

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97. DOI: 10.1056/NEJMoa0810625.

## NICE SUGAR Study Appendices:

### Appendix A: Eligibility criteria for the NICE-SUGAR study

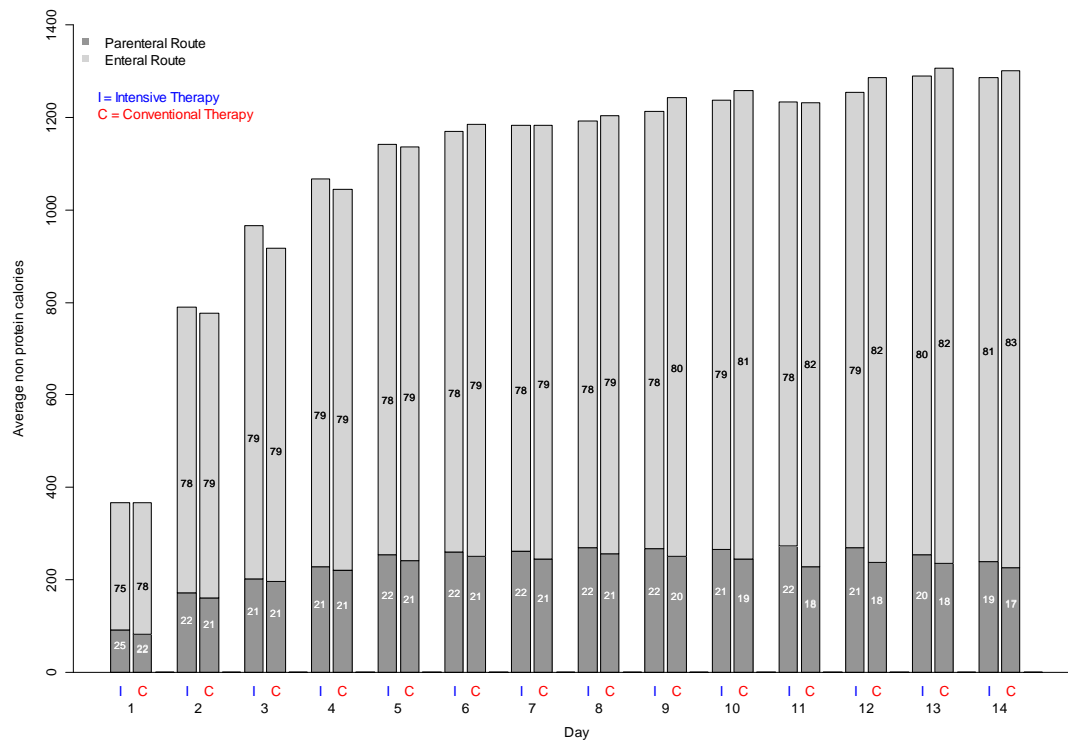
Patients are eligible for inclusion in the study if the following criteria are met:

1. At time of the patient's admission to the ICU the treating ICU specialist expects that 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 the placement of an arterial line is imminent (within the next hour) as part of routine ICU management.

Patients are excluded from the study if one or more of the following criteria are present:

1. Age less than 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 is confirmed by a documented treatment-limitation order that exceeds a "do-not-resuscitation" order.
3. Patients admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state.
4. Patients expected to be eating before the end of the day following the day of admission to the ICU.
5. Patients who have previously suffered hypoglycemia without documented full neurological recovery.
6. Patients considered at abnormally high risk of suffering hypoglycemia (e.g. known insulin secreting tumor or history of unexplained or recurrent hypoglycemia or fulminant hepatic failure)
7. Patient has previously been enrolled in the study.
8. Patient cannot provide prior informed consent and 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. Patient has been in the study ICU or another ICU for 24 hours or more for this admission.

Appendix B - Median non protein calories per patient administered by enteral and parenteral routes – days 1 – 14; Day 1 is the day of randomization from randomization to end of ICU day, day 2 is first full day after randomization. Numbers within bars represent percentage of total calories given by enteral or parenteral route.



