthesia matter? Abstract, *Annual Auckland Anaesthetic Consultants Meeting* August 2011.
24. Story DA, Fink M, Leslie K, Myles PS, Yap SJ, Beavis V, Kerridge RK, McNicol PL. Perioperative mortality risk score using pre- and post-operative risk factors in older patients. *Anaesth Intensive Care. 2009*; 37:392-8.
25. Gurman GM, Popescu M, Weksler N, Steiner O, Avinoah E, Porath A. Influence cortical activity level during general anaesthesia on the severity of immediate postoperative pain in the morbidly obese. Acta Anaesthesiologica Scandinavica 2003; 47:804-808.
26. Henneberg SW, Rosenborg D, Weber Jensen E, Ahn P, Burgdorff B, Thomsen LL. Perioperative depth of anaesthesia may influence postoperative opioid requirements. Acta Anaesthesiol Scand. 2005; 49:293-6.
27. Baldini G, Bagry H, Carli F. Depth of anesthesia with desflurane does not influence the endocrine-metabolic response to pelvic surgery. Acta Anaesthesiol Scand. 2008;52:99-105.
28. Perouansky M. General anesthetics and long-term neurotoxicity. *Handb Exp Pharmacol.* 2008; 182:143-57.
29. Salo M. Effects of anaesthesia and surgery on the immune response. *Acta Anaesth Scand.* 1992; 36:201-20.
30. Crozier TA, Muller JE, Quittkat D, Sydow M, Wuttke W, Kettler D. Effect of anaesthesia on the cytokine responses to abdominal surgery. *Br J Anaesth* 1994; 72:280-5.
31. Schneemilch CE, Bank U. Release of pro- and anti-inflammatory cytokines during different anaesthesia procedures. *Anaesthesiol Reanim.* 2001; 26:4-10.
32. Kudoh A, Katagai H, Takazawa T, Matsuki A. Plasma proinflammatory cytokine response to surgical stress in elderly patients. *Cytokine* 2001; 15:270-3.
33. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, Kuipers HM, Hanning CD, Siersma VD, Kristensen D, Canet J, Ibañaz MT, Moller JT; ISPOCD2 Investigators. Postoperative cognitive dysfunction in the middle-aged patients. *Anesthesiology* 2002; 96:1351-7.
34. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME: Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *JAMA 1995*; 274: 44-50.
35. Singleton PA, Moss J. Effect of perioperative opioids on cancer recurrence: a hypothesis. Future Oncol 2010; 6:1237-42.
36. Morimoto Y, Monden Y, Ohtake K, Sakabe T, Hagihira S. The detection of cerebral hypoperfusion with bispectral index monitoring during general anaesthesia. Anesth Analg, 2005; 100:158-61.

37. Liu N, Chazot T, Mutter C, Fischler M. Elevated burst suppression ratio: the possible role of hypoxemia. Anesth Analg, 2006; 103:1609-10.
38. Watson PL, Shintani AK, Tyson R, Pandharipande PP, Pun BT, Ely EW. Presence of electroencephalogram burst suppression in sedated critically ill patients is associated with increased mortality. Crit Care Med 2008; 36:3171-77.
39. Besch G, Liu N, Samain E, Pericard C, Boichut N, Mercier M, Chazot T, Pili-Floury S. Occurrence of and risk factors for electroencephalogram burst suppression during propofol-remifentanil anaesthesia. Br J Anaesth 2011; 107:749-56.
40. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index and low minimum alveolar concentration of volatile anaesthesia. Anesthesiology 2012; 116:1195-203.
41. Kheterpal S, Avidan MS. "Triple low" murderer, mediator or mirror (editorial). Anesthesiology 2012; 116:176-8.
42. Wahl KM, Moretti E, White W, Hale B, Gan T. Validation of a risk-stratification for predicting 1-year mortality. ASA Abstracts 2011, A014.
43. Ballard C, Jones E, Gauge N, Aarsland D, Nilsen OB, Saxby BK, Lowery D, Corbett A, Wesnes K, Katsaiti E, Arden J, Amaoko D, Prophet N, Purushothaman B, Green D. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomized controlled trial. Plos ONE 2012; 7(6): e37410.
44. Chan MTV, Cheng BCP, Lee TMC, Gin T and the CODA trial group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2012, *published ahead of press*.
45. Short TG, Chan MTV, Leslie K, Myles PS, O'Loughlin P, Campbell D, McAllister D, The Balanced pilot study. Abstract, *ANZCA Clinical Trials Group Annual Meeting.* Palm Cove, August 2011.
46. Weiser TG, Rewgenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; 372:193-44.
47. Peyton PJ, Myles PS, Silbert BS, Rigg JRA, Jamrozik K, Parsons RW, and the MASTER Anesthesia Trial Study Group. Perioperative epidural analgesia and outcome after major abdominal surgery in high risk patients. Anesth Analg 2003; 96:548-554.
48. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000 Dec 16; 321(7275):1493.
49. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu LS, Xu S, Málaga G, Avezum A, Chan MTV, Montori VM, Jacka M, Choi P, on behalf of POISE Investigators. Effects of metoprolol succinate extended-release in patients undergoing noncardiac surgery: a randomised controlled trial. Lancet 2008; 371:1839-47.
50. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet. 2004; 29:363(9423):1757-63.
51. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E; ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology, 2007; 107:221-31.

