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**National Institute for
Health Research**

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Abstract

A clinical and economic evaluation of Control of Hyperglycaemia in Paediatric intensive care (CHiP): a randomised controlled trial

Duncan Macrae,^{1*} Richard Grieve,² Elizabeth Allen,³ Zia Sadique,² Helen Betts,¹ Kevin Morris,⁴ Vithayathil John Pappachan,⁵ Roger Parslow,⁶ Robert C Tasker,⁷ Paul Baines,⁸ Michael Broadhead,⁹ Mark L Duthie,¹⁰ Peter-Marc Fortune,¹¹ David Inwald,¹² Paddy McMaster,¹³ Mark J Peters,⁹ Margrid Schindler,¹⁴ Carla Guerriero,² Deborah Piercy,³ Zdenek Slavik,¹ Claire Snowdon,³ Laura Van Dyck³ and Diana Elbourne³

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Background: Early research in adults admitted to intensive care suggested that tight control of blood glucose during acute illness can be associated with reductions in mortality, length of hospital stay and complications such as infection and renal failure. Prior to our study, it was unclear whether or not children could also benefit from tight control of blood glucose during critical illness.

Objectives: This study aimed to determine if controlling blood glucose using insulin in paediatric intensive care units (PICUs) reduces mortality and morbidity and is cost-effective, whether or not admission follows cardiac surgery.

Design: Randomised open two-arm parallel group superiority design with central randomisation with minimisation. Analysis was on an intention-to-treat basis. Following random allocation, care givers and outcome assessors were no longer blind to allocation.

Setting: The setting was 13 English PICUs.

Participants: Patients who met the following criteria were eligible for inclusion: ≥ 36 weeks corrected gestational age; ≤ 16 years; in the PICU following injury, following major surgery or with critical illness; anticipated treatment > 12 hours; arterial line; mechanical ventilation; and vasoactive drugs. Exclusion criteria were as follows: diabetes mellitus; inborn error of metabolism; treatment withdrawal considered; in the PICU > 5 consecutive days; and already in CHiP (Control of Hyperglycaemia in Paediatric intensive care).

Intervention: The intervention was tight glycaemic control (TGC): insulin by intravenous infusion titrated to maintain blood glucose between 4.0 and 7.0 mmol/l.

Conventional management (CM): This consisted of insulin by intravenous infusion only if blood glucose exceeded 12.0 mmol/l on two samples at least 30 minutes apart; insulin was stopped when blood glucose fell below 10.0 mmol/l.

Main outcome measures: The primary outcome was the number of days alive and free from mechanical ventilation within 30 days of trial entry (VFD-30). The secondary outcomes comprised clinical and economic outcomes at 30 days and 12 months and lifetime cost-effectiveness, which included costs per quality-adjusted life-year.

Results: CHiP recruited from May 2008 to September 2011. In total, 19,924 children were screened and 1369 eligible patients were randomised (TGC, 694; CM, 675), 60% of whom were in the cardiac surgery stratum. The randomised groups were comparable at trial entry. More children in the TGC than in the CM arm received insulin (66% vs. 16%). The mean VFD-30 was 23 [mean difference 0.36; 95% confidence interval (CI) -0.42 to 1.14]. The effect did not differ among prespecified subgroups. Hypoglycaemia occurred significantly more often in the TGC than in the CM arm (moderate, 12.5% vs. 3.1%; severe, 7.3% vs. 1.5%). Mean 30-day costs were similar between arms, but mean 12-month costs were lower in the TGC than in CM arm (incremental costs $-\pounds 3620$, 95% CI $-\pounds 7743$ to $\pounds 502$). For the non-cardiac surgery stratum, mean costs were lower in the TGC than in the CM arm (incremental cost $-\pounds 9865$, 95% CI $-\pounds 18,558$ to $-\pounds 11,172$), but, in the cardiac surgery stratum, the costs were similar between the arms (incremental cost $\pounds 133$, 95% CI $-\pounds 3568$ to $\pounds 3833$). Lifetime incremental net benefits were positive overall ($\pounds 3346$, 95% CI $-\pounds 11,203$ to $\pounds 17,894$), but close to zero for the cardiac surgery stratum ($-\pounds 919$, 95% CI $-\pounds 16,661$ to $\pounds 14,823$). For the non-cardiac surgery stratum, the incremental net benefits were high ($\pounds 11,322$, 95% CI $-\pounds 15,791$ to $\pounds 38,615$). The probability that TGC is cost-effective is relatively high for the non-cardiac surgery stratum, but, for the cardiac surgery subgroup, the probability that TGC is cost-effective is around 0.5. Sensitivity analyses showed that the results were robust to a range of alternative assumptions.

Conclusions: CHiP found no differences in the clinical or cost-effectiveness of TGC compared with CM overall, or for prespecified subgroups. A higher proportion of the TGC arm had hypoglycaemia. This study did not provide any evidence to suggest that PICUs should stop providing CM for children admitted to PICUs following cardiac surgery. For the subgroup not admitted for cardiac surgery, TGC reduced average costs at 12 months and is likely to be cost-effective. Further research is required to refine the TGC protocol to minimise the risk of hypoglycaemic episodes and assess the long-term health benefits of TGC.

Trial registration: Current Controlled Trials ISRCTN61735247.

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List of abbreviations

AKI	acute kidney injury	NICU	neonatal intensive care unit
CBCL	Child Behavioural Checklist	OLS	ordinary least squares
CHiP	Control of Hyperglycaemia in Paediatric intensive care	PbR	NHS Payments by Results database
CI	confidence interval	PCCMDS	<i>Paediatric Critical Care Minimum Data Set</i>
CM	conventional management	PI	principal investigator
CRF	case report form	PIC	paediatric intensive care
CRS-R:S	Conners' Rating Scales revised – short version	PICANet	Paediatric Intensive Care Audit Network
DCC	data co-ordinating centre	PICU	paediatric intensive care unit
DMEC	Data Monitoring and Ethics Committee	PIM2	Paediatric Index of Mortality version 2
EDD	expected date of delivery	QALY	quality-adjusted life-year
GCP	good clinical practice	QoL	quality of life
GM	general medical	R&D	research and development
GP	general practitioner	RACHS1	Risk-adjusted Classification for Congenital Heart Surgery 1
HRG	health-care resource group	RCT	randomised controlled trial
HTA	Health Technology Assessment	RR	relative risk
HUI	Health Utilities Index®	RRT	renal replacement therapy
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	SA	sensitivity analysis
ICU	intensive care unit	SAE	serious adverse event
INB	incremental net benefit	SD	standard deviation
LOS	length of stay	SUSAR	suspected, unexpected, serious adverse reaction
LSHTM	London School of Hygiene and Tropical Medicine	TBI	traumatic brain injury
MCRN	Medicines for Children Research Network	TGC	tight glycaemic control
MI	multiple imputation	TMG	Trial Management Group
MREC	Multicentre Research Ethics Committee	TSC	Trial Steering Committee
NEC	necrotising enterocolitis	VFD	ventilator-free day
NICE	National Institute for Health and Care Excellence	VFD-30	ventilator-free days 30 days post randomisation

Scientific summary

Background

Early research in adults admitted to intensive care suggested that tight control of blood glucose during acute illness can be associated with reductions in mortality, length of hospital stay and complications such as infection and renal failure. There was no clear information, however, about whether or not there were different effects for adults in surgical compared with medical intensive care; nor was there clear information concerning the longer-term economic implications of controlling blood glucose. In addition, despite over 10,000 children being admitted to paediatric intensive care units (PICUs) in England and Wales each year, the research did not include children.

Objectives

The objective of the Control of Hyperglycaemia in Paediatric intensive care (CHIP) trial was to determine if a policy of strictly controlling blood glucose [tight glycaemic control (TGC)] using insulin reduces mortality and morbidity and is cost-effective in children admitted to PICUs, whether or not admission follows cardiac surgery.

The primary hypothesis was that:

- TGC will increase the numbers of days alive and free of mechanical ventilation within 30 days of trial entry (VFD-30) for children aged ≤ 16 years on ventilatory support and receiving vasoactive drugs.

The secondary hypotheses were that:

- TGC will lead to improvement in a range of complications associated with intensive care treatment.
- TGC will be cost-effective.
- The clinical effectiveness of TGC will be similar whether children were admitted to a PICU following cardiac surgery or for other reasons.
- The cost-effectiveness of TGC will be similar whether children were admitted to a PICU following cardiac surgery or for other reasons.

Methods

Children were eligible for trial entry if they:

- were ≥ 36 weeks corrected gestational age and ≤ 16 years
- were admitted to the PICU following injury, following major surgery or in association with critical illness, and it was anticipated treatment would be required to continue for at least 12 hours
- had an arterial line in situ and were receiving both mechanical ventilation and vasoactive drugs.

Children were excluded prior to trial entry if they:

- were born preterm (≤ 36 weeks corrected gestational age)
- had diabetes mellitus
- had an established or suspected diagnosis of an inborn error of metabolism

- were children for whom treatment withdrawal or limitation of intensive care treatment was being considered
- had been in a PICU for > 5 consecutive days
- had already participated in the CHiP study during a previous PICU admission.

After consent by parents/guardians, children were randomised to either of the following:

- TGC: insulin by intravenous infusion titrated to maintain a blood glucose between the limits of 4.0 and 7.0 mmol/l.
- Conventional management (CM): insulin by intravenous infusion only if blood glucose levels exceeded 12 mmol/l on two blood samples taken at least 30 minutes apart and discontinued once blood glucose fell to < 10.0 mmol/l.

Patients not entered into the trial received standard care.

Standard insulin solutions were used and changes in insulin infusion rates were guided by the glucose levels from arterial blood sampling using commercially available 'point-of-care' blood gas analysers. Training in the use of the glucose control protocol was provided.

To reduce the risk of selection bias at trial entry, allocation was carried out through a central computerised 24-hour, 7-day-a-week randomisation service. Minimisation with a probabilistic element was used to ensure a balance of key prognostic factors between arms. The minimisation criteria were centre; age ≤ 1 year compared with between 1 year and ≤ 16 years; admission following cardiac surgery or not; for children admitted for cardiac surgery, Risk-adjusted Classification for Congenital Heart Surgery 1 (RACHS1) categories 1–4 compared with 5–6; for children not admitted for cardiac surgery, Paediatric Index of Mortality version 2 (PIM2) score categorised by probabilities of death of < 5%, 5% to < 15% and $\geq 15\%$; and accidental traumatic brain injury (TBI) or not.

Following randomisation, care-givers and outcome assessors were no longer blind to allocation.

The primary outcome measure was VFD-30. A difference of 2 days in VFD-30 was considered clinically important. Taking a type I error of 1% (with a two-sided test), with an overall standard deviation across both cardiac and non-cardiac strata of 7 days, a total sample size of 750 patients would have 90% power to detect this difference. The target size was inflated to 1000 to take account of possible dilution of effect. The trial was powered to be able to detect whether or not any effect of tight glucose control differed between the cardiac surgery and non-cardiac surgery strata. To have 80% power for an interaction test to be able to detect a difference of 2 days in the effect of intervention between the strata at the 5% level of statistical significance, the sample size was increased to 1500.

Secondary outcomes were assessed at PICU discharge or 30 days after randomisation (if on PICU ≥ 30 days) and at 12 months. The short-term outcomes included mortality; duration of ventilation, length of PICU and hospital stay; readmission rates; renal replacement therapy; infection; transfusions; seizures; paediatric organ dysfunction score; and hypoglycaemia. The 12-month outcomes included mortality; attention and behaviour in TBI patients; and total duration of PICU and hospital stay. Additional outcomes for the economic evaluation included hospital costs within 30 days of trial entry; hospital and community health service costs within 12 months of trial entry; and lifetime incremental net benefits calculated by valuing quality-adjusted life-years (QALYs) at the recommended threshold of £20,000 per QALY. All future costs and life-years were discounted at the recommended rate of 3.5%.

Resource-use data were collected on the trial case report forms. Data on the level of care for PICU bed-days were available through the *Paediatric Critical Care Minimum Data Set*, extracted via the Paediatric Intensive Care Audit Network. Other data on hospital and community service use at 12 months were collected from parents by postal questionnaire for patients randomised before 30 October 2010. Unit costs were taken

from the 2011 NHS Payments by Results database. For children who survived to hospital discharge, vital status at 12 months post randomisation was recorded using information from the participating PICUs, the children's general practitioners (GPs) or the NHS Information Centre and the NHS Central Register.

Primary analyses were by intention to treat. For the primary outcome, linear regression models were used to estimate a mean difference in VFD-30 between the two arms of the trial. For the secondary outcomes, appropriate generalised linear models were used to examine the effect of the intervention. Odds ratios and mean differences are reported with 95% confidence intervals (CIs). Non-parametric bootstrapping was used when appropriate. Multiple imputation was used to handle missing data. Sensitivity analyses (SAs) were undertaken to investigate whether or not results were robust to alternative approaches, including the approaches taken to unit costing, handling missing data and extrapolating survival in the lifetime cost-effectiveness analysis.

Prespecified subgroup analyses were planned for cardiac surgical compared with non-cardiac surgical cases, age (< 1 year or between 1 and ≤ 16 years), TBI or not, RACHS1 (cardiac cases) (groups 1–4 vs. 5 and 6), PIM2 risk of mortality (non-cardiac cases) (categorised by probabilities of death of < 5%, between 5% and < 15% and ≥ 15%) and run-in cases (first 100 randomised) compared with non-run-in cases. Likelihood ratio tests for interactions were used to assess whether or not there was any difference in the effect of the intervention in the different subgroups.

An independent Data Monitoring and Ethics Committee (DMEC) was established to review data from the trial in strict confidence, using the Peto–Haybittle stopping rule.

Results

Trial recruitment began on 4 May 2008 and was slower than expected, mainly because of delays in trial initiation at some sites, clinical constraints and a 'research learning curve' in many of the participating units that had no previous experience of recruiting critically ill children to clinical trials. The DMEC confidentially reviewed unblinded interim analyses on two occasions. In addition, they met to discuss serious adverse events and recruitment rates on three further occasions. Recruitment closed on 31 August 2011. A total of 19,924 children were screened from 13 sites. Of these, 1384 were recruited and randomised (701 to TGC and 683 to CM). Of the 1384, 15 were subsequently found to be ineligible, leaving 1369 eligible children (694 to TGC and 675 to CM) randomised into the trial – 91% of the original target of 1500.

The randomised groups were broadly comparable at trial entry. Sixty-two per cent were randomised within 1 day of admission to PICU. In terms of the prespecified stratifying factors, two-thirds were aged under 1 year, and 60% of the children were in the cardiac surgery stratum. In the cardiac surgery stratum, 7% of children were considered to be undergoing surgical procedures associated with a high risk of mortality (RACHS1 score 5 or 6), and 19% of children in the non-cardiac group had a PIM2 score indicative of > 15% risk of PICU mortality.

The management of blood glucose differed between the two arms of the study. In the TGC arm, 461 of the 694 children (66%) received insulin compared with 109 of 675 (16%) in the CM arm. Children in the TGC arm received more insulin, received insulin treatment earlier and continued insulin treatment for longer.

The primary outcome, the mean VFD-30, was 23 in both trial arms (mean difference 0.36; 95% CI –0.42 to 1.14).

The secondary outcomes up to 30 days were similar between the arms, although less renal replacement therapy was carried out in the TGC arm (odds ratio 0.63; 95% CI 0.45 to 0.89). Hypoglycaemia occurred in a greater proportion of patients in the TGC arm than in the CM arm of the study (moderate, 12.5% vs. 3.1%, $p < 0.001$; severe, 7.3% vs. 1.5%, $p < 0.001$).

None of the interaction tests between the intervention and prespecified subgroups for the primary outcome were statistically significant, suggesting that there was no difference in the effect of TGC on VFD-30 in the different strata.

For the index hospital episode, the mean number of PICU bed-days, the length of stay on general medical wards and the total length of stay were similar between arms. The mean total number of hospital days up to day 30, including both the initial episode and readmissions to the initial PICU before day 30, was also similar between arms. For the stratum admitted to PICUs following cardiac surgery, the mean total length of stay was again comparable between arms, but, for the non-cardiac surgery stratum, the mean numbers of PICU days and the length of stay on general medical wards and in total were lower for the TGC than the CM arm.

Overall, the mean total costs at 30 days post randomisation were similar between arms. For the cardiac surgery stratum, the mean total costs per patient were £16,228 (TGC) and £17,005 (CM). For the non-cardiac surgery stratum, the TGC arm had lower mean costs than the CM arm, with an incremental cost of -£2319 (95% CI -£4702 to £124).

Between 30 days and 12 months post randomisation, the mean numbers of days in a PICU, on general medical wards and in total were lower for the TGC than the CM arm. For the cardiac surgery stratum, the mean total length of stay at 12 months was similar between arms. For the non-cardiac surgery stratum, the TGC arm reported fewer days on PICUs, on general medical wards and in total at 12 months post randomisation (mean total hospital days at 12 months, 31.0 for the TGC arm vs. 44.5 for the CM arm).

Mortality at 12 months was similar between the randomised arms, and no differences were found between the two arms of the trial in attention and behaviour measures for the 13 patients with TBI.

The mean total costs at 12 months were lower in the TGC than in the CM arm (incremental costs -£3620, 95% CI -£7743 to £502). For the cardiac surgery stratum, the mean total costs were similar between arms (incremental costs £133, 95% CI -£3568 to £3833), but, for the patients not admitted for cardiac surgery, the mean costs were lower in the TGC than in the CM arm, with an incremental cost of -£9865 (95% CI -£18,558 to -£1172).

Sensitivity analyses showed that the results were robust to alternative approaches for calculating unit costs, or handling missing data.

Overall, the lifetime incremental net benefits were high (£3346, 95% CI -£11,203 to £17,894). For patients admitted for cardiac surgery, the incremental net benefits were close to zero (-£919, 95% CI -£16,661 to £14,823). For patients not admitted for cardiac surgery, the incremental net benefits were positive (£11,322, 95% CI -£15,791 to £38,615). The cost-effectiveness acceptability curves consider alternative thresholds of willingness to pay for a QALY gain, and show that overall, and for the cardiac surgery stratum, it is highly uncertain that TGC is cost-effective. For the non-cardiac stratum, the probability that TGC is cost-effective is relatively high. For example, at ceiling ratios of £10,000 to £30,000 per QALY, the probabilities that TGC is cost-effective range from 90% to 70%.

The SAs suggest that these findings are robust to alternative assumptions about the extrapolation of long-term survival, quality of life for PICU survivors or long-term costs.

Conclusions

Implications for health care

This study found no differences in the effectiveness of TGC compared with CM, according to the primary outcome measure, both overall and for prespecified subgroups. The secondary clinical outcomes were generally similar between the arms, but a lower proportion of the TGC arm had renal replacement therapy, and a higher proportion had hypoglycaemia. For the cardiac surgery subgroup, average costs at 12 months post randomisation were similar between arms, and TGC was unlikely to be cost-effective. For the subgroup not admitted for cardiac surgery, average costs at 12 months post randomisation were lower for the TGC than the CM arm. Therefore, TGC is likely to be cost-effective for patients not admitted for cardiac surgery.

The majority of PICUs in the NHS currently provide CM for patients who meet this study's inclusion criteria. For children following cardiac surgery, our study does not offer any evidence to suggest that PICUs should stop CM for these patients. For children admitted to PICUs for other reasons, TGC can reduce NHS costs. However, before a policy of TGC can be recommended for this subgroup, the potential for cost savings has to be weighed against the small increased risk of hypoglycaemia, and further investigation of the long-term clinical effectiveness and cost-effectiveness of TGC compared with CM is warranted.

Recommendations for research

The findings of the CHiP trial raise the following important questions to be addressed in follow-on studies:

1. Does the excess rate of moderate and severe hypoglycaemia during TGC for children admitted to PICUs for reasons other than cardiac surgery have an impact on long-term neurodevelopmental outcomes?
2. Can we improve the delivery of TGC to minimise the risk of hypoglycaemia?
3. Does TGC in critically ill children protect the kidneys from injury?
4. Do the findings from CHiP apply to routine clinical practice?
5. What can be learnt from triallists, clinicians, parents and older children about their experiences of participating in CHiP to aid the design and conduct of future PICU trials?

Trial registration

This trial is registered as ISRCTN61735247.

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Chapter 1 Introduction

Hyperglycaemia is a common element of the early phase of the neuroendocrine response to stress which is observed following the onset of illness or injury in both adults and children, and is sometimes referred to as the diabetes of critical illness,^{1–4} as a result of accelerated glucose production and acute development of relative insulin resistance.

Stress has long been recognised as a programmed, co-ordinated and adaptive process conferring survival advantage which may, if prolonged, lead to secondary harm.⁵ Stress hyperglycaemia was therefore usually explained as being an adaptive response whose purpose could potentially be beneficial by maintaining intravascular volume or increasing energy substrate delivery to vital organs, and it was not usually treated unless glucose levels were grossly and persistently elevated. These assumptions around the lack of harm from or benefits of stress hyperglycaemia have increasingly been questioned in the light of reports from a wide range of illnesses and populations which have shown hyperglycaemia to be related to worse clinical outcomes.

Myocardial infarction

In a meta-analysis,⁶ patients with acute myocardial infarction, and without diabetes mellitus, who had glucose concentrations in the range 6.1–8.0 mmol/l or higher had a 3.9-fold [95% confidence interval (CI) 2.9- to 5.4-fold] higher risk of death than patients who had lower glucose concentrations. Glucose concentrations higher than values in the range of 8.0–10.0 mmol/l on admission were associated with increased risk of congestive heart failure or cardiogenic shock.

Stroke

Capes *et al.*⁷ conducted a systematic review and meta-analysis of the literature relating glucose levels in the interval immediately post stroke to the subsequent course. A comprehensive literature search was carried out to identify cohort studies reporting mortality and/or functional recovery after stroke in relation to admission glucose level. In total, 32 studies were identified, and predefined outcomes could be analysed for 26 of these. After stroke, the unadjusted relative risk (RR) of in-hospital or 30-day mortality associated with an admission glucose level above the range of 6–8 mmol/l was 3.07 (95% CI 2.50 to 3.79) in non-diabetic patients and 1.30 (95% CI 0.49 to 3.43) in diabetic patients. Non-diabetic stroke survivors whose admission glucose level was above the range of 6.7–8 mmol/l also had a greater risk of poor functional recovery (RR 1.41; 95% CI 1.16 to 1.73).

Head injury and multisystem trauma

Hyperglycaemia has been shown to be an independent predictor of poor outcomes in adults with head injury⁸ and in cases of multiple trauma.⁹

Pulmonary function

Hyperglycaemia has been shown to be associated with diminished pulmonary function in adults, even in the absence of diabetes mellitus,¹⁰ and a range of risk factors for lung injury.¹¹

Gastrointestinal effects

Hyperglycaemia has been shown to be associated with delayed gastric emptying,¹² decreased small bowel motility and increased sensation and cerebral-evoked potentials in response to a range of gastrointestinal stimuli in adult volunteers.^{13–16}

Infections

The in vitro responsiveness of leucocytes stimulated by inflammatory mediators is inversely correlated with glycaemic control.¹⁷ This reduction in polymorphonuclear leucocyte responsiveness may contribute to the compromised host defence associated with sustained hyperglycaemia,¹⁷ and, indeed, hyperglycaemia has been shown to be associated with an increased rate of serious infections after adult cardiac¹⁸ and vascular surgery.¹⁹

These studies, which associate poorer outcomes with patients with the highest levels of stress glycaemia, raise the question of whether high blood glucose levels simply identify the more severely ill patients, in whom worse outcomes are inevitable, or whether specific homeostatic or allostatic glycaemic dysfunction influences outcomes independently. If the latter were true, then perhaps measures to prevent or limit stress-induced hyperglycaemia would improve clinical outcomes.

Does hyperglycaemia matter for adults in the critically ill setting?

Although the importance of good glycaemic control has long been established in minimising complications of chronic hyperglycaemia in patients with diabetes mellitus,^{20,21} and a number of mechanisms for glucotoxicity identified,²² in the era up to the year 2000, a permissive approach was typically adopted when managing non-diabetic patients in intensive care settings. A very reasonable question, however, is *Could shorter-term hyperglycaemia in non-diabetic populations be associated with clinically important adverse outcomes?* Early reports from adult populations started to explore the possible association between acute stress-induced hyperglycaemia and outcome in both diabetic and non-diabetic patients.

Furnary *et al.*¹⁸ noted that hyperglycaemia is associated with higher sternal wound infection rates following adult cardiac surgery and questioned whether more aggressive control of glycaemia might lead to lower infection rates. In a prospective study of 2467 consecutive diabetic patients who underwent open-heart surgical procedures, patients were classified into two sequential groups. The control group included 968 patients treated with sliding-scale-guided intermittent subcutaneous insulin injections. The study group included 1499 patients treated with a continuous intravenous insulin infusion in an attempt to maintain a blood glucose level of < 11.1 mmol/l. Compared with subcutaneous insulin injections, continuous intravenous insulin infusion induced a significant reduction in perioperative blood glucose levels, which was associated with a significant reduction in the incidence of deep-sternal wound infection in the continuous intravenous insulin infusion group [0.8% (12 of 1499) vs. 2.0% (19 of 968) in the intermittent subcutaneous insulin injection group; $p = 0.01$]. The use of perioperative, continuous intravenous insulin infusion in diabetic patients undergoing open-heart surgical procedures appeared to significantly reduce the incidence of major infections.

Malmberg *et al.*²³ randomly allocated patients with diabetes mellitus and acute myocardial infarction to intensive insulin therapy ($n = 306$) or standard treatment (controls, $n = 314$). The mean (range) follow-up was 3.4 (1.6–5.6) years. There were 102 (33%) deaths in the treatment group compared with 138 (44%) deaths in the control group (RR 0.72; 95% CI 0.55 to 0.92; $p = 0.011$). The effect was most pronounced among a predefined group that included 272 patients who had not received insulin treatment previously and who were at a low cardiovascular risk (0.49; 0.30 to 0.80; $p = 0.004$). Intensive insulin therapy

improved survival in diabetic patients with acute myocardial infarction. The effect seen at 1 year continued for at least 3.5 years, with an absolute reduction in mortality of 11%.

In 2001, Van den Berghe and colleagues from Leuven, Belgium,²⁴ extended this approach to non-diabetic hyperglycaemic populations. They performed a single-centre randomised trial in adults undergoing intensive care following surgical procedures which showed that the use of insulin to tightly control blood glucose led to a reduction in mortality from 10.9% to 7.2%, and a significantly lower incidence of a range of important complications of critical illness including renal failure, infection, inflammation, anaemia and polyneuropathy and need for prolonged ventilatory support.

The same group undertook a similar trial in non-surgical, adult, critically ill patients²⁵ and again found benefits from the control of blood glucose with intensive insulin therapy. Patients were randomly assigned to a regimen of strict normalisation of blood glucose (4.4–6.1 mmol/l) with use of insulin or conventional therapy whereby insulin was administered only when blood glucose levels exceeded 12 mmol/l, with the infusion tapered when the level fell below 10 mmol/l. In the intention-to-treat analysis of the 1200 patients, intensive care unit (ICU) and in-hospital mortality were not significantly altered by intensive insulin therapy; however, for those patients who stayed > 3 days in intensive care (an a priori subgroup), mortality was significantly reduced from 52.5% to 43% ($p = 0.009$). Morbidity was significantly reduced by intensive insulin therapy, with a lower incidence of renal injury and shorter length of mechanical ventilation and duration of hospital stay noted. For patients who stayed > 5 days in intensive care after trial entry, all morbidity end points were significantly improved in the intensive insulin therapy group.

Although the precise mechanisms by which different glucose control strategies might influence clinical outcomes had not been fully elucidated, the clinical effects of 'tight glycaemic control' (TGC) for adults in critical care appeared promising. As a result, TGC was widely adopted in adult critical care standards in the years following the publication of Van den Berghe *et al.* 2001 paper.²⁴

Stress hyperglycaemia in the critically ill child

Over 12,000 children are admitted to ICUs in England and Wales each year.²⁶ Hyperglycaemia occurs frequently during critical illness or after major surgery in children, with a reported incidence of up to 86%,³ but children in critical care may not respond to interventions in the same way as adults.

References to hyperglycaemia and its management in critically ill children were identified through searches in MEDLINE²⁷ from 1990 to December 2006. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the genesis of this research proposal. The search terms used were 'glycaemia', 'control', 'insulin', 'critical illness' and 'intensive care'; the limits applied were 'clinical trials', 'meta-analysis', 'randomised controlled trial' and 'humans' and 'age 0–18 years'. No randomised trials or meta-analyses of glycaemic control in childhood critical illness were identified.

The non-randomised studies identified included a number of reports of critically ill children receiving care in general,^{3,28,29} cardiac surgical,^{30,31} trauma^{9,32,33} and burns³⁴ ICUs, all showing that high blood glucose levels occur frequently and that levels are significantly higher in children who die than in children who survive. As in adults, the occurrence of hyperglycaemia was associated with poorer outcomes including death, sepsis and longer length of intensive care stay for critically ill children.

Srinivasan *et al.*³ studied the association of timing, duration and intensity of hyperglycaemia with mortality in critically ill children. The study had a retrospective, cohort design and included 152 critically ill children receiving vasoactive infusions or mechanical ventilation. A peak blood glucose of > 7 mmol/l occurred in 86% of patients. Non-survivors had a higher peak blood glucose [mean \pm standard deviation (SD)] than

survivors (17.3 ± 6.4 mmol/l vs. 11.4 ± 4.4 mmol/l, $p < 0.001$). Non-survivors had more intense hyperglycaemia during the first 48 hours in the paediatric intensive care unit (PICU) (7 ± 2.1 mmol/l) than survivors (6.4 ± 1.9 mmol/l, $p < 0.05$). Median blood glucose levels > 8.3 mmol/l were associated with a threefold increased risk of mortality compared with median levels of < 8.3 mmol/l. Univariate logistic regression analysis showed that peak blood glucose and the duration and intensity of hyperglycaemia were each associated with PICU mortality ($p < 0.05$). Multivariate modelling controlling for age and paediatric risk of mortality scores showed an independent association of peak blood glucose and duration of hyperglycaemia with PICU mortality ($p < 0.05$). This study demonstrated that hyperglycaemia is common among critically ill children. Peak blood glucose and duration of hyperglycaemia appear to be independently associated with mortality. The study was limited by its retrospective design, its single-centre location and the absence of cardiac surgical cases, a group which make up approximately 40% of paediatric intensive care (PIC) admissions in the UK.

Yates *et al.*³⁰ conducted a retrospective review of data from 184 children < 1 year of age who underwent major cardiac surgery over a 22-month period ending in August 2004. Factors analysed included peak glucose levels and duration of hyperglycaemia. The duration of hyperglycaemia was significantly longer in children who developed renal insufficiency, liver insufficiency and infection and those who required mechanical circulatory support or who died, and was associated with longer PICU and hospital lengths of stay (LOS).

Hall *et al.*³⁵ investigated the incidence of hyperglycaemia in infants with necrotising enterocolitis (NEC) and the relationship between glucose levels and outcome in these infants. Glucose measurements ($n = 6508$) in 95 neonates with confirmed NEC admitted to the surgical ICU were reviewed. Glucose levels ranged from 0.5 to 35.0 mmol/l; 69% of infants became hyperglycaemic (> 8 mmol/l) during their admission; and 32 infants died. The mortality rate tended to be higher in infants whose peak glucose concentration exceeded 11.9 mmol/l than in those with peak glucose concentrations of < 11.9 mmol/l, and the late (> 10 days after admission) mortality rate was significantly higher in the former infants (29% vs. 2%; $p = 0.0009$). Linear regression analysis indicated that peak glucose concentration was significantly related to LOS ($p < 0.0001$).

Branco *et al.*²⁹ showed an association between hyperglycaemia and increased mortality in children with septic shock. They prospectively studied children admitted to a regional PICU with septic shock refractory to fluid therapy over a period of 32 months. The peak glucose level in those with septic shock was 11.9 ± 5.4 mmol/l (mean \pm SD), and the mortality rate was 49.1% (28/57). In non-survivors, the peak glucose level was 14.5 ± 6.1 mmol/l, which was higher ($p < 0.01$) than that found in survivors (9.3 ± 3.0 mmol/l). The RR of death in patients with peak glucose levels of ≥ 9.9 mmol/l was 2.59 ($p = 0.012$).

Faustino and Apkon²⁸ demonstrated that hyperglycaemia occurs frequently among critically ill non-diabetic children and is associated with higher mortality and longer LOSs in PICUs. They performed a retrospective cohort study of 942 non-diabetic patients admitted to a PICU over a 3-year period. The prevalence of hyperglycaemia was based on initial PICU glucose measurement, peak value within 24 hours and peak value measured during PICU stay up to 10 days after the first measurement. Using three cut-off values (6.7, 8.3 and 11.1 mmol/l), the prevalence of hyperglycaemia was 16.7–75.0%. The RR for death increased for peak glucose within 24 hours of > 8.3 mmol/l (RR, 2.50; 95% CI 1.26 to 4.93) and peak glucose within 10 days of > 6.7 mmol/l (RR, 5.68; 95% CI 1.38 to 23.47).

Pham *et al.*³⁴ reviewed the records of children with $\geq 30\%$ total body surface area burn injury admitted to a regional paediatric burn centre during two consecutive periods, during the first of which patients received 'conventional insulin therapy' ($n = 31$), and during the second of which they were managed with TGC ($n = 33$). Intensive insulin therapy was positively associated with survival and a reduced incidence of infections. The authors concluded that intensive insulin therapy to maintain normoglycaemia in severely

burned children could be safely and effectively implemented in a paediatric burns unit and that this therapy seemed to lower infection rates and improve survival.

There was, therefore, mounting evidence to suggest that stress hyperglycaemia occurred in both neonates and children (as in adults). From adult studies, TGC appeared to offer the possibility of clinical benefits, particularly following surgery, but there was no convincing randomised controlled trial (RCT) evidence for children, whether or not admitted to PICUs following surgery. This was of particular importance as approximately one-third of admissions of children to UK PICUs are associated with surgery, in particular cardiac surgery.

Evidence on the cost-effectiveness of tight glycaemic control

The existing evidence on the clinical effectiveness of TGC is derived from studies in both critically ill adults and critically ill children. However, to inform whether or not the NHS should provide TGC rather than conventional management (CM) for critically ill children, it is important to consider whether or not the additional costs associated with implementing a TGC protocol are offset by subsequent reductions in resource use and improved health outcomes. Limited evidence suggests that any additional costs associated with implementing a TGC protocol may be relatively small.³⁶ A post-hoc analysis of the Van den Berge 2001 RCT^{24,37} for critically ill adults admitted for surgery reported that TGC can reduce ICU LOS, and hence hospital costs.³⁷ However, this study had several limitations. The study was not designed to measure costs; resource use after the initial hospital episode was not recorded; the study was undertaken in a single centre and lacked generalisability; and it is unclear whether the results apply to other patient groups (e.g. critically ill children, patients not admitted for surgery).

For critically ill children, any assessment of the effect of a TGC protocol compared with CM on resource use and costs is hindered by the lack of evidence from RCTs. The costs of each PICU bed-day are substantial (ranging from £1000 to £5000 per bed-day),³⁸ so if TGC reduces PICU LOS then it would be anticipated to also reduce short-term costs (i.e. those incurred within 30 days of admission to the PICU). It is also plausible that TGC may have an effect on longer-term costs. A previous study reported that around 10% of PICU survivors had residual long-term disability (median follow-up of 3.5 years from initial admission).³⁹ Therefore, the long-term costs following PICU survival may be substantial, and may be increased if TGC increases PICU survival, or reduced if improved blood glucose control reduces morbidity. There is little available evidence on the net effect of TGC compared with CM on longer-term morbidity and hence costs, either in general or specifically for critically ill children.

The previous evidence, therefore, raises the hypotheses that TGC may have an impact on costs, both in the short term (e.g. 30 days post PICU admission) and in the longer term (e.g. 12 months post PICU admission). It would, therefore, seem important to consider the net effect of TGC on costs alongside any change in clinical outcomes. No previous study has considered the effect of TGC on health service costs for paediatric patients.

The Control of Hyperglycaemia in Paediatric intensive care (CHiP) trial, therefore, sought to address the question of whether or not a policy of strictly controlling blood glucose using insulin in children admitted to PICU reduces mortality and morbidity and is cost-effective.

Chapter 2 Methods

Study design

The study was an individually randomised controlled open trial with two parallel arms. The allocation ratio was 1 : 1.

The planned flow of patients through the trial is summarised in *Figure 1*.

Primary hypothesis

The primary hypothesis was that TGC will increase the numbers of days alive and free of mechanical ventilation at 30 days post randomisation (VFD-30) for children aged ≤ 16 years on ventilatory support and receiving vasoactive drugs.

Secondary hypotheses

The secondary hypotheses were as follows:

- TGC will lead to improvement in a range of complications associated with intensive care treatment.
- TGC will be cost-effective.
- The clinical effectiveness of TGC will be similar whether children were admitted to PICU following cardiac surgery or for other reasons.
- The cost-effectiveness of TGC will be similar whether children were admitted to PICU following cardiac surgery or for other reasons.

Participants

Inclusion criteria

Included were children ≥ 36 weeks corrected gestational age and ≤ 16 years admitted to PICU who had an arterial line in situ and who were also receiving both mechanical ventilation and vasoactive drugs [catecholamines or similar (dopamine, dobutamine, adrenaline, noradrenaline), phosphodiesterase type III inhibitors (milrinone, enoximone), other vasopressors (vasopressin, phenylephrine or similar)] following injury, following major surgery or in association with critical illness, and in whom it was anticipated such treatment would be required to continue for at least 12 hours.

Exclusion criteria prior to trial entry

- Children born preterm (< 36 weeks corrected gestational age).
- Children with diabetes mellitus.
- Children with an established or suspected diagnosis of an inborn error of metabolism.
- Children for whom treatment withdrawal or limitation of intensive care treatment was being considered.
- Children who had been in a PICU for > 5 consecutive days.
- Children admitted to PICU who had already participated in the CHIP study during a previous PICU admission.

Consent

All parents/guardians of children in PICUs who wished to enter their child into the trial were asked by the principal investigator (PI) or delegated investigator to give consent. The trial team recognised that parents were likely to be stressed and anxious, and often had limited time to consider trial entry, but it was considered medically inappropriate to delay the start of treatment. Parents of children listed for cardiac

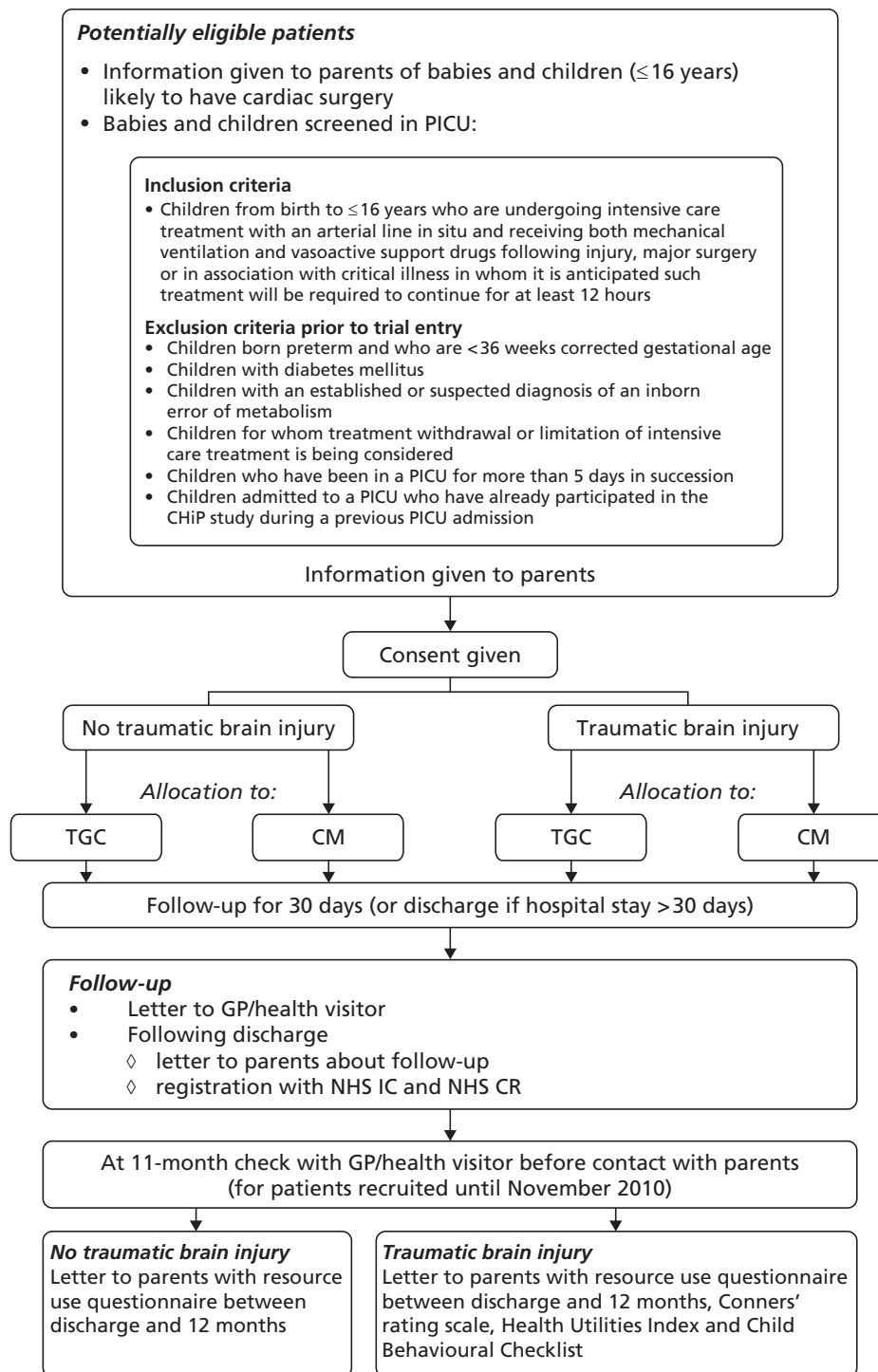


FIGURE 1 Flow chart summarising the planned flow of patients through the trial. CR, Central Register; GP, general practitioner; IC, Information Centre.

surgery were given information about the trial preoperatively by the PI or delegated investigator, and this afforded families some additional time to think about participation. Provisional consent was sought at this time, and confirmed later if the child was admitted to the PICU. In addition, when possible, older children were given information by the PI or delegated investigator and, if they wished to enter the trial, were asked to assent to their participation in the study. Information sheets and consent forms are shown in *Appendix 1*.

Patients not entered into the trial received standard care.

Ethical approval

The trial (protocol version 1) was approved by the Brighton East Research Ethics Committee (07/Q1907/24) in 2007. Subsequent amendments are detailed in *Appendix 2*. The final substantive version (protocol version 6, 23 August 2010) is shown in *Appendix 3*, and the published version is in *Appendix 4*.

Allocation of patients

After inclusion in the study, children were randomised to one of two arms:

- group 1 – CM
- group 2 – TGC.

To reduce the risk of selection bias at trial entry, allocation was administered through a central computerised 24-hour, 7-day-a-week randomisation service established at the London School of Hygiene and Tropical Medicine (LSHTM), with telephone backup if required. Minimisation was used, with the first child randomly allocated to a trial arm, and each subsequent child allocated randomly to a trial arm with a weighting in favour of the trial arm that minimises the imbalance on selected key prognostic factors.

The following factors were used:

- centre
- age ≤ 1 year compared with between 1 year and ≤ 16 years
- admitted following cardiac surgery or not
- for children who were admitted for cardiac surgery, risk-adjusted classification for congenital heart surgery (RACHS1)⁴⁰ categories 1–4 compared with 5 or 6
- for children who were not admitted for cardiac surgery, Paediatric Index of Mortality version 2 (PIM2) score at randomisation categorised by probabilities of death of $< 5\%$, 5% to $< 15\%$ and $\geq 15\%$
- accidental traumatic brain injury (TBI) or not.

Interventions

After inclusion in the study, children were randomised to one of two arms: arm 1 (CM) or arm 2 (TGC).