Total non protein calories by any route as mean and SD  
(P = Student's or Welch's t test as appropriate)

Day	Intensive Control Mean (SD)	Conventional control Mean (SD)	Difference (95%CI)	P value
1	466 (399)	462 (392)	5 (-16, 26)	0.65
2	921(597)	894 (605)	26 (-5, 58)	0.10
3	1070 (656)	1010 (652)	60 (24,96)	0.001
4	1150 (680)	1130 (669)	27 (-14,67)	0.95
5	1220 (672)	1210 (676)	8 (-36,52)	0.73
6	1240 (655)	1260 (677)	-15 (-62,32)	0.53
7	1260 (684)	1260 (695)	-0.4 (-53,52)	1.0
8	1270 (657)	1270 (670)	-5 (-59,49)	0.9
9	1280 (651)	1310 (675)	-26 (-84,32)	0.4
10	1300 (646)	1320 (674)	-21 (-83,40)	0.5
11	1300 (630)	1290 (680)	3 (-62,67)	0.9
12	1320 (676)	1340 (672)	-21 (-92,50)	0.6
13	1350 (617)	1360 (661)	-7 (-78,64)	0.8
14	1350 (631)	1350 (668)	-8 (-84,69)	0.8

Total non protein calories as IV glucose solution  
(Includes maintenance fluids and drug infusions) (P = Welch's t test)

Day	Intensive Control Mean (SD)	Conventional control Mean (SD)	Difference (95%CI)	P value
1	99 (123)	96 (123)	3 (-3,9.6)	0.3
2	131 (153)	118 (152)	13 (5,21)	0.0004
3	108 (133)	98 (134)	10 (3,18)	0.007
4	89 (126)	83 (121)	6 (-2,13)	0.3
5	79 (112)	76 (107)	3 (-4,10)	0.4
6	74 (106)	73 (113)	2 (-6,9)	0.7
7	72 (106)	73 (118)	-0.7 (-9,8)	0.9
8	74 (114)	68 (112)	6 (-3,15)	0.2
9	68 (103)	63 (104)	4 (-5,13)	0.3
10	61 (96)	62 (114)	-0.8 (-10,9)	0.9
11	63 (93)	61 (108)	2 (-8,12)	0.8
12	67 (108)	57 (105)	11 (-0.7,22)	0.07
13	63 (98)	55 (95)	8 (-2,19)	0.2
14	60 (100)	52 (93)	7 (-4,19)	0.2

Total non protein calories by enteral route  
(P = Student's or Welch's t test as appropriate)

Day	Intensive Control Mean (SD)	Conventional control Mean (SD)	Difference (95%CI)	P value
1	276 (356)	284 (362)	-8 (-27,11)	0.4
2	618 (602)	617 (606)	1 (-31,32)	1
3	764 (675)	720 (648)	45 (8,81)	0.07
4	839 (688)	825 (674)	13 (-27,54)	0.5
5	887 (690)	896 (693)	-9 (-54,36)	0.7
6	909 (688)	935 (700)	-26 (-75,22)	0.3
7	921 (703)	939 (716)	-18 (-71,36)	0.5
8	924 (693)	947 (702)	-23 (-80,34)	0.4
9	945 (693)	992 (722)	-48 (-109,14)	0.3
10	972 (704)	1010 (725)	-42 (-109,25)	0.3
11	960 (689)	1000 (728)	-44 (-114,25)	0.2
12	986 (703)	1050 (721)	-63 (-138,12)	0.1
13	1040 (692)	1070 (713)	-35 (-113,43)	0.4
14	1050 (703)	1080 (711)	-30 (-112,54)	0.5

Total non protein calories by parenteral route (P = Student's t test)