52. Ware JH, Hamel MB. Pragmatic trials –guides to better patient care? (Perspective) N Engl J Med 2011; 341:1685-87.
53. Horan T, Andrus M, Dudeck M. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control. 2008;36(5):309-32.
54. Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during general anaesthesia. BJA 1970; 42: 535-42.
55. Nordstrom O, Engstrom AM, Persson S, Sandin R. Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. Acta Anaesthesiol Scand 1997; 41: 978-84.
56. Ustun TB, Chatterji S, Kostanjsek N, Rehm J, Kennedy C, Epping-Jordan J, Saxena S, von Korff M, Pull C in collaboration with WHO/NIH Joint Project. Developing the World Health Organisation Disability Assessment Schedule 2.0. Bull World Health Organ 2010;88:818-23.
57. Charlson ME, Pompei P, Ales KL, MacKenzie CR, A new method of classifying prognostic comorbidity in longitudinal studies development and validation. J Chron Dis 1987; 40:373-83.
58. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. 2012. *in press.*
59. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. Pain Suppl 1986; 3: S1-226
60. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factorsand prevention. Lancet 2006; 367:1618-1625
61. Myles PS, Leslie K, Peyton P, Paech M, Forbes A, Chan MTV, Sessler S, Devereaux PJ, Silbert BS, Jamrozik K, Beattie S, Badner N, Tomlinson J, Wallace S. Nitrous oxide and perioperative cardiac morbidity (ENIGMA-II) trial: rationale and design. Am Heart J 2009; 157:488-94
62. Dellinger RP, Levy MM, Rhodes A et al. Surviving sepsis campaign: international guidelines for the management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580-637
63. Quan H, Couris CM, Fushimi K, Graham P, Hider P, Januel M, Sundararajan V. Updating and validting the Charlson comorbidity index and score for risk adjustment in hospital discharge abstract using data from 6 countries. Am J Epidemiol 2011; 2:1-7

23. APPENDICES

23.1 Charlson Score, with updated weightings [63]

Charlson Score	Assigned Weight	New weight
myocardial infarction	1	0
congestive heart failure	1	2
peripheral vascular disease	1	0
cerebrovascular disease	1	0
dementia	1	2
chronic pulmonary disease	1	1
connective tissue disease (rheumatologic disease)	1	1
ulcer disease	1	0
diabetes: mild/with end organ damage	1/2	0/1
hemiplegia	2	2
renal disease: mild/moderate/severe	1/2/3	1
any malignancy including leukemia and lymphoma	2	2
liver disease: Mild/moderate/severe	1/2/3	0/4/4
metastatic solid malignancy	6	6
AIDS	6	4

Definitions

Diabetes

Mild -requiring treatment with oral hypoglycaemics or insulin, not diet alone

With end organ damage -presence of retinopathy, nephropathy or neuropathy

Renal disease –

Mild –creatinine 170 – 260 mmol/L

Moderate –creatinine >260 mmol/L

Severe –renal dialysis, previous transplant or uraemia

Liver disease

Mild –cirrhosis but no portal hypertension

Moderate –patients with cirrhosis, portal hypertension, but no variceal bleeding

Severe –patients with cirrhosis, portal hypertension and variceal bleeding

23.2 QoR-15 Score

How have you been feeling in the last 24 hours ?

0 to 10 where 0 = none of the time (poor) and 10 = all of the time (excellent)

1	Able to breathe easy	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
2	Been able to enjoy food	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
3	Feeling rested	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
4	Have had a good sleep	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
5	Able to look after personal toilet and hygiene unaided	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
6	Able to communicate with family or friends	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
7	Getting support from hospital doctors and nurses	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
8	Able to return to work or usual home activities	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
9	Feeling comfortable and in control	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time
10	Having a feeling of general well-being	None of the time 0 1 2 3 4 5 6 7 8 9 10 all of the time

Have you had any of the following in the last 24 hours ?