Arm 1: conventional management

Children in this arm were treated according to a standard approach to blood glucose management. Insulin was given by intravenous infusion in this group only if blood glucose levels exceeded 12 mmol/l on two blood samples taken at least 30 minutes apart and was discontinued once blood glucose fell to < 10 mmol/l.

The protocol for glucose control in this arm is shown in *Appendix 3A*.

Arm 2: tight glycaemic control

Children in this arm received insulin by intravenous infusion titrated to maintain a blood glucose level between the limits of 4 and 7.0 mmol/l.

The protocol for glucose control in this arm is shown in *Appendix 3B*.

The protocol for glucose control in arm 2 was carefully designed to achieve tight glucose control while minimising the risk of hypoglycaemia, the principal side effect of insulin therapy. Standard insulin solutions were used and changes in insulin infusion rates were guided by both the current glucose level and its rate of change from previous measurements. Blood glucose levels were routinely measured as in all ICUs using commercially available 'point-of-care' blood gas analysers, usually with extended biochemical panels, which utilise very small blood samples, producing results in approximately 1 minute. All of the hospitals in this study have laboratories registered with Clinical Pathology Accreditation (UK) Ltd. The NHS executive accreditation standards specify the requirement for the operation and management of chemical pathology,

including the operation of a quality management system for all testing (see <http://www.cpa-uk.co.uk>). The CHiP protocol advised blood glucose testing using arterial rather than venous blood sampling.

Training in the use of the glucose control protocol was provided before the first patient was enrolled in each collaborating centre and for new staff throughout the trial. The clinical co-ordinating centre team liaised closely with local clinicians to ensure that glucose control algorithms were followed closely and safely.

Blinding

Following random allocation, care-givers and outcome assessors were no longer blind to allocation.

Outcome measures

Primary

Following the influential Acute Respiratory Distress Syndrome NETWORK (ARDSNET) study,⁴¹ VFD-30 was chosen as the primary outcome measure. Death is obviously an important outcome. Mechanical ventilation can be seen as a measure of disease severity, defining the need for complex intensive care. The concept of ventilator-free days (VFDs) brings together these two outcomes. Schoenfeld *et al.*⁴² define VFDs as follows: VFD = 0 if the child dies before 30 days; VFD = 30 – x if the child is successfully weaned from ventilator within 30 days (where x is the number of days on ventilator); or VFD = 0 if the child is ventilated for ≥ 30 days. This use of organ-failure-free days to determine patient-related morbidity surrogate end points in paediatric trials has been supported by influential paediatric triallists in the current low-mortality paediatric critical care environment.⁴³

Secondary

Clinical outcomes at discharge from paediatric intensive care unit or 30 days (if at paediatric intensive care unit ≥ 30 days)

- Death within 30 days of trial entry (or before discharge from hospital if duration of hospital stay was ≥ 30 days).
- Number of days in PICU.
- Duration of mechanical ventilation.
- Duration of vasoactive drug usage.
- Need for renal replacement therapy (RRT).
- Bloodstream infection (positive cultures associated with two or more features of systemic inflammation or any positive blood culture for fungi).
- Use of antibiotics for > 10 days.
- Number of red cell transfusions.
- Number of hypoglycaemic episodes either moderate (blood glucose < 2.5 mmol/l) or severe (blood glucose < 2.0 mmol/l).
- Occurrence of seizures (clinical seizures requiring anticonvulsant therapy).
- Paediatric organ dysfunction score.^{43–45}
- Number of children readmitted within 30 days of trial entry.

Thirty-day economic outcomes

- Hospital LOS within 30 days of trial entry.
- Hospital costs within 30 days of trial entry.

Twelve-month end points (resource use; survival; attention and behaviour in traumatic brain injury patients; costs)

- Number of days in PICU, and hospital LOS.
- Death within 12 months of trial entry.
- Assessment of attention and behaviour in patients with TBI as measured by the Health Utilities Index [HUI®, Health Utilities Inc. (HUInc), Dundas, ON, Canada; www.healthutilities.com], the King's outcome scale for childhood head injury (KOSCHI),⁴⁶ the Child Behavioural Checklist (CBCL) (ASEBA, University of Vermont, Burlington, VT, USA; www.ASEBA.org) and the Conners' rating scales revised – short version (CRS-R:S).⁴⁷
- Hospital and community health service costs within 12 months of trial.

Lifetime cost-effectiveness

- Cost per life-year (based on 12-month costs and survival for all cases).
- Cost per quality-adjusted life-year (QALY).
- Incremental net benefits (INB).
- Cost per disability-free survivor (based on 12-month cost and outcomes data for subgroup with TBI).

Follow-up at 12 months

Parents were informed about the follow-up study at trial entry and asked to give consent for their children to be included. The trial manager at the data co-ordinating centre (DCC) wrote to parents following discharge from hospital to remind them about the follow-up, ask them whether or not they wished to receive the trial results and ask them to keep the DCC informed about any change of address. A separate letter was sent to bereaved parents.

At hospital discharge, parents were given a sample copy of a questionnaire (see *Appendix 8*) about service use post discharge, and a letter explaining that they would be sent and asked to complete the same questionnaire at the 12-month follow-up. To help the parents record and later recall use of any NHS services, at hospital discharge parents were also given a diary (see *Appendix 5*). The purpose of this diary was to allow parents to prospectively note resource use and to help them to remember it when the time came to complete the questionnaire. They were not asked to return the diary. After 11 months, following checks with the patient's general practitioner (GP) to find out whether or not the patient was still alive, and whether or not the GP judged it was appropriate for the parents to receive the service-use questionnaire, the trial manager sent the questionnaire to the parents of those patients who met the eligibility criteria. For those parents who did not respond within 4 weeks, a first reminder was issued by post, and, if there was still no response after a further 4 weeks, the parent was contacted by telephone. Follow-up ended when a postal questionnaire was returned either complete or blank, when a refusal was obtained or after both reminders had been issued.

Because of the slower than expected recruitment rates, the funder, the National Institute for Health Research's Health Technology Assessment (HTA) programme, agreed a funding extension, but reduced the time period for which patients could be followed up, that is patients randomised after 30 October 2010 were ineligible for this 1-year follow-up. This also had implications for the analysis of total LOS and costs up to 12 months (see below).

Follow-up of traumatic brain injury subgroup

This subgroup is more likely to have longer-term morbidity. Although there were unlikely to be large numbers of such children in the trial, parents of children (aged ≥ 4 years) in this subgroup were asked to provide additional information at 12 months (for patients recruited until 2010), regarding overall health status, global neurological outcome, and attention and behavioural status. Further details are given in *Appendix 6*.

Survival up to 12 months

If parents gave their consent, all children who survived to hospital discharge were followed up for up to 12 months post randomisation to determine mortality using information from the participating PICUs, the children's GPs or the NHS Information Centre and the NHS Central Register. The NHS number was used to ensure accurate linkage to national death registration using the 'list cleaning' service of the Medical Research Information Service at the NHS Information Centre for Health and Social Care.

Adverse events and safety reporting

The Royal Brompton and Harefield NHS Trust, as sponsor of this study, had the responsibility of ensuring arrangements were in place to record, notify, assess, report, analyse and manage adverse events in order to comply with Medicines for Human Use (Clinical Trials) Regulations 2004.

All sites involved in the study were expected to inform the chief investigator and lead research nurse of any serious adverse events (SAEs)/reactions within 24 hours so that appropriate safety reporting procedures could be followed by the sponsor.

It was therefore important that all site investigators involved in the study were aware of the reporting process and timelines. Details of the mandatory adverse event and safety reporting requirements are detailed in *Appendix 3C*.

Expected side effects

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to insulin therapy qualified as adverse reactions. Whereas any suspected, unexpected, serious adverse reactions (SUSARs) involving insulin therapy were reported according to the timelines for SUSARs, expected side effects of insulin were reported in the annual safety report unless serious enough to warrant expedited reporting.

Hypoglycaemia is the principal side effect of insulin therapy. Moderate and severe hypoglycaemia were defined as a blood glucose < 2.5 mmol/l and < 2 mmol/l⁴⁸ respectively. The insulin administration protocols aimed to achieve blood glucose control with the lowest possible incidence of hypoglycaemia and the avoidance of neuroglycopenia (hypoglycaemia associated with neurological symptoms and signs such as seizures and cerebral oedema). By definition, children in the TGC arm were at increased risk of hypoglycaemia because the target range in this arm of the study (i.e. blood glucose 4–7 mmol/l) was much closer to the trial's predefined hypoglycaemic thresholds than the 10–12 mmol/l therapeutic window used as a target for the control of blood glucose in the CM arm of the study. The principal operating procedure used to avoid hypoglycaemia was blood glucose measurement every 30 minutes when insulin was first administered, and then every 45 minutes until blood glucose was controlled within the required range and stable glucose and insulin infusion rates were achieved, and then hourly once stabilised.

Insulin is reported to occasionally cause a rash which may be associated with itching.

Data collection

To minimise the data collection load for busy units, the trial collaborated with the Paediatric Intensive Care Audit Network (PICANet)⁴⁹ to make best use of the established data collection infrastructure which exists in all PICUs in the UK. The PICANet data set included many of the items being used in the trial and these data were transmitted from the participating centres to the DCC electronically using strong encryption. The remaining short-term data items were collected locally by the research nurses, and those for the longer-term follow-up were collected separately by telephone and postal questionnaires. These data were used to report the mean number of inpatient days following readmissions after 30 days, and the mean outpatient and community service use at 12 months for all patients randomised. The main data collection forms, questionnaires and covering letters are shown in *Appendix 7*.

All case report form (CRF) data were double entered onto electronic database storage systems at the DCC.

Sample size

The primary outcome was VFD-30. A difference of 2 days in VFD-30 was considered clinically important. Information from PICANet from a sample of PICUs for 2003–4 provided estimates that the mean VFD-30 in cardiac patients is 26.7 days, with a SD of 4.2 days. The corresponding figures for non-cardiac patients were a mean of 22.7 days and a SD of 6.8 days. As the SD is estimated with error, to be conservative a SD nearer 5.5 days for the cardiac and 8 days for the non-cardiac patients was assumed. There were likely to be more non-cardiac than cardiac patients eligible for the trial. An overall SD across both cardiac and non-cardiac strata of 7 days was therefore assumed. Assuming this was the same in both trial arms, and taking a type I error of 1% (with a two-sided test), a total sample size of 750 patients would have 90% power to detect this difference. Although minimal loss to follow-up at 30 days could be assumed, there was the possibility of some non-compliance (some patients allocated to TGC not receiving this, and some allocated to CM being managed with TGC). The target size was therefore inflated to 1000 to take account of possible dilution of effect.

As information from PICANet indicated that there were differences in outcome between cardiac and non-cardiac patients, not merely in VFD-30 but also in 30-day mortality (3.4% vs. 20%) and mean duration of ventilation (3.7 vs. 8.0 days, survivors and non-survivors combined), the trial was powered to be able to detect whether or not any effect of tight glucose control differed between the cardiac and non-cardiac strata. To have 80% power for an interaction test to be able to detect a difference of 2 days in the effect of intervention between the strata at the 5% level of statistical significance, the sample size was increased to 1500. If the interaction test was positive, this size would allow assessment of the effect of TGC separately in the two strata.

Centres

The following PICUs in the UK planned to recruit patients into the CHiP trial: Birmingham Children's Hospital; Bristol Royal Hospital for Children; Great Ormond Street Hospital; Leeds General Infirmary; University Hospitals of Leicester – Glenfield Hospital and Leicester Royal Infirmary; Royal Brompton and Harefield NHS Trust (Royal Brompton Hospital); Royal Liverpool Children's NHS Trust; Royal Manchester Children's Hospital; St George's Hospital; St Mary's Hospital; Sheffield Children's NHS Foundation Trust; Southampton General Hospital; and University Hospital of North Staffordshire.

Recruitment rate

There were estimated to be approximately 1300 eligible cardiac and 1550 eligible non-cardiac patients per year in collaborating PICUs at the start of the trial. About half of those eligible were anticipated to be recruited into the trial, predicting that the overall total sample size of 1500 would be accrued by September 2011.

Type of analysis for clinical outcomes at discharge from paediatric intensive care unit or at 30 days

Primary analyses were by intention to treat. For the primary outcome, linear regression models were used to estimate a mean difference in VFD-30 between the two arms of the trial. For the secondary outcomes, appropriate generalised linear models were used to examine the effect of the intervention. Odds ratios and mean differences are reported with 95% CIs. Where there was evidence of non-normality in the continuous outcome measures, non-parametric bootstrapping, with 1000 samples, was used to estimate the effect of the intervention⁵⁰ and bias-corrected CIs are reported.

Secondary analyses included the following prespecified subgroup analyses: cardiac surgical compared with non-cardiac cases, age (< 1 year or between 1 and ≤ 16 years), TBI or not, RACHS1 (cardiac cases) (groups 1–4 vs. 5 and 6), PIM2 risk of mortality (non-cardiac cases) (categorised by probabilities of death of < 5%, between 5% and < 15% and ≥ 15%), run-in cases (first 100 randomised) compared with non-run-in cases. Likelihood ratio tests for interactions were used to assess whether or not there was any difference in the effect of the intervention in the different subgroups. Where stratified results are presented, the effects in the different strata are estimated directly from the regression model with the interaction term included.

Frequency of analysis

An independent Data Monitoring and Ethics Committee (DMEC) planned to review, in strict confidence, data from the trial approximately half-way through the recruitment period. The chair of the DMEC could also request additional meetings/analyses. In the light of these data, and other evidence from relevant studies, the DMEC would inform the Trial Steering Committee (TSC) if in their view:

- i. There was proof that the data indicated that any part of the protocol under investigation was either clearly indicated or clearly contraindicated for either all patients or a particular subgroup of patients, using the Peto and Haybittle rule.^{51,52}
- ii. It was evident that no clear outcome would be obtained with the current trial design.
- iii. They had a major ethical or safety concern.

Except for those who supplied the confidential information, everyone (including the TSC, funders, collaborators and administrative staff) remained ignorant of the results of the interim analysis

Economic evaluation

Overview

Cost–consequence analyses were undertaken to assess whether or not any additional costs of achieving TGC were justified by subsequent reductions in hospitalisation costs and/or by improvements in patient outcomes. The evaluations were conducted in two phases: in the first phase, all hospital costs at 30 days post randomisation were compared across randomised arms alongside 30-day clinical outcomes; and, in the second phase, cost and outcomes at 12 months post randomisation were compared between arms, and used to project relative cost-effectiveness over the lifetime. This aspect of the costing study took the health and personal services perspective recommended by the National Institute for Health and Care Excellence (NICE).⁵³

Measurement of resource use up to 30 days post randomisation

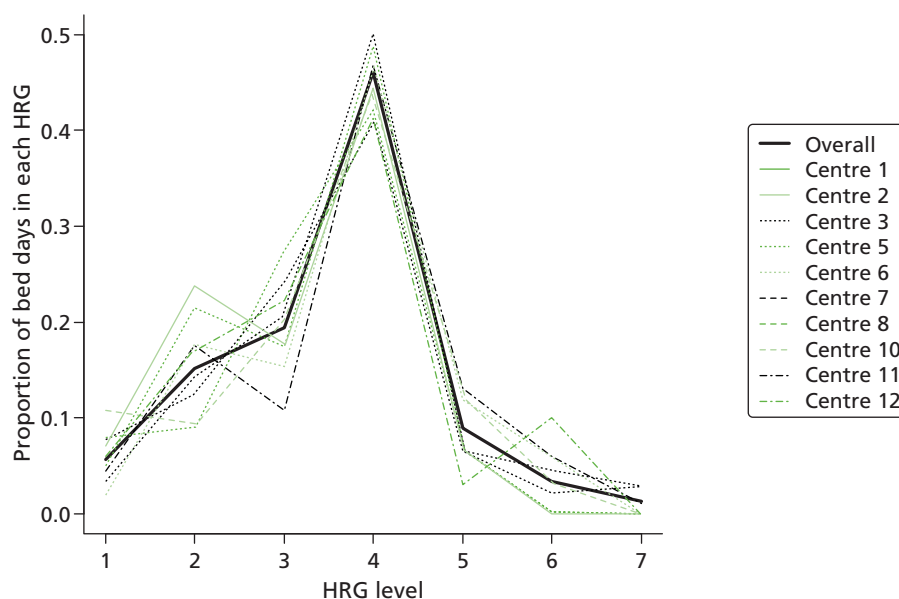
The trial CRFs recorded the number of inpatient days for the index hospital episode following randomisation, up to day 30. Within this index hospital episode, the CRFs recorded the number of PICU days spent on the unit where the patient was randomised, and any subsequent PICU bed-days following transfers to other hospitals. The CRFs also recorded the LOS on general medical (GM) wards, both within the acute hospital where the patient was randomised and following transfer to other hospitals. The number of day-case admissions was also noted. The total LOS for the initial hospital episode was calculated as the sum of the LOS at PICUs and GM wards up to a maximum of 30 days following randomisation. Any readmissions within 30 days to the PICU where the child was randomised were also recorded. The LOS following these readmissions was added to the total number of days for the initial episode, to give the total hospital LOS up to 30 days post randomisation.

Data on the level of care for PICU bed-days were available through routine collection of the *Paediatric Critical Care Minimum Data Set* (PCCMDS)⁵⁴ in 11 of the participating centres via the PICANet database. The PCCMDS consists of 32 items recorded for each PICU bed-day that can be used to define the level of care, that is the paediatric critical care health-care resource group (HRG).⁵⁵ The PCCMDS data items were extracted for each PICU bed-day after randomisation. Each PICU bed-day was then assigned to the appropriate HRG (HRG, version 4), using the HRG grouper.⁵⁵ [The HRG classification includes items for primary and secondary diagnosis, OPCS (Office of Population, Censuses and Surveys' *Classification of Surgical Operations and Procedures*) codes for high-cost drugs, and fields for critical care activity.] *Table 1* lists the HRG classifications for PICU with examples of procedures for each category. *Figure 2* reports the distribution of PICU bed-days across HRG categories for the 8954 PICU bed-days that were grouped during the first 30 days, both overall and for each site. The most common HRG category was 'intensive care basic enhanced' [HRG level 4 (HRG4)]. For 1862 bed-days in the 11 sites that provided information, PCCMDS data were missing or incomplete, and, for three centres (254 bed-days), no PCCMDS information

TABLE 1 Health-care resource groups for paediatric critical care: definitions and examples

HRG Level	Critical care unit	Examples of procedures
HRG1	HDU basic	ECG or CVP monitoring, oxygen therapy plus pulse oximetry
HRG2	HDU advanced	Non-invasive ventilation, acute haemodialysis, vasoactive infusion (inotrope, vasodilator)
HRG3	ICU basic	Invasive mechanical ventilation, or non-invasive ventilation + vasoactive infusion + haemofiltration
HRG4	ICU basic enhanced	Invasive mechanical ventilation + vasoactive infusion, or advanced respiratory support
HRG5	ICU advanced	Invasive mechanical ventilation or advanced respiratory support + haemofiltration
HRG6	ICU advanced enhanced	Invasive mechanical ventilation or advanced respiratory support + burns > 79% BSA
HRG7	ICU ECMO/ECLS	ECMO or ECLS, including VAD or aortic balloon pump

BSA, burns surface area; CVP, central venous pressure; ECG, electrocardiogram; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; HDU, high-dependency unit; VAD, ventricular assist device.

**FIGURE 2** Distribution of paediatric critical care bed-days within 30 days post randomisation across HRG categorises for CHIIP patients. Proportion of paediatric critical care bed-days within each HRG category, overall and by centre.

was available. All these bed-days were assigned to the modal HRG category (HRG4) (see *Sensitivity analysis*). For a total of 326 bed-days, the activity reported was categorised by the HRG grouper as 'not critical care activity', and designated as bed-days on GM wards.

Unit costs

Unit costs were taken from the 2011 NHS Payments by Results (PbR) database, which includes reference costs returns from each NHS trust.³⁸ For all critical care admissions, each bed-day was costed with the corresponding unit cost per bed-day from the PbR database.³⁸ The unit cost of bed-days classified as 'intensive care basic' was taken as the average across all CHIIP centres that returned reference costs for that HRG category (HRG3, *Table 2*) (see *Sensitivity analysis*). Few NHS trusts returned reference cost information for all seven paediatric critical care HRGs, so the relative unit costs for all HRGs apart from

'intensive care basic' (HRG3) were calculated by multiplying the unit costs for HRG 3 by the relative cost ratio from a previous detailed multicentre PICU costing study (see *Sensitivity analysis*).⁵⁶ This previous study assessed the relative staff input according to HRG category and reported the cost ratios listed (see *Table 2*). *Table 2* reports the PICU costs taken for the base case and subsequent sensitivity analyses (SAs). The unit costs for GM bed-days and day-case admissions were taken from previous studies (*Table 3*).^{58,59}

TABLE 2 Unit costs (£) of paediatric critical care for each HRG

HRG	Cost ratios (NHS information centre)	PCC reference costs (n = 11 CHIP centres)	PCC reference cost for ICU basic weighted by cost ratios
HDU basic	0.75	1112	1324
HDU advanced	0.91	1315	1607
ICU basic	1	1765	1765
ICU basic enhanced	1.22	2065	2154
ICU advanced	1.4	1998	2472
ICU advanced enhanced	2.12	3061	3743
ICU ECMO/ECLS	3.06	4026	5402

ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; HDU, high-dependency unit; PCC, paediatric critical care.

TABLE 3 Unit costs (£) of hospital and personal social services

Personal or social service	Unit cost ^a
Hospital inpatient bed-day	252
Hospital outpatient visit	147
Day cases	202
GP contact	47
GP practice nurse contact	11
Health visitor contact	11
District nurse contact	11
Social worker contact	9
Speech and language therapist contact	8
Occupational therapist contact	10
Physiotherapist contact	8
Children's disability team contact	7
Hospital discharge co-ordinator contact	6
Child psychologist contact	15
Dietitian contact	8
Mental health service contact	27
Specialist paediatric nurse contact	14
School nurse contact	3

a Source of unit costs and assumed duration of contacts was taken from Curtis 2011.⁵⁷

The base-case analysis assumed that all resource use required implementation of the TGC protocol or management of side effects and was recognised by the HRG categorisation, as including any additional resources could represent double-counting. A SA was also undertaken to investigate whether or not the results were robust to an alternative approach whereby the resources and unit costs of implementing the TGC protocol and managing hypoglycaemic events were considered as additional unit costs (see *Sensitivity analysis*). To inform these SAs, information was collected on the nurse time, clinical time, number of blood gas analyses and insulin required in managing a subsample of patients in either group during the first 48 hours in critical care after randomisation. Soluble insulin (Actrapid®, Novo Nordisk Limited) was assumed to be used over a 24-hour period, the unit costs of which were taken from the *British National Formulary*.⁶⁰ The additional resources required in managing patients who in the CRFs were recorded as having moderate or severe hypoglycaemic episodes were also considered. All unit costs were reported in 2010–11 prices.

Statistical analysis for the 30-day economic end points

All the economic analyses were based on the treatment arms as randomly allocated ('intention to treat'). Mean differences between treatment arms in resource use (e.g. total LOS summed across the index hospital episode and readmissions to PICU within 30 days) were reported for the overall cohort, and separately for subgroups admitted following either cardiac surgery (cardiac surgery) or no cardiac surgery (non-cardiac). Incremental costs were estimated as the mean difference (95% CI) in total costs at 30 days using ordinary least squares (OLS) regression analysis, with randomised arm as the only independent variable. To test the hypothesis that incremental costs differed according to cardiac surgery status, the OLS regression was repeated, including independent effects for randomised arm, cardiac surgery status and an interaction term for randomised arm by cardiac status. A likelihood ratio test was then employed to compare the model fit to that from an OLS model that included randomised arm and cardiac surgery status as independent effects. Finally, the above OLS regression models that included the interaction terms for randomised arm by cardiac status were used to report the incremental costs for each subgroup (cardiac surgery, non-cardiac).

Resource-use measurement between 30 days and 12 months post randomisation

Index hospital episode and readmissions to the paediatric intensive care unit within 30 days post randomisation

Information on PICU days and hospital LOS for up to 12 months was collected from the CHiP trial CRFs. For CHiP patients whose index hospital episode exceeded 30 days, the CRFs collected information on their continuing hospital stay up to a maximum of 12 months. The CRFs also noted any readmissions that were within 30 days to the PICU where the patient was randomised. For both initial hospital episodes and readmissions, the CRFs recorded subsequent transfers to other hospitals. For initial hospital admissions and readmissions, the CRFs distinguished between the total LOS in PIC and those on GM wards, and day cases. These data were used to report the total days in PIC and on GM wards up to 12 months. The last time point at which 12-month follow-up data were available from the CRFs was 31 March 2012, so, for patients randomised after 1 April 2011, it was possible that an index admission or a readmission was censored before 12 months post randomisation.

Other hospital and community service use

The postal questionnaires were used to collect information on hospital and community service use, from discharge from the index hospital episode up to 12 months post randomisation. This questionnaire was based on one previously developed for neonatal intensive care,⁶¹ and modified to include those items of service use most relevant to patients discharged from PIC. The items for the questionnaires were further amended following comments from a panel of parents from the Medicines for Children Research Network (MCRN). The final questionnaire is appended⁶¹ (see *Appendix 8*). The items considered covered readmissions to PIC other than those collected on the CRFs, readmissions to GM wards, outpatient visits, and contacts with the GP, practice nurse, health visitor, social worker, speech and language therapist and child psychologist.

Unit costs and calculation of total 12-month costs per patient

For PICU bed-days from 30 days to 12 months post randomisation, PCCMDS information was not available for categorising each bed-day into the appropriate HRG4 category. Each PICU bed-day was, therefore, assumed to be in the modal HRG4 category (intensive care basic enhanced) and assigned the corresponding unit cost. GM bed-days and outpatient and community service use were valued with national unit costs (see *Table 3*). Total costs for each patient were then calculated by summing the costs of all hospital and community health services used.

Statistical analysis for the 12-month end points (resource use, survival, costs)

Mean differences in resource use (e.g. days in PICU, on GM wards and combined) between the randomised arms were reported. The proportion of patients still in hospital (index admission) was plotted for up to 12 months post randomisation. Each of these items was reported for the overall cohort and separately for those admitted for cardiac surgery or not.

The effect of TGC compared with CM on 12-month mortality and cost was then reported, overall and for the cardiac and non-cardiac stratum. For a subsample of patients, 12-month health and community cost data were censored. Other patients were judged ineligible or did not respond to the 12-month service-use questionnaire. The cost data that were either censored or missing at 12 months were addressed with multiple imputation (MI).⁶²⁻⁶⁴ The imputation models included baseline covariates, the number of ventilated days, total LOS and costs at 30 days, and information on 12-month costs for those individuals for whom this end point was observed. Each imputation model assumed that the data were 'missing at random', that is conditional on the variables included in each imputation model.⁶² MI was employed based on predictive mean matching,⁶⁵ which offers relative advantages when dealing with data, such as costs that have irregular distributions.⁶⁶

Incremental costs were estimated as the mean difference (95% CI) in total costs at 12 months post randomisation with OLS regression analysis. Incremental costs were reported both overall and for the cardiac and non-cardiac strata.

As the missingness pattern may differ across treatment groups, separate imputation models were specified for each comparator. Five imputed data sets were generated for the imputation models (see *Sensitivity analysis*). After imputation, the analytical models were applied to estimate incremental costs overall, and by subgroup to each imputed data set. Each of the resultant estimates was combined with Rubin's formulae,⁶² which recognise uncertainty both within and between imputations. All MI models were implemented in R with multivariate imputation by chained equations.⁶⁷

Sensitivity analysis

The base-case cost analysis made the following assumptions that a priori were judged potentially important: (1) all relevant resource use relating to implementing the TGC protocol and managing side effects was recognised by the paediatric critical care HRG categorisation; (2) PICU bed-days for which PCCMDS data were missing or incomplete were in the HRG category for 'basic enhanced intensive care' (HRG4); (3) the cost ratios from a previous PICU costing study reflected the relative costs; (4) the average unit costs for HRG4 were taken just from CHiP sites; (5) the regression models had residuals that were normally distributed.

The following separate, univariate, SAs tested whether or not the results were robust to the following alternative assumptions.

1. *Inclusion of the costs of implementing the TGC protocol and managing hypoglycaemic episodes as specific additional items.* The HRG categorisation could be insensitive to the resource use required to implement the TGC protocol, and for managing hypoglycaemic episodes. SAs were therefore conducted that considered any additional staff times, blood gas analyses and insulin required for:
 - i. implementing the TGC protocol compared with CM
 - ii. as for i. but also including any further costs for managing the moderate or severe hypoglycaemic episodes recorded.
2. *Reassignment of PICU bed-days without HRG classification to either:*
 - i. 'ICU basic' (HRG3); or
 - ii. 'ICU advanced' (HRG5).
 - (a) *The unit costs for each level of care in PICU were taken directly from PbR.* Rather than using the cost ratios, unit costs from PbR were used for each HRG level.
 - (b) *PICU costs were taken as national averages:* the unit costs of PIC were taken as averages from all centres that returned the relevant costs in PbR including non-CHiP sites.
 - (c) *Assume gamma rather than normal distributions for costs at 30 days and 12 months.* The assumption that costs are normally distributed may not be plausible,⁶⁸ so here costs were allowed to follow a gamma distribution.⁶⁹
3. *The MI was rerun with 10 imputations.* In some circumstances, five imputations may be insufficient to test the impact of increasing the number of imputations; the imputation models were rerun but with 10 imputations.

For each SA, the effect of TGC compared with CM on 12-month costs was reported, overall and for the cardiac and non-cardiac subgroups.

Lifetime cost-effectiveness analysis

The cost and outcome data collected at 1 year were used to project the impact of the intervention on longer-term costs and outcomes. Kaplan–Meier survival curves were plotted out to the maximum time of follow-up, overall and then separately for cardiac and non-cardiac cases. Alternative parametric functions were considered for extrapolating mortality up to 5 years, by fitting commonly recommended alternative distributions to the CHiP survival data, excluding the first 365 days post randomisation, as the event rate during this early period was anticipated to be atypical and not to provide an appropriate basis for extrapolation. The base-case analysis used the 'most appropriate' parametric survival curves judged according to which gave the best fit to the observed data and the most plausible extrapolation relative to the age- and gender-matched general population.⁷⁰ Survival extrapolations were considered for the first 5 years from randomisation, as this was anticipated to be the period over which the risk of death would be higher than that for the age- and gender-matched general population. After 5 years post randomisation, all-cause death rates were assumed to be that of the age- and gender-matched general population. The parametric extrapolations for years 1–5 were combined, applying all-cause death rates for years 6 onwards to report life expectancy for each CHiP patient observed to survive at 1 year. The projected life expectancy was used to report life-years following TGC compared with CM both overall and for the cardiac and non-cardiac strata.

Previous evidence suggests that a minority of PICU survivors may suffer from long-term disability and reductions in quality of life (QoL), and therefore QALYs were reported. QoL data were not collected for the patients who did not have TBI in the CHiP trial. Instead, information was used from a previous study that

included a large sample of PICU patients with similar baseline characteristics to those of the patients of the CHiP study⁷¹ and reported QoL with the HUI questionnaire at 6 months after the index admission. The mean QoL from this previous study (0.73, on a scale anchored at 0, death, and 1, perfect health) was applied to weight each life-year of those CHiP patients predicted to be alive 12 months after randomisation.

To project costs attributable to the initial critical care admission for years 1–5, the inpatient, outpatient and community service costs reported from the service-use survey at 1 year were assumed to be maintained until the end of year 2. Previous studies have suggested that, between 3 and 4 years after the initial PICU admission, around 10% of survivors have relatively severe disability. Those predicted to survive in years 3–5 were, therefore, assumed to have incurred 10% of the mean costs reported at 12 months. Those patients who were observed or predicted to die before 12 months were assigned zero QALYs.

Lifetime incremental costs per life-year, and per QALY gained, were reported. INBs were calculated by valuing each QALY at the £20,000 per QALY threshold recommended by NICE.⁵³ All future costs and life-years were discounted at the recommended rate of 3.5%.⁵³ All incremental cost-effectiveness results are reported overall, and then for the cardiac and non-cardiac strata.

Sensitivity analysis on lifetime cost-effectiveness analysis

The following further SAs were run to test the assumptions made in the lifetime analyses:

1. An alternative parametric extrapolation was used to project survival from year 1 to 5.
2. Excess mortality compared with the age- and gender-matched general population was assumed to remain for 10 rather than 5 years post randomisation, that is the parametric extrapolation was applied for years 1–10, and then applied for all-cause death rates.
3. It was assumed that trial patients were not subject to any excess mortality other than that of the age- and gender-matched general population.
4. Rather than assuming the mean QoL (0.73) from a previous study, the values given by the lower and upper 95% CIs around that mean (0.71 to 0.75) were assumed.
5. Alternative assumptions were made about the duration and magnitude of the costs:
 - i. For all patients who survived beyond 1 year, it was assumed that costs were maintained until the end of year 3 (rather than 2).
 - ii. 10% of costs were assumed to be maintained over years 3–10 rather than years 3–5.
 - iii. The costs for years 2–5 were assumed to be 50% not 10% of those at 12 months.
 - iv. i. to iii. above were combined.

For each of these SAs, the lifetime INBs of TGC compared with CM overall and for the cardiac and non-cardiac strata were reported.

Ancillary studies

In addition to the main study, the grant holders welcomed more detailed or complementary studies, provided that proposals were discussed in advance with the TSC and appropriate additional research ethics approval was sought. These will not be discussed further in this monograph.

Publication policy

To safeguard the integrity of the trial, data from this study were not presented in public or submitted for publication without requesting comments and receiving agreement from the TSC. The primary results of the trial will be published by the group as a whole in collaboration with local investigators and local investigators will be acknowledged. The success of the trial was dependent on the collaboration of many people. The results were, therefore, presented first to the trial local investigators. A summary of the results of the trial will be sent to parents of participating children on request and also made available on the trial website.

Organisation

A TSC (see *Appendix 9*) and a DMEC were established (see *Appendix 10*). Day-to-day management of the trial was overseen by a Trial Management Group (TMG) (see *Appendix 11*). Each participating centre identified a paediatric intensivist as a PI (see *Appendix 12*). Each participating centre was allocated funding (from the core trial grant, from the MCRN and/or from local Comprehensive Local Research Networks) for research nursing time, and employed or reallocated a research nurse to support all aspects of the trial at the local centre.

Confidentiality

Patients were identified by their trial number to ensure confidentiality. However, as the patients in the trial were contacted about the study results (and patients recruited until November 2010 were followed up for 12 months following randomisation), it was essential that the team at the DCC had the names and addresses of the trial participants recorded on the data collection forms in addition to the allocated trial number. Stringent precautions were taken to ensure confidentiality of names and addresses at the DCC.

The chief investigator and local investigators ensured conservation of records in areas to which access is restricted.

Audit

To ensure that the trial was conducted according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) guidelines, site audits were carried out on a random basis. The local investigator was required to demonstrate knowledge of the trial protocol and procedures and ICH and GCP. The accessibility of the site file to trial staff and its contents were checked to ensure all trial records were being properly maintained. Adherence to local requirements for consent was examined.

If the site had full compliance, the site visit form was signed by the lead research nurse. In the event of non-compliance, the DCC and/or the lead research nurse addressed the specific issues to ensure that relevant training and instruction were given.

The CHiP trial also passed an inspection by the Medicines and Healthcare products Regulatory Agency (MHRA) (August 2009).

Termination of the study

At the termination of planned recruitment, the DCC contacted all sites by telephone, email or fax in order to terminate all patient recruitment as quickly as possible. After all recruited patients had been followed until 30 days post randomisation (or hospital discharge if stay > 30 days), a declaration of the end of trial form was sent to EudraCT and the Multicentre Research Ethics Committee (MREC). The following documents will be archived in each site file and kept for at least 5 years: original consent forms, data forms, trial-related documents and correspondence. At the end of the analysis and reporting phase, the trial master files at the clinical co-ordinating centre and DCC will be archived for 15 years.

Funding

The costs for the study itself were covered by a grant from the HTA programme. Clinical costs were met by the NHS under existing contracts.

Indemnity

If there is negligent harm during the clinical trial, when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS indemnity does not offer no-fault compensation.

Chapter 3 Results

Recruitment

Trial recruitment began on 4 May 2008. As indicated in *Chapter 2*, recruitment was slower than expected. This was mainly a result of delays in trial initiation at some sites, clinical constraints and a 'research learning curve' in many of the participating units which had no previous experience of recruiting critically ill children to clinical trials. These delays necessitated an application to the HTA programme for an extension to the trial. The HTA programme granted funding to allow recruitment to be extended to allow the trial to achieve sufficient power (1500 children) to identify whether or not there was a differential effect for the primary end point (VFD-30) in the two strata (cardiac and non-cardiac).

The DMEC confidentially reviewed unblinded interim analyses on two occasions. In addition, they met to discuss SAEs and recruitment rates on three further occasions.

Recruitment closed on 31 August 2011, as agreed in the HTA funding. A total of 19,924 children were screened from 13 sites. Of these, 1384 were recruited and randomised (701 to TGC and 683 to CM). The reasons for non-recruitment are shown in *Table 4*. Of the 1384, 15 were subsequently found to be ineligible (*Table 5*), leaving 1369 eligible children (694 to TGC and 675 to CM) randomised into the trial – 91% of the original target of 1500. The flow of patients is shown in *Figure 3* and cumulative recruitment in *Figure 4*. Recruitment by site is shown in *Table 6*.

TABLE 4 Numbers screened with reasons for non-recruitment

	Reason not recruited	All screened, non-recruited patients N = 18,540	
		n	n/N (%)
Inclusion criteria	> 16 years	211	1.14
	Mechanical ventilator and vasoactive drugs not likely to be continued for > 12 hours	2285	12.32
	Arterial line not in situ	1576	8.50
	Not ventilated	2637	14.22
	No inotropes	9601	51.79
Exclusion criteria	< 36 weeks corrected gestational age	565	3.05
	Diabetes mellitus	56	0.30
	Error of metabolism	268	1.45
	Treatment withdrawal/limitation	312	1.68
	> 5 days on PICU	135	0.73
	Already participated in CHiP	262	1.41
Other	Refused consent	1116	6.02
	Patient died	143	0.77
	Not asked within time frame	531	2.86
	Other (<i>further details in box below</i>)	1573	8.48

Text responses for category 'other'

Research nurse on leave/ill/unavailable (weekend)	322
ECMO/transplant	134
Language difficulties	127
In another trial/approached for another trial	116
Legal/social issues	109
No decision within time frame	97
PI – clinical decision	95
Parents not available/too upset	89
Transferred to another hospital	48
Non-TBI site	33
Other	403

ECMO, extracorporeal membrane oxygenation.

TABLE 5 Ineligible patients

TGC arm	CM arm
During a monitoring visit it was found that this patient had <i>not fully consented</i>	During the final data analysis the trial statistician found that this patient actually <i>met one of the exclusion criteria</i> , i.e. he or she was in PICU for > 5 days before he or she was randomised
In response to a query it was found that this patient was recruited in error. He or she <i>did not meet one of the eligibility criteria</i> (taking vasoactive drugs)	During the final data analysis the trial statistician found that this patient actually <i>met one of the exclusion criteria</i> , i.e. he or she was in PICU for > 5 days before he or she was randomised
Patient randomised incorrectly, possibly <i>met one of the exclusion criteria</i> , as when randomised had suspected metabolic illness; therefore treatment was stopped early	During the final data analysis the trial statistician found that this patient actually <i>met one of the exclusion criteria</i> , i.e. he or she was in PICU for > 5 days before he or she was randomised
Parents had forgotten that their child had previously been in the trial; therefore he or she was not eligible for the trial	During the final data analysis the trial statistician found that this patient actually <i>met one of the exclusion criteria</i> , i.e. he or she was in PICU for > 5 days before he or she was randomised
Patient randomised in error: <i>met the exclusion criterion</i> of having an inborn error of metabolism (Refsum's disease, which is a rare disorder of lipid metabolism)	Patient randomised in error: <i>met the exclusion criterion</i> of being in PICU for > 5 days but site did not realise until after randomised
During the final data analysis the trial statistician found that this patient actually <i>met one of the exclusion criteria</i> , i.e. he or she was in PICU for > 5 days before he or she was randomised	Patient randomised in error: <i>met the exclusion criterion</i> of being in PICU for > 5 days but site did not realise until after randomised
Patient randomised in error: <i>did not meet the inclusion criterion</i> of being on inotropes at randomisation	Patient randomised in error: <i>met the exclusion criterion</i> of having an inborn error of metabolism (Barth syndrome)
	Patient randomised in error: <i>did not meet the inclusion criterion</i> of being on inotropes at randomisation

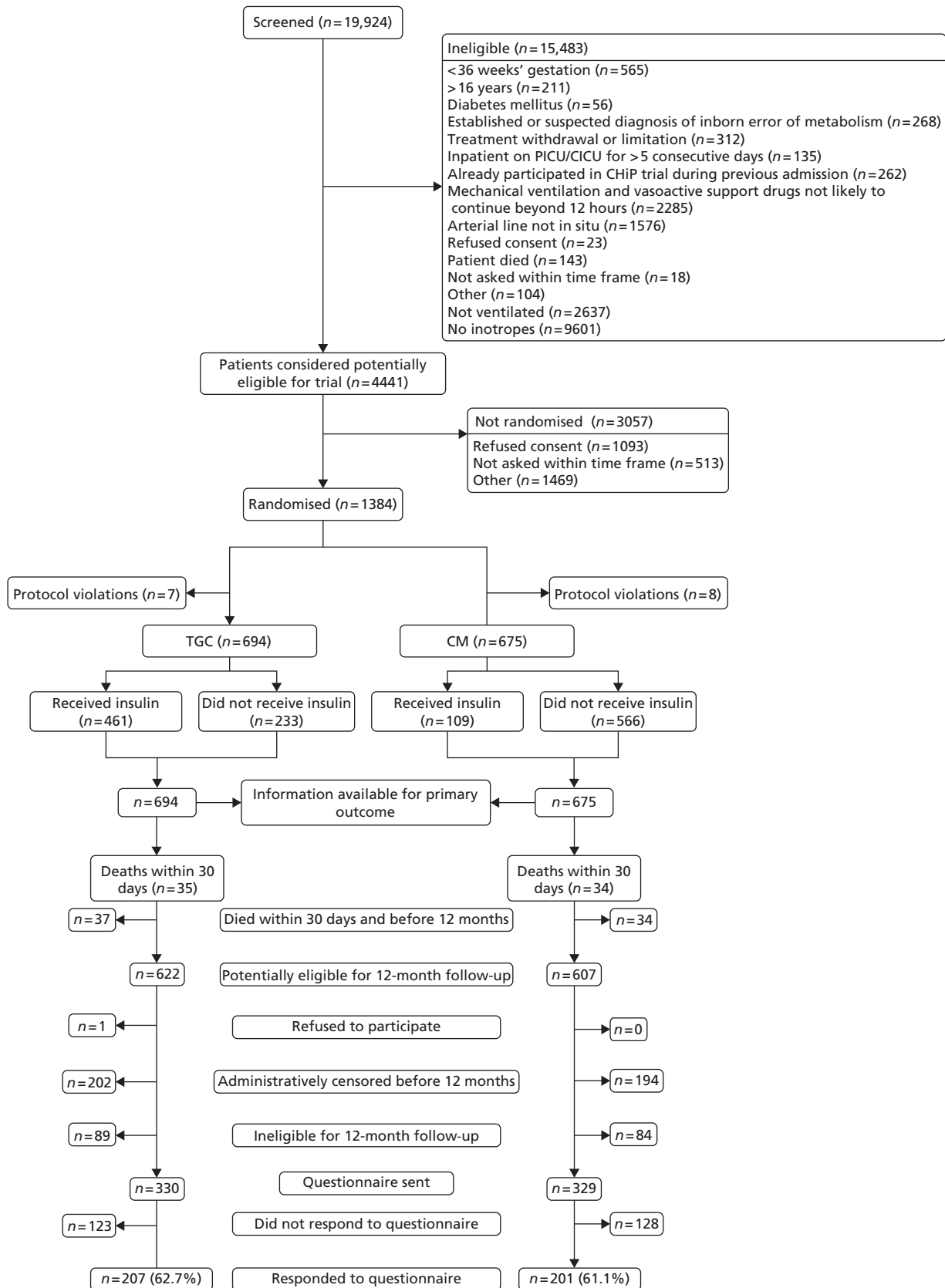


FIGURE 3 A flow chart showing the flow of patients. Note that the information on vital status up to 12 months was available from the Office for National Statistics, aside from for 17 non-UK nationals.