Day	Intensive Control (N=2969) Mean (SD)	Conventional control (N=2943) Mean (SD)	Difference (95%CI)	P value
1	91 (225)	82 (190)	10 (-1,21)	0.08
2	172 (406)	160 (386)	12 (-8,33)	0.2
3	201 (471)	196 (466)	5 (-21,31)	0.7
4	227 (515)	220 (501)	8 (-23,38)	0.7
5	255 (552)	241 (523)	14 (-21,49)	0.4
6	260 (549)	251 (535)	9 (-29,48)	0.6
7	262 (561)	244 (527)	18 (-23,59)	0.4
8	268 (569)	256 (535)	12 (-33,53)	0.6
9	268 (566)	251 (544)	17 (-31,65)	0.5
10	266 (556)	244 (542)	22 (-30,73)	0.4
11	273 (573)	228 (514)	46 (-8,99)	0.1
12	269 (589)	237 (546)	32 (-28,91)	0.3
13	255 (562)	235 (555)	20 (-42,82)	0.5
14	240 (557)	226 (553)	14 (-51,79)	0.7

Total non protein calories averaged over day 1-14 for each Patient  
(P = Student's or Welch's t test as appropriate)

	Intensive Control Mean (SD)	Conventional control Mean (SD)	Difference (95%CI)	P value
Non protein nutrition via all routes	891 (490)	872 (500)	19 (-6,44)	0.1
Non protein nutrition via IV route	93 (89)	87 994)	6 (2,11)	0.008
Non protein nutrition via enteral route	624 (496)	623 (496)	2 (-24,27)	0.9
Non protein nutrition via parenteral route	173 (359)	162 (345)	11 (-7,29)	0.2

## Appendix C – Cause of death methodology and withdrawal of therapy data instructions

### CAUSE OF DEATH CLASSIFICATION – DATA COMPLETION INSTRUCTIONS

#### Introduction

Accurate and consistent classification of cause of death is extremely important and the following completion notes are designed to aid that.

#### Classification

The cause of death is classified by giving **one** and only one **PROXIMATE** cause of death with, in addition, **all UNDERLYING** causes that apply. Although we have grouped **proximate** and **underlying** causes by system (neurological, cardiovascular, respiratory, metabolic and other), it is possible to have proximate cause in one system with underlying cause(s) in another system. For instance, death due to distributive or septic shock is listed in the cardiovascular system for proximate cause of death but this may be due to a number of underlying causes such as pneumonia which is listed under the respiratory system, meningococcal meningitis listed under the neurological system and/or sepsis with multi-organ failure listed under the cardiovascular system. The proximate cause of death should describe the predominant proximate cause in each case.

#### Withdrawal of therapy

Where death follows withdrawal of treatment, the proximate cause of death given should be that representing the pathological process that was most important in the decision to withdraw treatment. It should not represent the final mode of dying. For example, if a patient has severe sepsis with multi-organ failure and rapidly increasing inotrope requirements, a decision is made to withdraw treatment by discontinuing inotropes and extubation, following extubation the patient rapidly becomes hypoxic, hypotensive and dies, the proximate cause of death should be distributive (septic shock) rather than hypoxic respiratory failure as it was the refractory shock which was the cause for withdrawing treatment even though hypoxia was present at the time of death. Conversely, if treatment is withdrawn because the patient has severe refractory hypoxic respiratory failure due to ARDS as part of a picture of sepsis with multi-organ failure, if the refractory hypoxic respiratory failure is the cause of withdrawal of treatment, then hypoxic respiratory failure should be given as the proximate cause of death.

There are three mutually exclusive answers to the question on withdrawal of therapy. **One only** should be ticked. If the patient has CPR as a terminal event, it should be clear which one should be indicated. If the patient has maximum medical therapy but is clearly not responding and ultimately the decision is made to put a limit on that treatment, for example a limit on the amount of inotrope that is given or dialysis is not commenced because all other systems are deteriorating, then indicate that treatment was withdrawn or limited as a terminal event as the patient was dying despite maximum therapeutic efforts.

In the situation where a patient has a decision made not to have treatment with certain interventions such as inotropes, renal replacement therapy or intubation because it is felt that they will either not survive this treatment or if they do survive, their quality of life will be poor, then the option of “treatment withheld, as maximum medical therapy not indicated” should be chosen.