(0 to 10 where 0 = none of the time (excellent) and 10 = all of the time (poor))

11	Moderate pain all or nearly all of the time	None of the time 10 9 8 7 6 5 4 3 2 1 0 all of the time
12	Severe pain at any time	None of the time 10 9 8 7 6 5 4 3 2 1 0 all of the time
13	Nausea or vomiting	None of the time 10 9 8 7 6 5 4 3 2 1 0 all of the time
14	Feeling worried or anxious	None of the time 10 9 8 7 6 5 4 3 2 1 0 all of the time
15	Feeling sad or depressed	None of the time 10 9 8 7 6 5 4 3 2 1 0 all of the time

23.3 The World Health Organisation disability assessment schedule 2.0.

12 Item interviewer-administered version (self-administered and proxy-administered versions are also available)

SECTION 3: PREAMBLE

SAY TO RESPONDENT:
The interview is about difficulties people have because of health conditions. ***(HAND FLASHCARD #1 TO RESPONDENT)***. By health condition I mean diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems and problems with alcohol or drugs.

I remind you to keep all of your health problems in mind as you answer the questions. When I ask you about difficulties in doing an activity think about ***(POINT TO FLASHCARD #1)***.

- Increased effort
- Discomfort or pain
- Slowness
- Changes in the way you do the activity

(POINT TO FLASHCARD #1). When answering, I'd like you to think back over the last 30 days. I also would like you to answer these questions thinking about how much difficulty you have, on average over the past 30 days, while doing the activity as you usually do it.

(HAND FLASHCARD #2 TO RESPONDENT). Use this scale when responding. ***(READ SCALE ALOUD)***: None, mild, moderate, severe, extreme or cannot do.

(FLASHCARDS #1 AND #2 SHOULD REMAIN VISIBLE TO THE RESPONDENT THROUGHOUT THE INTERVIEW.)

Flashcard #1

Health Conditions:

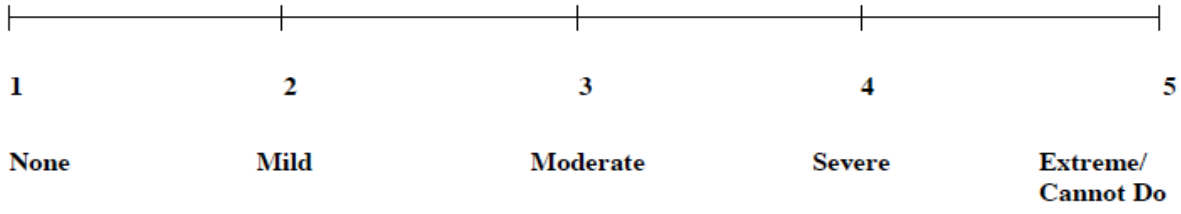
- **Diseases, illnesses or other health problems**
- **Injuries**
- **Mental or emotional problems**
- **Problems with alcohol**
- **Problems with drugs**

Having difficulty with an activity means:

- **Increased effort**
- **Discomfort or pain**
- **Slowness**
- **Changes in the way you do the activity**

Think about the past 30 days only

Flashcard #2



SECTION 4. CORE QUESTIONS

H1	How do you rate your overall health in the past 30 days? *Read choices to respondent.*	Very good	Good	Moderate	Bad	Very Bad

SHOW FLASHCARD #2 to participant

In the last 30 days how much difficulty did you have in:

		None	Mild	Moderate	Severe	Extreme /Cannot Do
S1	Standing for long periods such as 30 minutes?	1	2	3	4	5
S2	Taking care of your household responsibilities?	1	2	3	4	5
S3	Learning a new task, for example, learning how to get to a new place?	1	2	3	4	5
S4	How much of a problem did you have joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	1	2	3	4	5
S5	How much have you been emotionally affected by your health problems?	1	2	3	4	5

Continue to next page…

In the last 30 days how much difficulty did you have in:						
		None	Mild	Moderate	Severe	Extreme /Cannot Do
S6	Concentrating on doing something for ten minutes?	1	2	3	4	5
S7	Walking a long distance such as a kilometre [or equivalent]?	1	2	3	4	5
S8	Washing your whole body?	1	2	3	4	5
S9	Getting dressed?	1	2	3	4	5
S10	Dealing with people you do not know?	1	2	3	4	5
S11	Maintaining a friendship?	1	2	3	4	5
S12	Your day to day work?	1	2	3	4	5

		None	Mild	Moderate	Severe	Extreme /Cannot Do
H2	Overall, how much did these difficulties interfere with your life? *Read choices to respondent.*	1	2	3	4	5
H3	Overall, in the past 30 days, how many days were these difficulties present?	RECORD NUMBER OF DAYS ___/___				
H4	In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition?	RECORD NUMBER OF DAYS __/__				
H5	In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?	RECORD NUMBER OF DAYS __/__				

23.4 Modified Brice Questionnaire

1. What is the last thing you remember happening before you went to sleep?
2. What is the first thing you remember happening on waking?
3. Do you remember anything in between?
4. Did you have any dreams while you were asleep?