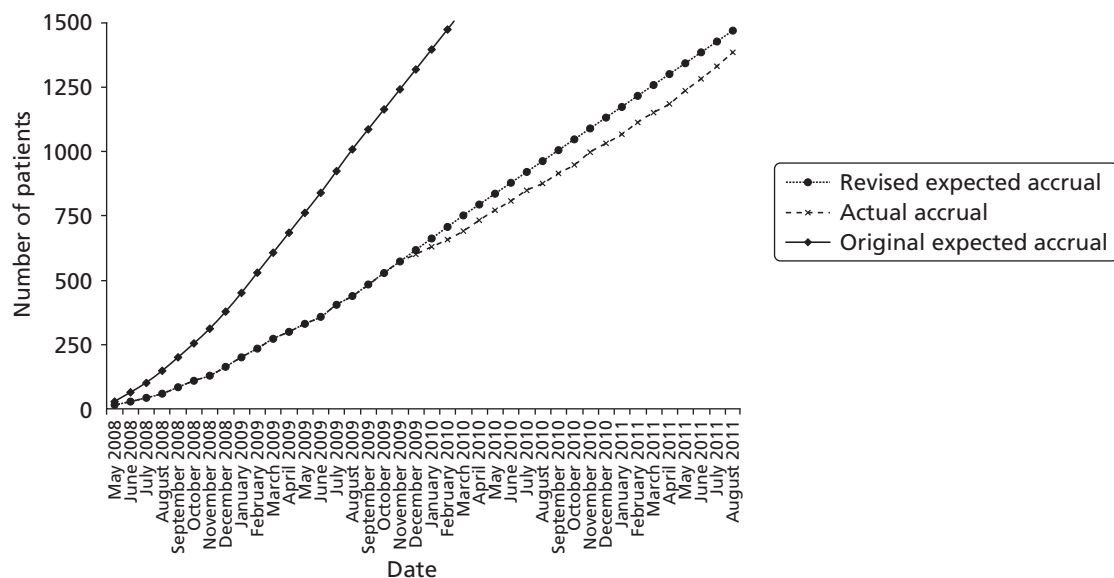


FIGURE 4 Cumulative recruitment – actual accrual vs. revised expected.

TABLE 6 Recruitment per site

Site	Screened (N)	Randomised [n (%)]
1. Birmingham Children's Hospital	3490	241 (6.9)
2. Bristol Royal Hospital for Children	1525	148 (9.7)
3. Great Ormond Street Hospital	3878	210 (5.4)
4. Leeds General Infirmary	278	3 (1.1)
5. Royal Brompton Hospital	1695	158 (9.3)
6. Royal Liverpool Children's NHS Trust	2145	164 (7.6)
7. Royal Manchester Children's Hospital	1806	75 (4.2)
8. St Mary's Hospital	935	60 (6.4)
9. Sheffield Children's NHS Foundation Trust	320	22 (6.9)
10. Southampton General Hospital	2416	219 (9.1)
11. University Hospital of North Staffordshire	419	15 (3.6)
12. University Hospitals of Leicester	946	63 (6.7)
14. St George's Hospital	71	6 (8.5)
<i>Total</i>	<i>19,924</i>	<i>1384</i>

Comparability at baseline

The characteristics of the children at baseline are shown in *Table 7*. The randomised groups were broadly comparable at trial entry. Sixty-two per cent were randomised within 1 day of admission to PICU. In terms of the prespecified stratifying factors, two-thirds were aged < 1 year, and 60% of the children were in the cardiac surgery stratum. Seven per cent of children in the cardiac surgery stratum were considered to be undergoing surgical procedures associated with a high risk of mortality (RACHS1 score 5 or 6), and 19% of children in the non-cardiac group had a PIM2 score indicative of a $\geq 15\%$ risk of PICU mortality.

TABLE 7 Characteristics at baseline

Characteristic	TGC (N = 694)	CM (N = 675)
Centre ^a		
1	122	119
2	71	75
3	101	106
4	1	2
5	78	76
6	82	80
7	41	34
8	31	28
9	10	12
10	111	106
11	9	6
12	34	29
14	3	2
Sex		
Male [n (%)]	389 (56.05)	363 (53.78)
Age (years) ^a		
0 to < 1 [n (%)]	432 (62.24)	421 (62.36)
1 to < 16 [n (%)]	262 (37.75)	254 (37.63)
Median (IQR)	0.49 (0.07–2.72)	0.53 (0.08–2.73)
Weight (kg) [mean (SD)]	12.13 (15.11)	11.31 (12.88)
Height (cm) [mean (SD)]	76.24 (32.67)	76.09 (31.75)
<i>Not measured</i>	65	63
Waist circumference (cm) [mean (SD)]	44.88 (14.30)	44.13 (12.82)
<i>Not measured</i>	140	150
Trial entry following cardiac surgery [n (%)] ^a	421 (60.66)	416 (61.63)
Other trial entry [n (%)] ^a	273 (39.34)	259 (38.37)
Undergoing cardiopulmonary bypass	N = 421 ^b	N = 416 ^b
n (%)	396 (94.06)	392 (94.23)
RACHS1 score ^{a,c}	N = 421 ^b	N = 416 ^b
1–4 [n (%)]	388 (92.16)	393 (94.47)
5–6 [n (%)]	33 (7.84)	23 (5.53)
Predicted risk of mortality (PIM2) ^{a,c}	N = 273 ^b	N = 259 ^b
< 5% [n (%)]	74 (27.11)	67 (25.87)
5–15% [n (%)]	144 (52.75)	144 (55.60)
≥ 15% [n (%)]	55 (20.15)	48 (18.53)

TABLE 7 Characteristics at baseline (continued)

Characteristic	TGC (N = 694)	CM (N = 675)
Time from admission to trial entry (days) [median (IQR)]	1 (0–2)	1 (0–1)
Inotrope score [mean (SD)]	15.00 (21.58)	16.22 (21.07)
Blood glucose (mmol/l) [mean (SD)]	7.10 (2.76)	7.02 (2.86)
Not measured		1
Plasma creatinine ($\mu\text{mol/l}$) [mean (SD)]	50.69 (44.33)	54.54 (40.58)
Not measured	69	52
PELOD score ^c [mean (SD)]	7.46 (7.04)	7.70 (6.58)

IQR, interquartile range; PELOD, paediatric organ dysfunction.

a Minimisation factor.

b Number who entered the trial following cardiac surgery.

c Higher score indicates poorer performance.

Actual management

Table 8 describes the observed management of blood glucose after randomisation, and shows a clear difference between the two arms of the study. In the TGC arm, 461 of the children (66%) received insulin compared with 109 of 675 (16%) in the CM arm. Children in the TGC arm received more insulin, and continued on insulin for longer. Figure 5 shows the mean daily blood glucose level by arm. There was a clear separation between the two randomised arms, with children in the TGC arm having a significantly lower blood glucose profile than those in the CM arm.

TABLE 8 Actual management after randomisation

Actual management	TGC (N = 694)	CM (N = 675)
Insulin administered (yes) [n (%)]	461 (66.43)	109 (16.15)
Total insulin given (IU/kg body weight) [mean (SD)]	2.56 (6.18) (N = 461)	1.29 (2.85) (N = 109)
Number of days on insulin [mean (SD)]	3.24 (3.32)	1.71 (1.19)
Time from randomisation to starting insulin (hours) [median (IQR)]	3.37 (0.78–17.93)	3.1 (0.09–42.18)

IU, international unit.

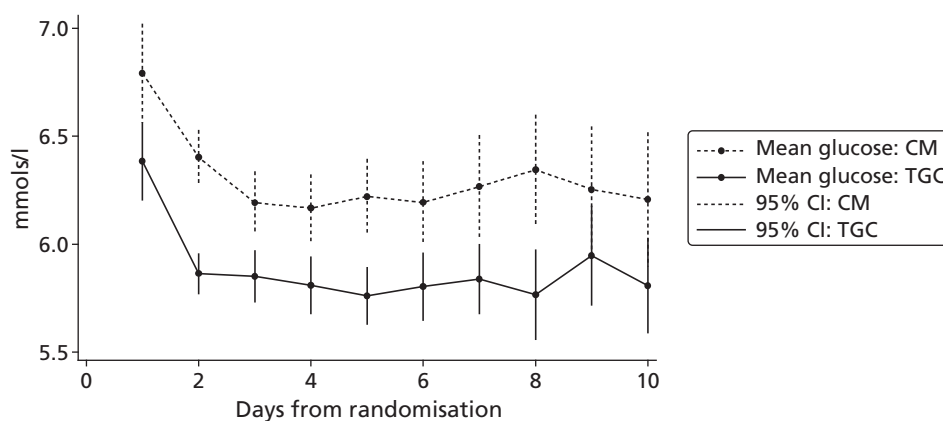


FIGURE 5 Mean glucose level.

Thirty-day clinical outcomes

Primary outcome

Results for the primary outcome are shown in *Table 9*. The mean number of VFD-30 from randomisation was 23 in both trial arms (mean difference 0.36; 95% CI -0.42 to 1.14).

Secondary outcomes

The secondary outcomes up to 30 days are shown in *Table 10*, and the duration of ventilation in *Figure 6* and of vasoactive drug use in *Figure 7*. In general, the secondary outcomes are similar between the arms over the 30-day period, although less RRT was undertaken in the TGC arm (odds ratio 0.63; 95% CI 0.45 to 0.89). Additionally, mean caloric intake (*Figure 8*) was similar between the two groups.

TABLE 9 Primary outcome 30 days post randomisation

Outcome	TGC (n = 694) [mean (standard error)]	CM (n = 675) [mean (standard error)]	Mean difference/odds ratio (95% CI)
VFD-30	23.61 (0.27)	23.24 (0.29)	0.36 (-0.42 to 1.14)

TABLE 10 Secondary outcomes 30 days post randomisation

Outcome	TGC (N = 694)	CM (N = 675)	Mean difference/odds ratio (95% CI)
Death within 30 days of trial entry [n (%)]	35 (5.04) ^a	34 (5.04) ^a	1.00 (0.62 to 1.63)
Number of days in PICU [mean (SE)]	6.50 (0.21)	6.96 (0.24)	-0.47 (-1.12 to 0.15)
Number of days in hospital [mean (SE)]	16.40 (0.34)	16.73 (0.36)	-0.33 (-1.24 to 0.62)
Duration of mechanical ventilation (days) [mean (SE)]	5.30 (0.19)	5.61 (0.21)	-0.31 (-0.87 to 0.25)
PELOD score [mean (SE)]	9.79 (0.19)	9.79 (0.21)	-0.31 (-0.87 to 0.25)
Duration of vasoactive drug use (days) [median (IQR)]	3 (2 to 6)	4 (2 to 6)	-0.20 (-0.64 to 0.25)
RRT [n (%)]	62 (8.93)	91 (13.48)	0.63 (0.45 to 0.89)
Bloodstream infection [n (%)]	38 (5.48)	43 (6.37)	0.85 (0.54 to 1.34)
Use of antibiotics > 10 days [n (%)]	62 (8.93)	74 (10.96)	0.80 (0.56 to 1.14)
Number of red blood cell transfusions [mean (SE)]	1.00 (0.11)	1.12 (0.11)	-0.11 (-0.43 to 0.18)
Number of patients who experienced at least one hypoglycaemic episode (moderate or severe) [n (%)]	110 (15.85)	25 (3.70)	4.90 (3.13 to 7.67)
Number of moderate hypoglycaemic episodes (< 2.0–2.5 mmol/l)			
Number of episodes	127	30	
Number of patients who experienced at least one episode ^b [n (%)]	87 (12.54)	21 (3.11)	4.46 (2.73 to 7.28)
Mean number of episodes per patient (SE)	0.18 (0.03)	0.04 (0.01)	
Number of severe hypoglycaemic episodes (< 2.0 mmol/l)			
Number of episodes	70	11	
Number of patients who experienced at least one episode ^b [n (%)]	51 (7.35)	10 (1.48)	5.27 (2.65 to 10.48)
Mean number of episodes per patient (SE)	0.1 (0.02)	0.02 (0.005)	
Seizures given pharmacological treatment [n (%)]	23 (3.31)	15 (2.22)	1.15 (0.77 to 2.98)

PELOD, paediatric organ dysfunction; SE, standard error.

a Outcome missing for two patients (one in TGC arm and one in CM arm).

b Patients who experienced moderate episodes may also have experienced a severe episode and vice versa.

In terms of adverse effects, there were 135 patients whose blood glucose level was below the threshold that defined moderate hypoglycaemia; 61 of these had one or more episodes that were considered severe. Hypoglycaemia occurred in 33 (4.1%) patients not given insulin, but was more commonly observed in patients who received insulin [102 (17.9%)].

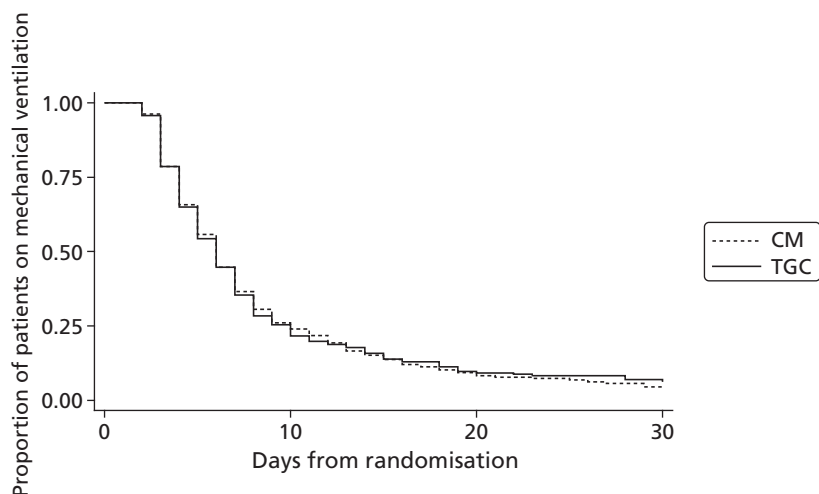


FIGURE 6 Proportion of patients on mechanical ventilation.

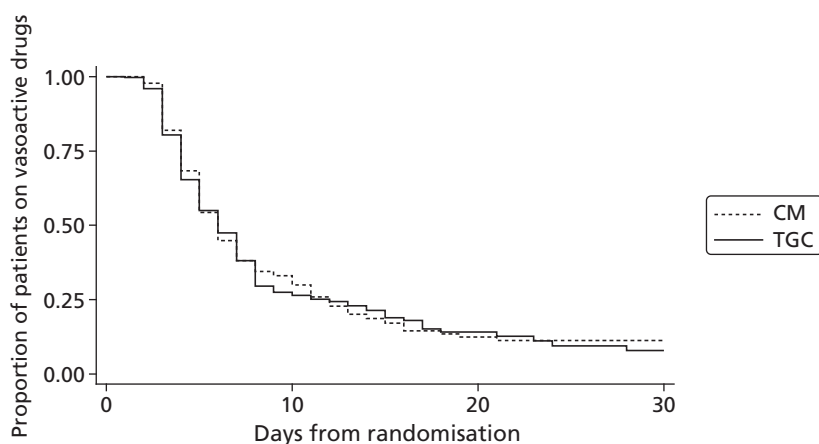


FIGURE 7 Proportion of patients receiving vasoactive drugs.

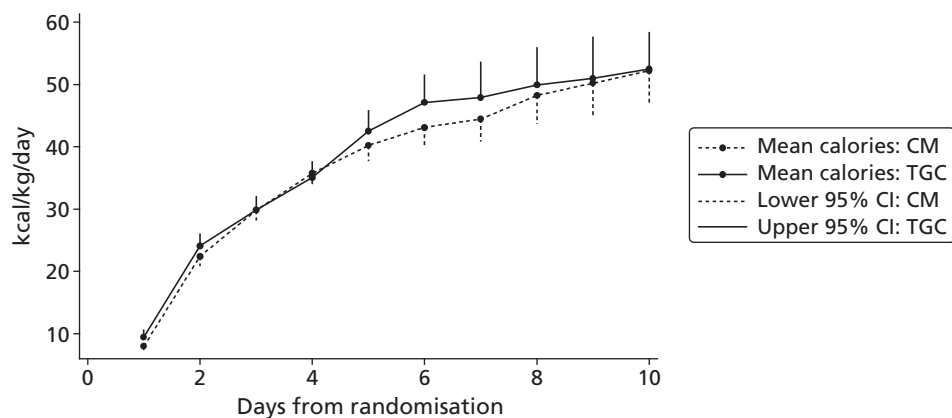


FIGURE 8 Mean caloric intake.

RESULTS

Hypoglycaemia occurred in a greater proportion of patients in the TGC arm than in the CM arm of the study (moderate, 12.5% vs. 3.1%, $p < 0.001$; severe, 7.3% vs. 1.5%, $p < 0.001$). Of the patients who experienced any hypoglycaemic episode, 11.1% died as opposed to 4.4% of those who did not experience any hypoglycaemic episode ($p = 0.001$).

Stratified analyses

Table 11a–e shows the primary outcome for the main prespecified stratification factors. None of the interaction tests between the intervention and prespecified subgroups was statistically significant, suggesting that there is no difference in the effect of TGC on VFD-30 in the different strata [$p = 0.63$ (cardiac vs. non-cardiac); $p = 0.28$ (age < 1 vs. ≥ 1 year); $p = 0.09$ (RACHS1 1–4 vs. 5–6); $p = 0.88$ (PIM2 $< 5\%$ vs. 5–15% vs. $\geq 15\%$) and $p = 0.66$ (run-in cases vs. non-run-in cases)]. One of the prespecified stratified analyses (TBI or not) was not included, as only 13 TBI patients were followed up at 1 year.

TABLE 11a Ventilator-free days at 30 days post randomisation stratified by cardiac and non-cardiac patients

	TGC (N = 694)	CM (N = 675)	Mean difference (95% CI)
Cardiac			
<i>n</i>	421	416	
Mean (SE)	25.05 (0.27)	24.80 (0.31)	0.25 (–0.71 to 1.22)
Non-cardiac			
<i>n</i>	273	259	
Mean (SE)	21.37 (0.52)	20.74 (0.54)	0.63 (–0.58 to 1.84)

SE, standard error.

TABLE 11b Ventilator-free days at 30 days post randomisation stratified by age < 1 year and age ≥ 1 year

	TGC (N = 694)	CM (N = 675)	Mean difference (95% CI)
Age < 1 year			
<i>n</i>	432	421	
Mean (SE)	23.59 (0.35)	23.56 (0.36)	0.03 (–0.96 to 1.02)
Age ≥ 1 year			
<i>n</i>	262	254	
Mean (SE)	23.63 (0.44)	22.72 (0.49)	0.91 (–0.36 to 2.18)

SE, standard error.

TABLE 11c Ventilator-free days at 30 days post randomisation stratified by operative complexity (cardiac)

Operative complexity	TGC (N = 421)	CM (N = 416)	Mean difference (95% CI)
RACHS 1–4			
<i>n</i>	388	393	
Mean (SE)	25.29 (0.27)	25.13 (0.29)	0.17 (–0.66 to 0.99)
RACHS 5 or 6			
<i>n</i>	33	23	
Mean (SE)	22.21 (1.32)	19.26 (2.27)	2.95 (–0.15 to 6.06)

SE, standard error.

TABLE 11d Ventilator-free days at 30 days post randomisation stratified by predicted risk of mortality (non-cardiac)

Predicted risk of mortality	TGC (N = 272)	CM (N = 261)	Mean difference (95% CI)
PIM2 < 5%			
<i>n</i>	74	67	
Mean (SE)	24.22 (0.70)	22.82 (0.87)	1.40 (−1.42 to 4.42)
PIM2 5–15%			
<i>n</i>	144	144	
Mean (SE)	21.22 (0.72)	20.59 (0.70)	0.63 (−1.33 to 2.58)
PIM2 ≥ 15%			
<i>n</i>	55	48	
Mean (SE)	17.95 (1.39)	18.29 (1.50)	−0.35 (−3.63 to 2.94)

SE, standard error.

TABLE 11e Ventilator-free days at 30 days post randomisation stratified by run-in (first 100 cases) and non-run-in

	TGC (N = 694)	CM (N = 675)	Mean difference (95% CI)
Run-in – first 100 cases			
<i>n</i>	47	53	
Mean (SE)	23.62 (1.04)	22.64 (1.05)	0.98 (−1.91 to 3.86)
Non-run-in			
<i>n</i>	647	254	
Mean (SE)	23.61 (0.28)	23.30 (0.30)	0.31 (−0.50 to 1.12)

SE, standard error.

In both cardiac and non-cardiac strata, hypoglycaemia occurred in a greater proportion of patients in the TGC arm than in the CM arm of the trial (moderate: cardiac 10.9% vs. 1.4%, $p < 0.001$; non-cardiac 15.4% vs. 5.8% $p < 0.001$; severe: cardiac 5.5% vs. 0.5%, $p < 0.001$; non-cardiac 10.3% vs. 3.1%, $p = 0.001$). Cardiac cases receiving insulin were not at a greater risk of hypoglycaemia than non-cardiac cases (16.4% vs. 20.3%).

Thirty-day economic outcomes

For the index hospital episode, the mean PICU bed-days, LOS on GM wards and total LOS for the index hospital episode were similar between arms (*Table 12*). The mean total number of hospital days up to day 30, including both the initial episode and readmissions to the initial PICU before day 30, were similar between arms (see *Table 12*). For the stratum admitted for cardiac surgery, the mean total LOS was again comparable between arms (*Table 13*). As regards the non-cardiac stratum, for the initial hospital episode, the mean numbers of PICU days, LOS on GM wards and total LOS were lower for the TGC than the CM arm (*Table 14*).

TABLE 12 Lengths of stay (days) within 30 days post randomisation: whole study cohort

	TGC (N = 694)	CM (N = 675)
Index hospital episode		
Mean (SD) PICU days	6.50 (5.50)	6.96 (6.12)
Mean (SD) days on general wards	9.91 (7.43)	9.77 (7.52)
Mean (SD) total days	16.40 (8.84)	16.73 (9.26)
Readmission		
n (%)	39 (5.62)	37 (5.48)
Mean (SD) total days	0.21 (1.02)	0.25 (1.27)
Mean (SD) total hospital days ^a	16.62 (8.81)	16.98 (9.25)

a Total days for the index episode and readmissions, from randomisation up to day 30.

TABLE 13 Lengths of stay (days) within 30 days post randomisation: cardiac surgery subgroup

	TGC (N = 421)	CM (N = 416)
Index hospital episode		
Mean (SD) PICU days	5.69 (4.79)	5.89 (5.37)
Mean (SD) days on general wards	9.26 (6.83)	8.32 (6.34)
Mean (SD) total days	14.96 (8.29)	14.22 (8.19)
Readmission		
n (%)	35 (8.31)	26 (6.25)
Mean (SD) total days	0.31 (1.20)	0.32 (1.49)
Mean (SD) total hospital days ^a	15.27 (8.29)	14.54 (8.25)

a Total days for the index episode and readmissions, from randomisation up to day 30.

TABLE 14 Lengths of stay (days) within 30 days post randomisation: non-cardiac surgery subgroup

	TGC (N = 273)	CM (N = 259)
Index hospital episode		
Mean (SD) PICU days	7.74 (6.25)	8.68 (6.83)
Mean (SD) days on general wards	10.90 (8.18)	12.10 (8.62)
Mean (SD) total days	18.63 (9.22)	20.78 (9.46)
Readmission		
n (%)	4 (1.47)	11 (4.25)
Mean (SD) total days	0.07 (0.64)	0.13 (0.80)
Mean (SD) total hospital days ^a	18.70 (9.20)	20.91 (9.43)

a Total days for the index episode and readmissions, from randomisation up to day 30.

Tables 15–17 report that the mean numbers of PICU bed-days, by HRG level, were similar between arms.

Overall, the mean total costs at 30 days post randomisation were similar between arms (Table 18). For the cardiac subgroup, the mean total costs per patient were £16,228 (TGC) and £17,005 (CM) (Table 19). For the non-cardiac subgroup, the TGC arm had lower mean costs than the CM group, with an incremental cost of –£2319 (95% CI –£4702 to £124) (Table 20). Including the treatment by cardiac interaction term led to a statistically significant improvement in model fit ($p < 0.001$).

TABLE 15 Mean (SD) PICU bed-days by HRG level within 30 days post randomisation: whole study cohort

HRG level	TGC ($n = 694$)	CM ($n = 675$)
1	0.31 (0.80)	0.26 (0.63)
2	0.74 (1.32)	0.90 (1.83)
3	0.93 (2.08)	1.10 (2.44)
4	2.59 (3.13)	2.48 (3.14)
5	0.52 (2.20)	0.48 (1.44)
6	0.18 (0.63)	0.22 (0.74)
7	0.11 (1.49)	0.05 (0.50)

TABLE 16 Mean (SD) PICU bed-days by HRG level within 30 days post randomisation: cardiac surgery subgroup

HRG level	TGC ($n = 421$)	CM ($n = 416$)
1	0.17 (0.48)	0.19 (0.55)
2	0.81 (1.26)	0.96 (1.77)
3	0.57 (1.46)	0.60 (1.57)
4	2.44 (2.99)	2.42 (2.79)
5	0.42 (1.62)	0.37 (1.21)
6	0.14 (0.65)	0.11 (0.39)
7	0.09 (1.40)	0.03 (0.35)

TABLE 17 Mean (SD) PICU bed-days by HRG level within 30 days post randomisation: non-cardiac surgery subgroup

HRG level	TGC ($n = 273$)	CM ($n = 259$)
1	0.53 (1.07)	0.37 (0.73)
2	0.63 (1.40)	0.80 (1.90)
3	1.48 (2.69)	1.91 (3.26)
4	2.80 (3.33)	2.61 (3.65)
5	0.68 (2.88)	0.65 (1.74)
6	0.25 (0.59)	0.40 (1.10)
7	0.14 (1.62)	0.08 (0.66)

TABLE 18 Total and incremental costs (£) within 30 days post randomisation: whole study cohort

	TGC (<i>n</i> = 694) [mean (SD)]	CM (<i>n</i> = 675) [mean (SD)]	Incremental [mean (95% CI)]
Index hospital episode			
PICU costs	13,607 (13,579)	14,446 (12,938)	
GM costs	2497 (1872)	2463 (1895)	
Total costs	16,104 (13,499)	16,908 (12,923)	
Readmission			
PICU costs	58 (658)	26 (499)	
GM costs	54 (240)	64 (316)	
Total costs	112 (750)	90 (612)	
Total costs (index admission and readmissions)	16,228 (13,504)	17,005 (12,913)	-776 (-2183 to 632)

TABLE 19 Total and incremental costs (£) within 30 days post randomisation: cardiac surgery subgroup

	TGC (<i>n</i> = 421) [mean (SD)]	CM (<i>n</i> = 416) [mean (SD)]	Incremental [mean (95% CI)]
Index hospital admission			
PICU costs	11,956 (12,379)	12,119 (11,200)	
GM costs	2336 (1722)	2098 (1597)	
Total costs	14,291 (12,413)	14,216 (11,272)	
Readmissions			
PICU costs	80 (771)	42 (635)	
Other ward costs	76 (288)	82 (367)	
Total costs	156 (873)	124 (761)	
Total costs (index admission and readmissions)	14,465 (12,437)	14,350 (11,285)	114 (-1496 to 1725)

TABLE 20 Total and incremental costs (£) within 30 days post randomisation: non-cardiac surgery subgroup

	TGC (<i>n</i> = 273) [mean (SD)]	CM (<i>n</i> = 259) [mean (SD)]	Incremental [mean (95% CI)]
Index hospital admission			
PICU costs	16,153 (14,915)	18,184 (14,587)	
GM costs	2746 (2060)	3048 (2172)	
Total costs	18,899 (14,609)	21,232 (14,195)	
Readmission			
PICU costs	26 (427)	0 (0)	
GM costs	19 (129)	36 (207)	
Total costs	45 (501)	36 (207)	
Total costs (index admission and readmissions)	18,949 (14,614)	21,268 (14,183)	-2319 (-4762 to 124)

Twelve-month results

Index hospital episode and readmissions to paediatric intensive care unit within 30 days post randomisation

Table 21 reports the mean total number of hospital days up to 12 months post randomisation, including the initial hospital episode and any readmissions to PICU within 30 days. A lower proportion of patients in the TGC than in CM arm had an index hospital admission or relevant readmission that continued beyond day 30. Between 30 days and 12 months post randomisation, the mean number of days in PICU, on GM wards and in total, was lower for the TGC than the CM arm (see Table 21).

Four patients were still in hospital at the date of administrative censoring, with LOS ranging from 119 to 359 days. Each of these patients was assumed to have the mean total LOS taken across the whole sample still in hospital at the respective time point. (For example, for the patient censored at a LOS of 119 days, the assumed LOS was 228 days, according to the mean across the 46 patients still in hospital 118 days post randomisation.) One patient withdrew consent for participation in the study, after 8 days in hospital, and was assumed to have a total hospital LOS of 60 days, the mean across the whole sample of patients who were still in hospital after day 8.

For the cardiac stratum, the mean total LOS at 12 months was similar between arms (Table 22). For the non-cardiac subgroup, the TGC arm had a lower proportion of patients who had a hospital admission that continued beyond 30 days post randomisation, and on average reported fewer days on PICUs, and on GM wards (Table 23), than the CM arm. For the non-cardiac stratum, the mean total LOS for the initial episode

TABLE 21 Lengths of stay (days) within 12 months post randomisation: whole study cohort

	TGC (N = 694)	CM (N = 675)
Mean (SD) total days up to 30 days post randomisation	16.62 (8.81)	16.98 (9.25)
30 days to 1 year		
n (%) continuing admission	130 (18.73)	152 (22.52)
Mean (SD) PICU days	1.98 (11.86)	2.79 (15.19)
Mean (SD) days on general wards	5.67 (25.89)	9.75 (36.22)
Mean (SD) total days	7.64 (31.18)	12.54 (41.47)
Mean (SD) total hospital days ^a	24.26 (35.40)	29.52 (46.18)

a Includes hospital days between randomisation and 12 months for initial hospital episode and readmissions to initial PICU that were within 30 days.
Source: CRFs.

TABLE 22 Lengths of stay (days) within 12 months post randomisation: cardiac surgery subgroup

	TGC (N = 421)	CM (N = 416)
Mean (SD) days at 30 days post randomisation	15.27 (8.29)	14.54 (8.25)
30 days to 1 year		
n (%) continuing admission	59 (14.01)	52 (12.50)
Mean (SD) PICU days	1.39 (8.81)	1.26 (6.70)
Mean (SD) days on general wards	3.25 (18.54)	4.40 (26.48)
Mean (SD) total days	4.64 (22.17)	5.65 (29.30)
Mean (SD) total hospital days ^a	19.90 (26.40)	20.19 (33.19)

a Includes hospital days between randomisation and 12 months for initial hospital episode and readmissions to initial PICU that were within 30 days.
Source: CRFs.

TABLE 23 Lengths of stay (days) within 12 months post randomisation: non-cardiac surgery subgroup

	TGC (N = 273)	CM (N = 259)
Mean (SD) days at 30 days post randomisation	18.70 (9.20)	20.91 (9.43)
30 days to 1 year		
<i>n</i> (%) continuing admission	71 (26.01)	100 (38.61)
Mean (SD) PICU days	2.88 (15.40)	5.25 (22.82)
Mean (SD) days on general wards	9.40 (33.97)	18.35 (46.66)
Mean (SD) total days	12.27 (41.03)	23.60 (53.98)
Mean (SD) total hospital days ^a	30.98 (45.18)	44.51 (58.59)

a Includes hospital days between randomisation and 12 months for initial hospital episode and readmissions to initial PICU that were within 30 days.
Source: CRFs.

and readmissions to PICU within 30 days was 31.0 days for the TGC arm compared with 44.5 days for the CM arm (see *Table 23*).

Figure 9 plots the proportion of patients over time who were still in hospital following the index admission. For the overall sample, and the cardiac patients, the proportion still in hospital was similar between arms at each time point. For the non-cardiac patients, a higher proportion of the CM than the TGC arm were still in hospital 60 and 90 days post randomisation.

Mortality

Mortality at 12 months was similar between the randomised groups (*Table 24*). The CIs around each of the odds ratios all encompassed 1.

Assessment of attention and behaviour in patients with traumatic brain injury

No differences were found between the two arms of the trial in attention and behaviour measures for those patients with TBI (*Table 25*).

Other hospital and community service use (after discharge from index hospital episode but excluding any readmissions to the initial paediatric intensive care unit within 30 days)

Figure 10 shows the flow of patients from randomisation to response to the service-use questionnaire. In the overall sample, a total of 397 patients (203 in the TGC arm, 194 in the CM arm) were randomised after 30 October 2010 and could not be followed up for 1 year; that is, for the purposes of collecting information on service use, these patients were administratively censored. Patients were also ineligible for the service-use questionnaire if their GP did not confirm that it was appropriate to contact them to administer the questionnaire. Of the eligible patients, the response rate to the service-use questionnaire was 63% in the TGC arm and 61% in the CM arm. For those who responded to the questionnaire, the mean LOS following hospital readmissions after 30 days post randomisation, and the mean number of contacts with hospital and personal social services, was similar between the randomised arms (*Tables 26–28*). The mean total costs of hospital and community health services were also similar between the randomised arms (*Tables 29–31*).

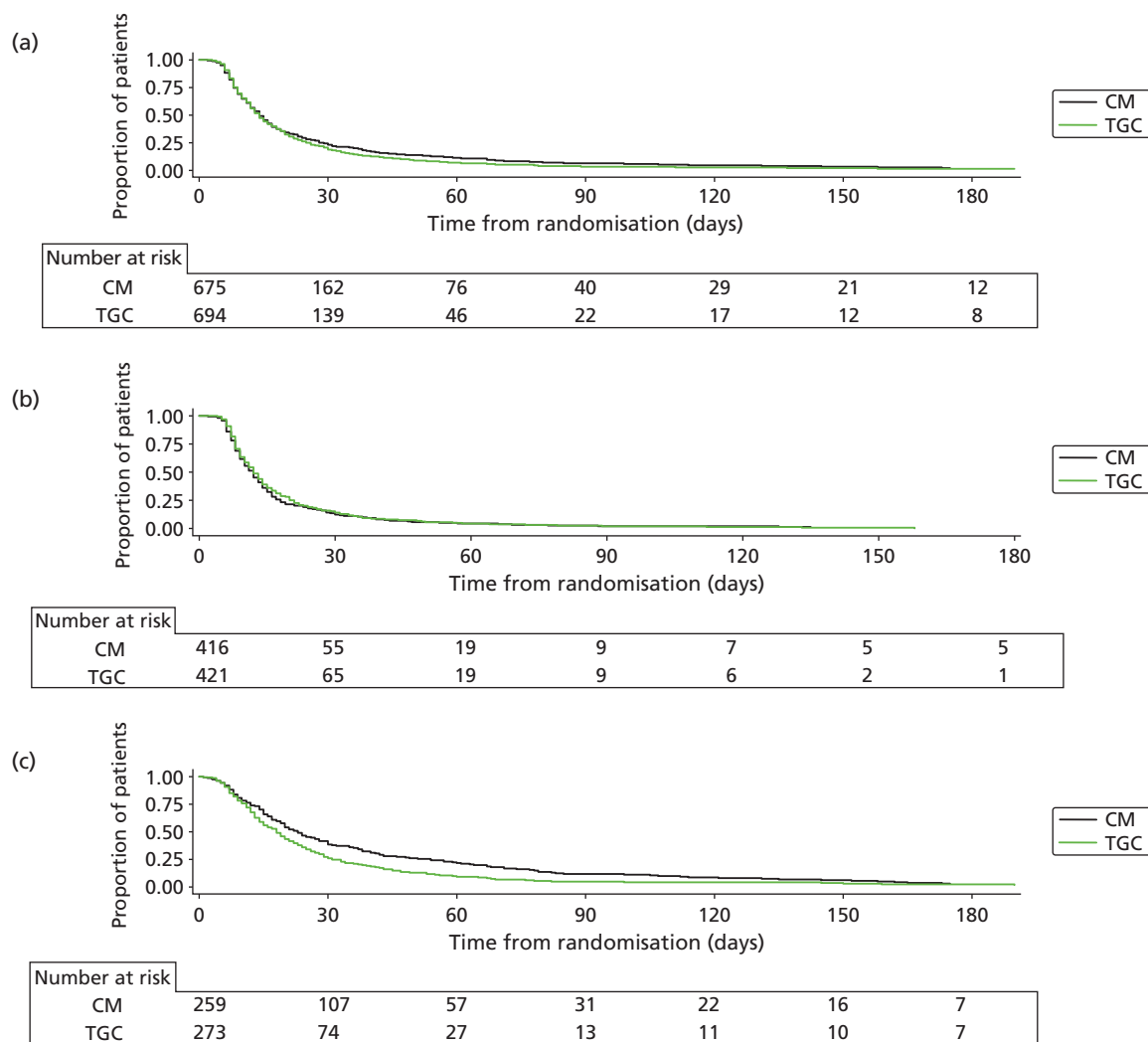


FIGURE 9 Proportion of patients remaining in hospital (index admission) up to 180 days post randomisation. Proportion of patients remaining in hospital: (a) whole study cohort; (b) cardiac surgery subgroup; and (c) non-cardiac surgery group.

TABLE 24 Vital status within 12 months post randomisation: overall, cardiac and non-cardiac

	Deaths within 12 months by group [n (%)]		Odds ratio (95% CI)
	TGC	CM	
Overall (TGC, N = 694; CM, N = 675)	73 (10.52)	71 (10.52)	1.00 (0.71 to 1.41)
Cardiac (TGC, N = 421; CM, N = 416)	31 (7.36)	30 (7.21)	1.02 (0.61 to 1.72)
Non-cardiac (TGC, N = 273; CM, N = 259)	42 (15.38)	41 (15.83)	0.97 (0.61 to 1.54)

Information on vital status at 12 months was not available for 17 patients who were non-UK nationals.

TABLE 25 Attention and behaviour measures at 12 months (subgroup comprising children diagnosed with brain injury at trial entry)

Measure	TGC (N = 6)	CM (N = 7)
KOSCHI ^a		
1–4A [n (%)]	2 (33.3)	2 (28.7)
4B–5B [n (%)]	4 (66.7)	5 (71.4)
HUI ^a [mean (SE)]	0.74 (0.15)	0.97 (0.03)
Behaviour – CBCL total score ^b [mean (SD)]	62.8 (5.66)	55.6 (4.22)
CRS-R:S total score ^b [mean (SE)]	51.2 (5.53)	54.4 (5.40)

SE, standard error.

a Lower score indicates lower health status.

b Higher score indicates lower health status.

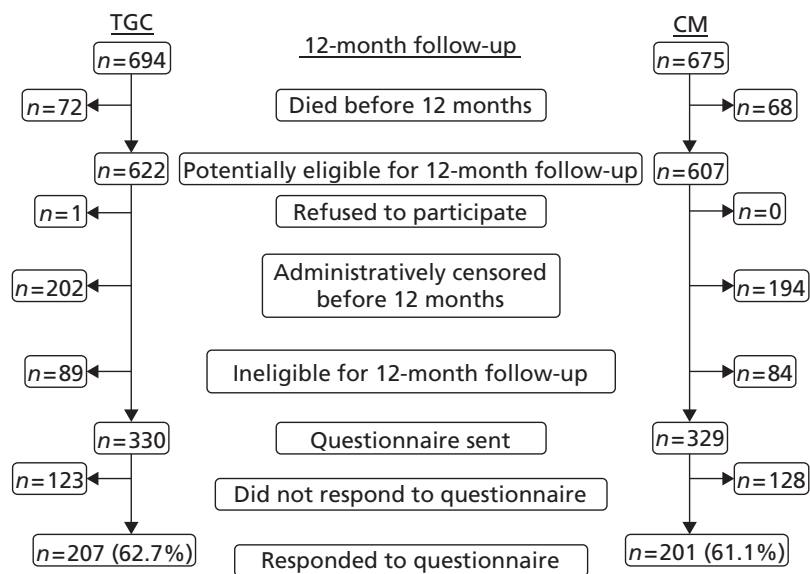


FIGURE 10 Flow chart for 12-month follow-up for service-use questionnaire.

TABLE 26 Levels of service use for questionnaire responders within 12 months post randomisation: whole study cohort

Service	TGC (n = 207) [mean (SD)]	CM (n = 201) [mean (SD)]
Inpatient hospital days following readmission ^a	6.12 (1.01)	6.63 (1.29)
Hospital outpatient visits	6.81 (0.46)	6.93 (0.45)
GP contacts	1.23 (0.12)	1.08 (0.99)
Practice nurse contacts	1.76 (0.21)	2.14 (0.29)
Health visitor contacts	5.85 (0.74)	6.87 (0.69)
Social worker contacts	0.10 (0.02)	0.08 (0.02)
Speech and language therapist contacts	2.18 (0.38)	1.88 (0.32)
Occupational therapist contacts	7.83 (1.80)	11.94 (2.30)
Other health service contacts	9.52 (1.13)	10.04 (1.11)

^a Readmissions to GM wards, to PICUs other than the one the patient was originally randomised to or readmissions to the same PICU that were after day 30.
Source: service-use questionnaire.

TABLE 27 Levels of service use for questionnaire responders within 12 months post randomisation: cardiac surgery subgroup

Service	TGC (n = 127) [mean (SD)]	CM (n = 121) [mean (SD)]
Inpatient hospital days following readmission ^a	7.10 (1.50)	8.25 (2.03)
Hospital outpatient visits	6.81 (0.59)	6.64 (0.55)
GP contacts	1.37 (0.17)	1.19 (0.13)
Practice nurse contacts	1.88 (0.25)	2.11 (0.05)
Health visitor contacts	6.24 (0.78)	8.24 (0.98)
Social worker contacts	0.05 (0.02)	0.03 (0.01)
Speech and language therapist contacts	2.32 (0.71)	1.77 (0.50)
Occupational therapist contacts	5.84 (1.99)	7.20 (2.26)
Other health service contacts	8.86 (1.31)	9.06 (1.44)

^a Readmissions to GM wards, to PICUs other than the one the patient was originally randomised to or readmissions to the same PICU that were after day 30.
Source: service-use questionnaire.

TABLE 28 Levels of service use for questionnaire responders within 12 months post randomisation: non-cardiac surgery subgroup

Service	TGC (n = 79) [mean (SD)]	CM (n = 80) [mean (SD)]
Inpatient hospital days ^a	4.54 (1.00)	4.15 (1.00)
Hospital outpatient visits	6.82 (0.75)	7.36 (0.75)
GP contacts	1.02 (0.19)	0.91 (0.13)
Practice nurse contacts	1.58 (0.39)	2.18 (0.53)
Health visitor contacts	5.22 (1.47)	4.78 (0.86)
Social worker contacts	0.17 (0.04)	0.17 (0.04)
Speech and language therapist contacts	2.32 (0.71)	1.77 (0.50)
Occupational therapist contacts	11.04 (3.45)	11.17 (4.58)
Other health service contacts	10.60 (2.08)	10.63 (1.97)

a Readmissions to GM wards, to PICUs other than the one the patient was originally randomised to or readmissions to the same PICU that were after day 30.
Source: service-use questionnaire.

TABLE 29 Costs (£) of health and personal social services for questionnaire responders, between discharge from the index admission and 12 months post randomisation: whole study cohort

Service	TGC (n = 207) [mean (SD)]	CM (n = 201) [mean (SD)]
Inpatient hospital days ^a	1367 (243)	1402 (264)
Hospital outpatient visits	1019 (66)	1002 (68)
GP contacts	51 (5)	58 (6)
Practice nurse contacts	13 (3)	10 (4)
Health visitor contacts	67 (8)	78 (8)
Social worker contacts	3 (1)	3 (1)
Speech and language therapist contacts	18 (3)	15 (3)
Other health service contacts	115 (15)	119 (15)

a Refers to readmissions to GM wards, to PICUs other than the one the patient was originally randomised to or readmissions to the same PICU that were after day 30.
Source: service-use questionnaire.