This option should also be used for a patient who has had a period of maximal medical therapy and who recovers to a point but ultimately has treatment limited, and for patients who are discharged to the ward but die on the ward after a decision is made that they not be readmitted to the Intensive Care Unit or who die on the ward after a treatment limitation order has been documented in the medical record.

**Time of Withdrawal or Limitation of Treatment**

Please record the date that limitation, withdrawal or withholding of treatment leading to death, was documented in the patient’s chart.

**Place of Death:**

We have also asked for you to indicate the place of death. There are 4 options:

1. In the Intensive Care Unit ( or an Intensivist managed HDU)
2. In the General Ward
3. Home
4. Other (please specify)

If the patient is discharged from the Intensive Care Unit to a High Dependency Unit or a Step-Down Unit that is not managed by the Intensivists, then they are considered to have died on a General Ward.

**Causes of death - Proximate causes:**

CAUSES OF DEATH	
<b>Proximate cause</b>	
<b>Neurological</b>	Neurological - traumatic brain injury, with brain death
	Neurological - traumatic brain injury, without brain death
	Neurological - no traumatic brain injury, with brain death
	Neurological - no traumatic brain injury, without brain death
<b>Cardiovascular</b>	Arrhythmia
	Cardiogenic Shock
	Distributive (Septic) Shock
	Hypovolaemic Shock
<b>Respiratory</b>	Hypoxic respiratory failure
<b>Metabolic</b>	Metabolic
<b>Other</b>	Other

## Appendix C – Underlying causes of death:

CAUSES OF DEATH	
Underlying cause	
<b>Neurological</b>	Traumatic brain injury (unsurvivable primary injury)
	Traumatic brain injury (refractory intracranial hypertension)
	Haemorrhagic stroke
	Ischaemic stroke
	Meningoencephalitis
	Cerebral abscess
	Status epilepticus
	Hypoxic brain injury
	Aneurysmal SAH (Primary or secondary haemorrhage)
	Metabolic encephalopathy
	Other Neurological
<b>Cardiovascular</b>	AMI
	Myocarditis
	Ruptured or leaking AAA
	Ruptured or leaking Thoracic AA
	Pericardial tamponade
	Sepsis with multi-organ failure
	Haemorrhage due to trauma
	Haemorrhage not due to trauma
	Hepatic Failure
	Anaphylaxis
	Pancreatitis
	Aortic valvular disease
	Mitral valve disease
	Massive pulmonary thromboembolism
	Other Cardiovascular
<b>Respiratory</b>	COPD
	Cancer
	Asthma
	Pulmonary fibrosis
	Pneumonia
	Aspiration pneumonitis
	ARDS - pulmonary
	ARDS - non-pulmonary
	Pulmonary haemorrhage
	Other Respiratory
<b>Metabolic</b>	Vasculitis
	Hepatitis
	Drug overdose
	Anorexia/cachexia
	Diabetes
	Hypoadrenalism
	Drug induced
Renal Failure	
<b>Other</b>	Other cause not listed

## **Appendix D:**

### **Limitation of potentially life sustaining treatment in patients who died**

Treatment limitation status was known for 1557 of the 1580 patients who died; potentially life sustaining treatments were withheld or withdrawn prior to death in 1415/1557 (90.9%) patients; 746/816 (91.4%) in the lower range group, 669/741 (90.3%) in the higher range group, (OR 1.15, 95%CI 0.81 - 1.62, P=0.44). Treatment was withheld as not indicated in 429 (27.6%) patients; 219 (26.8%) in the lower range group, 210 (28.3%) in the higher range group, (OR 0.93, 95%CI 0.74 - 1.16, P=0.51). Treatment was withdrawn or withheld because the patient was judged terminally ill in 986 (63.3%) patients; 527 (64.6%) in the lower range group, 459 (61.9%) in the higher range group, (OR 1.12, 95%CI 0.91 - 1.38, P=0.28). The median (IQR) time from randomization to withdrawal or withholding of treatment was 6 (3-16) days in the lower range group and 6 (2-15) in the higher range group (P=0.42).