23.5 Modified Brief Pain Inventory

We want you to rate the severity of your pain, using a number from 0 to 100. For example, if you have no pain, you would rate it '0'. If you have the worst pain imaginable, you would rate it "100".

1. Please rate your pain with the number that best describes your pain at its WORST in the last 24 hours. | | |

2. Please rate your pain with the number that best describes your pain at its LEAST in the last 24 hours. | | |

3. Please rate your pain with the number that best describes your pain on the AVERAGE in the last 24 hours. | | |

4. Please rate your pain with the number that tells how much pain you have RIGHT NOW. | | |

5. Using a number from 0 to 100 as shown below describe how, during the past 24 hours, pain has interfered with your:

0 …… 100
does not interfere *interferes completely*

A. General activity ……..

B. Mood ……..

C. Walking ability ……..

D. Normal Work (includes both work outside the home and housework) ….

E. Relations with other people ……..

F. Sleep ……

G. Enjoyment of life ……..

23.6 Neuropathic pain questionnaire

We need to understand exactly what type of pain you have from your operation a year ago and how it may not change over time. You may have only one site of pain, or you may have more than one.

1. With regard to the pain from your operation, please name the site of pain which is most disturbing for you.
2. Was the pain there before your surgery or has it developed since the operation ?
3. For your pain at this site, please describe your pain in your own words.
4. For the following types of pain, please rate your pain at this site as it usually feels, using a number from 0 to 100. For example, if you have no pain, rate it "0". If you have the worst pain imaginable, you would rate it "100". If neither of those fits your pain because it is in between, choose a number that fits your pain.

1. Burning Pain
0 ◁——▷ 100 ☐☐☐
No Burning Pain — Worst Burning Pain Imaginable

2. Overly Sensitive to Touch
0 ◁——▷ 100 ☐☐☐
No Oversensitivity — Worst Oversensitivity Imaginable

3. Shooting Pain
0 ◁——▷ 100 ☐☐☐
No Oversensitivity — Worst Oversensitivity Imaginable

4. Numbness
0 ◁——▷ 100 ☐☐☐
No Numbness — Worst Numbness Imaginable

5. Electric Pain
0 ◁——▷ 100 ☐☐☐
No Electric Pain — Worst Electric Pain Imaginable

6. Tingling Pain
0 ◁——▷ 100 ☐☐☐
No Tingling Pain — Worst Tingling Pain Imaginable

7. Squeezing Pain
0 ◁——▷ 100 ☐☐☐
No Squeezing Pain — Worst Squeezing Pain Imaginable

8. Freezing Pain
0 ◁——▷ 100 ☐☐☐
No Freezing Pain — Worst Freezing Pain Imaginable

9. How Unpleasant is your usual pain?
0 ◁——▷ 100 ☐☐☐
No Unpleasant Pain — Worst Over-Whelming Pain

10. How overwhelming is your usual pain?
0 ◁——▷ 100 ☐☐☐
No Over-whelming Pain — Worse Over-Whelming Pain Imaginable

We are also interested in learning in what circumstances cause changes in your pain. Please indicate the amount youexperience each of the following:

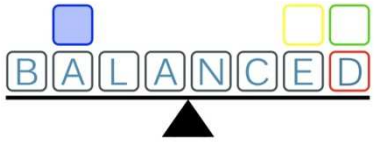
11. Increased Pain due to Touch
0 ◁——▷ 100 ☐☐☐
No Increase At All — Greatest Increase Imaginable

12. Increased pain due to weather changes
0 ◁——▷ 100 ☐☐☐
No Increase At All — Greatest Increase Imaginable

21.5 Study Flow Chart

	Pre-operative	**Day of Surgery**	**Day1 post op**	**Day 2 Post op**	**Day 3 post op**	**Day of discharge**	**Day 30 post op**	**1 Year post op**
Entry criteria	X							
Informed consent	X							
Demographics	X							
Charlson score	X							
Randomisation	X							
Intra-operative data		X						
PACU data record		X						
Discharge data						X		
Outcomes *			X	X	X		X	X
Brice (awareness)			X				X	
QoR-15			X	X	X		X	
WHODAS score	X						X	X
Pain: mBPI (if needed)							X	X
Pain : neuropathic (if needed)								X
Cancer staging (if needed)							X	X

*Outcomes: survival, MI, cardiac arrest, PE, stroke, sepsis, surgical site infection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