TABLE 30 Costs (£) of health and personal social services for questionnaire responders, between discharge from the index admission and 12 months post randomisation: cardiac surgery subgroup

Service	TGC (n = 127) [mean (SD)]	CM (n = 121) [mean (SD)]
Inpatient hospital days ^a	1576 (358)	1732 (414)
Hospital outpatient visits	976 (82)	1001 (87)
GP contacts	56 (6)	65 (8)
Practice nurse contacts	12 (5)	5 (3)
Health visitor contacts	71 (9)	94 (11)
Social worker contacts	2 (1)	1 (1)
Speech and language therapist contacts	17 (16)	16 (3)
Other health service contacts	107 (19)	104 (19)

a Readmissions to GM wards, to PICUs other than the one the patient was originally randomised to or readmissions to the same PICU that were after day 30.

Source: service-use questionnaire.

TABLE 31 Costs (£) of health and personal social services for questionnaire responders, between discharge from the index admission and 12 months post randomisation: non-cardiac subgroup

Service	TGC (n = 79) [mean (SD)]	CM (n = 80) [mean (SD)]
Hospital inpatient days ^a	1029 (256)	900 (211)
Hospital outpatient visits	1082 (111)	1004 (111)
GP contacts	48 (7)	48 (9)
Practice nurse contacts	16 (7)	17 (8)
Health visitor contacts	59 (17)	54 (10)
Social worker contacts	4 (11)	5 (11)
Speech and language therapist contacts	19 (6)	14 (4)
Other health service contacts	127 (25)	141 (26)

a Readmissions to GM wards, to PICUs other than the one the patient was originally randomised to or readmissions to the same PICU that were after day 30.

Source: service-use questionnaire.

Twelve-month total costs

Tables 32–34 report the total costs at 12 months across all the resource-use items recorded. The values presented are the results after using MI to handle missing values for health and community service costs at 12 months. Table 32 reports that, overall, the mean total costs were lower in the TGC than in the CM group, but with 95% CIs that encompass zero. For the cardiac surgery stratum, the mean total costs were similar between the groups (see Table 33), but, for non-cardiac patients, the mean costs were lower in the TGC than in the CM group, with an incremental cost of –£9865 (95% CI –£18,558 to –£1172) (see Table 34).

TABLE 32 Total costs (£) at 12 months post randomisation: whole study cohort

	TGC (n = 694) [mean (SD)]	CM (n = 675) [mean (SD)]	Incremental [mean (95% CI)]
Hospital costs at 30 days	16,228 (13,504)	17,005 (12,913)	
Hospital costs between 30 days and 12 months ^a	5683 (27,978)	8463 (35,366)	
Other hospital and community health service costs at 12 months ^b	2388 (3659)	2452 (4010)	
<i>Grand total costs up to 1 year</i>	<i>24,300 (34,503)</i>	<i>27,920 (42,775)</i>	<i>-3620 (-7743 to 502)</i>

a Includes index hospital admissions and readmissions to initial PICU that were within 30 days but that continued beyond day 30. Source: CRF.

b Includes other hospital readmissions, and other hospital and community service use. Source: service-use questionnaire.

TABLE 33 Total costs (£) at 12 months post randomisation: cardiac surgery subgroup

	TGC (n = 421) [mean (SD)]	CM (n = 416) [mean (SD)]	Incremental [mean (95% CI)]
Hospital costs at 30 days	14,465 (12,437)	14,350 (11,285)	
Hospital costs between 30 days and 12 months ^a	3811 (20,497)	3815 (17,720)	
Other hospital and community health service costs at 12 months ^b	2652 (3890)	2630 (4319)	
<i>Grand total costs up to 1 year</i>	<i>20,929 (27,385)</i>	<i>20,796 (26,520)</i>	<i>133 (-3568 to 3833)</i>

a Includes index hospital admissions and readmissions to initial PICU that were within 30 days but that continued beyond day 30. Source: CRF.

b Includes other hospital readmissions, and other hospital and community service use. Source: service-use questionnaire.

TABLE 34 Total costs (£) at 12 months post randomisation: non-cardiac surgery subgroup

	TGC (n = 273) [mean (SD)]	CM (n = 259) [mean (SD)]	Incremental [mean (95% CI)]
Hospital costs at 30 days	18,949 (14,614)	21,268 (14,183)	
Hospital costs between 30 days and 12 months ^a	8569 (36,495)	15,927 (51,688)	
Other hospital and community health service costs at 12 months ^b	1979 (3056)	2167 (3437)	
<i>Grand total costs up to 1 year</i>	<i>29,498 (4267)</i>	<i>39,363 (58,551)</i>	<i>-9865 (-18,558 to -1172)</i>

a Includes index hospital admissions and readmissions to initial PICU that were within 30 days but that continued beyond day 30. Source: CRF.

b Includes other hospital readmissions, and other hospital and community service use. Source: service-use questionnaire.

Figures 11–13 report SAs that investigate whether or not the base-case results are robust to alternative assumptions. The results show that the incremental costs under these alternative scenarios are similar to the base case. For example, in the SAs that include additional costs of staff time and tests associated with monitoring TGC, and further costs for managing hypoglycaemic episodes, the mean incremental costs of TGC overall and for the non-cardiac subgroup are similar to the base case (see Figures 11–13). Moreover, when alternative approaches were taken to unit costing, this had little impact on the results.

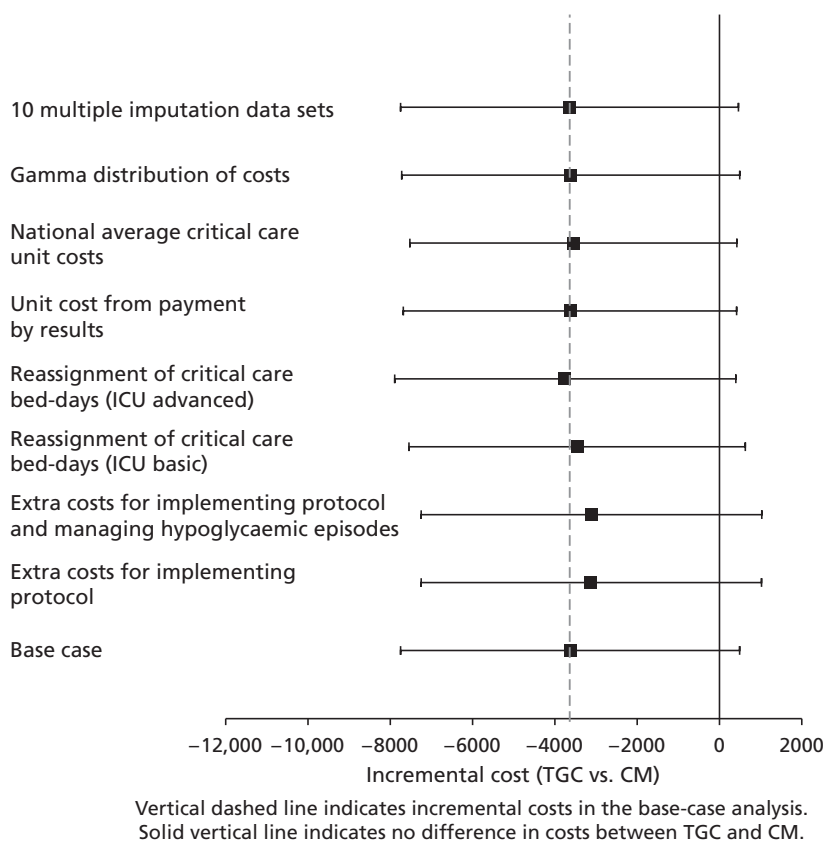


FIGURE 11 Sensitivity analysis reporting mean total costs at 12 months post randomisation according to alternative assumptions: whole study cohort.

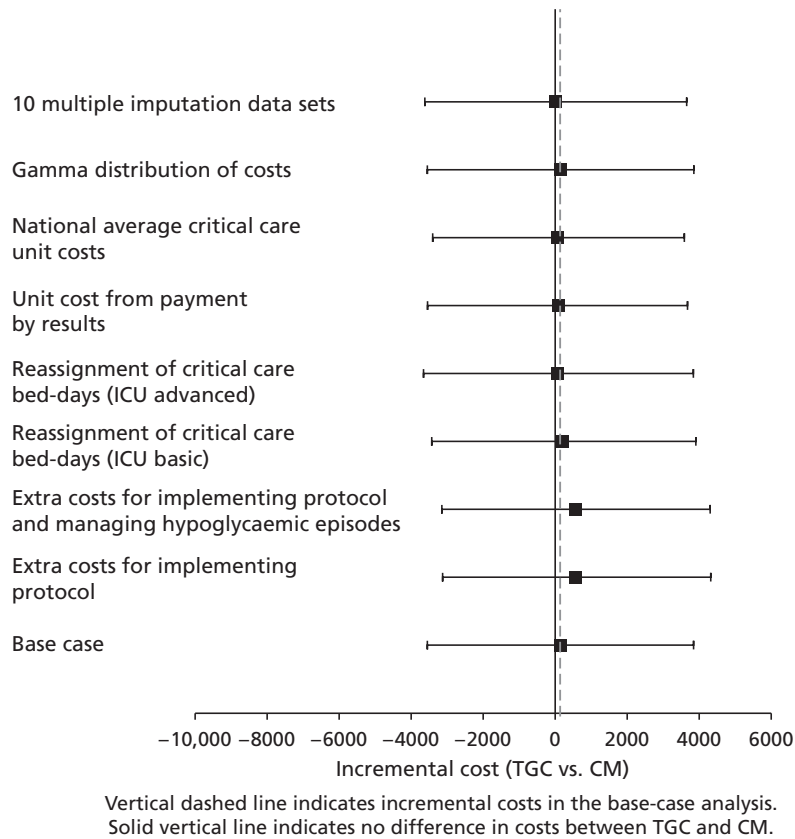


FIGURE 12 Sensitivity analysis reporting mean total costs at 12 months post randomisation according to alternative assumptions: cardiac surgery subgroup.

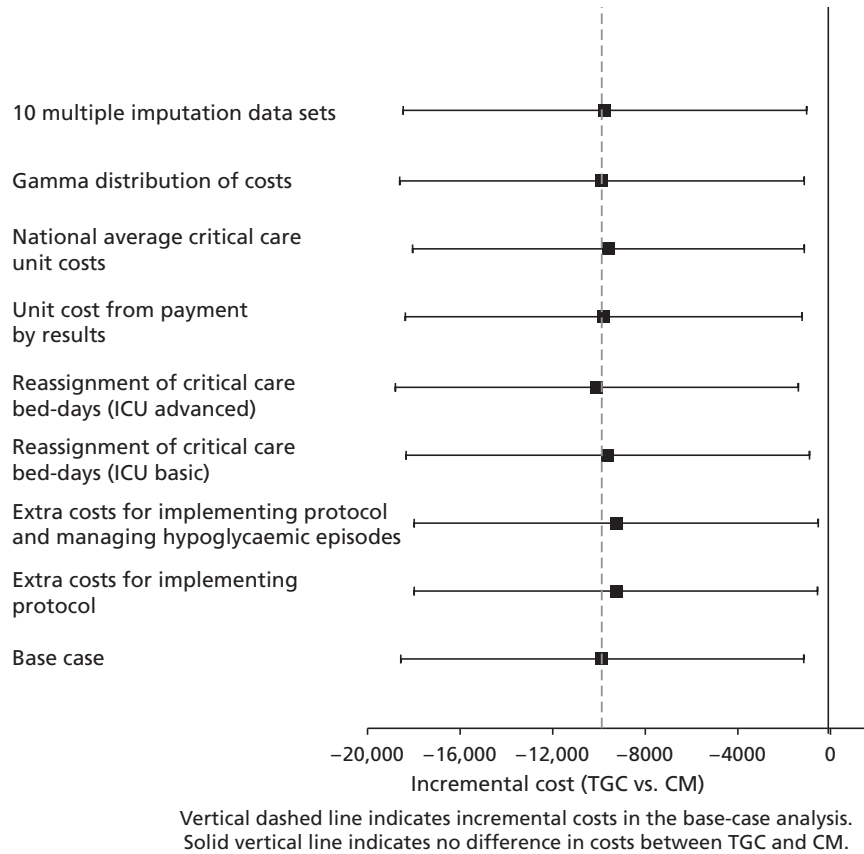


FIGURE 13 Sensitivity analysis reporting mean total costs at 12 months post randomisation according to alternative assumptions: non-cardiac surgery subgroup.

Lifetime cost-effectiveness results

The Kaplan–Meier survival curves show that when the time horizon was extended beyond 1 year, for those for whom survival data were available, the probability of survival remained similar between arms (*Figure 14*).

Figure 15 considers alternative parametric extrapolations for both treatment arms combined, using the observed survival data after day 30. Of the alternative survival functions, the Gompertz function appears to fit the observed data best in that it reports the lowest Akaike and Bayesian information criterion (*Table 35*). The Gompertz function also offers the most plausible projections of future survival (*Table 36*), in that the levels of excess death compared with those for the age- and gender-matched general population remain constant over time from 2 years post randomisation onwards.

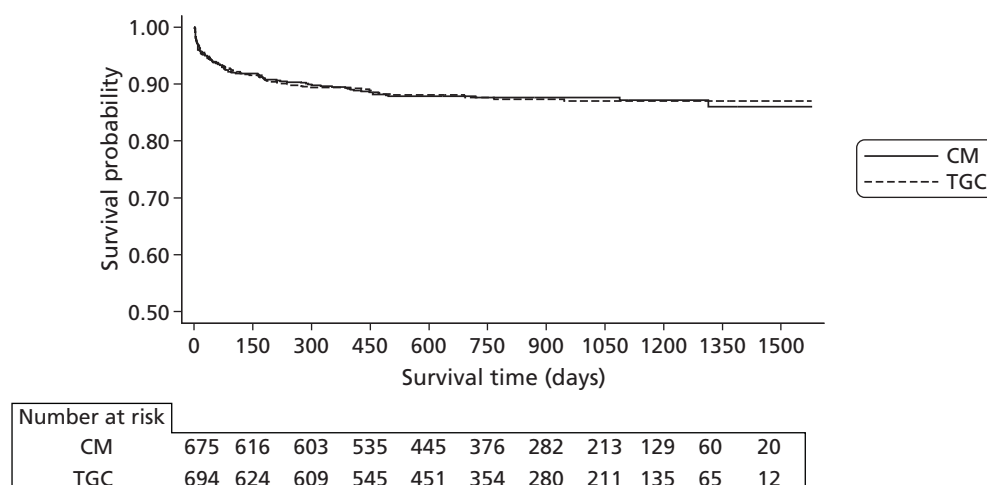


FIGURE 14 Kaplan–Meier survival curves. Overall cohort, TGC vs. CM.

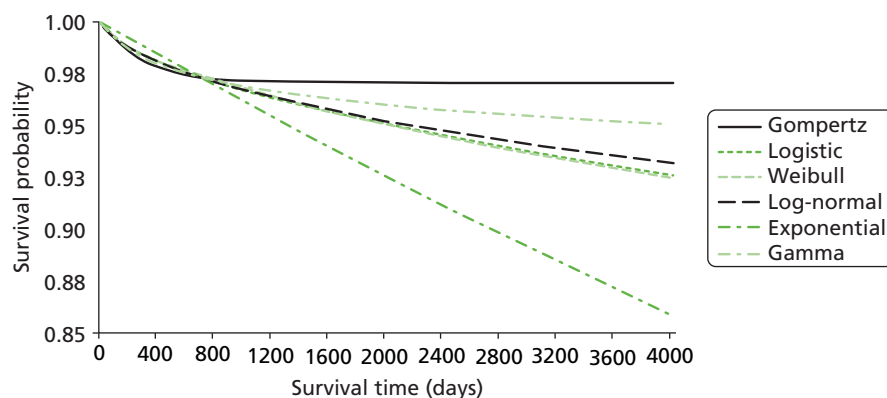


FIGURE 15 Comparison of alternative parametric extrapolations for survival from 12 months to 5 years post randomisation, across both randomised arms.

TABLE 35 Fit of alternative parametric survival functions applied to the CHiP study data after day 365

Distribution	AIC	BIC
Gompertz	305.9559	326.3428
Gamma	302.0634	327.547
Log-normal	306.6391	327.026
Logistic	310.0006	330.3875
Weibull	310.2893	330.6762
Exponential	315.8474	331.1376

AIC, Akaike information criterion; BIC, Bayesian information criterion.

TABLE 36 Ratios of the death rates from applying alternative parametric extrapolations for all patients from the CHiP Study compared with the age- and gender-matched general population

Year	Gompertz	Logistic	Weibull	Log-normal	Exponential	Gamma
1	6.51	5.60	5.57	5.65	3.55	6.05
2	4.86	4.49	4.46	4.58	4.25	4.72
3	5.28	5.85	5.82	5.90	6.67	5.67
4	5.31	6.96	6.95	6.91	8.97	6.28
5	5.23	7.89	7.89	7.73	11.12	6.70

Tables 37–39 present the resultant life-years, QALYs, lifetime costs and INBs according to the base-case assumptions. Overall, at a threshold of £20,000 per QALY, the INBs are positive, but with wide 95% CIs that include zero. For cardiac patients, the INBs are close to zero with wide CIs. For non-cardiac patients, the INBs are positive but with 95% CIs that include zero.

The cost-effectiveness acceptability curves consider alternative thresholds of willingness to pay for a QALY gain, and show that, overall and for the cardiac surgery stratum, it is highly uncertain whether or not TGC is cost-effective (Figures 16 and 17). For the non-cardiac stratum, the probability that TGC is cost-effective is relatively high. For example, at ceiling ratios of £10,000 to £30,000 per QALY, the probability that TGC is cost-effective ranges from 90% to 70% (Figure 18).

The SA on the lifetime results suggests that these findings are robust to alternative assumptions about the extrapolation of long-term survival, QoL for PICU survivors or long-term costs (Figures 19–21).

TABLE 37 Lifetime cost-effectiveness analysis: mean (SD) costs (£), life-years and INBs (£): whole study cohort

	TGC (<i>n</i> = 694) [mean (SD)]	CM (<i>n</i> = 675) [mean (SD)]	Incremental [mean (95% CI)]
Lifetime costs	27,330 (34,262)	30,951 (42,600)	-3620 (-7723 to 482)
Life-years	24.99 (8.58)	25.01 (8.58)	-0.02 (-0.93 to 0.89)
QALY	18.25 (6.26)	18.26 (6.27)	-0.01 (-0.68 to 0.65)
INBs			3346 (-11,203 to 17,894)

Costs, QALYs and life-years all discounted at 3.5%; INBs calculated by valuing a QALY gain at a threshold of £20,000 per QALY.

TABLE 38 Lifetime cost-effectiveness analysis: mean (SD) costs (£), life-years and INBs (£): cardiac surgery subgroup

	TGC (<i>n</i> = 421) [mean (SD)]	CM (<i>n</i> = 416) [mean (SD)]	Incremental [mean (95% CI)]
Lifetime costs	24,066 (27,139)	23,939 (26,304)	128 (-3542 to 3797)
Life-years	25.97 (7.33)	26.03 (7.26)	-0.05 (-1.04 to 0.94)
QALY	18.96 (5.35)	19.00 (5.30)	-0.04 (-0.76 to 0.68)
INBs			-919 (-16,661 to 14,823)

Costs, QALYs and life-years all discounted at 3.5%; INBs calculated by valuing a QALY gain at a threshold of £20,000 per QALY.

TABLE 39 Lifetime cost-effectiveness analysis: mean (SD) costs (£), life-years and INBs (£): non-cardiac surgery subgroup

	TGC (<i>n</i> = 273) [mean (SD)]	CM (<i>n</i> = 259) [mean (SD)]	Incremental [mean (95% CI)]
Lifetime costs	32,364 (42,515)	42,214 (58,432)	-9850 (-18,521 to -1180)
Life-years	23.48 (10.03)	23.38 (10.15)	0.10 (-1.62 to 1.82)
QALY	17.14 (7.32)	17.07 (7.41)	0.07 (-1.18 to 1.33)
INBs			11,322 (-15,791 to 38,615)

Costs, QALYs and life-years all discounted at 3.5%; INBs calculated by valuing a QALY gain at a threshold of £20,000 per QALY.

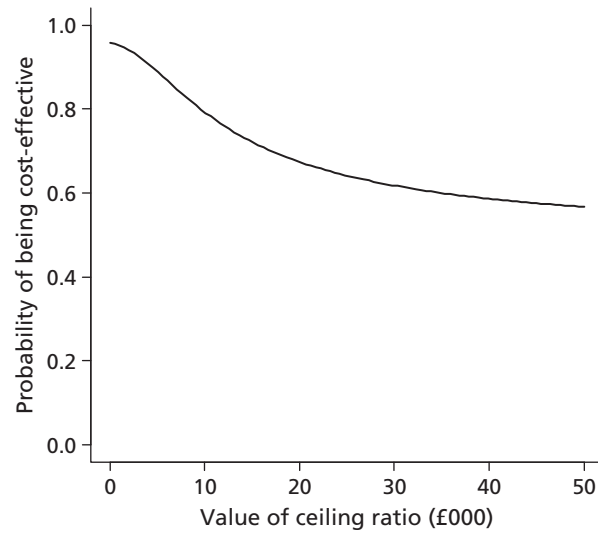


FIGURE 16 Probability that TGC vs. CM is cost-effective at alternative levels of willingness to pay for a life-year gained: whole study cohort.

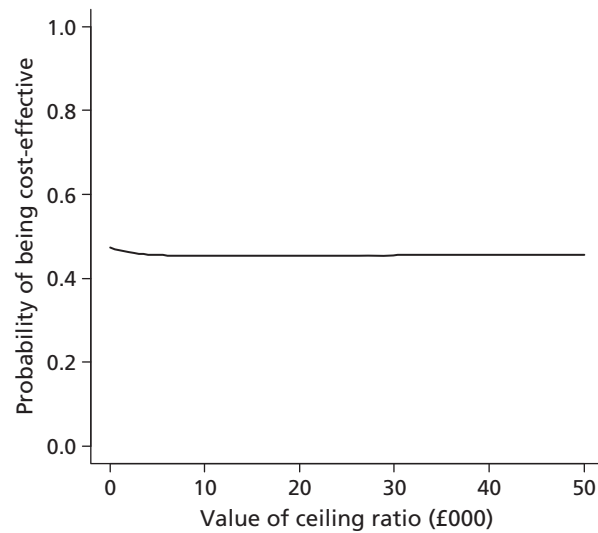


FIGURE 17 Probability that TGC vs. CM is cost-effective at alternative levels of willingness to pay for a life-year gained: cardiac surgery subgroup.

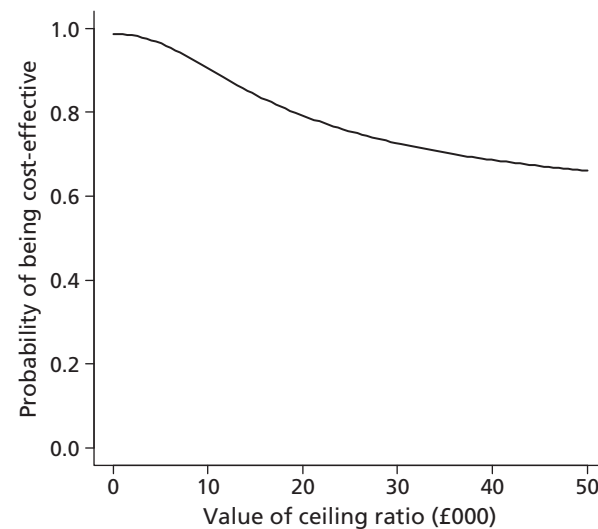


FIGURE 18 Probability that TGC vs. CM is cost-effective at alternative levels of willingness to pay for a life-year gained: non-cardiac surgery subgroup.

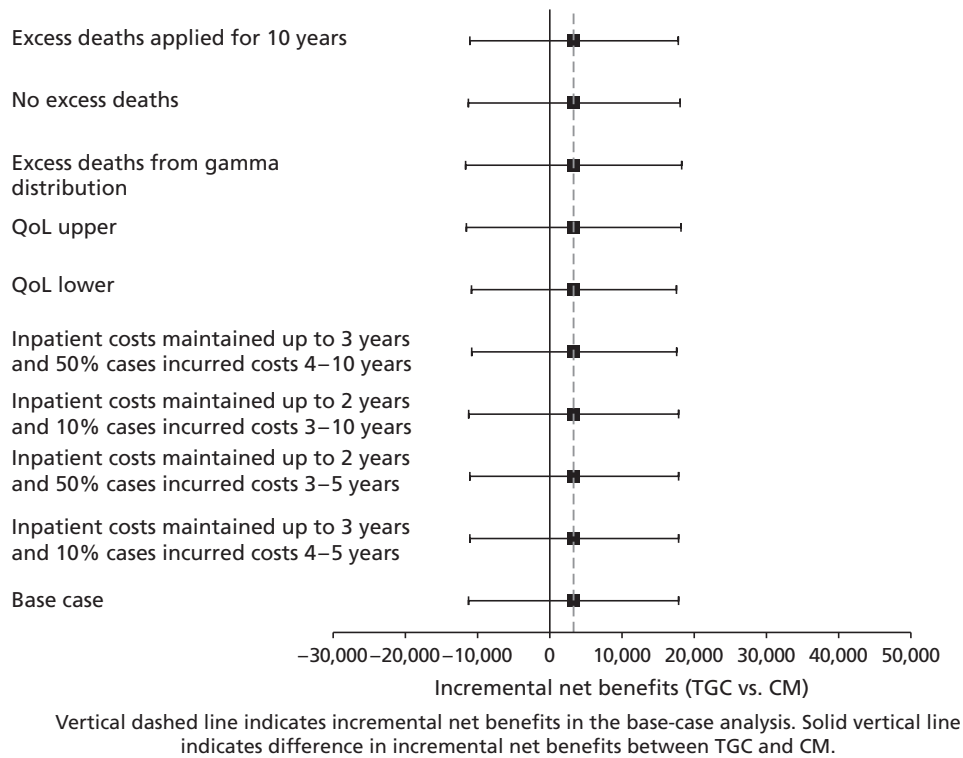


FIGURE 19 Sensitivity analysis reporting lifetime INBs (£) according to alternative assumptions: whole study cohort.

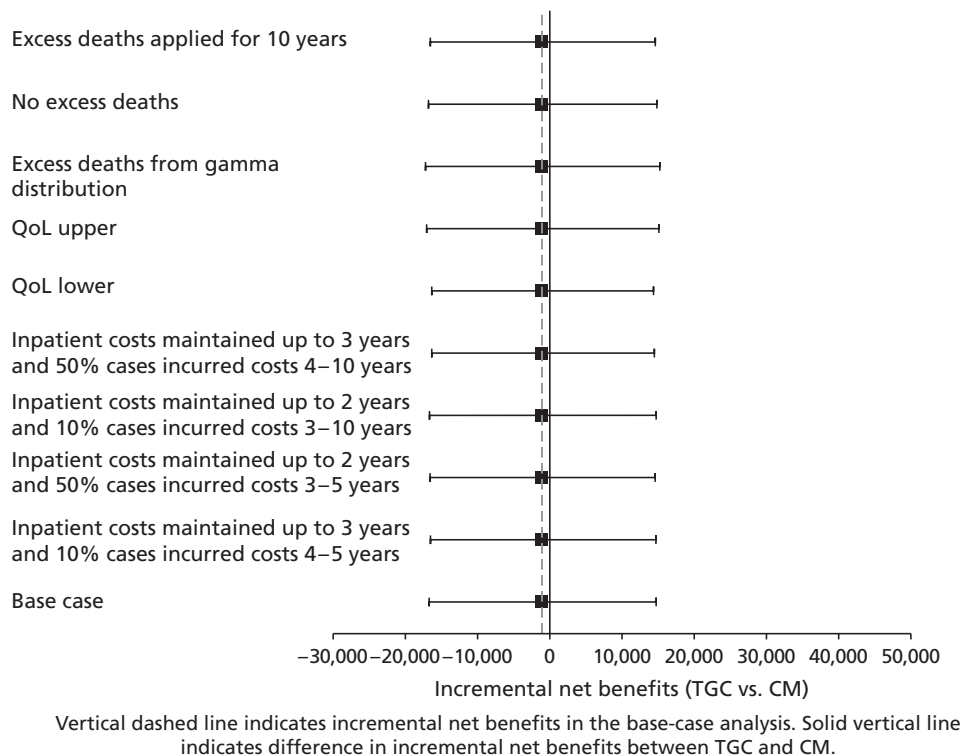


FIGURE 20 Sensitivity analysis reporting lifetime INBs (£) according to alternative assumptions: cardiac surgery subgroup.

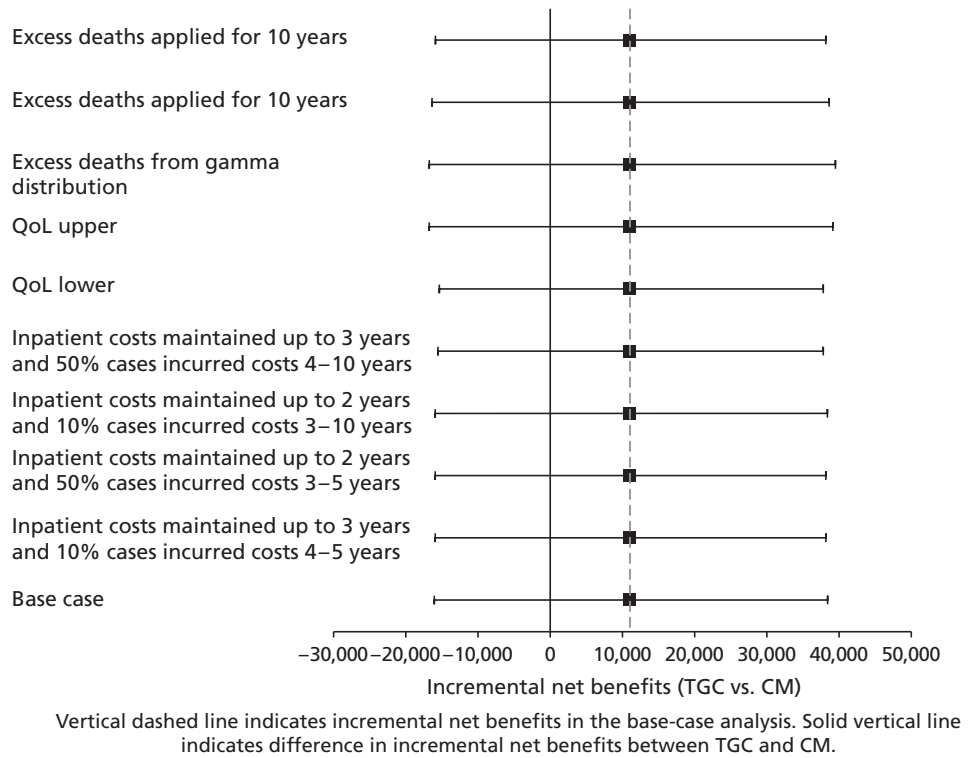


FIGURE 21 Sensitivity analysis reporting lifetime INBs (£) according to alternative assumptions: non-cardiac surgery subgroup.

Chapter 4 Discussion

The aims of the CHiP trial were to evaluate the clinical effectiveness, safety and cost-effectiveness of a policy of TGC compared with CM for an overall population of children in PICUs and for subgroups admitted to PICU following cardiac surgery or for other reasons. The results suggest that, overall, TGC has no effects on major clinical outcomes such as death and/or ventilator days, whether at 30 days or at 1 year. However, the secondary outcomes reveal a complex relationship of gains and potential harm from the intervention. TGC results in a slight reduction in the proportion of patients receiving RRT, but hypoglycaemia occurs in a greater proportion of patients in the TGC arm than in the CM arm of the study (severe hypoglycaemia 7.3% vs. 1.5%). TGC reduces mean hospital LOS and total costs at 12 months after PICU admission. The lower costs reflect the reductions in PICU days and total hospital LOS for the subgroup not admitted for cardiac surgery. For children admitted for cardiac surgery, the LOS and costs are similar between the randomised arms.

It is interesting to speculate why there might be a differential effect of TGC on non-cardiac surgery cases as opposed to cardiac surgery cases. Hyperglycaemia is known to be associated with the activation of alternative metabolic pathways for glucose, some of which have the potential to generate reactive metabolites or trigger inflammatory pathways. Insulin, in contrast, can promote an anti-inflammatory milieu. Cardiopulmonary bypass has often been proposed as a proxy model for inflammation, in that it is known to be associated with the activation of major inflammatory pathways. Recent developments in clinical strategies are thought to have improved outcomes in children undergoing cardiopulmonary bypass. For instance, corticosteroids, modified ultrafiltration, low-prime-volume circuits and newer circuit components have been shown to, or are assumed to, favourably modify these inflammatory processes. It may be, therefore, that cardiac surgery in children is no longer associated with 'sufficient' inflammatory pathway activation for TGC to result in significant clinical benefit. In contrast, in the non-cardiac surgery cases, stress hyperglycaemia from sepsis and a variety of other medical conditions may, in fact, be truly detrimental,²⁹ and hence control of the derangement is important for survival and limiting renal injury. Given that these problems may take days to manifest, it is entirely possible that the effects may be more identifiable at later time points, for example at 60 or even 90 days.

The finding that TGC leads to an average reduction in 12-month costs of approximately £10,000 for the non-cardiac surgery subgroup is robust to alternative stand points (such as the inclusion of any additional costs from monitoring the increased number of hypoglycaemic episodes in the TGC arm). The lifetime cost-effectiveness analysis suggests that it is highly uncertain that TGC is cost-effective in the cardiac surgery subgroup, whereas, for children admitted for other reasons, TGC appears relatively cost-effective. Therefore, for the patients not admitted for cardiac surgery, the findings from this study suggest that a TGC protocol would lead to earlier discharge from PICUs and hospital, leading to possible cost savings.

The potential NHS cost savings from a TGC policy can be estimated by combining the CHiP findings with projections of the annual incidence of eligible cases using the trial screening logs, or the PICANet⁴⁹ database. The trial screening logs suggest that approximately 1300 admissions per year from the 13 CHiP centres would be eligible for TGC in routine practice, approximately 500 of which (around 40%) would be admitted for reasons other than cardiac surgery. If implementing TGC rather than CM for this subgroup does reduce average costs per patient by £10,000, then TGC could yield annual cost savings of around 5 million pounds in the CHiP centres alone. This approach underestimates total cost reductions, as not all potentially eligible cases were screened in CHiP centres, and some PICUs in England and Wales did not participate in the study.

PICANet provides an alternative source for calculating the annual incidence of eligible cases; it includes all PICUs in England and Wales and avoids undercounting the incidence of eligible cases from incomplete screening. We applied the main CHiP eligibility criteria to PICANet data from 2004–11. This includes all children who stayed for > 2 days in PIC in England and Wales, who received inotropes and mechanical ventilation and who were not admitted following cardiac surgery. The result was approximately

1500 admissions per year. To allow for the other CHiP eligibility criteria, which could not be applied to PICANet data, we reduced the anticipated number of admissions by 20% to 1200 per year, which gives annual cost savings to the NHS in England and Wales of approximately £12M. This approximation recognises that most, but not all, of the inclusion criteria required for children to be eligible for TGC could be applied to the PICANet data. More fundamentally, it should be recognised that introducing a policy of TGC would not realise full financial cost savings. Instead, PICU and hospital beds would be 'released' if patients were discharged earlier and other patients were allowed to use these resources.

Limitations

The primary end point in the study was selected based on the best evidence at the time and took into account usual practice in reporting short-term outcomes in studies conducted on critically ill patients. Our results, however, indicate that for non-cardiac surgical cases, it may be better to assess VFDs or QoL at a later time point, for example day 60, in future studies.

The cost-effectiveness analysis has some limitations. First, the level of activity was measured only within PICUs and only for up to day 30, after which general PICU costs were assumed. But analysis using different assumptions made little difference to the results. Second, there were some missing data on follow-up costs and at 12 months from administrative censoring owing to study funding, but also non-response to questionnaire. This was handled using MI, which assumes that data are missing conditional on baseline factors and other end point and process measures that are observed; therefore, if missingness is driven by unobserved prognostic factors, this could have led to biased estimates. However, for questionnaire responders, the follow-up costs were similar between the groups. Third, like previous RCTs in PIC, this study did not measure QoL. Instead, the cost-effectiveness analysis used QoL data from a previous study that included children admitted to UK PICUs who were at least 6-months-old.⁷¹ It is unclear whether or not the QoL values from this sample of older children (median age of approximately 5-years-old) apply directly to the population represented by CHiP patients. However, the results of the SA suggest that the lifetime cost-effectiveness results were robust to the QoL value assumed for PICU survivors. Four, the cost-effectiveness analysis required that survival data from the CHiP trial were extrapolated over the lifetime. The analysis took a standard approach and applied the parametric survival function that was judged most plausible. There was no evidence from the survival data available from CHiP of any differences in survival up to 24 months, and the SA again shows results were robust to alternative assumptions.

Strengths

The CHiP trial addressed both clinical and economic questions, with follow-up at 12 months. The trial was the largest RCT in PIC, and was rigorously designed and conducted. Randomisation reduced the potential for selection bias at trial entry, and there was no loss to follow-up for the primary outcome. Although the local clinicians could not be blinded to allocation post randomisation, the use of a hard outcome (mortality) as an integral component of the 30-day primary outcome ensured the risk of biased outcome assessment was low, and it is not plausible that LOS would be influenced by allocation across the range of PICUs involved. The reasonably small number of secondary outcomes reduced the risks of problems associated with multiple testing.

There was careful preparation and training for the introduction of the clinical management protocol with a run-in period and minor adjustments to address any concerns about risks of hypoglycaemia. The delivery of TGC may be further improved by the use of continuous glucose monitoring systems,⁷² including those with paediatric decision support.

The biggest drivers of cost differences between the arms were PICU and total hospital LOS. For the vast majority of patients (99%), these resource-use data were measured until they were discharge from their

index hospital admission or following readmission to the PICU within 30 days, and up to a maximum of 12 months from randomisation. The study employed careful resource-use and cost measurement, estimated from large sample patient-level data drawing on the PCCMDS, which provided reasonable inference on costs. State-of-the-art approaches to handling missing 12-month cost data were used. The study also recorded use of other hospital and community health services and found that reductions in hospital LOS for the TGC arm were not offset by increased use of other services.

The CHiP trial was conducted in a large proportion of the PICUs in England, increasing the generalisability of the clinical and cost-effectiveness results to other UK PICUs, and other settings with similar populations and systems of care.

As the largest PICU trial to date, CHiP had sufficient power to reliably assess whether the balance of costs and benefits differed depending on if the admission was following cardiac surgery or not and to provide reasonable inference on costs.

The results of the economic evaluation were subject to extensive SAs and were robust to alternative assumptions, including, for example, the approaches taken to unit costing or the projection of life expectancy from the trial data.

The CHiP trial results in context

In considering how the CHiP trial results compare with other research, we have drawn on the trials of TGC with adults in critical care, with preterm neonates in neonatal ICUs (NICU) and with children in PICUs, using studies published prior to CHiP's initiation and reviewed in *Chapter 1*, and later relevant studies in different populations of critically ill patients. The particular emphases here are the size and type of effect of the intervention, the rate of hypoglycaemia and the differential effect in medical and surgical populations. There are some distinctions in these classifications between the CHiP trial and the adult studies. About a third of the patients in the Leuven surgical trial²⁴ underwent surgery that was not cardiovascular, and, in the CHiP trial, general surgery was incorporated in the non-cardiac surgery group. The CHiP trial stratification of cardiac surgical and non-cardiac surgical does, however, allow direct comparison with the Leuven paediatric study⁷³ and the ongoing US paediatric cardiac surgical study.⁷⁴

Adults

The CHiP trial findings differ from those of the initial adult study from the Leuven group.²⁴ In patients randomised to receive TGC in an adult surgical intensive care setting, Van den Berghe *et al.*²⁴ reported substantial reductions in mortality, other important complications of intensive care, and length of PICU and hospital stay. By contrast, the CHiP trial found no difference in mortality or VFD-30, and only minimal differences in secondary outcomes in the cardiac surgical subgroup. For the non-cardiac surgical subgroup from the CHiP trial, however, findings follow those from the Leuven²⁵ study in critically ill, adult patients not admitted for surgery. Neither study found benefits for TGC on major clinical end points, but both studies found that TGC reduced hospital LOS, and reduced hospital costs.

Since these studies, several more trials and two meta-analyses have been published. The largest trial, the Normoglycaemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE SUGAR),⁷⁵ was an international RCT that enrolled 6104 adults undergoing intensive care to undergo TGC (target blood glucose range 4.5–6.0 mmol/l) or conventional blood glucose control (target ≤ 10.0 mmol/l). Contrary to the Leuven studies, the NICE SUGAR investigators found that TGC increased mortality. A total of 829 patients in the TGC group (27.5%) died compared with 751 (24.9%) in the conventional-control group (odds ratio for intensive control 1.14, 95% CI 1.02 to 1.28, $p = 0.02$). Treatment effects did not differ significantly between surgical and non-surgical groups. There was no significant difference between the treatment groups in the median number of days in ICU, but severe hypoglycaemia (blood glucose level ≤ 2.2 mmol/l) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014

(0.5%) in the conventional-control group (odds ratio 14.7, 95% CI 9.0 to 25.9, $p < 0.001$). No long-term sequelae of severe hypoglycaemia were reported.

In 2008, Wiener *et al.*⁷⁶ reported a meta-analysis of TGC in critically ill adults. In total, the authors identified 8432 patients in 34 randomised trials (23 full publications, 9 abstracts, 2 unpublished studies) and did not find a survival benefit of TGC, but showed that TGC was associated with an increased risk of hypoglycaemia (glucose ≤ 2.2 mmol/l; 13.7% vs. 2.5%; RR, 5.13; 95% CI 4.09 to 6.43). This increased risk was fairly consistent across different ICU settings (surgical, medical and mixed). Most trials reported that very few of the hypoglycaemic events were associated with overt symptoms, but some studies found that patients who experienced hypoglycaemia had a higher risk of death.

A later meta-analysis,⁷⁷ which contained 26 adult studies including the NICE SUGAR trial, also concluded that TGC conferred no overall benefit among critically ill patients. A subanalysis of five trials that included only surgical patients suggested possible benefits from TGC, although the predominant influence on this subgroup was the original Leuven study,²⁴ which contributed 765 of the 1037 patients in the TGC group and 783 of 935 patients in the control group. The differences between the two meta-analyses were likely to be a result of their inclusion criteria, with the positive results for surgical patients in the Griesdale meta-analysis reflecting publication bias from excluding unpublished trials with negative results.

A major impetus for the CHiP trial was the concern that the results of trials in adult ICUs may not be easily transferable to children. In 2008 and 2009, two trials did report results for children.

Preterm neonates

The NIRTURE (neonatal insulin therapy in Europe) study⁷⁸ enrolled 389 very low-birthweight neonates from eight NICUs in the UK and mainland Europe. The trial sought to determine whether or not early insulin replacement (continuous infusion of insulin at a dose of 0.05 IU/kg/hour with 20% dextrose support) on days 1–7 reduced hyperglycaemia and affected outcomes in preterm newborns compared with standard neonatal care, the primary outcome being death at the expected date of delivery (EDD).

The early insulin group had significantly more carbohydrate infused and less weight loss in the first week than infants in the control group. However, more infants in the early insulin group had episodes of hypoglycaemia (< 2.6 mmol/l) than in the control group (29% vs. 17%; odds ratio 2.21; 95% CI 1.34 to 3.65; $p < 0.005$). In prespecified subgroup analyses, the increase in hypoglycaemia was significant only in the infants with a birth weight of > 1 kg (34% vs. 12% in the control group; odds ratio 3.96; 95% CI 1.85 to 8.47; $p < 0.001$). There was no increase in hypoglycaemia in infants with a birth weight of < 1 kg (26% in the early insulin group vs. 23% in the control group; odds ratio 1.17; 95% CI 0.60 to 2.28; $p = 0.7$). Clinicians reported episodes of hypoglycaemia in 17 infants in the early insulin group (8.8%) (including two who had protocol violations and four who were withdrawn from the study) and in three in the control group (1.6%). Episodes of hypoglycaemia were not associated with clinical alterations in physiology.

The trial was stopped early by the TSC on the advice of the independent Data Monitoring Committee for a combination of futility in terms of the primary mortality outcome, and concerns about potential harm in terms of an excess of ventricular haemorrhage and parenchymal lesions on cerebral ultrasound scans. There was no statistically significant difference in the primary outcome of mortality at EDD (14% vs. 9%; odds ratio 1.64; 95% CI 0.87 to 3.03; $p = 0.2$), or duration of neonatal intensive care, but mortality at 28 days was increased in the TGC group (12% vs. 6%; odds ratio 2.22; 95% CI 1.04 to 4.76; $p = 0.04$).

The authors speculated that the results might be due to a smaller difference in the levels of glucose control than seen in their pilot study, or too short a period (7 days) of insulin replacement. The design of this study was fundamentally different from other TGC studies in that a constant dose of insulin was infused, and blood glucose levels normalised by increasing the amount of glucose infused. This different methodology and the obvious developmental differences between the preterm infants included in this study and term or older infants and children in the CHiP trial make direct comparisons difficult to interpret.

Children

We are aware of only one published RCT that has investigated the effects of TGC in critically ill infants and children. This single-centre trial⁷³ evaluated whether or not targeting age-adjusted normoglycaemia (TGC) would improve outcomes. This trial enrolled 700 children, 317 of whom were < 1 year of age, with 75% admitted for cardiac surgery. Patients were randomly assigned to normoglycaemia/TGC, defined as 2.8–4.4 mmol/l in infants and 3.9–5.6 mmol/l in children, with insulin infusion throughout their PICU stay. Primary end points were duration of PICU stay and inflammation, C-reactive protein.

Hypoglycaemia (blood glucose \leq 2.2 mmol/l) occurred in 87 (25%) patients in the intensively targeted blood glucose group ($p < 0.0001$) compared with five (1%) patients in the conventional group; hypoglycaemia, defined as blood glucose < 1.7 mmol/l, arose in 17 (5%) patients in the intensive insulin group (15 infants and 2 children) and in 3 (1%) in the conventional group (two infants and one child) ($p = 0.001$). Hypoglycaemia (\leq 2.2 mmol/l) occurred at a median of day 2 (interquartile range 1–5) in the intensive insulin group compared with day 1 (1–3) in the conventional group ($p = 0.29$). Hypoglycaemia (\leq 2.2 mmol/l) on more than two occasions occurred in 18 patients (5%) treated with intensive insulin compared with none in the conventional group.

The study found that TGC reduced the duration of PICU stay from a mean of 6.15 days (95% CI 5.25 days to 7.05 days) in the control group to 5.51 days (95% CI 4.65 days to 6.37 days; $p = 0.017$). The number of patients whose stay in the ICU was extended (> median) was 132 (38%) in the intensively targeted blood glucose group compared with 165 (47%) in the conventional group ($p = 0.013$). TGC resulted in a greater reduction in C-reactive protein at day 5 compared with baseline [–9.75 mg/l (95% CI –19.93 mg/l to 0.43 mg/l) vs. 8.97 mg/l (95% CI –0.9 mg/l to 18.84 mg/l), $p = 0.007$], indicating an attenuated inflammatory response.

As in the CHiP trial, Vlasselaers *et al.*⁷³ noted a lower requirement for RRT in those children managed by TGC (0.6% vs. 1.7%) than in their control group. This difference did not reach statistical significance, perhaps owing to small numbers requiring dialysis, but a reduction in RRT was shown in the meta-analysis by Wiener *et al.*⁷⁶ (RR 0.64, 95% CI 0.45 to 0.92) when analysing their data using a fixed-effects model.

There were 20 deaths in the conventional group (5.7%), compared with nine deaths in the TGC group (2.6%, $p = 0.38$), but, given the substantially lower mortality rates in PIC than usually experienced in adult populations, the study was not powered for a mortality end point.

During the course of the CHiP trial, the results of these trials and meta-analyses were noted by the CHiP TSC and DMEC. The continuing uncertainty with regards to the clinical effectiveness and safety of TGC were noted, together with the absence of evidence on its long-term clinical effectiveness and cost-effectiveness.

Although the Leuven paediatric trial is the most similar to the CHiP trial, the two trials differ in a number of important respects. First, the CHiP trial is twice as large, giving more power to determine whether or not TGC led to different outcomes in the cardiac surgical and non-cardiac surgical subpopulations. Three-quarters of the Leuven trial population underwent cardiac surgery, but the two strata are not reported separately. Second, the CHiP trial is also a test of the potential diffusibility of TGC across a range of PICUs, contrasting with the Leuven paediatric study, which was a single-centre trial from an 'early adopting' setting. Third, the hypoglycaemia rates were lower in the CHiP trial, possibly as a result of the choice of lower glucose control ranges for TGC in the Leuven paediatric study. Finally, the CHiP trial measured the impact of TGC over a longer follow-up period and included a rigorous economic evaluation.⁷³

Vlasselaers and colleagues are conducting a longer-term follow-up of the children enrolled in their study (D Vlasselaers, Catholic University of Leuven, 2011, personal communication). In addition, other groups are planning or are recruiting to⁷⁴ similar clinical trials, the findings of which will add to those of the Leuven and CHiP trials, and further inform clinicians about the risks and benefits of TGC.

Chapter 5 Conclusions

Implications for health care

For the cardiac surgery subgroup, average costs at 12 months post randomisation were similar between arms and TGC was unlikely to be cost-effective. For children admitted to PICUs following cardiac surgery, our study suggests that PICUs should not adopt TGC and should continue with CM.

For children admitted to PICUs for other reasons, although TGC did not improve short-term clinical outcomes compared with CM, children in this subgroup were discharged earlier from hospital. This clinical benefit (earlier discharge) was associated with substantially reduced NHS costs. These average reductions in NHS costs were not offset by increased use of community health services in the TGC versus CM arm.

This is the first study to find that TGC may be cost-effective in children in PIC who were not admitted for cardiac surgery. Before a policy of TGC can be recommended for this important subgroup of NHS patients (around 1200 patients per year), careful consideration should be given to the balance of risk and benefit of this intervention: between the small increased risk of hypoglycaemia and the potential reduction in length of hospital stay and associated cost savings.

Recommendations for further research

The findings of the CHiP trial raise the following important questions:

- *Does the excess rate of moderate and severe hypoglycaemia during TGC for children admitted to PICUs for reasons other than cardiac surgery have an impact on long-term neurodevelopmental outcomes?*

Before a policy of TGC can be recommended for children admitted to PICUs for reasons other than cardiac surgery, further information is needed about the long-term implications of the small increased risk of hypoglycaemia. Over 100 children in the CHiP trial experienced at least one episode of moderate or severe hypoglycaemia. In the first instance, we will undertake a post-hoc analysis of the data along the lines of the recent analysis of hypoglycaemia complicating TGC in adults that was published in the *New England Journal of Medicine*. One of the CHiP investigators has been in contact with the lead investigator of NICE SUGAR and plans are being made for the post-hoc data evaluation. Subsequently, a neurodevelopmental follow-up study of these children would inform clinicians of the long-term risk of hypoglycaemia in this population.

- *Can we improve the delivery of TGC to minimise the risk of hypoglycaemia?*

If a policy of TGC is to be recommended for children admitted to PICUs for reasons other than cardiac surgery, research is needed to further refine clinical algorithms for the delivery of TGC, and to assess whether or not delivery of TGC may be further improved by the use of continuous glucose monitoring systems,⁷² including those with paediatric decision support.

- *Does TGC in critically ill children protect the kidneys from injury?*

One hypothesis raised by the CHiP trial is that TGC can reduce acute kidney injury (AKI). AKI is a common complication of critical illness, which in its most severe form requires RRT. Children requiring RRT have a prolonged stay in PICU and increased mortality ($\approx 40\%$). Children in the TGC arm in CHiP

had a lower incidence of RRT than those in the CM arm. However, RRT represents the most severe end of the spectrum of AKI and is a rare outcome compared with lesser degrees of AKI. An add-on study in CHiP patients could provide more precise measures of AKI, through estimation of daily glomerular filtration rate from sequential plasma creatinine values obtained as part of routine clinical care. Creatinine values would be retrieved from laboratory databases and statistical analysis would be undertaken to investigate this research question.

- *Do the findings from CHiP apply to routine clinical practice?*

The CHiP RCT had a pragmatic design, included the majority of English PICUs and had broad patient eligibility criteria. However, as with any RCT, the findings might not apply directly to routine clinical practice. Inevitably, the CHiP centres did not screen all potential patients, and eligible patients were excluded for various reasons, for example because of refused consent. Further, the CM delivered in the CHiP study may differ from that provided routinely. These potential concerns illustrate the general challenge that RCT findings might not apply directly to routine clinical practice. To address these issues, further research is required that develops an approach for maximising external validity. One possible approach to extending the CHiP findings would be to carefully assess the external validity of the study findings using PICANet data. This further research could examine whether or not the patients' baseline characteristics, resource use, costs and outcomes following CM in CHiP differed from those observed in routine clinical practice. This setting, with a large RCT nested within an observational data set, would provide an opportunity for considering whether or not results from pragmatic trials such as CHiP have external validity.

- *What can be learnt from triallists, clinicians, parents and older children about their experiences of participating in CHiP, to aid the design and conduct of future PICU trials?*

As more PICU RCTs assessing treatments in the NHS are funded, it is important for their success to learn from the experiences of participants in existing trials. A substantial body of research on participants' experiences of NICU trials aided development of CHiP trial procedures, but there is currently no equivalent literature from PICUs. As the largest UK PICU trial to date, CHiP offers a timely opportunity for such work. Qualitative research exploring clinician and family experiences of implementing the CHiP protocol would inform the conduct of future PICU trials.

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The UK Paediatric Intensive Care Society Study Group

Publication

Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, *et al.* A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med* 2014;**370**:107–18.

Contributions of authors

Duncan Macrae (Consultant in Paediatric Intensive Care) was the chief investigator. He was involved in the design and conduct of research and was a member of the trial development group, the project management group and the TSC. He was also involved in the development and refinement of the trial protocol, the conduct of the research interpretation and the reporting of results, and he revised the manuscript for important intellectual content.

Richard Grieve (Reader in Health Economics) led the health economic evaluation and was involved in the design and conduct of research, the trial development group, the project management group and the TSC, the statistical analysis, and the interpretation and reporting of results. He wrote the economic evaluation sections of the report and revised the manuscript for important intellectual content.

Elizabeth Allen (Senior Lecturer in Medical Statistics) was the lead statistician and was involved in the design and conduct of research, the Data Monitoring Committee, the project management team, the interpretation and reporting of results, and the draft and revision of the manuscript for important intellectual content.

Zia Sadique (Research Fellow in Health Economics) undertook the majority of the health economics analysis and was involved in the design and conduct of research, the project management team, the interpretation and reporting of results, and revision of the manuscript for important intellectual content.

Helen Betts (Lead Research Nurse, London) was involved in the set up, conduct and acquisition of data of this research and in the preparation of the manuscript.

Kevin Morris (Consultant Paediatric Intensivist) was a member of the trial development group, the TMG and the TSC. He was the PI for Birmingham Children's Hospital. He was involved in the development and refinement of the trial protocol, the conduct of the research, acquisition of data, the interpretation and reporting of results, and revision of the manuscript for important intellectual content. In addition, he was chief investigator for an add-on study to CHIP investigating the mechanism of hyperglycaemia in critically ill children.

Vithayathil John Pappachan (Consultant Paediatric Intensivist) was the PI for University Hospitals Southampton NHS Foundation Trust and was involved in the conduct of research, trial design and management acquisition of data, the interpretation and reporting of result and manuscript preparation.

Roger Parslow (Senior Lecturer at the University of Leeds) was the PI for PICANet and was a member of the TMG involved in the conduct of research facilitating the acquisition of data, the interpretation and reporting of results and revision of the manuscript for important intellectual content.

Robert C Tasker (Professor of Neurology and Anaesthesia) was part of the senior management structure for the trial: he was involved with the conception and design of the trial, its conduct of research, and interpretation and reporting of results. He helped draft and revise the manuscript for important intellectual content.

Paul Baines (Consultant Paediatric Intensivist) was the PI at Alder Hey Hospital and was involved in the conduct of research, acquisition of data, and interpretation and reporting of results.

Michael Broadhead (Consultant Cardiac Intensivist) was the PI at Great Ormond Street Hospital for Children and was involved in the conduct of research, patient consent, data review and reporting.

Mark L Duthie (Consultant Paediatric Intensivist) was the PI for University Hospitals of Leicester and was involved in conduct of the trial, recruitment of subjects, reporting and interpretation of acquired data.

Peter-Marc Fortune (Consultant Paediatric Intensivist) was the PI for Royal Manchester Children's Hospital and was involved with the drafting of the trial protocols, conduct of the research and acquisition of data.

David Inwald (Senior Lecturer and Honorary Consultant Paediatric Intensivist) was the PI for Imperial College Healthcare NHS Trust and was involved in the conduct of research, acquisition of data, and interpretation and reporting of results.

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Carla Guerriero (Research Fellow in Health Economics) helped with the design and analysis of the health economic evaluation and was involved in the project management team and in the interpretation and reporting of results.

Deborah Piercy (Trial Manager) was the trial manager (until 2009) and was involved in the set up, running and management of the trial.

Zdenek Slavik (Consultant Paediatric Cardiologist/Intensivist) originally suggested carrying out a prospective study involving TGC in paediatric patients requiring intensive care treatment, and was involved in the initial discussion of its merits and initial planning stages of the trial.

Claire Snowdon (Qualitative Researcher) was a member of the TSC, was involved in the design of the trial communication strategies with parents, advised on the conduct of research and the acquisition of data in her role as TSC member and contributed to the reporting of results.

Laura Van Dyck (Trial Manager) was involved in the day-to-day running of the trial, in particular the data management, and was a member of the project management team.

Diana Elbourne (Professor of Healthcare Evaluation) was the lead investigator for trial design and management, and was involved in the design and conduct of the research, the trial development group, the project management group and the TSC, the statistical analysis, the interpretation and reporting of results, and revision of the manuscript for important intellectual content.

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Appendix 1 Consent/assent forms and patient information leaflets

Appendix 1a

CARDIAC Version 5 August 2010
PROTOCOL Version 6, August 2010

	Patient Name		
	CHiP Patient Study Number		
<h2>CONSENT FORM</h2> <p><i>Please initial box</i></p> <p><input type="checkbox"/> I confirm that I have read and understand the information sheet <i>CHiP: The Control of Hyperglycaemia In Paediatric Intensive Care Information</i> version 5, August 2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.</p> <p><input type="checkbox"/> I understand that my participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without his/her medical care or legal rights being affected.</p> <p><input type="checkbox"/> I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from The Royal Brompton Hospital, from regulatory authorities, from the NHS Trust or from the Data Coordinating Centre at the London School of Hygiene and Tropical Medicine where it is relevant to my child taking part in this research. I give permission for these individuals to have access to this information.</p> <p><input type="checkbox"/> I agree to my child's GP and Health Visitor (if relevant) being informed of his/her participation in the study.</p> <p><input type="checkbox"/> I agree that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my child's health status.</p> <p><input type="checkbox"/> I agree for researchers to contact me about the study after my child has been discharged from the hospital.</p> <p><input type="checkbox"/> I agree for my child to take part in the above study.</p>	Site Number		
		Principal Investigator	
Name of parent/ authorised legal representative	Relationship to child	date	signature
Name of person taking consent		date	signature



Patient name

CHIP Patient Study Number

Centre number

Please initial box

I re-confirm consent given pre-operatively.

Name of parent/ authorised legal representative

Relationship to child

date

signature

Name of person taking consent

date

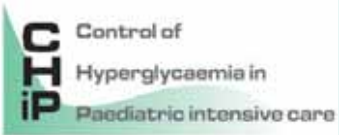
signature

ISRCTN61735247
EudraCT No: 2006/-005715/-10

Copies: Original to be kept in research site file 1 for hospital notes
1 for parent/authorised legal representative 1 for CRF

Appendix 1b

PICU Version 5 August 2010
 PROTOCOL Version 6, August 2010

	Patient Name	<input type="text"/>	
	CHiP Patient Study Number	<input type="text"/>	
<h1>CONSENT FORM</h1> <p><i>Please initial box</i></p> <p><input type="checkbox"/> I confirm that I have read and understand the information sheet <i>CHiP: The Control of Hyperglycaemia In Paediatric Intensive Care Information</i> version 5, August 2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.</p> <p><input type="checkbox"/> I understand that my participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without his/her medical care or legal rights being affected.</p> <p><input type="checkbox"/> I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from The Royal Brompton Hospital, from regulatory authorities, from the NHS Trust or from the Data Coordinating Centre at the London School of Hygiene and Tropical Medicine where it is relevant to my child taking part in this research. I give permission for these individuals to have access to this information.</p> <p><input type="checkbox"/> I agree to my child's GP and Health Visitor (if relevant) being informed of his/her participation in the study.</p> <p><input type="checkbox"/> I agree that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my child's health status.</p> <p><input type="checkbox"/> I agree for researchers to contact me about the study after my child has been discharged from the hospital.</p> <p><input type="checkbox"/> I agree for researchers to ask me if I would like to be sent a summary of the results of the study when available.</p> <p><input type="checkbox"/> I agree for my child to take part in the above study.</p>	Site Number	<input type="text"/>	<input type="text"/>
		Principal Investigator	<input type="text"/>
Name of parent/ authorised legal representative	<input type="text"/>		<input type="text"/>
Relationship to child	<input type="text"/>	date	
Name of person taking consent	<input type="text"/>		<input type="text"/>
	<input type="text"/>	date	

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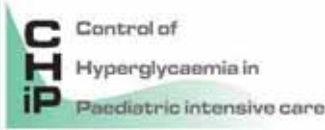
EudraCT No: 2006/-005715/-10

Copies: Original to be kept in research site file
 1 for parent/authorised legal representative

1 for hospital notes
 1 for CRF

Appendix 1c

YP Version 5 August 2010
 PROTOCOL Version 6, August 2010



Patient Name

CHIP Patient Study Number

Site Number

Principal Investigator

ASSENT FORM

Young person to circle all they agree with

YES **NO** Have you read about this project?

YES **NO** Has somebody else explained about this project to you?

YES **NO** Do you understand what this project is about?

YES **NO** Have you asked all the questions you want?

YES **NO** Have you had your questions answered in a way you understand?

YES **NO** Do you understand it is OK to stop taking part at any time?

YES **NO** Are you happy to take part?

If any answers are 'No' or you do not want to take part, don't sign your name!

If you do want to take part, you can write your name below

Your name

Date

The doctor who explained this project needs to sign too:

Name of doctor

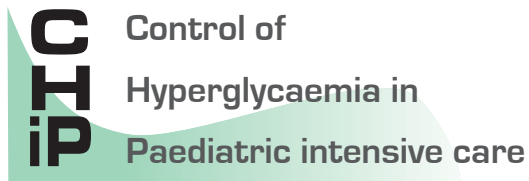
Date

ISRCTN61735247
 EudraCT No: 2006/-005715/-10

Copies: Original to be kept in research site file
 1 for parent/authorised legal representative

1 for hospital notes
 1 for CRF

Appendix 1d



PATIENT INFORMATION LEAFLET

For parents/guardians of children likely to have cardiac surgery

CARDIAC

1. Introduction

Your child is being invited to take part in a nationwide medical research study called CHiP. This information sheet gives you details about the study. We explain why we are asking you to think about taking part, and what you can expect if you agree. Please remember, you do not have to take part and the quality of your child's care will not be affected in any way, whatever you decide.

This information sheet is in two parts:

Part 1 tells you about why we are doing this study and what will happen if you agree for your child to take part.

Part 2 gives you some more information about how research studies like CHiP are run.

PART 1 2. Why is a study needed?

When babies, children and adults are in intensive care, the levels of sugar in their blood can go up. This is called hyperglycaemia. It can happen because they have had a serious illness, an injury, or surgery. In Paediatric Intensive Care we take small samples of blood regularly. We use these to check sugar levels. Babies and children with high blood sugar are usually treated with a drug called insulin, but only if the blood sugar reaches quite a high level. We measure the level of sugar with a scale called millimoles per litre, shortened to mmol/L. When the level reaches 12 (mmol/L), we would say that this is too high and should be treated.

In adults, some research has suggested that controlling the blood sugar levels *tightly* may speed recovery time. *Tight* control means checking the blood more often. If the sugar level is going up, we give insulin at around level 7, rather than waiting until it goes up to level 12 (we will tell you more about insulin later in this leaflet). This *tight* control may also be a promising treatment for children, but we do not know whether children will respond in the same way as adults.

If blood sugar levels are raised above normal this is called hyperglycaemia

3. Why has my child been chosen for this study?

Your child has been chosen for this study because s/he is likely to have a heart operation. After the operation s/he may need to spend a few days in the Paediatric Intensive Care Unit being helped to breathe by a machine called a ventilator and medicines to support his/her blood pressure. We are hoping that 1500 children on a ventilator will take part in the CHiP study. Doctors and nurses from Paediatric Intensive Care Units in ten hospitals are helping with the study. You have been given this information leaflet and asked if you would like to join the CHiP Study because your child is in one of these ten hospitals.

4. What is the study testing?

We are comparing two different ways of controlling blood sugar levels using insulin. Insulin is a drug that is used by lots of people who have diabetes. It is also used for

patients like your child who are in intensive care. It helps to control the level of sugar in their blood. Although we would use insulin, this does not mean that your child has diabetes.

We are doing the study to help us find out whether it is better to *tightly* control the sugar levels by giving insulin when the blood sugar rises above level 7 or to treat only when the sugar level reaches level 12. For each approach there might be advantages and disadvantages. The best way of finding out is to carry out a randomised study such as the CHiP Study. A randomised study is a way of comparing the effects of the two approaches. This is a good and a fair test of the two approaches.

We want to test whether tight control of blood sugar levels will help children and not do any harm.

5. What will happen to my child if we agree to take part?

For the CHiP Study, half of the children will be treated using one approach, *tight* control using insulin to keep the blood sugar between level 4 and 7. The other half will be treated using the *usual* approach, to treat with insulin if the sugar goes up to level 12 on two checks, tested 30 minutes apart. A computer is used to put each child into one of these two groups. It does this in a random way. This means that it uses chance, a bit like flipping a coin, to organise the two treatment groups.

A small blood sample will be taken without any pain from one of the drip lines which has already been inserted as part of the care of your child. It will be used to measure the level of blood sugar. Whichever treatment group your child is in, the insulin (if used) is given through a tube into a vein. Treatment if necessary will take place during the time your child is in Intensive Care. If your child is in the tight control group s/he is likely to receive more insulin than children in the usual treatment group. If his/her blood sugar levels do not go up then insulin will not be given, whichever group s/he is in.

Information about all of the children in the study will be collected while they are in hospital. The study team do not want to lose contact with you afterwards. Once you have taken your child home, the Study Manager from the CHiP Data Co-ordinating Centre in the London School of Hygiene and Tropical Medicine will write to you. She will ask if you will help with some more information later, as the CHiP Study team need to try to follow-up everyone who has been in the study. It would also be very helpful if you would agree that your child's name could be registered with the NHS Information Centre and the NHS Central Register. This would make it easier for the study team to contact you in the future and provide the study team with information about your child's health status even if you move house.

If you are happy for your child to take part in the CHiP Study, and are comfortable with the explanations from the doctors and nurses at this hospital, you will be asked to sign a consent form. We will check with you again if your child is admitted to

paediatric intensive care and become eligible for the study, to make sure that you are still happy to go ahead. A member of staff from the Unit will then make a telephone call to the study centre. The staff member will give the centre some details about your child and find out which study group your child will be in. This will tell the intensive care staff which of the two treatment approaches they will follow if sugar levels go up.

6. Does my child have to take part?

No, it is up to you to decide whether or not your child takes part. You are free to withdraw at any time without giving a reason. This would not affect the quality of care your child receives.

7. What treatment will my child get if s/he does not take part?

We will give your child the same treatment that all patients in paediatric intensive care would receive. This means that we would give insulin if the blood sugar levels go up to level 12 on two tests. The tests would be taken 30 minutes apart. If the blood sugar levels do not go up, then we would not need to use any insulin.

8. What are the possible benefits to my child from taking part?

We are doing this study because we do not know whether *tight* control of blood sugar produces better results. Some studies carried out in adults in intensive care have shown that patients treated with *tight* control of blood sugar do better but others have not shown any benefit of *tight* control. If children benefit in the same way as adults did in some of these studies, then *tight* control of blood sugar levels may be helpful in speeding up recovery time. We cannot promise the study will help your child but the information that we get might help other children in the future.

9. What are the possible side effects of the treatment and possible risks of taking part?

There is a possibility that for children in the *tight* control group, giving insulin at an earlier stage might mean that the level of sugar in the blood will drop BELOW normal. This is called hypoglycaemia (the opposite of hyperglycaemia where sugar levels are high). Mild hypoglycaemia can cause confusion and/or dizziness. Severe hypoglycaemia could cause brain damage but only if left untreated for a long time. Be reassured that the doctors and nurses in the CHiP Study will be carefully watching your child. If your child shows signs of hypoglycaemia, this will be picked up very quickly while still very mild and prompt action will be taken to treat it. The staff will stop the insulin treatment straightaway and will give extra sugar either by mouth or as a sugar solution through a drip.

For the children who are in the *usual* care group, who will receive insulin if the blood sugar level goes up to 12, the possible risks are different. For them there is the possibility that their sugar levels might get too high. This can affect how the organs of the body work, but as we have said, all the children in the study will be very carefully monitored. There are not thought to be any other risks to your child from taking part in the study.

10. Are there any other possible disadvantages?

If your child is in the *tight* control group he/she is likely to have more blood samples taken than if in the *usual* care group

Also we do appreciate that we are asking you to consider a research study when you are naturally feeling worried about your child and that this might be adding to your stress now.

11. What if there is a problem?

If you have any complaint about the way you or your child is dealt with during the study or feel that you had suffered any sort of harm, this will be addressed. The detailed information about this is given in Part 2.

12. Will taking part in the study be kept confidential?

Yes, all information about your child's participation in the study will be kept confidential. The details are included in Part 2.

13. Involvement of the Family Doctor (GP) and Health Visitor

With your permission, we will let your GP and health visitor know that your child is taking part in the study.

14. Your contact people for the study in this hospital are:

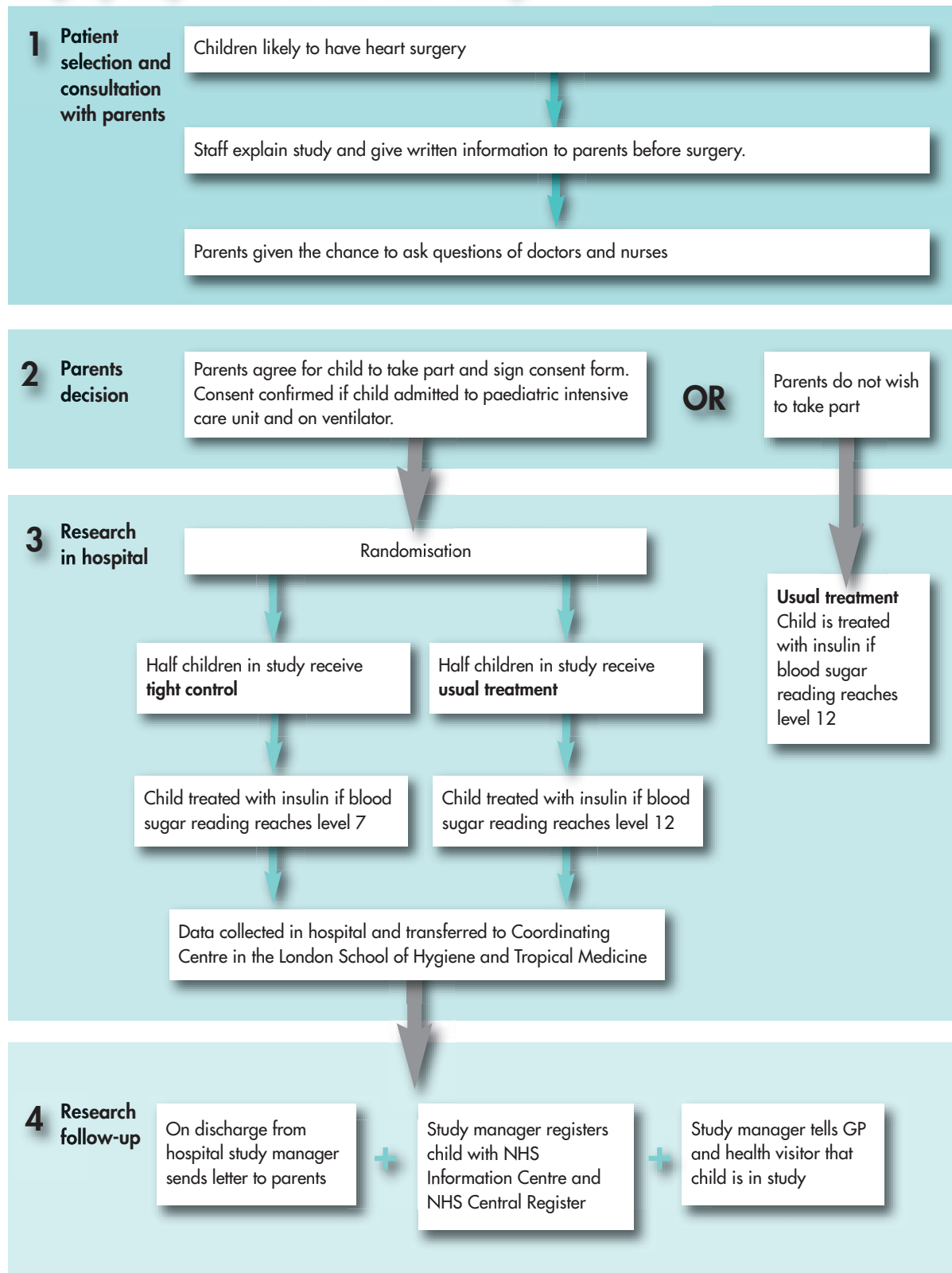
If the information in Part 1 has interested you and you are considering taking part in the CHiP Study, please continue to read the additional information in Part 2 before making a decision.

Principal Investigator name
Hospital address
tel:

CHiP Research Nurse name
CHiP Research Nurse
Hospital address
tel:

Complaints Manager name
Complaints Manager Title
tel:

Step by Step Guide to the CHiP Study



PART 2 *Part 2 gives you some more information about the conduct of research studies. Please read it before you agree to take part in the study.*

What will happen if I don't want my child to carry on with the study?

If you decide to take part in the study but then change your mind, just tell the research nurse or doctor. We will stop collecting information about your child and if you wish, any information we have already collected can be destroyed. If your child is in the *tight* control, s/he will instead be given usual care which is to give insulin at level 12. If your child is in the *usual* care group nothing will change.

Will my child's taking part in the study be kept confidential?

All information about your child (including your contact details) which is collected for the study will be kept securely and strictly confidentially within the study team (the hospital and the Data Co-ordinating Centre at the London School of Hygiene and Tropical Medicine), and your child's doctor (GP) and health visitor. We will not use your child's name in any analysis or in any reports that we write. The study team are responsible for analysing, storing and eventually destroying the data according to guidelines set by the National Health Service Research & Development Unit. Information will be kept for up to 15 years at the study centre.

What will happen to the results of the research study?

The results will be available when all the children have been followed up and the results analysed. This is likely to be in 2012. The research will be published in a scientific journal and the results publicised widely. A summary of the research and details of how to find the scientific publication will be posted on the study website (website www.chip-trial.org.uk). A summary of the results will be sent to parents if you let the Study Manager know that you would like to have this.

What if there is a problem?

If you have a concern about any aspect of the study you should ask to speak to Helen Betts (Lead Research nurse tel: 07854 980 072 or to the Chief Investigator, Dr. Duncan Macrae 020-7351 8546) who will do their best to answer your questions. If you remain unhappy and wish to make a formal complaint, you can do this through the NHS Complaints Procedure at this hospital (name and tel number to inserted for each collaborating hospital). The Royal Brompton and Harefield Trust is the sponsor of this research project. In the very unlikely event that your child is harmed due to someone's negligence, then you may have grounds for legal action against the sponsor of the research or NHS Trust but you may have to pay for it. This is the normal procedure, whether or not there is a research study. If you wish to complain about any aspect of the way your child has been approached or treated during the course of this study, all the normal health service complaints mechanisms are available to you.

Who is organising and funding the research?

The study is funded by the Health Technology Assessment Programme of the NHS. This study is co-ordinated by the Royal Brompton and Harefield NHS Trust and the London School of Hygiene and Tropical Medicine (LSHTM). The Royal Brompton Hospital is responsible for the conduct of the study. The research grant from the Health Technology Assessment Programme pays for the employment of research nurses and the study team at the LSHTM.

ChiP Study Team

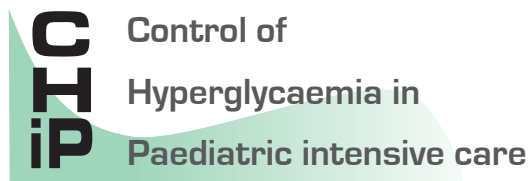
Dr Duncan Macrae, Chief Investigator CHiP Study
Royal Brompton Hospital
Tel: 020-7351 8546
Email: d.macrae@rbht.nhs.uk

Laura Van Dyck/Lucy Brooks, Study Manager
CHiP Data Co-ordinating Centre
London School of Hygiene and Tropical Medicine
Tel: 020-7927 2075
Email: Laura.VanDyck@lshtm.ac.uk/Lucy.Brooks@lshtm.ac.uk

This study was given a favourable ethical opinion for conduct in the NHS by the Brighton East Research Ethics Committee.

Thank you for taking the time to read this information

Appendix 1e



PATIENT INFORMATION LEAFLET

For parents/guardians of children in paediatric intensive care

PICU

1. Introduction

Your child is being invited to take part in a nationwide medical research study called CHiP. This information sheet gives you details about the study. We explain why we are asking you to think about taking part, and what you can expect if you agree. Please remember, you do not have to take part and the quality of your child's care will not be affected in any way, whatever you decide.

This information sheet is in two parts:

Part 1 tells you about why we are doing this study and what will happen if you agree for your child to take part.

Part 2 gives you some more information about how research studies like CHiP are run.

PART 1 2. Why is a study needed?

When babies, children and adults are in intensive care, the levels of sugar in their blood can go up. This is called hyperglycaemia. It can happen because they have had a serious illness, an injury, or surgery. In Paediatric Intensive Care we take small samples of blood regularly. We use these to check sugar levels. Babies and children with high blood sugar are usually treated with a drug called insulin, but only if the blood sugar reaches quite a high level. We measure the level of sugar with a scale called millimoles per litre, shortened to mmol/L. When the level reaches 12 (mmol/L), we would say that this is too high and should be treated.

In adults, some research has suggested that controlling the blood sugar levels *tightly* may speed recovery time. *Tight* control means checking the blood more often. If the sugar level is going up, we give insulin at around level 7, rather than waiting until it goes up to level 12 (we will tell you more about insulin later in this leaflet). This *tight* control may also be a promising treatment for children, but we do not know whether children will respond in the same way as adults.

If blood sugar levels are raised above normal this is called hyperglycaemia

3. Why has my child been chosen for this study?

Your child has been chosen for this study because s/he has developed a serious illness that needs the support of a ventilator and medicines to support his/her blood pressure. We are hoping that 1500 children on a ventilator will take part in the CHiP Study. Doctors and nurses from Paediatric Intensive Care Units in ten hospitals are helping with the study. You have been given this information leaflet and asked if you would like to join the CHiP Study because your child is in one of these ten hospitals.

4. What is the study testing?

We are comparing two different ways of controlling blood sugar levels using insulin. Insulin is a drug that is used by lots of people who have diabetes. It is also used for patients like your child who are in intensive care. It helps to control the level of sugar in their blood. Although we would use insulin, this does not mean that your child has diabetes.

We are doing the study to help us find out whether it is better to *tightly* control the sugar levels by giving insulin when the blood sugar rises above level 7 or to treat only when the sugar level reaches level 12. For each approach there might be advantages and disadvantages. The best way of finding out is to carry out a randomised study such as the CHiP Study. A randomised study is a way of comparing the effects of the two approaches. This is a good and a fair test of the two approaches.

We want to test whether tight control of blood sugar levels will help children and not do any harm.

5. What will happen to my child if we agree to take part?

For the CHiP Study, half of the children will be treated using one approach, *tight* control using insulin to keep the blood sugar between level 4 and 7. The other half will be treated using the *usual* approach, to treat with insulin if the sugar goes up to level 12 on two checks, tested 30 minutes apart. A computer is used to put each child into one of these two groups. It does this in a random way. This means that it uses chance, a bit like flipping a coin, to organise the two treatment groups.

A small blood sample will be taken without any pain from one of the drip lines which has already been inserted as part of the care of your child. It will be used to measure the level of blood sugar. Whichever treatment group your child is in, the insulin (if used) is given through a tube into a vein. Treatment if necessary will take place during the time your child is in Intensive Care. If your child is in the *tight* control group s/he is likely to receive more insulin than children in the *usual* treatment group. If his/her blood sugar levels do not go up then insulin will not be given, whichever group s/he is in.

Information about all of the children in the study will be collected while they are in hospital. The study team do not want to lose contact with you afterwards. Once you have taken your child home, the Study Manager from the CHiP Data Co-ordinating Centre in the London School of Hygiene and Tropical Medicine will write to you. She will ask if you will help with some more information later, as the CHiP Study team need to try to follow-up everyone who has been in the study. It would also be very helpful if you would agree that your child's name could be registered with the NHS Information Centre and the NHS Central Register. This would make it easier for the study team to contact you in the future and provide the study team with information about your child's health status even if you move house.

If you are happy for your child to take part in the CHiP Study, and are comfortable with the explanations from the doctors and nurses at this hospital, you will be asked to sign a consent form. A member of staff from the Unit will then make a telephone call to the study centre. The staff member will give the centre some details about your child and find out which study group your child will be in. This will tell the intensive care staff which of the two treatment approaches they will follow if sugar levels go up.

6. Does my child have to take part?

No, it is up to you to decide whether or not your child takes part. You are free to withdraw at any time without giving a reason. This would not affect the quality of care your child receives.

7. What treatment will my child get if s/he does not take part?

We will give your child the same treatment that all patients in paediatric intensive care would receive. This means that we would give insulin if the blood sugar levels go up to level 12 on two tests. The tests would be taken 30 minutes apart. If the blood sugar levels do not go up, then we would not need to use any insulin.

8. What are the possible benefits to my child from taking part?

We are doing this study because we do not know whether *tight* control of blood sugar produces better results. Some studies carried out in adults in intensive care have shown that patients treated with *tight* control of blood sugar do better but others have not shown any benefit of *tight* control. If children benefit in the same way as adults did in some of these studies, then *tight* control of blood sugar levels may be helpful in speeding up recovery time. We cannot promise the study will help your child but the information that we get might help other children in the future.

9. What are the possible side effects of the treatment and possible risks of taking part?

There is a possibility that for children in the *tight control* group, giving insulin at an earlier stage might mean that the level of sugar in the blood will drop BELOW normal. This is called hypoglycaemia (the opposite of hyperglycaemia where sugar levels are high). Mild hypoglycaemia can cause confusion and/or dizziness. Severe hypoglycaemia could cause brain damage but only if left untreated for a long time. Be reassured that the doctors and nurses in the CHiP Study will be carefully watching your child. If your child shows signs of hypoglycaemia, this will be picked up very quickly while still very mild and prompt action will be taken to treat it. The staff will stop the insulin treatment straightaway and will give extra sugar either by mouth or as a sugar solution through a drip.

For the children who are in the *usual* care group, who will receive insulin if the blood sugar level goes up to 12, the possible risks are different. For them there is the possibility that their sugar levels might get too high. This can affect how the organs of the body work, but as we have said, all the children in the study will be very carefully monitored. There are not thought to be any other risks to your child from taking part in the study.

10. Are there any other possible disadvantages?

If your child is in the *tight* control group he/she is likely to have more blood samples taken than if in the *usual* care group

Also we do appreciate that we are asking you to consider a research study when you are naturally feeling worried about your child and that this might be adding to your stress now.

11. What if there is a problem?

If you have any complaint about the way you or your child is dealt with during the study or feel that you had suffered any sort of harm, this will be addressed. The detailed information about this is given in Part 2.

12. Will taking part in the study be kept confidential?

Yes, all information about your child's participation in the study will be kept confidential. The details are included in Part 2.

13. Involvement of the Family Doctor (GP) and Health Visitor

With your permission, we will let your GP and health visitor know that your child is taking part in the study.

14. Your contact people for the study in this hospital are:

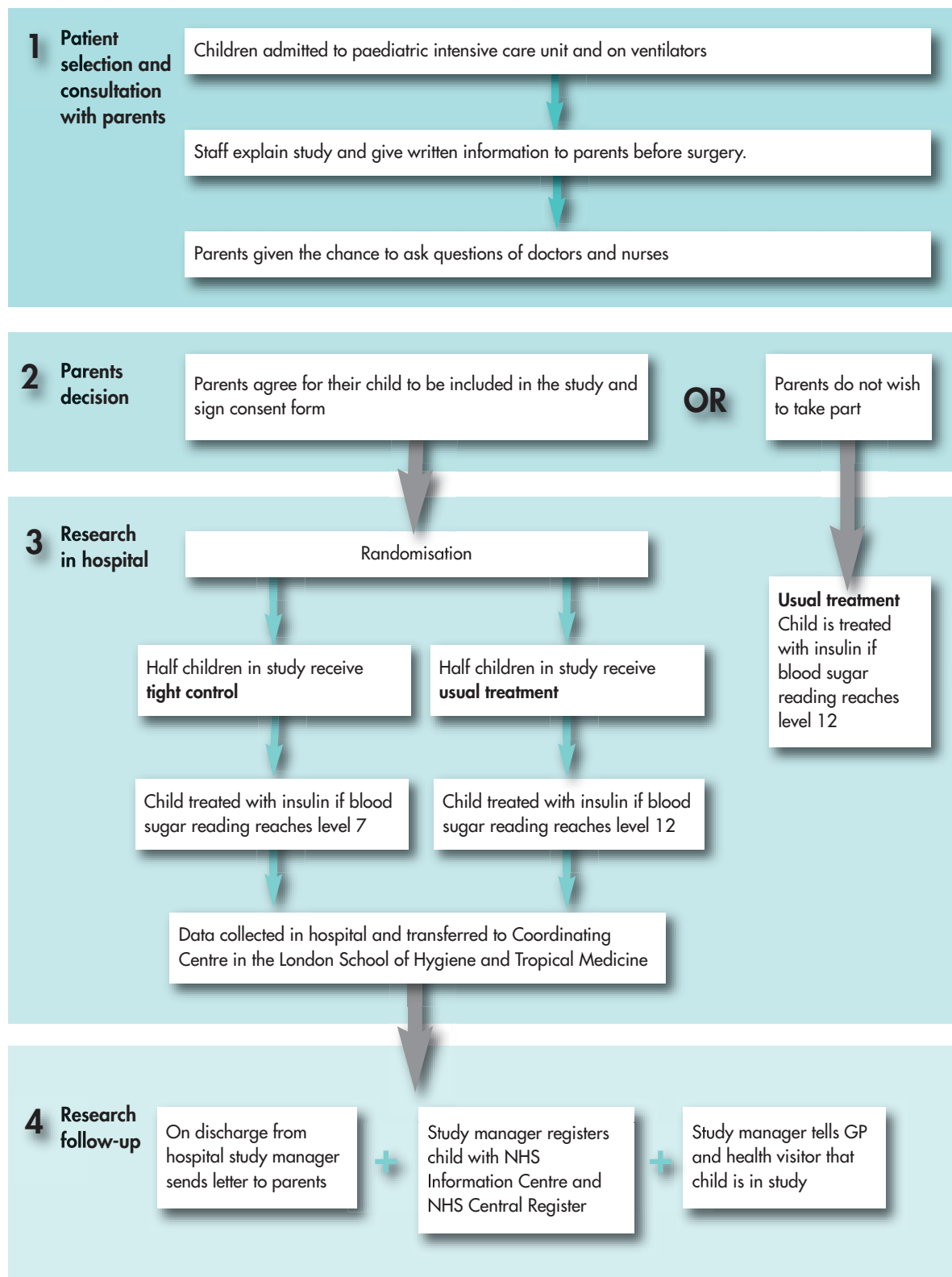
If the information in Part 1 has interested you and you are considering taking part in the CHiP Study, please continue to read the additional information in Part 2 before making a decision.

Principal Investigator name
Hospital address
tel:

CHiP Research Nurse name
CHiP Research Nurse
Hospital address
tel:

Complaints Manager name
Complaints Manager Title
tel:

Step by Step Guide to the CHiP Study



PART 2 *Part 2 gives you some more information about the conduct of research studies. Please read it before you agree to take part in the study.*

What will happen if I don't want my child to carry on with the study?

If you decide to take part in the study but then change your mind, just tell the research nurse or doctor. We will stop collecting information about your child and if you wish, any information we have already collected can be destroyed. If your child is in the *tight* control, s/he will instead be given *usual* care which is to give insulin at level 12. If your child is in the *usual* care group nothing will change.

Will my child's taking part in the study be kept confidential?

All information about your child (including your contact details) which is collected for the study will be kept securely and strictly confidentially within the study team (the hospital and the Data Co-ordinating Centre at the London School of Hygiene and Tropical Medicine), and your child's doctor (GP) and health visitor. We will not use your child's name in any analysis or in any reports that we write. The study team are responsible for analysing, storing and eventually destroying the data according to guidelines set by the National Health Service Research & Development Unit. Information will be kept for up to 15 years at the study centre.

What will happen to the results of the research study?

The results will be available when all the children have been followed up and the results analysed. This is likely to be in 2012. The research will be published in a scientific journal and the results publicised widely. A summary of the research and details of how to find the scientific publication will be posted on the study website (website www.chip-trial.org.uk). A summary of the results will be sent to parents if you let the Study Manager know that you would like to have this.

What if there is a problem?

If you have a concern about any aspect of the study you should ask to speak to Helen Betts (Lead Research nurse tel: 07854 980 072 or to the Chief Investigator, Dr Duncan Macrae 020-7351 8546) who will do their best to answer your questions. If you remain unhappy and wish to make a formal complaint, you can do this through the NHS Complaints Procedure at this hospital (name and tel number to inserted for each collaborating hospital). The Royal Brompton and Harefield Trust is the sponsor of this research project. In the very unlikely event that your child is harmed due to someone's negligence, then you may have grounds for legal action against the sponsor of the research or NHS Trust but you may have to pay for it. This is the normal procedure, whether or not there is a research study. If you wish to complain about any aspect of the way your child has been approached or treated during the course of this study, all the normal health service complaints mechanisms are available to you.

Who is organising and funding the research?

The study is funded by the Health Technology Assessment Programme of the NHS. This study is co-ordinated by the Royal Brompton and Harefield NHS Trust and the London School of Hygiene and Tropical Medicine (LSHTM). The Royal Brompton Hospital is responsible for the conduct of the study. The research grant from the Health Technology Assessment Programme pays for the employment of research nurses and the study team at the LSHTM.

ChiP Study Team

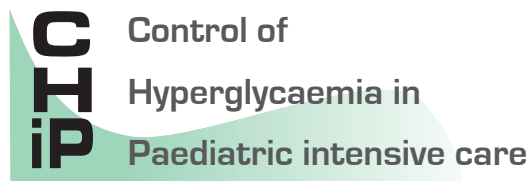
Dr Duncan Macrae, Chief Investigator CHiP Study
Royal Brompton Hospital
Tel: 020-7351 8546
Email: d.macrae@rbht.nhs.uk

Laura Van Dyck/Lucy Brooks, Study Manager
CHiP Data Co-ordinating Centre
London School of Hygiene and Tropical Medicine
Tel: 020-7927 2075
Email: Laura.VanDyck@lshtm.ac.uk/Lucy.Brooks@lshtm.ac.uk

This study was given a favourable ethical opinion for conduct in the NHS by the Brighton East Research Ethics Committee.

Thank you for taking the time to read this information

Appendix 1f



PATIENT INFORMATION LEAFLET

For young people likely to have heart surgery

YP

1. Introduction

We are asking if you would take part in a nationwide medical research study. This information sheet gives you details about the study. We explain why we are asking you to consider joining in. Please read this leaflet carefully. Talk about it with your parents/guardians and also with the doctor or nurse if you want to. Please remember that you do not have to take part.

This information sheet is in two parts:

Part 1 tells you about why we are doing this study and what will happen if you agree to join in.

Part 2 gives you some more information which you will need if you want to take part.

PART 1 2. Why are we doing this research?

Young people usually go into a Paediatric Intensive Care Unit after a heart operation. The levels of sugar in their blood can go up. This is called hyperglycaemia. It can happen because they have had an operation. In Paediatric Intensive Care, we take small samples of blood regularly. We use these to check sugar levels. Young people as well as children with high blood sugar are usually treated with a drug called insulin, but only if the blood sugar reaches quite a high level. We measure the level of sugar with a scale called millimoles per litre, shortened to mmol/L. When the level goes up to 12 (mmol/L), we would say that this is too high and should be treated.

Research with adults makes us think that controlling the blood sugar levels *tightly* may speed recovery time. *Tight* control means checking the blood more often. If the sugar level is going up, we give a drug called insulin at around level 7, rather than waiting until a higher level is reached. This *tight* control may also be a promising treatment for young people. However we do not know whether young people will respond in the same way as adults.

If blood sugar levels are raised above normal this is called hyperglycaemia

3. Why have I been asked to take part in this study?

We have given you this information leaflet because you may have an operation on your heart. After the operation you may need to spend a few days in the Paediatric Intensive Care Unit as you recover. You may need the help of a breathing machine (ventilator) and medicines to support your blood pressure. If you are on the ventilator you may be the sort of patient who could take part in this study. We are inviting 1500 children and young people to take part. Doctors and nurses from Paediatric Intensive Care Units in ten hospitals are helping with this study.

4. What is the study testing?

We are testing two different ways of controlling blood sugar levels using insulin. Insulin is a drug that helps to control the level of sugar in the blood. It is also used by people who have diabetes. Although we might use insulin for you, this does not mean that we think you have diabetes.

We are doing the study to help us find out whether it is better to *tightly* control the sugar levels. This means giving insulin when the blood sugar rises above level 7 or to treat only when the sugar level reaches level 12. For each way there might be advantages and disadvantages. The best method of finding out is to carry out a randomised study such as CHiP. This is a good and a fair test of the two ways of controlling blood sugar levels.

We want to test whether tight control of blood sugar levels will benefit young people and not do any harm.

5. What will happen to me if I agree to take part?

For CHiP half of the young people will be treated using one way. That is *tight* control using insulin to keep the blood sugar between level 4 and 7. The other half will be treated in the *usual* way. That is to treat with insulin if the sugar goes up to level 12 on two tests. A computer is used to put each young person into one of these two groups. It does this in a random way. This means that it uses chance, a bit like flipping a coin, to organise the two treatment groups.

A small blood sample will be taken without any pain from this tube which has already been put into your vein as part of your care. It will be used to measure the level of blood sugar. Whichever treatment group you are in, the insulin (if used) is given through this tube into a vein. Treatment will take place during the time you would be in the Intensive Care Unit. Young people in the *tight* control group are likely to receive more insulin than young people in the *usual* treatment group. If the blood sugar levels are not raised then insulin will not be given, whichever group you are in.

Information about you will be collected while you are in hospital. After you leave hospital the CHiP Study Manager from the Data Co-ordinating Centre in the London School of Hygiene and Tropical Medicine will write to your parents to follow-up your progress. We are also asking your parents if they will agree for the study team to give your name to the NHS Information Centre and the NHS Central Register. This will make it easier for the study team to contact you in the future even if you move house.

If you are admitted to the Paediatric Intensive Care Unit your parents will be asked if they still agree for you to be in the study. The staff will then make a telephone call to the study centre. They will give your details and find out which treatment group you are in.

6. Do I have to take part?

No it is up to you and your parents. If you are happy to take part, and have had your questions answered you will be asked to sign the form at the end of this leaflet. If you do not take part it would not affect the quality of care that you receive.

7. What treatment will I be given if I do not take part?

We will give your child the same treatment that all patients in paediatric intensive care would receive. This means that we would give insulin if the blood sugar levels go up to

level 12 on two tests. The tests would be taken 30 minutes apart. If the blood sugar levels do not go up, then we would not need to use any insulin.

8. What are the possible benefits from taking part?

We are doing this study because we do not know whether *tight* control of blood sugar produces better results. Some studies carried out in adults have shown that patients treated with *tight* control of blood sugar do better but others have not shown any benefit of *tight control*. If young people benefit in the same way as adults did in some of these studies, then *tight* control may be helpful in speeding recovery time. We cannot promise the study will help you. However the information we get might help other young people in the future.

9. What are the possible side effects of the treatment and possible risks of taking part?

For young people in the *tight* control group, there is a possibility that blood sugar levels will drop BELOW normal. This is called hypoglycaemia (the opposite of hyperglycaemia where sugar levels are high). Mild hypoglycaemia can cause confusion and/or dizziness. Severe hypoglycaemia could cause brain damage but only if left untreated for a long time. Be reassured that the doctors and nurses in the CHiP study will be carefully watching you. If you show signs of hypoglycaemia, this will be picked up very quickly while it still very mild. The staff will stop the insulin treatment straightaway and will give you extra sugar either by mouth or as a sugar solution through a drip.

For young people who are in the *usual* care group, who will receive insulin if the blood sugar level goes up to 12, the possible risks are different. For them there is the possibility that their sugar levels might go too high. This can affect how the organs of the body work, but as we have said, you will be very carefully checked. There are not thought to be any other risks to you from taking part.

10. Your contact people for the study in this hospital are:

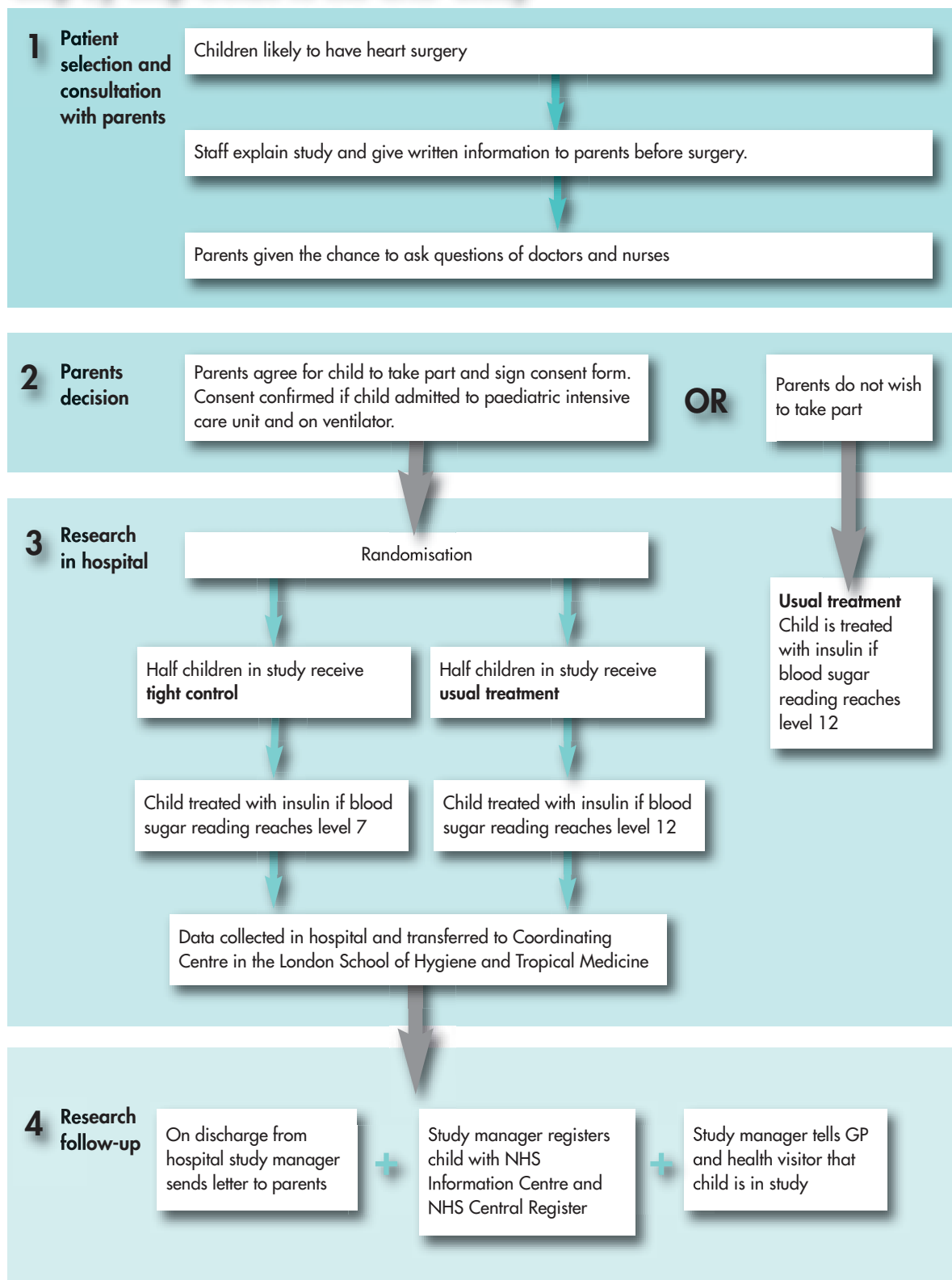
Principal Investigator name
Hospital address
tel:

CHiP Research Nurse name
CHiP Research Nurse
Hospital address
tel:

Complaints Manager name
Complaints Manager Title
tel:

Thank you for reading so far. If you are still interested please go to Part 2.

Step by Step Guide to the CHiP Study



PART 2 *Part 2 gives you some more information about the conduct of research studies. Please read it before you agree to take part in the study.*

What will happen if I don't want to carry on with the study?

If you decide to take part in the study but then change your mind, just tell the research nurse or doctor before you have your operation. Your parents may change their mind after you have had your operation. We will stop collecting information about you. If you wish, any information we have already collected can be destroyed. If you are in the *usual* care group nothing will change. If you are in the *tight* control group you will instead be given *usual* care which is to give insulin at level 12.

What if there is a problem or something goes wrong?

Information about who to contact if there is a problem is given in the information sheet for parents.

Will anyone else know that I am in a research study?

Yes – the study team in this hospital and at the Data Co-ordinating Centre at the London School of Hygiene and Tropical Medicine will know that you are taking part in the study. We will also tell your family doctor. If you agree to take part in the research, any of your medical records may be looked at to check that the study is being carried out correctly.

What will happen to the results of the research study?

The results will not be available until 2012 when everyone taking part has been followed up and the results analysed. The research will be published in a scientific journal and the results publicised widely. A research summary will be posted on the study website www.chip-trial.org.uk. A summary of the results will be sent to you and your parents if you let the Study Manager know that you would like to have this.

Who is organising and funding the research?

This study is run by the Royal Brompton and Harefield NHS Trust and the London School of Hygiene and Tropical Medicine. The study is funded by the Health Technology Assessment Programme of the NHS. The Royal Brompton Hospital is responsible for the conduct of the study. The doctor who is co-ordinating the study at this hospital is not being paid to include you in the study.

Dr Duncan Macrae, Chief Investigator CHiP Study, Royal Brompton Hospital
Tel: 020-7351 8546 Email: d.macrae@rbht.nhs.uk

Laura Van Dyck/Lucy Brooks, Study Manager
CHiP Data Co-ordinating Centre, London School of Hygiene and Tropical Medicine
Tel: 020-7927 2075 Email: Laura.VanDyck@lshtm.ac.uk/Lucy.Brooks@lshtm.ac.uk

Who has reviewed the study?

Before any research goes ahead it has to be checked by an Ethics Committee to make sure that the research is suitable. This study has been checked by the East Brighton Ethics Committee.

Thank you for taking the time to read this information. Please ask any questions if you need to.

Appendix 2 CHiP: summary of protocol amendments

Amendment 1 (protocol version 2, 20 November 2007)

- Changes to the Patient Information Sheets and Consent Forms for parents to include why their child had been chosen for this study, that blood taken specifically for this study would be painless and taken only from a line that already been inserted, and clarity on where and who was signing the consent form.
- Changes to the protocol to more clearly define how the insulin infusions should be prepared and managed.

Amendment 2 (protocol version 3, 13 February 2008)

- Changes to the protocol to clarify the dosing in the control group.

Amendment 3 (16 October 2008)

- Poster to be displayed in intensive care units.

Amendment 4 (17 March 2009)

- Addition of the following two sites:
 - Leicester Royal Infirmary and Glenfield Hospital (in Leicester).
 - University Hospital of North Staffordshire (in Stoke on Trent).

Amendment 5 (5 February 2009)

- Letter to be sent to parents at discharge.
- Diary to be given to parents at discharge.
- Letter to be sent to parents at 12 months.
- Questionnaire to be sent to parents at 12 months.

Amendment 6 (protocol version 4, 15 May 2009)

- Changes to the protocol to make minor alterations to the insulin control guidelines for the tight group.

Amendment 7 (not applicable)

- Not applicable, due to misnumbering by ethics (incorrectly number amendment 6 as amendment 7, and then unable to correct the numbering in their database).

Amendment 8 (28 June 2009)

- Follow-up questionnaires to be sent at 1 year to TBI patients (Conners' Parent Rating Scale - Revised, Health Utilities Index-2, and Child Behaviour Checklist).

Amendment 9 (18 November 2009)

- Letter to parents of children who have died.

Amendment 10 (protocol version 5, 5 March 2010)

- Changes in the protocol, patient information sheets and GP and parent letters to reflect changes in the TBI follow-up (all questionnaires now to be sent to them, rather than one to be completed over the telephone).
- Changes in the protocol to add the publication policy.
- Letter for parents of children who are inpatients for over 1 year.

Amendment 11 (protocol version 6, 23 August 2010)

- Changes in the protocol, patient information sheets, consent forms, GP and parent letters due to the 1 year follow-up questionnaires no longer being sent out to parents (due to reasons of cost).
- Changes in patient information sheets and consent forms to reflect the change in name of the NHS information centre.
- Changes in the protocol, patient information sheets and consent forms to make it clearer that their patient data (including personal details) would be sent to the London School of Hygiene and Tropical Medicine.
- Changes in the protocol to update the study background section to include more recent studies and literature.

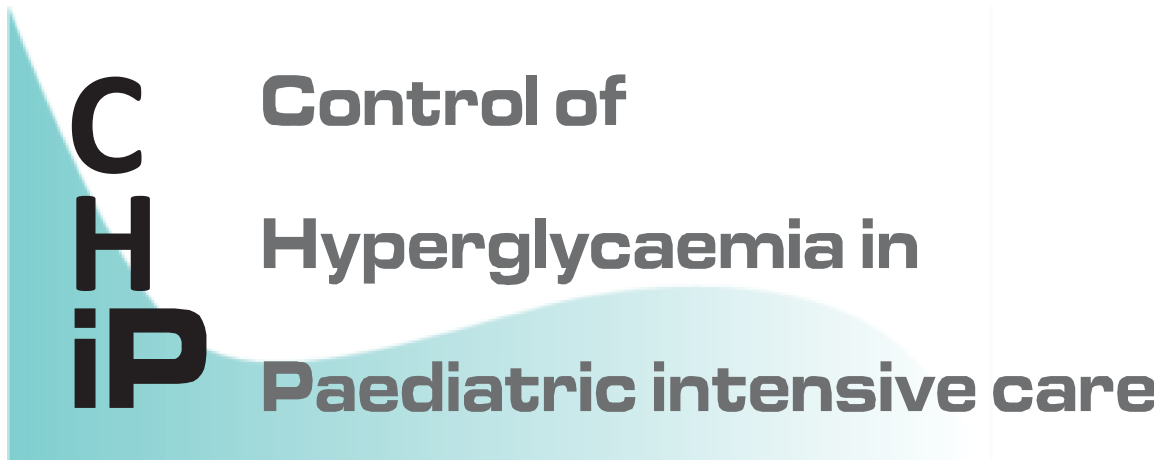
Amendment 12 (23 August 2010)

- Addition of the following site:
 - St George's Healthcare NHS Trust (in London).

Amendment 13 (14 December 2010)

- Change in PI at University Hospitals of North Staffordshire NHS Trust.

Appendix 3 Protocol version 6 (August 2010)



PROTOCOL

Version 6 August 2010

www.chip-trial.org.uk

ISRCTN61735247

Sponsor

Royal Brompton and Harefield NHS Trust

EurodrCT number 2006/005715/-10
ISRCTN61735247

SUMMARY

There is evidence that tight glucose control (TGC) of blood glucose (BG) favorably influences outcomes in adults who are critically ill or recovering from major surgery. Children have been shown to exhibit similar hyperglycaemic responses to 'stresses' of surgery or critical illness. However it is not known whether TGC will benefit children because of factors including maturational differences and the different disease spectrum seen in children. We are therefore seeking in this clinical trial to determine whether a policy of strictly controlling BG using insulin in children admitted to paediatric intensive care reduces mortality, morbidity and/or the use of healthcare resources.

BACKGROUND

Glucose homeostasis is known to be impaired in patients subjected to the stress of major surgery or critical illness resulting in hyperglycaemia[1]. This may in part result from insulin resistance, as insulin-dependent glucose uptake has been shown to be reduced in various organs and tissues during critical illness. Glucose uptake is however increased in non-insulin dependent tissues such as brain, red blood cells and wounds. This imbalance of glucose metabolism has previously been interpreted as the body's plea for tolerating moderately high levels of glucose during critical illness and injury and treatment of 'stress-induced' hyperglycaemia has typically only been initiated if BG levels are persistently and substantially elevated.

HYPERGLYCAEMIA IN CRITICALLY ILL ADULTS

Over recent years several studies have associated hyperglycaemia with adverse outcomes during acute illness in adults:

Myocardial infarction

In a meta-analysis [2], patients with acute myocardial infarction without diabetes who had glucose concentrations more than or equal to range 6.1-8.0 mmol/L had a 3.9-fold (95% CI 2.9-5.4) higher risk of death than patients without diabetes who had lower glucose concentrations. Glucose concentrations higher than values in the range of 8.0-10.0 mmol/L on admission were associated with increased risk of congestive heart failure or cardiogenic shock in patients without diabetes. Stress hyperglycaemia with myocardial infarction is associated with an increased risk of in-hospital mortality and increased risk of congestive heart failure or cardiogenic shock in patients without diabetes.

Stroke

Capes et al. conducted a systematic review and meta-analysis of the literature relating acute post stroke glucose levels to the subsequent course [3]. A comprehensive literature search was done for cohort studies reporting mortality and/or functional recovery after stroke in relation to admission glucose level. Thirty-two studies were identified for which pre-defined outcomes could be analysed in 26. After stroke, the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level >6 to 8 mmol/L was 3.07 (95% CI, 2.50 to 3.79) in non-diabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients. Non-diabetic stroke survivors whose admission glucose level was >6.7 to 8 mmol/L also had a greater risk of poor functional recovery (relative risk=1.41; 95% CI, 1.16 to 1.73).

Head injury and multi-system trauma

Hyperglycaemia has been shown to be an independent predictor of poor outcome in adult patients[4] and children with head injury[5-6] and multiple trauma[7].

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Pulmonary function

Hyperglycaemia has been shown to be associated with diminished pulmonary function in adults even in the absence of diabetes mellitus[8] and a range of other effects with potential to injure the lung [9].

Gastrointestinal effects

Hyperglycaemia has been shown to be associated with delayed gastric emptying[10], decreased small bowel motility and to increase sensation and cerebral evoked potentials to a range of gastrointestinal stimuli in adult volunteers [11-14].

Infections

In vitro responsiveness of leukocytes stimulated by inflammatory mediators is inversely correlated with glycaemic control [15]. This reduction in polymorphonuclear leucocyte responsiveness may contribute to the compromised host defence associated with sustained hyperglycaemia [15], and indeed, hyperglycaemia has been shown to be associated with an increased rate of serious infections after adult cardiac[16] and vascular[17] surgery.

STUDIES OF CONTROL OF GLYCAEMIA IN ADULTS

Recent reports from adult populations suggest that control of glycaemia during acute illness can be associated with improved outcomes [18-22].

Furnary et al.[21] studied the hypothesis that since hyperglycaemia was associated with higher sternal wound infection rates following adult cardiac surgery, aggressive control of glycaemia might lead to lower infection rates. In a prospective study of 2,467 consecutive diabetic patients who underwent open heart surgical procedures, patients were classified into two sequential groups. A control group included 968 patients treated with sliding-scale-guided intermittent subcutaneous insulin injections. A study group included 1,499 patients treated with a continuous intravenous insulin infusion in an attempt to maintain a BG level of less than 11.1 mmol/l. Compared with subcutaneous insulin injections, continuous intravenous insulin infusion induced a significant reduction in perioperative BG levels, which led to a significant reduction in the incidence of deep sternal wound infection in the continuous intravenous insulin infusion group (0.8% [12 of 1,499]) versus the intermittent subcutaneous insulin injection group (2.0% [19 of 968], $p = 0.01$). The use of perioperative continuous intravenous insulin infusion in diabetic patients undergoing open heart surgical procedures appears to significantly reduce the incidence of major infections.

Malmberg et al.[19] randomly allocated patients with diabetes mellitus and acute myocardial infarction to intensive insulin therapy ($n=306$) or standard treatment (controls, $n= 314$). The mean (range) follow up was 3.4 (1.6-5.6) years. There were 102 (33%) deaths in the treatment group compared with 138 (44%) deaths in the control group (relative risk (95% confidence interval) 0.72 (0.55 to 0.92); $P = 0.011$). The effect was most pronounced among the predefined group that included 272 patients without previous insulin treatment and at a low cardiovascular risk (0.49 (0.30 to 0.80); $P = 0.004$). Intensive insulin therapy improved survival in diabetic patients with acute myocardial infarction. The effect seen at one year continued for at least 3.5 years, with an absolute reduction in mortality of 11%.

In 2001 Van den Berghe and colleagues from Leuven, Belgium, [18] reported the results of a randomised trial in adults undergoing intensive care following surgical procedures. This trial showed that the use of insulin to tightly control BG led to a reduction in mortality (32%), mean length of intensive care stay (22%), and significantly lower occurrence of a range of complications of critical illness such as renal failure, infection, inflammation, anaemia and polyneuropathy. Duration of intensive care stay was 3.4 days shorter in the insulin group.

In 2006 the Leuven group [22] have reported that, in addition to adult surgical intensive care patients, intensive insulin therapy reduces morbidity in adults who require intensive care for treatment of medical conditions. In this prospective randomised controlled trial, patients were randomly assigned to a regime of

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strict normalisation of BG (4.4-6.1 mmol/l) with use of insulin, or conventional therapy where insulin is administered only when BG levels exceeded 12 mmol/l, with the infusion tapered when the level fell below 10 mmol/l. In the intention to treat analysis of the 1200 patients included, ICU and in-hospital mortality were not significantly altered by intensive insulin therapy, however for those patients requiring more than 3 days intensive care, mortality was significantly reduced from 52.5 to 43% ($p=0.009$). Morbidity was significantly reduced by intensive insulin therapy with a lower incidence of renal injury and shorter length of mechanical ventilation and duration of hospital stay noted. Beyond the fifth day of intensive insulin therapy, all morbidity endpoints were beneficially affected, whereas for those patients staying less than 3 days, none of the morbidity end-points were significantly different between the two treatment groups.

On the basis of these studies, several groups have recommended that tight glycaemic control with intensive insulin therapy become a standard of care for the critically ill adult patients. The Joint Commission on Accreditation of Healthcare Organization (JACHO) recently proposed tight glucose control for the critically ill as a core quality of care measure for all U.S. hospitals that participate in the Medicare program[23]. The Institute for Healthcare Improvement, together with an international initiative by several professional societies including the American Thoracic Society, is promoting a care "bundle" for severe sepsis that also includes intensive glycaemic control for critically ill adults [24]. Both the Society of Critical Care Medicine and European Society of Intensive Care Medicine have incorporated TGC into their recently publicised 'Surviving Sepsis' guidelines. These initiatives represent important attempts to translate research findings into improved care at the bedside[25].

Since then, the NICE-SUGAR Study [26], a large international multicentre study which compared two glucose control strategies (targets of 4.5 – 6.0 mmol/l versus < 10 mmol/l) in 6104 adults undergoing intensive care, has reported. This found that intensive glucose control as compared to conventional glucose control led to a statistically significant increase in the rate of the primary end-point, death by 90 days, with intensive insulin control (27.5% v. 24.9%; odds ratio (OR) 1.14, 95%CI 1.02-1.28, $p=0.02$). There was also more severe hypoglycaemia (<40 mg per decilitre) in the intensive control group (6.8% v. 0.5%; OR 14.7, 95%CI 9-25.9, $p<0.001$).

The authors discuss possible explanations for why their results differ from those of the Leuven group [17,22] in terms of their specific treatment algorithm, the fact that most of their patients received enteral nutrition, or that their greater power and longer follow up allowed more accurate determination of effects. They speculate that the mechanism for the increased mortality may be the reduced blood glucose level, increased insulin administration, more hypoglycaemia, or other factors. They conclude by not recommending the use of a lower blood glucose target in critically ill adults.

In the accompanying editorial [27], Inzucchi and Siegel caution against over-reaction to the NICE-SUGAR study. They point out that the trial's weaknesses include open label design (although they do recognise that this is understandable), and an imbalance between the groups in corticosteroid therapy (but this is post-randomisation and may be a consequence of the intervention, not a weakness of the trial). The editorial also comments on the intention to treat analysis and that 10% of intensive control discontinued this intervention. However, both these approaches are appropriate – statistically and clinically. Like the authors, they draw attention to the differences between this trial and those of the Leuven group, in particular that the latter was single-centre and their results may therefore be less generalisable, and that they used parenteral rather than enteral nutrition. Also, the standard management in the Leuven studies (reduction of glucose levels above 215 mg per decilitre) was contrasted to a milder range 144-180 mg per decilitre in NICE-SUGAR. Inzucchi and Siegel suggest a number of further exploratory analyses in the NICE-SUGAR trial and recommend that, while awaiting further evidence, ICUs continue with where intensive glucose control in adult critical care where this practice is already strongly embedded.

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Griesdale et al. [28] have recently published a meta-analysis which summarises data from a total of 26 trials of intensive glucose control involving a total of 13,567 adult patients, including the NICE-SUGAR trial. The meta-analysis did not show an overall benefit of tight glucose control on mortality (RR 0.93, 95% CI 0.83-1.04). There was some evidence of heterogeneity between effects by the type of ICU ($p < 0.01$) such that patients in surgical intensive care appeared to benefit from intensive glucose control (RR 0.63, 95% CI 0.44-0.91) whereas patients in other ICU settings did not (medical ICU RR 1.0, 95% CI 0.78 – 1.28; mixed ICU RR 0.99, 95% CI 0.87 – 1.12). Whereas the results from the trials in surgical and in medical ICU settings were mainly similar, there was more heterogeneity in the results from the mixed ICUs ($P < 0.01$). The results of this meta-analysis from the mixed ICUs were dominated by the largest trial [26]. Griesdale et al conclude that, while their results “do not support widespread adoption of intensive insulin therapy in critically ill **[adult]** patients” further research is needed to identify which, if any, patients might benefit from tight glucose control.

The possible mechanisms by which different glucose control strategies might influence clinical outcomes are yet to be fully elucidated. There is a substantial body of published research which points to an association between hyperglycaemia and organ/tissue dysfunction. In models of both focal and global cerebral ischaemia, hyperglycaemia has been shown to be associated with exacerbation of intracellular acidosis [29-31], accumulation of extracellular glutamate [32], cerebral oedema formation and disruption [33] of the blood-brain barrier [34]. In ischaemic brain injury, hyperglycaemia may worsen injury by promoting anaerobic metabolism and consequent intracellular acidosis. In the rat myocardium, hyperglycaemia leads to up-regulation of inducible nitric oxide synthase, resulting ultimately in an increase in production of superoxide, a condition favouring the production of the powerful pro-oxidant peroxynitrite. This highly reactive free radical has the power to cause direct oxidant damage to myocardial cells or to induce myocardial cell apoptosis [35-36]. Similar adverse mechanisms have been shown to exist in hyperglycaemic patients [37-38]. Improved clinical outcomes may arise not necessarily solely as a result of control of BG. Insulin lowers free fatty acids and normalises endothelial function [39]; is associated with anabolic effects [40-41]; has been shown to have anti-inflammatory effects [42-43] and to have cardio-protective effects [44], all of which may contribute independently to better outcomes in critical illness.

HYPERGLYCAEMIA IN LOW BIRTHWEIGHT NEONATES

The population for the NIRTURE trial [45] was 389 very low birthweight neonates, recruited from 8 NICUs in the UK and mainland Europe. The primary outcome was death at the expected date of delivery (EDD). The trial was stopped early by the trial steering committee on the advice of the independent data monitoring committee for a combination of futility in terms of the primary mortality outcome, and concerns about potential harm in terms of an excess of ventricular haemorrhage and parenchymal lesions on cerebral ultrasound scans. More infants in the early insulin group had episodes of hypoglycaemia (< 47 mg per decilitre) than in the control group (29% v. 17%; OR 2.21, 95%CI 1.34-3.65, $p < 0.005$). There was no statistically significant difference in the primary outcome of mortality at EDD (14% v. 9%; OR 1.64, 95%CI 0.87-3.03, $p < 0.2$), but the secondary mortality outcome of death at 28 days was increased in the tight glucose control group (12% v. 6%; OR 2.22, 95%CI 1.04-4.76, $p < 0.04$). The authors speculate that the results might be due to a smaller difference in the levels of glucose control than seen in their pilot study; or too short a period (7 days) of tight control. They stress the importance of long term follow up for the surviving babies. An accompanying editorial [46] recommends caution in the use of this therapy in very low birth weight infants.

HYPERGLYCAEMIA IN CRITICALLY ILL CHILDREN

Over 10,000 children are admitted to intensive care units in England and Wales each year [47]. Hyperglycaemia, defined as BG > 7 mmol/l, occurs frequently during critical illness or after major surgery in children, with a reported incidence of up to 86% [48]. As in adults, the occurrence of hyperglycaemia has been shown to be associated with poorer outcomes including death, sepsis, and longer length of intensive care stay in critically ill children [48-51]. on-randomised research in children includes a number of reports from

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general paediatric intensive care units [48-50, 52] and paediatric cardiac intensive care units [51] showing that high BG levels occur frequently in critically ill children and that BG levels are significantly higher in children who die than in children who survive.

Srinivasan et al.[48] studied the association of timing, duration, and intensity of hyperglycaemia with paediatric intensive care unit (PICU) mortality in critically ill children. The study was a retrospective, cohort design and included 152 critically ill children receiving vasoactive infusions or mechanical ventilation. Peak BG of >7 mmol/L occurred in 86% of patients. Compared with survivors, non-survivors had higher peak BG (17.3mmol/L +/- 6.4 vs. 11.4 +/- 4.4 mmol/L, $p < .001$). Non-survivors had more intense hyperglycaemia during the first 48 hrs in the PICU (7 +/-2.1 mmol/L) vs. survivors (6.4 +/- 1.9 mmol/L, $p < .05$). Univariate logistic regression analysis showed that peak BG and the duration and intensity of hyperglycaemia were each associated with PICU mortality ($p < .05$). Multivariate modelling controlling for age and Paediatric Risk of Mortality scores showed independent association of peak BG and duration of hyperglycaemia with PICU mortality ($p < .05$). This study demonstrated that hyperglycaemia is common among critically ill children. Peak BG and duration of hyperglycaemia appear to be independently associated with mortality. The study was limited by its retrospective design; its single-centre location and the absence of cardiac surgical cases, a group which make up approximately 40% of paediatric intensive care admissions in the UK.

Halverson-Steele et al.[51] have recently shown in a retrospective study, that hyperglycaemia was associated with poor outcomes in 526 children following cardiac surgery. Nineteen patients (3.6%) died postoperatively (median 11 days, range 1-17 days). Peak plasma glucose concentrations in survivors (mean 10.7 mmol/l,SD 3.7) was significantly lower than the peak value recorded in non-survivors (mean 14.3 mmol/l,SD 4.2; $p=0.0017$). The 147 patients who were discharged from ICU within 24 hours had lower plasma glucose concentrations on admission (mean 7.5mmol/l,SD 2.3) and peak plasma glucose concentrations (mean 9.2 mmol/l,SD 2.3) than the remaining patients staying longer than 24 hours (mean 8.1 mmol/l,SD 4.0; $p=0.003$ and mean 11.3mmol/l,SD 3.9; $p<0.0001$, respectively). Peak plasma glucose concentrations were also lower in 387 patients admitted for up to 5 days (mean 10.1mmol/l,SD 2.9) when compared with those patients with ICU stays of > 5 days (mean 12.7mmol/l,SD 4.6; $p<0.0001$).

Hall et al.[50] investigated the incidence of hyperglycaemia in infants with necrotizing enterocolitis (NEC) and the relationship between glucose levels and outcome in these infants. Glucose measurements ($n = 6508$) in 95 neonates with confirmed NEC admitted to the surgical intensive care unit were reviewed. Glucose levels ranged from 0.5 to 35.0 mmol/L. 69% of infants became hyperglycaemic (>8 mmol/L) during their admission. Thirty-two infants died. Mortality rate tended to be higher in infants when maximal glucose concentration exceeded 11.9 mmol/L compared with those with maximum glucose concentrations of less than 11.9 mmol/L, and late (>10 days admission) mortality rate was significantly higher in these infants (29% v, 2%; $P = .0009$). Linear regression analysis indicated that maximum glucose concentration was significantly related to length of stay ($P < .0001$).

Branco et al. [49] have shown that there is an association between hyperglycaemia and increased mortality in children with septic shock. They prospectively studied all children admitted to a regional PICU with septic shock refractory to fluid therapy over a period of 32 months. The peak glucose level in those with septic shock was 11.9 +/- 5.4 mmol/L (mean +/- SD), and the mortality rate was 49.1% (28/57). In non-survivors, the peak glucose level was 14.5 +/- 6.1 mmol/L, which was higher ($p < .01$) than that found in survivors (9.3 +/- 3.0 mmol/L). The relative risk of death in patients with peak glucose levels of ≥ 9.9 mmol/L was 2.59 (range, 1.37-4.88).

Faustino [52] demonstrated that hyperglycaemia occurs frequently among critically ill non-diabetic children and is associated with higher mortality and longer lengths of stay. They performed a retrospective cohort study of 942 non-diabetic patients admitted to a PICU over a 3 year period. The prevalence of hyperglycaemia was based on initial PICU glucose measurement, highest value within 24 hours, and highest value measured

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during PICU stay up to 10 days after the first measurement. Through the use of three cut-off values (6.7 mmol/L, 8.3 mmol/L, and 11.1 mmol/L), the prevalence of hyperglycaemia was 16.7% to 75.0%. The relative risk (RR) for dying increased for maximum glucose within 24 hours >8.3 mmol/L (RR, 2.50; 95% confidence interval (CI), 1.26 to 4.93) and highest glucose within 10 days >6.7 mmol/L (RR, 5.68; 95% CI, 1.38 to 23.47).

Pham *et al.* [53] have recently reported their experience of adopting a policy of 'intensive' insulin therapy to achieve BG levels 5 mmol/L to 6.7 mmol/L. They reviewed the records of children with $\geq 30\%$ total body surface area burn injury admitted over a 3 year period. The first cohort of 31 children received 'conventional insulin therapy', whilst the subsequent cohort of 33 children received 'intensive insulin therapy'. The demographic characteristics and injury severity were similar between the groups. Intensive insulin therapy was positively associated with survival and a reduced incidence of infections. The authors therefore concluded that intensive insulin therapy to maintain normoglycaemia in severely burned children could be safely and effectively implemented in a paediatric burns unit and that this therapy seemed to lower infection rates and improve survival.

The study by **Vlasselaers *et al.*** [54] was a single centre study from the Leuven group of Van den Berghe, and involved 700 PICU patients who were randomly assigned to either intensive glucose control (targeted to achieve blood glucose concentrations of 2.8-4.4 mmol/L in infants and 3.9-5.6 mmol/L in children), or to insulin infusion only to prevent blood glucose from exceeding 11.9 mmol/L (conventional care). Three quarters of the patients were admitted following cardiac surgery. There was more hypoglycaemia (defined as a blood glucose of <2.2 mmol/L) in the intensive control vs conventional arm (25% v. 1%, $p=0.0001$). Patients in the intensive control arm had reduced PICU stay (5.51 vs 6.15 days, $p=0.017$). The study was not powered for mortality but showed a reduction in deaths with intensive control (3% v. 6%, $p=0.038$). The authors consider their trial as a 'proof of concept' and call for further multicentre trials with a broader case-mix, powered to address mortality and with longer term follow up.

While there is therefore mounting evidence to suggest that a policy of TGC *may* be beneficial to children undergoing paediatric intensive care, none of this evidence is from large multicentre rigorous randomized controlled trials with longer term follow up. The aim of the present study is to determine whether a policy of strictly controlling BG using insulin in children admitted to paediatric intensive care reduces mortality, morbidity and / or the use of healthcare resources.

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STUDY DESIGN

Main hypothesis

For children aged from birth to ≤ 16 years on ventilatory support, Tight glucose control (TGC) will increase the numbers of days alive and free of mechanical ventilation at 30 days.

Secondary hypotheses

That TGC will lead to improvement in a range of complications associated with intensive care treatment and be cost effective.

Inclusion criteria

- Children from birth to < 16 years who are undergoing intensive care treatment with an arterial line in-situ and receiving both mechanical ventilation and vasoactive support drugs* following injury, major surgery or in association with critical illness in whom it is anticipated such treatment will be required to continue for at least 12 hours.

Exclusion criteria prior to trial entry

- Children born pre-term and who are < 36 weeks corrected gestation
- Children with diabetes mellitus
- Children with an established or suspected diagnosis of an inborn error of metabolism
- Children for whom treatment withdrawal or limitation of intensive care treatment is being considered
- Children who have been in a PICU for more than 5 days in succession
- Children admitted to a PICU who have already participated in the CHIP study during a previous PICU admission.

Consent

Parents/guardians of babies and children in intensive care will be asked to give consent in their role of legal representatives. We understand that parents will be stressed and anxious. However they will usually have limited time to consider trial entry as it may not be medically appropriate to delay the start of treatment. Parents of babies and children listed for cardiac surgery will be given information about the trial pre-operatively and consent provisionally obtained to be confirmed later if the child is admitted to intensive care. In addition, where possible, older children will be given information and asked to assent to their participation in the study.

Patients not entered into the trial will receive standard care.

Allocation of patients

After inclusion in the study, children will be randomised to one of two groups:

Group 1 - Standard treatment

* Vasoactive drugs : Catecholamines or similar (dopamine, dobutamine, adrenaline, noradrenaline), PDEIII inhibitors (milrinone, enoximone), other vasopressors (vasopressin, phenylephrine or similar).

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Group 2 - Tight glycaemic control

To reduce the risk of selection bias at trial entry, allocation will be administered through a 24 hour, 7 day a week central randomisation service. Minimisation with a probabilistic element will be used to ensure a balance of key prognostic factors between groups using the following criteria:

- Centre
- age <1 year v. 1year – ≤16 years
- admitted following cardiac surgery or not
- For cardiac surgical children, RACHS1[55] category 1 to 4 versus 5 to 6
- For non-cardiac surgical children, PIM2 score at randomization categorised by probabilities of death of <5%, 5% - <15% and ≥15%.
- accidental traumatic brain injury or not

Interventions

Group 1 - Standard treatment

Children in this group will be treated according to a standard, current, approach to BG management. Insulin will be given by intravenous infusion in this group only if BG levels exceed 12mmol/l on two blood samples taken at least 30 minutes apart and will be discontinued once BG falls to <10mmol/l.

A protocol for glucose control in this group is attached as Appendix A.

Group 2 - Tight glycaemic control

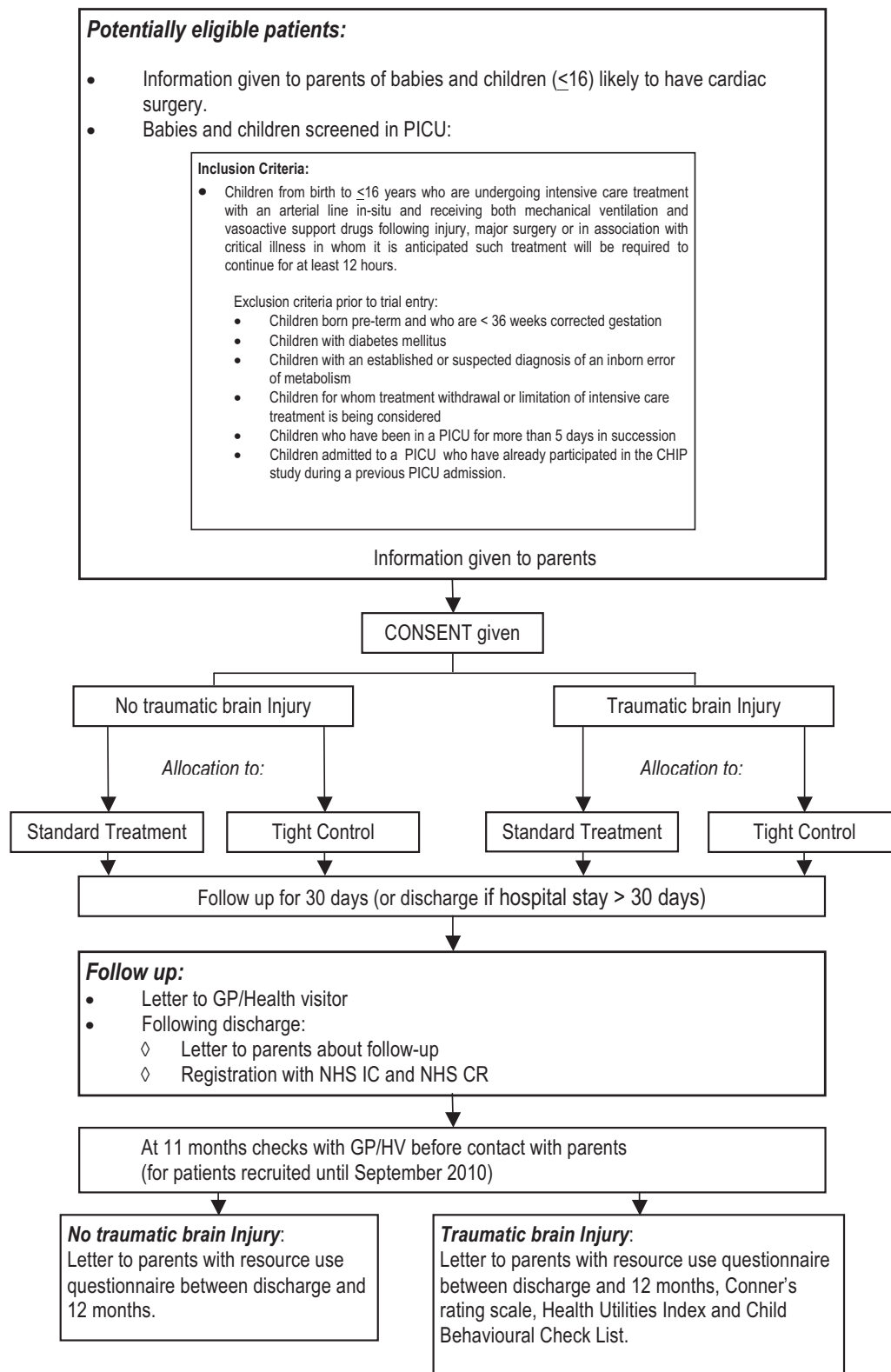
Children in this group will receive insulin by intravenous infusion titrated to maintain a BG between the limits of 4 and 7.0 mmol/l.

A protocol for glucose control in this group is attached as Appendix B.

The protocol for glucose control in group 2 has been carefully designed to achieve a tight glucose control whilst minimizing the risk of hypoglycaemia, the principal side effect of insulin therapy. Standard insulin solutions will be used and changes in insulin infusion rates will be guided both by the current glucose levels and its rate of change from previous measurements. BG levels will be routinely measured as in all intensive care units using commercially available 'point of care' analysers which utilise very small blood samples, producing results in approximately 1 minute. Analysers are rigorously maintained and subjected to laboratory-standard quality assurance programmes.

Training in use of the glucose control protocol will be provided before the first patient is enrolled in each collaborating centre and for new staff throughout the trial. The Clinical Co-ordinating centre team will liaise closely with local clinicians to ensure that glucose control algorithms are followed closely and safely.

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Outcome measures

Primary:

Following the influential ARDSNET study [56] we will use as the primary outcome the number of days alive and free from mechanical ventilation within the 30 days after trial entry. Death is obviously an important outcome. Mechanical ventilation can be seen as a measure of disease severity, defining the need for complex intensive care. The concept of ventilator free days (VFDs) brings together these two outcomes. Schoenfeld et al [57] define ventilator free days (VFDs) as: $VFD=0$ if the child dies before 30 days; $VFD=(30-x)$ if the child is successfully weaned from ventilator within 30 days (where x is the number of days on ventilator); or $VFD=0$ if the child is ventilated for 30 days or more. The use of organ failure free days to determine patient-related morbidity surrogate end-points in paediatric trials has been supported by influential paediatric trialists in the current low mortality paediatric critical care environment [58].

Secondary:

Death within 30 days after trial entry (or before discharge from hospital if duration is greater than 30 days)
 Death within 12 months of trial entry
 Number of days in ICU
 Duration of mechanical ventilation
 Duration of vasoactive drug usage (adrenaline, noradrenaline, dopamine, dobutamine, or PDEIII inhibitors or vasopressors)
 Need for renal replacement therapy
 Blood stream infection (positive cultures associated with two or more features of systemic inflammation or any positive blood culture for fungus)
 Use of antibiotics >10 days
 Number of red cell transfusions
 Number of hypoglycaemic episodes moderate (less than 2.5 mmol/L), severe (less than 2.0 mmol/L)
 Occurrence of seizures (clinical seizures requiring anticonvulsant therapy)
 Organ dysfunction score (PELOD)[58-60],
 Hospital length of stay
 Number of children readmitted within 30 days of trial entry
 Cost and cost-effectiveness measures
 Hospital costs within 30 days of trial entry
 Cost per life year (based on 30 days costs and survival)
 Hospital and community health service costs within 12 months of trial entry†
 Cost per life year (based on 12 month costs and survival for all cases)†
 Cost per disability-free survivor (based on 12 month cost and outcome data for sub group with traumatic brain injury)†

Follow-up at 12 months:

If parents give their consent all children surviving to hospital discharge will be followed up to 12 months post-randomisation to determine mortality using the NHS Information Centre and the NHS Central Register. Parents will be informed about the follow-up study at trial entry and asked to give consent. The Trial Manager at the Data Co-ordinating Centre (DCC) will write to parents following discharge home to remind them about the follow-up and ask them to keep the DCC informed about any change of address. At around 11 months†, following checks with the GP/Health Visitor to determine that this is appropriate, the Trial Manager will send a questionnaire to parents to determine the use of health care resources between discharge and 12 months. Non-responders will be followed-up by letter and telephone.

† For patients recruited until September 2010

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Follow-up of traumatic brain Injury sub-group:

This sub-group is more likely to have longer-term morbidity and parents of children (aged 4 or over) in this sub-group will be asked to provide additional information at 12 months[†], regarding overall health status, global neurological outcome, attention and behavioural status. Further details are given in Appendix D

Adverse events and safety reporting

The Royal Brompton & Harefield NHS Trust, as sponsor of this study, has responsibility to ensure arrangements are in place to record, notify, assess, report, analyse and manage adverse events in order to comply with the UK regulations of Medicines for Human Use (Clinical Trials) Regulations 2004.

All sites involved in the study are expected to inform the Chief Investigator and Study nurse of any serious adverse events/reactions within 24 hours so that appropriate safety reporting procedures can be followed by the Sponsor.

It is therefore important that all site investigators involved in the study are aware of the reporting process and timelines. Details of the mandatory Adverse Event and Safety Reporting requirements are detailed in Appendix C of this protocol.

Expected side effects

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to insulin therapy qualify as adverse reactions.

Whilst any suspected, unexpected, serious adverse reaction (SUSAR) involving insulin therapy will be reported according to the timelines for SUSARs, expected side effect of insulin will be reported in the annual safety report unless serious enough to warrant expedited reporting.

The most prominent adverse effect of insulin treatment is hypoglycaemia. We are aiming to control BG within the range 4 – 7 mmol/l which is well above the 2 mmol/l threshold for clinically important hypoglycaemia[61]. The principal measure to avoid clinically important hypoglycaemia will be hourly measurement of BG when insulin is first administered. The insulin administration protocols aim to achieve glucose control with the lowest possible incidence of hypoglycaemia and the avoidance of neuroglycopenia. Hypoglycaemic events will be reported to the Clinical Co-ordinating Centre and if necessary, the BG control protocols will be revised, whilst still aiming to achieve BG levels within the target ranges.

Insulin is reported to occasionally cause a rash which may be associated with itching.

Data collection

To minimise the data collection load for busy units, the trial will collaborate with the Paediatric Intensive Care Audit Network (PICANet) to make best use of the established data collection infrastructure which exists in all PICUs in the UK. The PICANet dataset includes most of the items being used in the trial and these data will be transmitted from the participating centres to the Data Co-ordinating Centre electronically using strong encryption. The remaining short term data items will be collected locally by the research nurses, and those for the longer term follow-up will be collected separately by telephone and postal questionnaires. These data will be double entered onto electronic database storage systems at the Data Co-ordinating Centre.

Economic evaluation

[†] For patients recruited until September 2010

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Cost-consequence and cost-effectiveness analyses will be undertaken as part of the proposed study. These economic evaluations will assess whether the costs of achieving tight blood glucose control are justified by subsequent reductions in hospitalisation costs and/or by improvements in patient outcomes. The evaluations will be conducted in two phases, in the first phase all hospital costs at 30 days post randomisation will be compared across treatment groups alongside 30-day outcomes, in the second phase cost and outcomes at 12-months[†] will be compared across the groups.

For the first phase evaluations, detailed resource use data will be collected for each patient enrolled in CHIP using the Paediatric Critical Care Minimum Dataset (PCCMDS)[62] which will be collected by each PICANet unit. Where information on resource use is required in CHIP is not available from these sources datasheets similar to those developed as part of the INNOVO study will be used [63]. Information will also be collected on the resources required to achieve tight blood glucose control, in particular all medication use and the staff time involved in monitoring the patients and managing adverse events (e.g. hypoglycaemia) will be noted.

Unit costs for hospital services will be taken from the NHS reference costs database [64]. Where more detailed unit costs are required, for example those associated with staff time and the use of insulin infusion, these will be collected on site visits to centres. Hospital costs up to 30 days will be estimated by valuing each resource use item by the appropriate unit cost.

In the second phase of the study the time horizon of the economic evaluation will be extended to 12 months[†], and resource use data on hospital re-admissions will be collected for all cases. For the sub-sample of patients diagnosed as having traumatic brain injury at study entry, information on the patient's disability at one-year will be collected by postal questionnaire's[†] to the patients' relatives based on previously developed interview schedules [63].

All the economic analyses will be based on the treatment groups as randomly allocated ('intention to treat'). The initial analysis will include a cost-consequence analysis and will report mean differences (95% CI) between treatment groups in resource use (e.g. length of hospital stay) and total hospital costs per patient, alongside the primary clinical endpoint. The initial analysis will also combine costs and outcomes at 30 days post-randomisation in a cost-effectiveness analysis, which will report cost per death averted and cost per adverse event averted. The subsequent analysis will use 12-month cost and outcome data[†] to report the cost per death averted for all patients. For the sub-sample of patients diagnosed as having brain injury at study entry, the cost-effectiveness analysis will also report the cost per death or disabled case averted.

The sensitivity analysis will test whether the results are robust to key assumptions made, for example to the choice of unit costs and the time horizon of the analysis. The cost and outcome data collected at one-year[†] will be used to project the impact of the intervention on longer-term costs and outcomes.

Sample size

The primary outcome is the number of ventilator-free days within the first 30 days post-randomisation. A difference of 2 days in the number of ventilator-free days (VFD) is considered clinically important for the trial to be able to detect. Information from PICANet from a sample of PICUs for 2003-4 estimates that the mean number of VFDs in cardiac patients is 26.7, with a standard deviation (SD) of 4.2. Corresponding figures for non-cardiac patients are a mean of 22.7 days, with a standard deviation (SD) of 6.8 days. As the SD is estimated with error, to be conservative we have assumed the SD is nearer 5.5 days for the cardiac and 8 days for the non-cardiac patients. There are likely to be more non-cardiac than cardiac patients eligible for the trial. We have therefore assumed an overall SD across both cardiac and non-cardiac strata of 7 days. Assuming this is the same in both trial arms, and taking a type I error of 1% (with a 2-sided test), a total sample size of 750 patients would have 90% power to detect this difference. Whereas we can assume

[†] For patients recruited until September 2010

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minimal loss to follow up to 30 days, there may be some non-compliance (some patients allocated to tight control not receiving this, and some allocated to usual care being managed with tight control). The target size will therefore be inflated to 1000 to take account of possible dilution of effect.

As information from PICANet indicates that there are differences in outcome between cardiac and non-cardiac patients not merely in VFDs but also in 30 day mortality rate (3.4% vs. 20%) and mean duration of time on a ventilator (3.7 vs. 8.0 days, survivors and non-survivors combined), we also wish to be able to detect whether any effect of tight glucose control differs between the cardiac and non-cardiac strata. To have 80% power for an interaction test to be able to detect a difference of two days in the effect of intervention between the strata at the 5% level of statistical significance, we would need to increase the sample size to 1500. If the interaction test was positive this size would allow us to assess the effect of tight glucose control separately in the two strata.

Recruitment rate

There are approximately eligible 1300 cardiac and 1550 non-cardiac patients per year in collaborating PICUs we estimate about half of those eligible will be recruited into the trial. The overall total sample size of 1500 should be accrued by September 2011.

Type of analysis

Analysis will be by intention to treat. The following sub-group analyses will be conducted: age (<1year or 1- <16years), severity of illness, traumatic brain injury or not, cardiac surgical versus non-cardiac cases, RACHS1 (cardiac cases) (Groups 1-4 versus 5 and 6), PIM2 group (non-cardiac cases) (categorised by probabilities of death of <5%, 5% - <15% and ≥15%), run in cases v. non-run in cases.

Frequency of analysis

An independent Data Monitoring and Ethics Committee (DMEC) will review, in strict confidence, data from the trial approximately half way through the recruitment period. The Chair of the DMEC may also request additional meeting/analyses. In the light of these data and other evidence from relevant studies, the DMEC will inform the Steering Committee if in their view:

- i. There is proof that the data indicate that any part of the protocol under investigation is either clearly indicated or clearly contra-indicated either for all patients or a particular subgroup of patients. using the Peto and Haybittle rule [65-66]
- ii. It is evident that no clear outcome will be obtained with the current trial design.
- iii. That they have a major ethical or safety concern

Ancillary studies

In addition to the main study, some collaborators may wish to conduct other more detailed or complementary studies. The grant holders welcome this provided that proposals are discussed in advance with the Trial Steering Committee and appropriate additional Research Ethics approval is sought.

Publication policy

To safeguard the integrity of the trial, data from this study will not be presented in public or submitted for publication without requesting comments and receiving agreement from the Trial Steering Committee. The primary results of the trial will be published by the group as a whole with local investigators acknowledged. The success of the trial depends on the collaboration of many people. The results will be presented first to the trial

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local investigators. A summary of the results of the trial will be sent to parents of participating children on request and also made available on the trial website.

The full Publication Policy is shown in Appendix H

ORGANISATION

A Data Monitoring and Ethics Committee (DMEC) and a Trial Steering Committee (TSC) have been established. Day to day management of the trial will be overseen by a Trial Management Group.

Trial Management Group

A Trial Management Group will be established and will be responsible for the day to day management of the trial. The group will comprise the grant holders and project staff from the Clinical Co-coordinating Centre at the Royal Brompton Hospital NHS Trust and the Data Co-coordinating Centre at the LSHTM. The group will meet regularly in person and by telephone.

The responsibilities of the TMG are:

- a) To establish and monitor recruitment of participating centres
- b) To distribute and supply of data collection forms and other appropriate documentation for the trial
- c) Data collection and management
- d) Data entry and cleaning
- e) Data analysis
- f) Organising and servicing the Data Monitoring and Ethics Committee
- g) Assure data security and quality and observe data protection laws
- h) Ensure trial is conducted in accordance with ICH GCP

Data Co-coordinating Centre responsibilities

- To ensure that all members of the study team are able by knowledge, training and experience to undertake the roles assigned to them and to comply with requirements as specified by the host organisation.
- To provide overall efficient day to day management of the trial ensuring compliance with Good Clinical Practice (GCP).
- To ensure each centre is put on-line with the randomization service after LREC, R&D approval and the signed local collaborator agreement have been received from the sponsor.
- To provide site folders and relevant documentation to each centre
- To contribute to the development of the protocol, and all study documentation including data sheets
- To design, produce and regularly update all trial materials and arrange printing and supply of documentation.
- To monitor recruitment and advise on remedial action if targets are not being met.
- To set up and maintain the website
- To service the Project management Committee, Steering Committee and any other relevant advisory groups.

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- To use all reasonable efforts to ensure that the data collected and reported are accurate, complete and identifiable at source; and that record keeping and data transfer procedures adhere to the Data Protection Act 1998
- To undertake the interim and final analyses and report regularly to the Data Monitoring and Ethics Committee in a timely way at their request.
- To supply documentation and reports as deemed necessary by the sponsors to fulfill their obligations.
- To co-ordinate the preparation and publication of data, reports and information, ensuring that these meet legislative, contractual and ethical requirements.
- To co-operate with audits or inspections undertaken by the host institution, the sponsors and regulatory authorities including the MHRA as required.
- To assist investigations into any alleged research misconduct undertaken by or on behalf of the co-sponsors
- To ensure safe storage of data, including trial site file, data sheets and other records for a period of 15 years after the conclusion of the trial.
- To inform the Chief Investigator of any changes in the trial protocol that effect the conduct of the Trial.

Trial Steering Committee

The Trial Steering Committee (TSC) responsibilities are to approve the main study protocol and any amendments, monitor and supervise the trial towards its interim and overall objectives, review relevant information from other sources, consider the recommendations of the DMEC, and resolve problems brought by the trial co-coordinating centres.

Face to face meetings will be held at regular intervals determined by need and not less than once a year. Routine business is conducted by telephone, email and post. The TSC will be chaired by Professor Michael Preece. The TSC membership is shown below and its terms of reference shown in Appendix F.

Membership

<i>Professor Michael Preece (Chair)</i>	Consultant Paediatrician, Great Ormond Street Children's Hospital
<i>Mrs. Pamela Barnes</i>	Lay member
<i>Ms Sian Edwards</i>	Paediatric Pharmacist, Royal Brompton Hospital,
<i>Professor David Field</i>	Neonatologist, Leicester Royal Infirmary and the University of Leicester
<i>Dr. James Hooper</i>	Consultant Clinical Biochemist, Royal Brompton Hospital,
<i>Mrs. Tara Quick</i>	Lay member, Parent
<i>Dr Claire Snowdon</i>	Centre for Family Research, University of Cambridge.
<i>Ms Lyvonne Tume</i>	Research Nurse, Royal Liverpool Children's Hospital
<i>Dr. Dirk Vlasselaers</i>	Consultant Paediatric Intensivist, Leuven, Belgium
<i>Professor Paula Williamson</i>	Professor of Medical Statistics, University of Liverpool
<i>In attendance</i>	
<i>Mr. Michael Loveridge (till Mar. 2008)</i>	Royal Brompton Hospital (Trial sponsor)
<i>HTA representative</i>	
<i>Trial Management Group:- (see below)</i>	
<i>Dr. Duncan Macrae (Chief Investigator)</i>	Director of Paediatric Intensive Care, Royal Brompton Hospital
<i>Dr Elizabeth Allen</i>	Lecturer, Medical Statistics Unit, LSHTM

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<i>Miss Helen Betts</i>	Lead Study Nurse, Royal Brompton Hospital
<i>Professor Diana Elbourne</i>	Professor of Healthcare Evaluation, Medical Statistics Unit, London School of Hygiene and Tropical Medicine (LSHTM)
<i>Dr Richard Grieve</i>	Senior Lecturer in Health Economics, Health Services Research Unit, LSHTM
<i>Dr. Kevin Morris</i>	Consultant in Paediatric Intensive Care, Birmingham Children's Hospital
<i>Dr. Roger Parslow</i>	Senior research fellow, University of Leeds
<i>Dr. Robert Tasker</i>	Clinical Senior Lecturer, Department of Paediatrics, University of Cambridge
<i>Mrs Ann Truesdale (till 2008)</i>	Trials Advisor, Medical Statistics Unit, LSHTM
<i>Miss Laura Van Dyck (from Aug. 2009)</i>	Study Manager, Medical Statistics Unit, LSHTM

Data Monitoring and Ethics Committee (DMEC)

A DMEC has been established, chaired by Professor David Dunger (membership listed below). The terms of reference of the DMEC are set out in Appendix G

Membership

<i>Professor David Dunger (CHAIR)</i>	Department of Paediatrics, University of Cambridge
<i>Dr David Harrison</i>	Statistician, Intensive Care Audit and Research Network (ICNARC),
<i>Professor David Hatch</i>	Emeritus Professor of Paediatric Anaesthesia and Intensive Care, Great Ormond Street Hospital
<i>Dr Jon Smith (from Sept. 2009)</i>	Consultant Cardiothoracic Anaesthetist, Newcastle General Hospital
<i>Mr. Giles Peek (till Sept. 2009)</i>	Consultant Cardiac Surgeon, Glenfield Hospital, Leicester

Principal Investigator's Responsibilities

Each participating centre will identify a paediatric intensivist as a principal investigator (PI). Each participating centre will be allocated funding for research nursing time and will be expected to employ or second a Research Nurse to support all aspects of the trial at the local centre.

The responsibility of the principal investigator will be to:

- a) Ensure local research ethics and R&D approval is obtained
Discuss the trial with medical, and nursing staff who see eligible patients and ensure that they are updated on the current state of knowledge, the trial and its procedures.
- b) Provide clinical support for the trial research nurse ensuring that relevant staff are trained in the trial procedures.
- c) Ensure that potentially eligible patients are considered for the trial.
- d) Report promptly to the Clinical Co-coordinating Centre any problems in meeting recruitment targets so that support can be provided.
- e) Maintain good contact with the paediatric cardiac unit to ensure that potentially eligible patients are given information about the trial.
- f) Ensure that mechanisms for consent and recruitment are in place.
- g) Ensure that data collection forms are completed and returned to the Data Co-coordinating Centre promptly and to deal with any queries.
- h) Inform and advise the relevant Co-coordinating Centre promptly.
- i) Facilitate other aspects of co-ordination as relevant.
- j) Make data available for verification, audit and inspection purposes as necessary.
- k) Respond to requests for data from the Economics team.
- l) Ensure that the confidentiality of all information about trial participants is respected by all persons and that records are kept in areas to which access is restricted.
- m) Ensure the trial is conducted in accordance with ICH GCP.

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- n) Allow access to source data for audit and verification.
- o) Ensure that adverse events are reported in line with statutory guidelines.

Confidentiality

Patients will be identified by their trial number to ensure confidentiality. However, as the patients in the trial will be contacted about the study results (and patients recruited until September 2010 will be followed up to 12 months following randomisation), it is essential that the team at the Data Co-coordinating Centre has the names and addresses of the trial participants recorded on the data collection forms in addition to the allocated trial number. Stringent precautions will be taken to ensure confidentiality of names and addresses at the Data Co-coordinating Centre.

The Chief Investigator and local investigators will ensure conservation of records in areas to which access is restricted.

Audit

To ensure that the trial is conducted according to ICH GCP guidelines, site audits will be carried out on a random basis. The local investigator will be required to demonstrate knowledge of the trial protocol and procedures and Good Clinical Practice. The accessibility of the site file to trial staff and its contents will be checked to ensure all trial records are being properly maintained. Adherence to local requirements for consent will be examined.

If the site has full compliance the Site Visit Form will be signed by the Trial Manager. In the event of non-compliance the Data Coordinating Centre will address the specific issues to ensure that relevant training and instruction is given.

Termination of the study

At the termination of planned recruitment the Data Co-coordinating Centre will contact all sites by telephone, email or fax in order to terminate all patient recruitment as quickly as possible. If the study is terminated prematurely by the Steering Committee all sites will be informed immediately. When all recruited patients have been followed until 30 days post randomisation (or hospital discharge if stay longer than 30 days) a declaration of the end of trial form will be sent to EurdraCT and the MREC. The following documents: original consent forms, data forms, trial related documents and correspondence will be archived in each Site File and kept for at least five years. At the end of the analysis and reporting phase, the Trial Master Files at the Clinical and Data Co-coordinating Centres will be archived for 15 years.

Funding

The costs for the study itself are covered by a grant from the Health Technology Assessment Programme (HTA). Clinical costs will be met by the NHS under existing contracts.

Indemnity

If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation.

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Appendix A

Insulin management of control group**Introduction**

- The guidelines are only indicative and are to be used with common sense.

Preparation of insulin infusion

ACTRAPID: Actrapid® is a short-acting human insulin solution for injection.

Actrapid contains: glycerol hydrochloric acid and/or sodium hydroxide if pH adjusted, insulin soluble human, metacresol, water for injections, zinc chloride.

Draw up 5 units per Kg of Actrapid and further dilute up to a total volume of 50mls with 0.9% sodium chloride - (1ml/hr is equal to 0.1Units /kg/ hour)

OR

Make up an infusion of Actrapid diluted in 0.9% sodium chloride according to own local drug policy.

- Insulin sticks to the syringe and tubing, so flush with several times the volume of the tubing before starting the infusion.
- Insulin infusions should be changed every 12 hours or according to local unit policy.
- Make sure the insulin infusion line is connected as close as possible to the patient to avoid flushes and to assure that small adjustments of the infusion speed are delivered in time to the patient.
- Glucose and insulin makes potassium go into the cells (hence its value in hyperkalaemia) Monitor the potassium closely.
- Blood glucose levels should be monitored using blood taken from arterial sampling. However if for any reason this is not possible the blood glucose level should be monitored for safety reasons according to the usual local practice.
- The frequency of blood glucose measurements should be adapted to the speed and magnitude of changes in glycaemia. It is recommended that following any change of the insulin infusion rate the following blood glucose level should be monitored within 45 minutes.
- The half life of intravenously injected insulin is short (7-9 minutes) and blood glucose may rise rapidly if the infusion is stopped. Similarly If feed or parenteral glucose-containing fluids are restricted or suspended blood glucose levels may fall rapidly therefore monitor the blood glucose levels closely and reduce or discontinue insulin in anticipation of a fall in blood glucose.

CONTROL GROUP (permissive) BG management**a. Start up and initial stabilising**

Eligible for insulin if BG > 12 mmol/l on 2 BG measurements at least 30 minutes apart

- If BG is >12.0 – 15.0 mmols start the insulin infusion at 0.05 Units / Kg / bodyweight / hour. Check BG within 30 minutes.

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- If BG is >15.0 mmols start the insulin infusion at 0.1 Units /Kg / bodyweight / hour
Check BG within 30 minutes.
- If control BG is 10-12 mmol/l maintain insulin at same dose (unless BG fall since last reading has been $\geq 50\%$ in which case reduce the infusion by 50%, if fall has been 25-49% reduce infusion by 25%)
- When BG < 10 mmols discontinue insulin
- If BG > 15mmol/l: increase insulin infusion by 0.1 Units/kg/h (unless BG fall since last reading has been $\geq 50\%$ in which case reduce the infusion by 50%, if fall has been 25-49% reduce infusion by 25%)
- If BG is > 12 and ≤ 15 mmol/l mg/dl: increase insulin infusion by 0.05 Units/kg/h (unless BG fall since last reading has been $> 50\%$ in which case reduce the infusion by 50%, if fall has been 25-50% reduce infusion by 25%)
- Check BG at least every 45 minutes until BG controlled within required range and stable glucose and insulin infusion rates have been achieved.

If the insulin infusion is stopped and restarted at a later time, always go back and use the start up and initial stabilising regime.

b. Adjustments after stabilisation

- Hourly BG checks should be maintained.
- If BG drops $> 50\%$: decrease insulin infusion rate by 50% and recheck BG within 45 minutes
- If BG < 10 mmol/l: stop insulin infusion and check BG within 1 hour
- If BG < limit for hypoglycaemia: **Stop insulin infusion and IV bolus 5mls / kg of 10% glucose. Alternatively for a smaller fluid bolus 2.5mls / kg of 20% glucose can be used.** Check BG after 15 minutes and repeat bolus until normalisation of BG.
- Restart insulin infusion only if BG > 12 mmol/l

When a child no longer requires an infusion of insulin to maintain their blood glucose within the range specified by their study arm, Blood glucose measurements should be recorded 12 hourly until discharge from PICU or day 30, whichever is sooner.

Control group BG ranges

Starting insulin:

Insulin will be started when BG levels exceed 12mmol/l on two blood samples taken at least 30 minutes apart

Stopping insulin:

Insulin must be discontinued if BG falls below 10 mmol/l

Hypoglycaemia BG < 2.5 mmol/l

Appendix B

Insulin management of tight glycaemic control

Introduction

- The guidelines are only indicative and are to be used with common sense.

Preparation of insulin infusion

ACTRAPID: Actrapid® is a short-acting human insulin solution for injection.

Actrapid contains: glycerol hydrochloric acid and/or sodium hydroxide if pH adjusted, insulin soluble human, metacresol, water for injections, zinc chloride.

Draw up 5 units per Kg of Actrapid and further dilute up to a total volume of 50mls with 0.9% sodium chloride - (1ml/hr is equal to 0.1Units /kg/ hour)

OR

Make up an infusion of Actrapid diluted in 0.9% sodium chloride according to own local drug policy.

- Insulin sticks to the syringe and tubing, so flush with several times the volume of the tubing before starting the infusion.
- Insulin infusions should be changed every 12 hours or according to local unit policy.
- Make sure the insulin infusion line is connected as close as possible to the patient to avoid flushes and to assure that small adjustments of the infusion speed are delivered in time to the patient.
- Glucose and insulin makes potassium go into the cells (hence its value in hyperkalaemia) Monitor the potassium closely.
- Blood glucose levels should be monitored using blood taken from arterial sampling. However if for any reason this is not possible the blood glucose level should be monitored for safety reasons according to the usual local practice.
- The frequency of blood glucose measurements should be adapted to the speed and magnitude of changes in glycaemia. It is recommended that following any change of the insulin infusion rate the blood glucose level should be monitored within 45 minutes.
- The half life of intravenously injected insulin is short (7-9 minutes) and blood glucose may rise rapidly if the infusion is stopped. Similarly If feed or parenteral glucose-containing fluids are restricted or suspended blood glucose levels may fall rapidly therefore monitor the blood glucose levels closely and reduce or discontinue insulin in anticipation of a fall in blood glucose.

TIGHT GLYCAEMIC CONTROL (TGC) management

a. Start up and initial stabilising

If BG is > than the upper limit (> 7.0 mmols) start the insulin infusion at 0.05 Units/ Kg/ bodyweight /hour.
Check BG within 30 minutes.

If BG is > twice upper limit (>14.0 mmols) start the insulin infusion at 0.1 Units/Kg/ bodyweight /hour.
Check BG within 30 minutes.

If BG > 2mmol/l above upper limit: increase insulin infusion by 0.1 IU/kg/h (unless BG fall since last reading has been \geq 50 % in which case stop the infusion. if fall has been 25-49% reduce infusion by 50%)

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If BG \leq 2 mmol/l mg/dl above upper limit: increase insulin infusion by 0.05 IU/kg/h (unless BG fall since last reading has been > 50 % in which case stop the insulin infusion. if fall has been 25-50% reduce infusion by 50%. if fall has been <25% continue checking at 30 min intervals and if after 2 hours still in this range only then increase insulin infusion by 0.05 IU/kg/h)

If the blood glucose level has dropped by <25% but is within the tight glycaemic range we recommend reducing the infusion by 25%.

If there has been no drop in blood glucose level and the blood glucose is within the tight glycaemic range we recommend continuing the infusion at the same infusion rate.

Check BG every 45 minutes until BG controlled within required range and stable glucose and insulin infusion rates have been achieved.

If the insulin infusion is stopped and restarted at a later time, always go back and use the start up and initial stabilising regime.

b. Adjustments after stabilisation

- Hourly BG checks should be maintained.
- If BG < lower TGC limit: stop insulin infusion and check BG within 1 hour
- If BG < limit for hypoglycaemia: **Stop insulin infusion and IV bolus 5mls / kg of 10% glucose. Alternatively for a smaller fluid bolus, 2.5mls / kg of 20% glucose can be used.** Check BG after 15 minutes and repeat bolus until normalisation of BG.
- Restart insulin infusion only if BG > upper TGC limit (>7mmols)

When a child no longer requires an infusion of insulin to maintain their blood glucose within the range specified by their study arm, Blood glucose measurements should be recorded 12 hourly until discharge from PICU or day 30, whichever is sooner.

TGC ranges and target BG

Target range for TGC 4-7 mmol/l

Target range A 5-7 mmol/l
Used by all centres when randomising first cohort of children

Target range B 4-6 mmol/l
Used by centres comfortable with experience of 5-7 mmol/l

Hypoglycaemia Treatment required if BG < 2.5 mmol/l

All trial centres will initially use Target range A. Subsequently, when centres are fully conversant with achieving TGC to Target A, they may with the agreement of the Clinical Coordinating centre move to Target range B. Both ranges are consistent with the treatment aims of the TGC arm of the protocol. Range B will however ensure a greater difference in effect compared to the control group but will not be imposed on investigators to ensure that the risk of hypoglycaemia is minimised, ensuring that centres are safely applying the higher Target A before moving to Target B.

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Appendix C

Adverse Events and Safety Reporting**This document must remain in the Trial Master File at all times**

Royal Brompton & Harefield NHS Trust, as sponsor of this study, has responsibility to ensure arrangements are in place to record, notify, assess, report, analyse and manage adverse events in this study in order to comply with the UK regulations of Medicines for Human Use (Clinical Trials) Regulations 2004.

It is therefore important that all site investigators involved in the study are aware of the regulatory reporting process and timelines. In addition, the following people at the Royal Brompton & Harefield NHS Trust should be notified immediately or within 24 hours of being made aware of a serious adverse event.

Helen Betts (Lead Study Nurse) Royal Brompton Hospital 020 7351 8546 h.betts@rbht.nhs.uk	Dr Duncan Macrae Chief Investigator CHIP Trial Royal Brompton Hospital 020 7351 8546 d.macrae@rbht.nhs.uk
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DefinitionsAdverse Event (AE)

Any untoward medical occurrence in a subject to whom insulin has been administered. This includes occurrences which are not necessarily caused by or related to insulin

Adverse Reaction (AR)

Any untoward and unintended response in a subject to insulin which is related to any dose administered to that subject.

Unexpected Adverse Reaction

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about insulin in the summary of product characteristics.

Serious Adverse Reaction/Event

An adverse reaction is 'serious' if it:

- results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect.

Suspected Serious Adverse Reaction (SSAR)

Any adverse reaction that is classed as serious and which is consistent with the information about insulin listed in the Summary of Product Characteristics (SPC) Information on known adverse reactions can be found at <http://emc.medicines.org.uk>

Appendix C

Suspected Unexpected Serious Adverse Reactions (SUSARs)

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Any adverse reaction that is classed as serious and is suspected to be caused by insulin that is **not** consistent with the information about the product in the Summary of Product Characteristics, i.e. it is suspected and unexpected.

The trial protocol includes a list of known side effects for insulin. This should be checked with each serious adverse event that occurs in terms of expectedness. If the event is not listed as expected, or has occurred in a more serious form than anticipated, this should be considered a SUSAR.

Causality

Adverse reactions should be assessed for causality using the definitions below.

Not Related - There is no evidence of any causal relationship

Unlikely - There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of insulin). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possibly Related* - There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of insulin). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probably Related* - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely Related* - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not Assessable - There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

*** If the AE is serious and unexpected, the possible, probable and definitely related should be notified to the MHRA, the relevant REC and the Sponsor as SUSAR**

Reporting Timeline

Adverse Events that are not considered serious should be reported in accordance with each Trust's policy for such events.

A SUSAR which is *fatal or life-threatening* must be reported to the Pharmacovigilance Unit at the MHRA and the main REC as soon as possible and in any event within **7 days** after the sponsor became aware of the event. Any additional relevant information must be reported within **8 days** of sending the first report.

A SUSAR which is *not fatal or life-threatening* must be reported to the MHRA and the MREC as soon as possible and in any event within **15 days** after the sponsor first became aware of the event.

In the case of double-blinded trials, the European Commission guidance recommends that reports of SUSARs should normally be unblinded. So far as the UK is concerned, both the MHRA and the main REC will expect all such reports to be unblinded.

Other expedited safety reports

The European Commission guidance recommends that expedited reports on the following occurrences should also be sent to the MHRA and the MREC according to the same timelines as SUSARs:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. death)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important

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Other Reports**Annual Progress Reports and End of Study Reports****Ethics Committee**

NHS Research Ethics Committees are required to monitor research with a favourable opinion. A progress report should be submitted to the MREC 12 months after the date on which the favourable opinion was given using the form available at.

[http://www.corec.org.uk/applicants/apply/docs/Progress_Report_Form_\(CTIMPs\)v3.1.doc](http://www.corec.org.uk/applicants/apply/docs/Progress_Report_Form_(CTIMPs)v3.1.doc)

All SAEs should also be reported.

Annual progress reports should be submitted thereafter until the end of the study, when the following form should be used.

<http://eudract.emea.eu.int/docs/Declarationoftheendoftrialform170805withfields.doc>

This form should be sent to the MREC no later than 12 months after the end of the study.

MHRA

An Annual report is required to be sent to the MHRA 12 months after the CTA is granted and then annually until the end of the study. All SAE s should also be reported

At the end of the study the sponsor is responsible for notifying the MHRA that the trial has ended. This notification should be sent by the sponsor within 90 days of its conclusion. An end of trial notification form is available from the EudraCT website. Reports should be sent to

Clinical Trials Unit, MHRA, Market Towers, 1 Nine Elms Lane, London SW8 5NQ

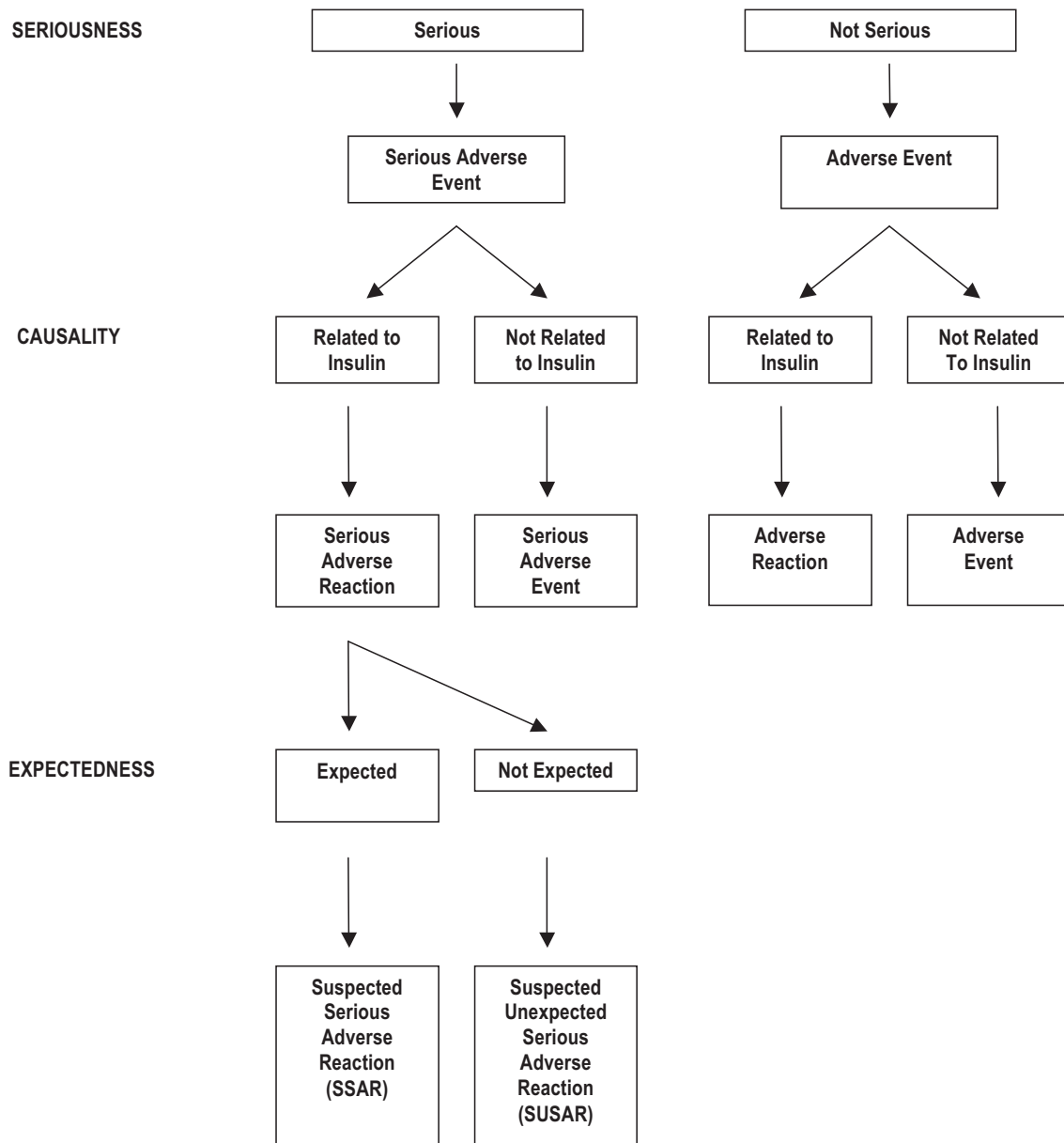
The end of the trial is defined as when the last patient recruited has completed their scheduled involvement in the trial e.g. last follow-up visit.

Early Termination

If a trial is terminated before the specified date for its conclusion then the investigators should notify the R&D Office immediately so that the Royal Brompton & Harefield NHS Trust, as sponsor, can notify the MHRA and the MREC within 15 days of the date of termination.

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Adverse Events



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Follow-up – Traumatic brain Injury sub-group

The sub group of children with traumatic brain injury (TBI) is more likely to have longer-term morbidity and parents of children in this sub-group will be asked to provide additional information at 12 months[†]. We will specifically include assessments of attention and behaviour as patients with TBI are commonly left with deficits in these areas.

Definition of TBI

Accidental trauma to the head resulting in need for intubation and mechanical ventilation

Population

750 ICU admissions per year in UK. Estimate of 150 recruited to the trial

Outcomes assessment

This will comprise four components:

Overall health status: measured by the Health Utilities Index (HUI)

Global neurological outcome: measured by the Kings Outcome Scale for Childhood Head Injury (KOSCHI)

Attention and behavioural assessment: measured by the Child Behavioural Check List (CBCL) and the Conner's Rating Scales revised – short version (CRS-R:S)

The HUI, CBCL and CRS are written questionnaires that will be posted out to the families. They take approximately 30 minutes to complete.

Health Utilities Index is a multi-attribute health status classification system. Seven attributes (sensation, mobility, emotion, cognition, self-care, pain, fertility) are categorised according to one of 4 or 5 levels. In this population fertility will be excluded. The algorithm (from death to perfect health scale) provides a single numerical value.

KOSCHI is a 5 point categorical scale, ranging from death to normal neurological function, and is similar in structure to the Glasgow Outcome Scale, which is widely used in adult studies. In addition the KOSCHI is further subdivided into two subcategories at points 4 and 5 on the scale (moderate outcome and good outcome). Patient outcomes will be dichotomized between patients in categories 1, 2, 3, 4A and those in 4B, 5A, 5B.

Child behaviour checklist (CBCL/4-18), problem scales

The CBCL is based on parent's report and assesses problematic child behaviour that is summarised in internalising behaviour (anxious/depressed, withdrawn/depressed, somatic complaints), externalising behaviour (rule-breaking, aggressive) and other (social problems, thought problems, attention problems).

In reference to 1991 normative data:

T-score (whole)	Guideline	T-score (individual scale)	Guideline
<60	Normal	<65	Normal
60-63	Borderline	65-69	Borderline
>63	Clinical	>69	Clinical

Patient outcome can be summarised according to placement within one of the three groups, or according to the T-score.

[†] For patients recruited until September 2010

Appendix D

Conners' rating scales revised – short version (CRS-R:S)

The CRS assesses symptoms of attention-deficit/hyperactivity disorder and related problem behaviour in children and adolescents based on parent's report [67].

In reference to 1993 normative data:

T-score	Guideline
≥70	Markedly atypical (significant problem)
66-69	Moderately atypical (significant problem)
61-65	Mildly atypical (possible significant problem)
56-60	Slightly atypical (borderline)
45-55	Average (no concern)
≤44	Good

Patient outcome can be summarised according to placement within one of the three groups (marked + moderate, mild + slight, average + good), or according to the T-score.

EurodrCT number 2006/-005715/-10
ISRCTN61735247

Information Sheets

See *Appendix 1a–d*.

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Trial Steering Committee (TSC): Terms of reference.**Appendix F**

The role of the TSC is to provide overall supervision for CHIP on behalf of the HTA and the Royal Brompton and Harefield NHS Trust (sponsor) and to ensure that the trial is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the trial is the responsibility of the Investigators and the Chief Investigator will set up a separate Trial Management Group (TMG) to assist with this function.

- The TSC should approve the protocol and trial documentation in a timely manner.
- In particular the TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and consideration of new information of relevance to the research question.
- The safety and well being of the trial participants are the most important consideration and should prevail over the interests of science and society.
- The TSC should provide advice, through its chair, to the Chief Investigator, the Trial Sponsor, the Trial Funder, on all appropriate aspects of the trial. Specifically the TSC will:-
 - Monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems.
 - Monitor completion of data sheets and comment on strategies from TMG to encourage satisfactory completion in the future.
 - Monitor follow-up rates and review strategies from TMG to deal with problems including sites that deviate from the protocol.
 - Approve any amendments to the protocol, where appropriate
 - Approve any proposals by the TMG concerning any change to the design of the trial, including additional sub-studies
 - Oversee the timely reporting of trial results
 - Approve and comment on the statistical analysis plan
 - Approve and comment on the publication policy
 - Approve and comment on the main trial manuscript
 - Approve and comment on any abstracts and presentations of any results *during* the running of the trial
 - Approve external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples.
 - Receive reports from the Data Monitoring and Ethics Committee.
 - The TSC will make decisions as to the future continuation (or otherwise) of the trial.
- Membership of the TSC should be limited and include an independent Chair, at least two other independent members, two collaborators and two members of the public. The Investigators and the trial project staff are ex-officio.
- Representatives of the trial sponsor and the HTA should be invited to all TSC meetings.
- Responsibility for calling and organising the TSC meetings lies with the Chief Investigator. The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.
- There may be occasions when the Trial sponsor or the HTA will wish to organise and administer these meetings in exceptional circumstances.
- The TSC will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.
- The TSC will maintain confidentiality of all trial information that is not already in the public domain.

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Data Monitoring and Ethics Committee (DMEC): Terms of reference

To safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the CHIP study.

The DMEC should receive and review information on the progress and accruing data of CHIP and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

The DMEC should inform the Chair of the TSC if, in their view the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.

Interim review of the trial's progress including updated figures on recruitment, data quality, adherence to protocol, follow-up, and main outcomes and safety data. Specifically, these roles include to:

- monitor evidence for treatment differences in the main efficacy outcome measures
- monitor evidence for treatment harm (e.g. toxicity, SAEs and SARs, treatment related deaths)
- assess the impact and relevance of external evidence
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- decide whether trial follow-up should be stopped earlier
- assess data quality, including completeness (and by so doing encourage collection of high quality data)
- maintain confidentiality of all trial information that is not in the public domain
- monitor recruitment figures and losses to follow-up
- monitor compliance with the protocol by participants and investigators
- consider the ethical implications of any recommendations made by the DMEC
- monitor planned sample size assumptions, preferably with regards to
 - (i) a priori assumptions about the control arm outcome and/or
 - (ii) emerging differences in clinically relevant subgroups, rather than on emerging, unblinded differences between treatment groups, overall
- suggest additional data analyses if necessary
- advise on protocol modifications proposed by investigators or HTA (e.g. to inclusion criteria, trial endpoints, or sample size)
- monitor continuing appropriateness of patient information
- monitor compliance with previous DMEC recommendations

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Appendix H

Publication Policy

To safeguard the integrity of the trial, data from this study will not be presented in public or submitted for publication without requesting comments and receiving agreement from the Trial Steering Committee. The primary results of the trial will be published by the group as a whole with local investigators acknowledged. The success of the trial depends on the collaboration of many people. The results will be presented first to the trial local investigators. A summary of the results of the trial will be sent to parents of participating children on request and also made available on the trial website.

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Appendix 4 Published protocol

Macrae *et al.* *BMC Pediatrics* 2010, **10**:5
<http://www.biomedcentral.com/1471-2431/10/5>



STUDY PROTOCOL

Open Access

Control of hyperglycaemia in paediatric intensive care (CHiP): study protocol

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Abstract

Background: There is increasing evidence that tight blood glucose (BG) control improves outcomes in critically ill adults. Children show similar hyperglycaemic responses to surgery or critical illness. However it is not known whether tight control will benefit children given maturational differences and different disease spectrum.

Methods/Design: The study is a randomised open trial with two parallel groups to assess whether, for children undergoing intensive care in the UK aged ≤ 16 years who are ventilated, have an arterial line in-situ and are receiving vasoactive support following injury, major surgery or in association with critical illness in whom it is anticipated such treatment will be required to continue for at least 12 hours, tight control will increase the numbers of days alive and free of mechanical ventilation at 30 days, and lead to improvement in a range of complications associated with intensive care treatment and be cost effective.

Children in the tight control group will receive insulin by intravenous infusion titrated to maintain BG between 4 and 7.0 mmol/l. Children in the control group will be treated according to a standard current approach to BG management. Children will be followed up to determine vital status and healthcare resources usage between discharge and 12 months post-randomisation. Information regarding overall health status, global neurological outcome, attention and behavioural status will be sought from a subgroup with traumatic brain injury (TBI).

A difference of 2 days in the number of ventilator-free days within the first 30 days post-randomisation is considered clinically important. Conservatively assuming a standard deviation of a week across both trial arms, a type I error of 1% (2-sided test), and allowing for non-compliance, a total sample size of 1000 patients would have 90% power to detect this difference. To detect effect differences between cardiac and non-cardiac patients, a target sample size of 1500 is required. An economic evaluation will assess whether the costs of achieving tight BG control are justified by subsequent reductions in hospitalisation costs.

Discussion: The relevance of tight glycaemic control in this population needs to be assessed formally before being accepted into standard practice.

Trial Registration: Current Controlled Trials ISRCTN61735247

Background

The ability to control blood sugar is known to be impaired in patients subjected to the stress of major surgery or critical illness resulting in high blood sugar levels (hyperglycaemia)[1]. This may in part result from insulin resistance, as insulin-dependent glucose uptake

has been shown to be reduced in various organs and tissues during critical illness. Glucose uptake is however increased in non-insulin dependent tissues such as brain, red blood cells and wounds. This imbalance of glucose metabolism has previously been interpreted as the body's plea for tolerating moderately high levels of glucose during critical illness and injury and treatment of 'stress-induced' hyperglycaemia has typically only

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been initiated if BG levels are persistently and substantially elevated.

Hyperglycaemia in Critically Ill Adults

Over recent years several studies have associated hyperglycaemia with adverse outcomes during acute illness in adults:

Myocardial infarction

In a meta-analysis [2], patients with acute myocardial infarction without diabetes who had glucose concentrations more than or equal to range 6.1-8.0 mmol/L had a 3.9-fold (95% CI 2.9-5.4) higher risk of death than patients without diabetes who had lower glucose concentrations. Glucose concentrations higher than values in the range of 8.0-10.0 mmol/L on admission were associated with increased risk of congestive heart failure or cardiogenic shock in patients without diabetes. Stress hyperglycaemia with myocardial infarction is associated with an increased risk of in-hospital mortality and increased risk of congestive heart failure or cardiogenic shock in patients without diabetes.

Stroke

Capes et al. conducted a systematic review and meta-analysis of the literature relating acute post stroke glucose levels to the subsequent course [3]. A comprehensive literature search was done for cohort studies reporting mortality and/or functional recovery after stroke in relation to admission glucose level. Thirty-two studies were identified for which pre-defined outcomes could be analysed in 26. After stroke, the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level >6 to 8 mmol/L was 3.07 (95% CI, 2.50 to 3.79) in non-diabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients. Non-diabetic stroke survivors whose admission glucose level was >6.7 to 8 mmol/L also had a greater risk of poor functional recovery (relative risk = 1.41; 95% CI, 1.16 to 1.73).

Head injury and multi-system trauma

Hyperglycaemia has been shown to be an independent predictor of poor outcome in adult patients[4] and children with head injury[5,6] and multiple trauma[7].

Pulmonary function

Hyperglycaemia has been shown to be associated with diminished pulmonary function in adults even in the absence of diabetes mellitus[8] and a range of other effects with potential to injure the lung[9].

Gastrointestinal effects

Hyperglycaemia has been shown to be associated with delayed gastric emptying[10], decreased small bowel motility and to increase sensation and cerebral evoked potentials to a range of gastrointestinal stimuli in adult volunteers [11-14].

Infections

In vitro responsiveness of leukocytes stimulated by inflammatory mediators is inversely correlated with glycaemic control[15]. This reduction in polymorphonuclear leucocyte responsiveness may contribute to the compromised host defence associated with sustained hyperglycaemia[15], and indeed, hyperglycaemia has been shown to be associated with an increased rate of serious infections after adult cardiac[16] and vascular [17] surgery.

Studies of Control of Glycaemia in Adults

Recent reports from adult populations suggest that control of glycaemia during acute illness can be associated with improved outcomes[18-22].

Furnary[21] studied the hypothesis that since hyperglycaemia was associated with higher sternal wound infection rates following adult cardiac surgery, aggressive control of glycaemia might lead to lower infection rates. In a prospective study of 2,467 consecutive diabetic patients who underwent open heart surgical procedures, patients were classified into two sequential groups. A control group included 968 patients treated with sliding-scale-guided intermittent subcutaneous insulin injections. A study group included 1,499 patients treated with a continuous intravenous insulin infusion in an attempt to maintain a BG level of less than 11.1 mmol/l. Compared with subcutaneous insulin injections, continuous intravenous insulin infusion induced a significant reduction in perioperative BG levels, which led to a significant reduction in the incidence of deep sternal wound infection in the continuous intravenous insulin infusion group (0.8% [12 of 1,499]) versus the intermittent subcutaneous insulin injection group (2.0% [19 of 968], $p = 0.01$). The use of perioperative continuous intravenous insulin infusion in diabetic patients undergoing open heart surgical procedures appears to significantly reduce the incidence of major infections.

Malmberg[19] randomly allocated patients with diabetes mellitus and acute myocardial infarction to intensive insulin therapy ($n = 306$) or standard treatment (controls, $n = 314$). The mean (range) follow up was 3.4 (1.6-5.6) years. There were 102 (33%) deaths in the treatment group compared with 138 (44%) deaths in the control group (relative risk (95% confidence interval) 0.72 (0.55 to 0.92); $p = 0.011$). The effect was most pronounced among the predefined group that included 272 patients without previous insulin treatment and at a low cardiovascular risk (0.49 (0.30 to 0.80); $p = 0.004$). Intensive insulin therapy improved survival in diabetic patients with acute myocardial infarction. The effect seen at one year continued for at least 3.5 years, with an absolute reduction in mortality of 11%.

In 2001 Van den Berghe and colleagues from Leuven, Belgium[18] reported the results of a randomised trial in adults undergoing intensive care following surgical procedures. This trial showed that the use of insulin to tightly control BG led to a reduction in mortality (32%), mean length of intensive care stay (22%), and significantly lower occurrence of a range of complications of critical illness such as renal failure, infection, inflammation, anaemia and polyneuropathy. Duration of intensive care stay was 3.4 days shorter in the insulin group.

Recently the Leuven group[22] have reported that, in addition to adult surgical intensive care patients, intensive insulin therapy reduces morbidity in adults who require intensive care for treatment of medical conditions. In this prospective randomised controlled trial, patients were randomly assigned to a regime of strict normalisation of BG (4.4-6.1 mmol/l) with use of insulin, or conventional therapy where insulin is administered only when BG levels exceeded 12 mmol/l, with the infusion tapered when the level fell below 10 mmol/l. In the intention to treat analysis of the 1200 patients included, ICU and in-hospital mortality were not significantly altered by intensive insulin therapy, however for those patients requiring more than 3 days intensive care, mortality was significantly reduced from 52.5 to 43% ($p = 0.009$). Morbidity was significantly reduced by intensive insulin therapy with a lower incidence of renal injury and shorter length of mechanical ventilation and duration of hospital stay noted. Beyond the fifth day of intensive insulin therapy, all morbidity endpoints were beneficially affected, whereas for those patients staying less than 3 days, none of the morbidity end-points were significantly different between the two treatment groups.

On the basis of these studies, several groups have recommended that tight glycaemic control with intensive insulin therapy become a standard of care for the critically ill adult patients. The Joint Commission on Accreditation of Healthcare Organization (JACHO) recently proposed tight glucose control for the critically ill as a core quality of care measure for all U.S. hospitals that participate in the Medicare program[23]. The Institute for Healthcare Improvement, together with an international initiative by several professional societies including the American Thoracic Society, is promoting a care "bundle" for severe sepsis that also includes intensive glycaemic control for critically ill adults[24]. Both the Society of Critical Care Medicine and European Society of Intensive Care Medicine have incorporated TGC into their recently publicised 'Surviving Sepsis' guidelines. These initiatives represent important attempts to translate research findings into improved care at the bedside[25].

The possible mechanisms by which different glucose control strategies might influence clinical outcomes are

yet to be fully elucidated. There is a substantial body of published research which points to an association between hyperglycaemia and organ/tissue dysfunction. In models of both focal and global cerebral ischaemia, hyperglycaemia has been shown to be associated with exacerbation of intracellular acidosis[26-28], accumulation of extracellular glutamate[29], cerebral oedema formation and disruption[30] of the blood-brain barrier[31]. In ischaemic brain injury, hyperglycaemia may worsen injury by promoting anaerobic metabolism and consequent intracellular acidosis. In the rat myocardium, hyperglycaemia leads to up-regulation of inducible nitric oxide synthase, resulting ultimately in an increase in production of superoxide, a condition favouring the production of the powerful pro-oxidant peroxynitrite. This highly reactive free radical has the power to cause direct oxidant damage to myocardial cells or to induce myocardial cell apoptosis[32,33]. Similar adverse mechanisms have been shown to exist in hyperglycaemic patients [34,35]. Improved clinical outcomes may arise not necessarily solely as a result of control of BG. Insulin lowers free fatty acids and normalises endothelial function[36], is associated with anabolic effects[37,38], has been shown to have anti-inflammatory effects[39,40] and to have cardio-protective effects[41], all of which may contribute independently to better outcomes in critical illness.

Hyperglycaemia in Critically Ill Children

Over 10,000 children are admitted to intensive care units in England and Wales each year[42]. Hyperglycaemia, defined as BG > 7 mmol/l, occurs frequently during critical illness or after major surgery in children, with a reported incidence of up to 86%[43]. As in adults, the occurrence of hyperglycaemia has been shown to be associated with poorer outcomes including death, sepsis, and longer length of intensive care stay in critically ill children[43-46]. Non-randomised research in children includes a number of reports from general[43-45,47] and cardiac PICUs[46] showing that high BG levels occur frequently in critically ill children and that BG levels are significantly higher in children who die than in children who survive.

Srinivasan[43] studied the association of timing, duration, and intensity of hyperglycaemia with PICU mortality in critically ill children. The study was a retrospective, cohort design and included 152 critically ill children receiving vasoactive infusions or mechanical ventilation. Peak BG of > 7 mmol/L occurred in 86% of patients. Compared with survivors, non-survivors had higher peak BG (17.3 mmol/L +/- 6.4 vs. 11.4 +/- 4.4 mmol/L, $p < .001$). Non-survivors had more intense hyperglycaemia during the first 48 hrs in the PICU (7 +/- 2.1 mmol/L) vs. survivors (6.4 +/- 1.9 mmol/L, p

<.05). Univariate logistic regression analysis showed that peak BG and the duration and intensity of hyperglycaemia were each associated with PICU mortality ($p < .05$). Multivariate modelling controlling for age and Paediatric Risk of Mortality scores showed independent association of peak BG and duration of hyperglycaemia with PICU mortality ($p < .05$). This study demonstrated that hyperglycaemia is common among critically ill children. Peak BG and duration of hyperglycaemia appear to be independently associated with mortality. The study was limited by its retrospective design, its single-centre location and the absence of cardiac surgical cases, a group which make up approximately 40% of paediatric intensive care (PICU) admissions in the UK.

Halverson-Steele[46] has recently shown in a retrospective study, that hyperglycaemia was associated with poor outcomes in 526 children following cardiac surgery. Nineteen patients (3.6%) died postoperatively (median 11 days, range 1-17 days). Peak plasma glucose concentrations in survivors (mean 10.7 mmol/l, SD 3.7) was significantly lower than the peak value recorded in non-survivors (mean 14.3 mmol/l, SD 4.2; $p = 0.0017$). The 147 patients who were discharged from ICU within 24 hours had lower plasma glucose concentrations on admission (mean 7.5 mmol/l, SD 2.3) and peak plasma glucose concentrations (mean 9.2 mmol/l, SD 2.3) than the remaining patients staying longer than 24 hours (mean 8.1 mmol/l, SD 4.0; $p = .003$ and mean 11.3 mmol/l, SD 3.9; $p < 0.0001$, respectively). Peak plasma glucose concentrations were also lower in 387 patients admitted for up to 5 days (mean 10.1 mmol/l, SD 2.9) when compared with those patients with ICU stays of > 5 days (mean 12.7 mmol/l, SD 4.6; $p < 0.0001$).

Hall[45] investigated the incidence of hyperglycaemia in infants with necrotizing enterocolitis (NEC) and the relationship between glucose levels and outcome in these infants. Glucose measurements ($n = 6508$) in 95 neonates with confirmed NEC admitted to the surgical intensive care unit were reviewed. Glucose levels ranged from 0.5 to 35.0 mmol/L. 69% of infants became hyperglycaemic (>8 mmol/L) during their admission. Thirty-two infants died. Mortality rate tended to be higher in infants when maximal glucose concentration exceeded 11.9 mmol/L compared with those with maximum glucose concentrations of less than 11.9 mmol/L, and late (>10 days admission) mortality rate was significantly higher in these infants (29% v, 2%; $p = .0009$). Linear regression analysis indicated that maximum glucose concentration was significantly related to length of stay ($p < .0001$).

Branco[44] showed that there is an association between hyperglycaemia and increased mortality in children with septic shock. They prospectively studied all children admitted to a regional PICU with septic shock

refractory to fluid therapy over a period of 32 months. The peak glucose level in those with septic shock was 11.9 +/- 5.4 mmol/L (mean +/- SD), and the mortality rate was 49.1% (28/57). In non-survivors, the peak glucose level was 14.5 +/- 6.1 mmol/L, which was higher ($p < .01$) than that found in survivors (9.3 +/- 3.0 mmol/L). The relative risk of death in patients with peak glucose levels of ≥ 9.9 mmol/L was 2.59 (range, 1.37-4.88).

Faustino[47] demonstrated that hyperglycaemia occurs frequently among critically ill non-diabetic children and is associated with higher mortality and longer lengths of stay. They performed a retrospective cohort study of 942 non-diabetic patients admitted to a PICU over a 3 year period. The prevalence of hyperglycaemia was based on initial PICU glucose measurement, highest value within 24 hours, and highest value measured during PICU stay up to 10 days after the first measurement. Through the use of three cut-off values (6.7 mmol/L, 8.3 mmol/L, and 11.1 mmol/L), the prevalence of hyperglycaemia was 16.7% to 75.0%. The relative risk (RR) for dying increased for maximum glucose within 24 hours >8.3 mmol/L (RR, 2.50; 95% confidence interval (CI), 1.26 to 4.93) and highest glucose within 10 days >6.7 mmol/L (RR, 5.68; 95% CI, 1.38 to 23.47).

Pham[48] have recently reported their experience of adopting a policy of 'intensive' insulin therapy to achieve BG levels 5 mmol/L to 6.7 mmol/L. They reviewed the records of children with $\geq 30\%$ total body surface area burn injury admitted over a 3 year period. The first cohort of 31 children received 'conventional insulin therapy', whilst the subsequent cohort of 33 children received 'intensive insulin therapy'. The demographic characteristics and injury severity were similar between the groups. Intensive insulin therapy was positively associated with survival and a reduced incidence of infections. The authors therefore concluded that intensive insulin therapy to maintain normoglycaemia in severely burned children could be safely and effectively implemented in a paediatric burns unit and that this therapy seemed to lower infection rates and improve survival.

There is therefore mounting evidence to suggest that a policy of TGC may be beneficial to neonates and children undergoing neonatal and paediatric intensive care, but none of this evidence is from large rigorous randomized controlled trials. The aim of the present study is to determine whether a policy of strictly controlling BG using insulin in children admitted to paediatric intensive care reduces mortality, morbidity and is cost-effective.

Methods/Design

Study Design

The study is an individually randomised controlled open trial with two parallel groups. The protocol is summarised in Figure 1.

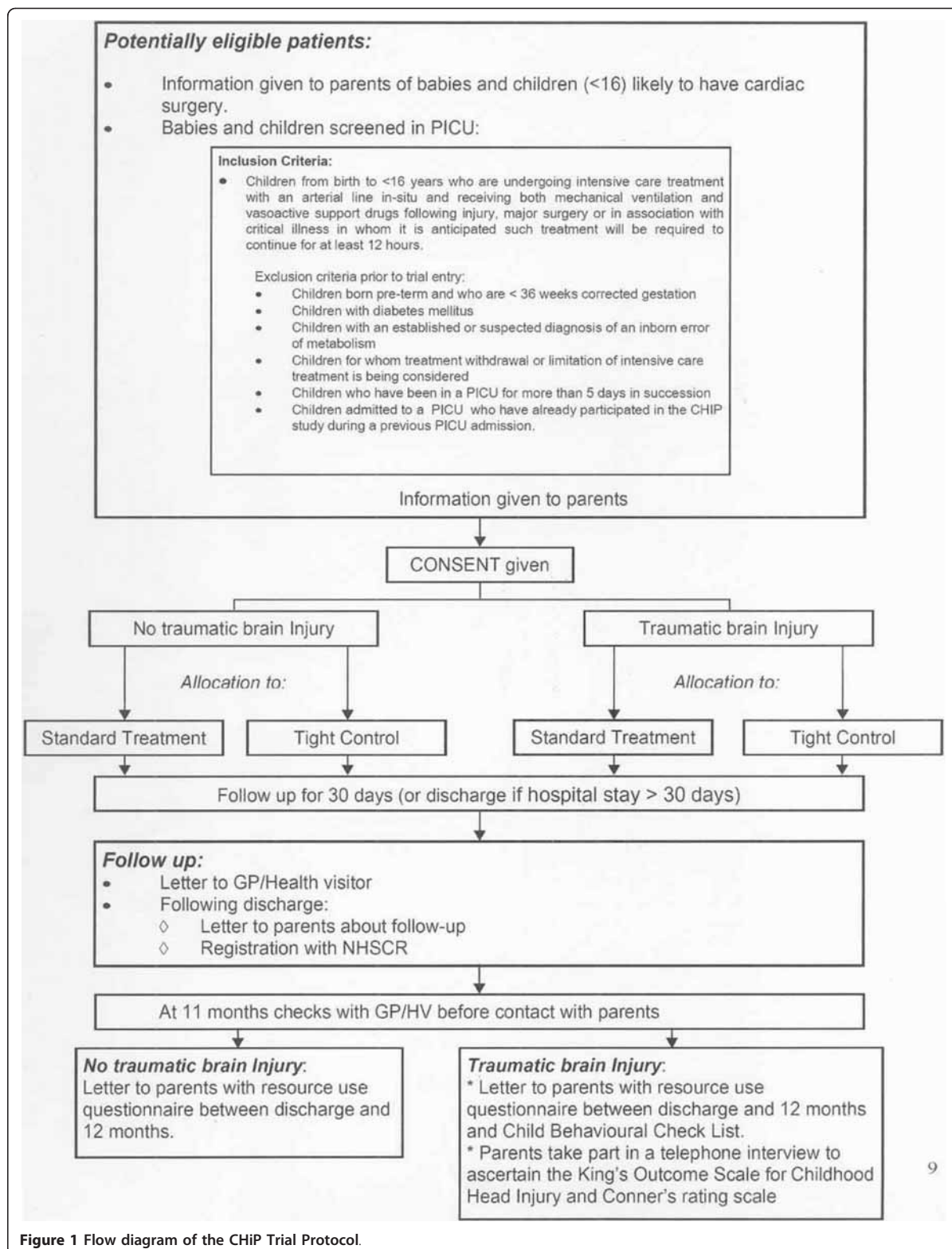


Figure 1 Flow diagram of the CHIP Trial Protocol.

Main hypothesis

For children aged from birth to ≤ 16 years on ventilatory support and vasoactive support drugs, tight glucose control (TGC) will increase the numbers of days alive and free of mechanical ventilation at 30 days.

Secondary hypotheses

That TGC will lead to improvement in a range of complications associated with intensive care treatment and be cost effective.

Setting

The following PICUs in the United Kingdom (UK) will be recruiting patients into the CHiP trial: Birmingham Children's Hospital; Bristol Royal Hospital for Children; Great Ormond Street Hospital; Leeds General Infirmary; University Hospitals of Leicester - Glenfield Hospital; Royal Brompton & Harefield NHS Trust (Royal Brompton Hospital); Royal Liverpool Children's NHS Trust; Royal Manchester Children's Hospital; St Mary's Hospital; Sheffield Children's NHS Foundation Trust; Southampton General Hospital; University Hospital of North Staffordshire.

Ethical Approval

MREC approval obtained from the Brighton East Research Ethics Committee (re 07/Q1907/24) in 2007 and SSIs have been successfully completed for all 10 participating centres. Over 500 children have thus far been recruited.

Type of participants**Inclusion criteria**

Children from birth (≥ 36 weeks corrected gestation) to ≤ 16 years who are undergoing treatment on a PICU with an arterial line in-situ and who are receiving both mechanical ventilation and vasoactive drugs (Table 1) following injury, major surgery or in association with critical illness in whom it is anticipated that such treatment will be required to continue for at least 12 hours.

Exclusion criteria prior to trial entry

- Children born pre-term and who are < 36 weeks corrected gestation
- Children with diabetes mellitus

Table 1 Definition of vaso-active drugs

Vaso-active drug name	Dose
Dobutamine	> 5 mcg/kg/min
Dopamine	> 5 mcg/kg/min
Epinephrine	Any dose
Norepinephrine	Any dose
Milrinone	Any dose
Vasopressin	Any dose

- Children with an established or suspected diagnosis of an inborn error of metabolism
- Children for whom treatment withdrawal or limitation of intensive care treatment is being considered
- Children who have been in a PICU for more than 5 days
- Children admitted to a PICU who have already participated in the CHIP study during a previous PICU admission.

Consent

Parents/guardians of babies and children in intensive care are likely to be stressed and anxious. However they will be asked to give consent in their role of legal representatives and will usually have limited time to consider trial entry as it may not be medically appropriate to delay the start of treatment. Parents of babies and children listed for cardiac surgery will be given information about the trial pre-operatively and consent provisionally obtained to be confirmed later if the child is admitted to intensive care. In addition, where possible, older children will be given information and asked to assent to their participation in the study.

Patients not entered into the trial will receive standard care**Allocation**

To reduce the risk of selection bias at trial entry, allocation will be administered through a 24 hour, 7 day a week central randomisation service. Minimisation with a probabilistic element will be used to ensure a balance of key prognostic factors between groups using the following criteria:

- Centre
- Age ≤ 1 year versus between 1 year and ≤ 16 years
- Admitted following cardiac surgery or not
- For cardiac surgical children, Risk adjusted classification for Congenital Heart Surgery 1 (RACHS1)[49] category 1 to 4 versus 5 to 6
- For non-cardiac surgical children, Paediatric index of mortality version 2 (PIM2) score at randomization categorised by probabilities of death of $< 5\%$, $5\% - < 15\%$ and $\geq 15\%$
- Accidental TBI or not

Interventions

After inclusion in the study, children will be randomised to one of two groups: Group 1 (Standard treatment) or Group 2 (Tight glycaemic control).

Group 1 - Standard treatment

Children in this group will be treated according to a standard, current, approach to BG management. Insulin will be given by intravenous infusion in this group only if BG levels exceed 12 mmol/l on two blood samples

taken at least 30 minutes apart and will be discontinued once BG falls to <10 mmol/l. A protocol for glucose control in this group is in Figure 2.

Group 2 - Tight glycaemic control

Children in this group will receive insulin by intravenous infusion titrated to maintain a BG between the limits of 4 and 7.0 mmol/l. A protocol for glucose control in this group is in Figure 3.

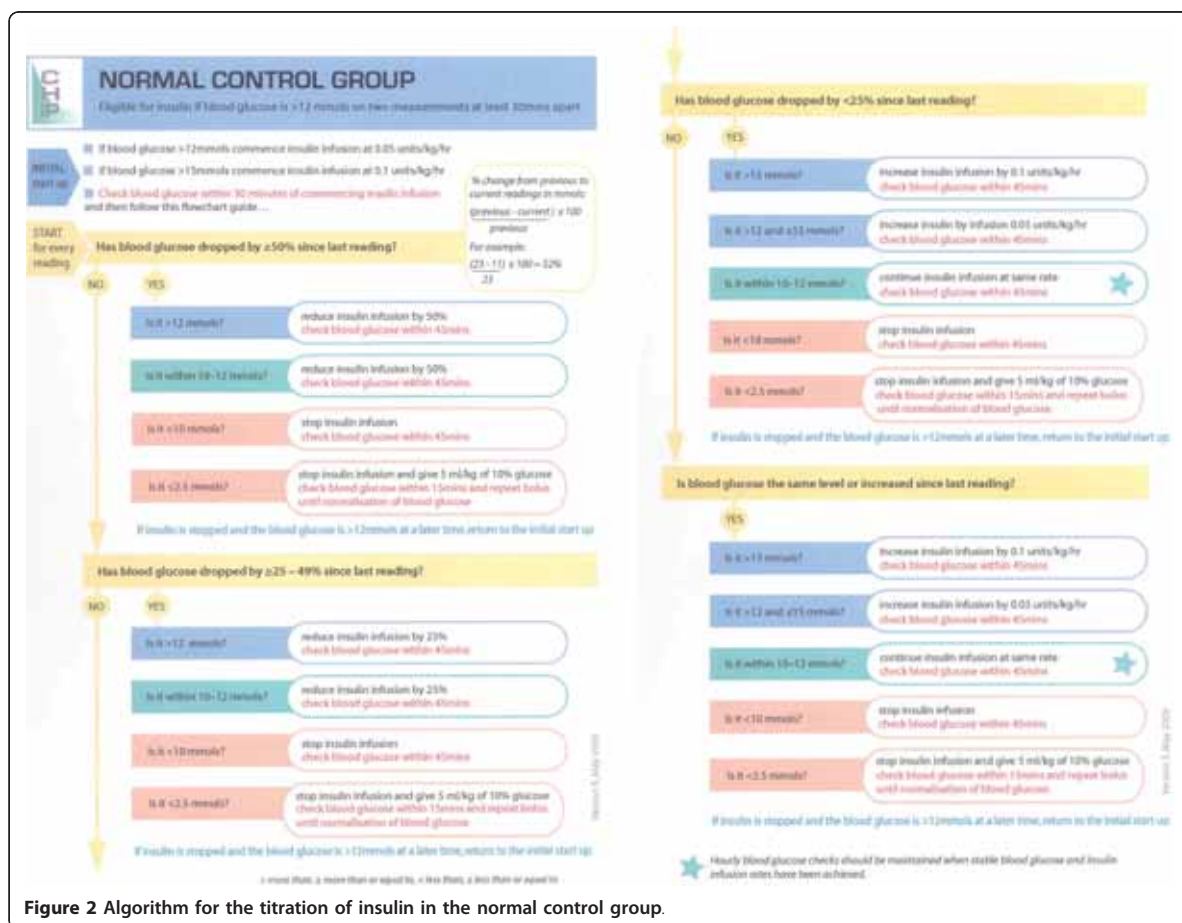
The protocol for glucose control in group 2 has been carefully designed to achieve tight glucose control whilst minimizing the risk of hypoglycaemia, the principal side effect of insulin therapy. Standard insulin solutions will be used and changes in insulin infusion rates will be guided both by the BG and its rate of change from previous measurements. BG levels will be routinely measured as in all PICUs using commercially available 'point of care' analysers which utilise very small blood samples, producing results in approximately 1 minute. Analysers are rigorously maintained and subjected to laboratory-standard quality assurance programmes.

Training in use of the BG control protocol will be provided before the first patient is enrolled in each collaborating centre and for new staff throughout the trial. The Clinical Co-ordinating centre team will liaise closely with local clinicians to ensure that BG control algorithms are followed closely and safely.

Outcome measures

Primary outcome

Following the influential ARDSNET study[50] the primary outcome for CHiP trial is the number of days alive and free from mechanical ventilation within the 30 days after trial entry. Death is obviously an important outcome. Mechanical ventilation can be seen as a measure of disease severity, defining the need for complex intensive care. The concept of ventilator free days (VFDs) brings together these two outcomes. Schoenfeld[51] define VFDs as: $VFD = 0$ if the child dies before 30 days; $VFD = (30-x)$ if the child is successfully weaned from ventilator within 30 days (where x is the number of days on ventilator); or $VFD = 0$ if the child is



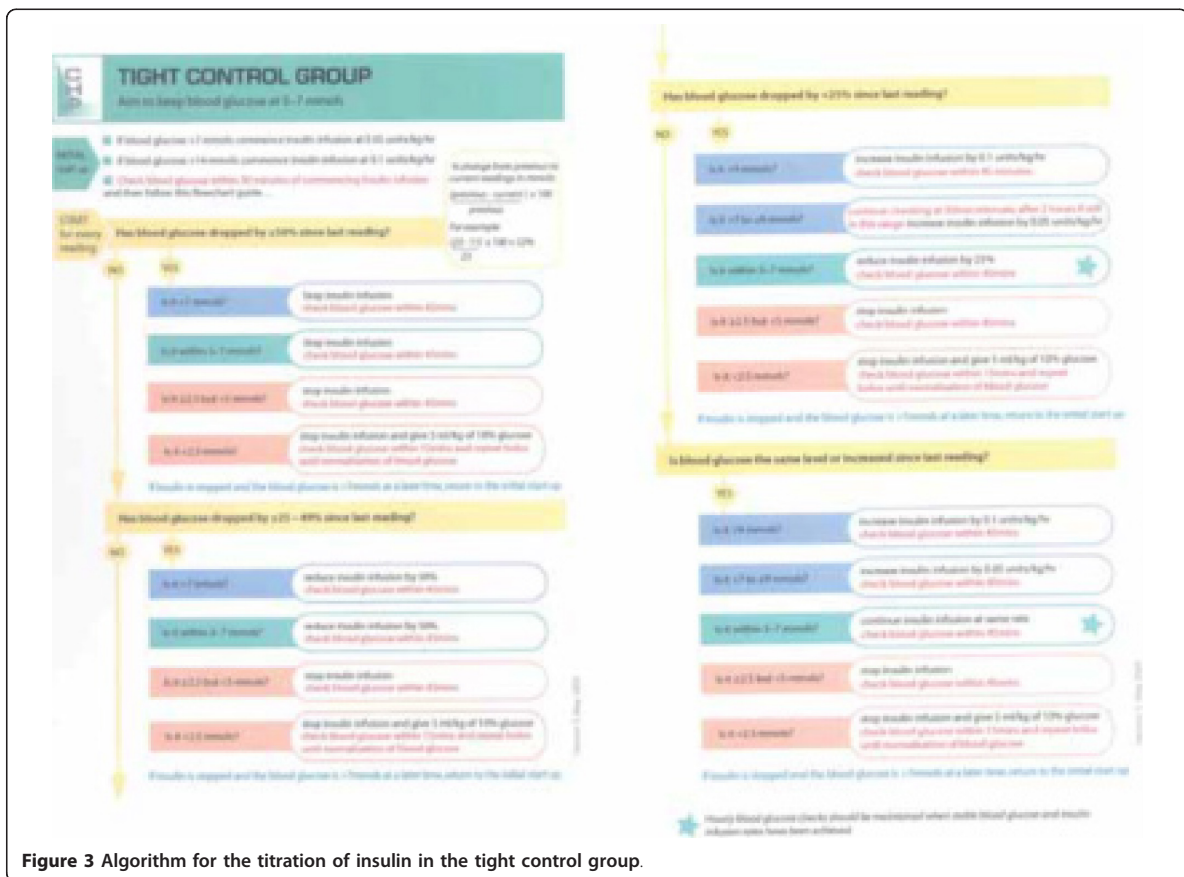


Figure 3 Algorithm for the titration of insulin in the tight control group.

ventilated for 30 days or more. The use of organ failure free days to determine patient-related morbidity surrogate end-points in paediatric trials has been supported by influential paediatric trialists in the current low mortality paediatric critical care environment[52].

Secondary outcomes

- Death within 30 days after trial entry (or before discharge from hospital if duration is greater than 30 days)
- Death within 12 months of trial entry
- Number of days in PICU
- Duration of mechanical ventilation
- Duration of vasoactive drug usage (adrenaline, nora-drenaline, dopamine, dobutamine, or Phosphodiesterase type III [PDEIII] inhibitors or vasopressors)
- Need for renal replacement therapy
- Blood stream infection (positive cultures associated with two or more features of systemic inflammation or any positive blood culture for bacteria or fungi)
- Use of antibiotics >10 days
- Number of red cell transfusions
- Number of hypoglycaemic episodes moderate (≤ 2.5 mmol/L), severe (≤ 2.0 mmol/L)

Occurrence of seizures (clinical seizures requiring anticonvulsant therapy)

Paediatric logistic organ dysfunction (PELOD) score [52-54],

Hospital length of stay

Number of children readmitted to PICU within 30 days of trial entry

Cost and cost-effectiveness measures

Hospital costs within 30 days of trial entry

Cost per life year (based on 30 days costs and survival)

Hospital and community health service costs within 12 months of trial entry

Cost per life year (based on 12 month costs and survival for all cases)

Cost per disability-free survivor (based on 12 month cost and outcome data for sub group with traumatic brain injury)

Follow-up at 12 months

If parents give their consent, all children surviving to hospital discharge will be followed up to 12 months post-randomisation to determine mortality using the NHS Central Register of the Office of National Statistics

(ONS). Parents will be informed about the follow-up study at trial entry and asked to give consent. The Trial Manager at the Data Co-ordinating Centre (DCC) will write to parents following discharge home to remind them about the follow-up and ask them to keep the DCC informed about any change of address. At hospital discharge parents will be given a diary to help them record their child's service use post discharge. At around 11 months, following checks with the GP/Health Visitor to determine that this is appropriate, the Trial Manager will send a questionnaire to parents to determine the use of health care resources between discharge and 12 months. Non-responders will be followed-up by letter and telephone.

Follow-up of traumatic brain Injury sub-group

TBI is defined for this study as accidental trauma to the head resulting in need for intubation and mechanical ventilation. There are approximately 750 ICU admissions per year in the UK, and an estimated 150 will be recruited into CHiP.

This sub-group is more likely to have longer-term morbidity and parents of children (aged 4 or over) in this sub-group will be asked to provide additional information at 12 months, regarding overall health status, global neurological outcome, attention and behavioural status.

Outcome assessment will comprise four components:
Overall health status: measured by the Health Utilities Index (HUI)

Global neurological outcome: measured by the Kings Outcome Scale for Childhood Head Injury (KOSCHI)

Attention and behavioural assessment: measured by the Child Behavioural Check List (CBCL) and the Connor's Rating Scales revised - short version (CRS-R:S)

The HUI and KOSCHI will be completed using a structured telephone interview (around 10 minutes). The CBCL and CRS are both written questionnaires that will be posted out to the families. They take approximately 30 minutes to complete.

The Health Utilities Index is a multi-attribute health status classification system. Seven attributes (sensation, mobility, emotion, cognition, self-care, pain, fertility) are categorised according to one of 4 or 5 levels. In this population fertility will be excluded. The algorithm (from death to perfect health scale) provides a single numerical value.

KOSCHI is a 5 point categorical scale, ranging from death to normal neurological function, and is similar in structure to the Glasgow Outcome Scale, which is widely used in adult studies. In addition the KOSCHI is further subdivided into two subcategories at points 4 and 5 on the scale (moderate outcome and good outcome). Patient outcomes will be dichotomized between patients in categories 1, 2, 3, 4A and those in 4B, 5A, 5B.

Child behaviour checklist (CBCL/4-18) (problem scales) is based on parental report and assesses problematic child behaviour that is summarised in internalising behaviour (anxious/depressed, withdrawn/depressed, somatic complaints), externalising behaviour (rule-breaking, aggressive) and other (social problems, thought problems, attention problems).

In reference to 1991 normative data (Table 2) Patient outcome can be summarised according to placement within one of the three groups, or according to the T-score.

The Conners' rating scales (revised - short version CRS-R:S) assesses symptoms of attention-deficit/hyperactivity disorder and related problem behaviour in children and adolescents based on parent's report.

In reference to 1993 normative data (Table 3) Patient outcome can be summarised according to placement within one of the three groups (marked + moderate, mild + slight, average + good), or according to the T-score.

Adverse events and safety reporting

The Royal Brompton & Harefield NHS Trust, as sponsor of this study, has responsibility to ensure arrangements are in place to record, notify, assess, report, analyse and manage adverse events in order to comply with the UK regulations of Medicines for Human Use (Clinical Trials) Regulations 2004.

All sites involved in the study are expected to inform the Chief Investigator and Study nurse of any serious adverse events/reactions within 24 hours so that appropriate safety reporting procedures can be followed by the Sponsor.

Expected side effects

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to insulin therapy qualify as adverse reactions.

Whilst any suspected, unexpected, serious adverse reaction (SUSAR) involving insulin therapy will be reported according to the timelines for SUSARs, expected side effects of insulin will be reported in the annual safety report unless serious enough to warrant expedited reporting.

The most prominent adverse effect of insulin treatment is hypoglycaemia. This is particularly important in

Table 2 Child behavior checklist (CBCL/4-18) assessment of outcome according to T-score

T-score (Whole)	Guideline	T-score (Individual scale)	Guideline
<60	Normal	<65	Normal
60-63	Borderline	65-69	Borderline
>63	Clinical	>69	Clinical

Table 3 The Conner's' rating scales (revised - short version CRS-R:S) assessment of outcome according to T-score

T-score	Guideline
≥ 70	Markedly atypical (significant problem)
66-69	Moderately atypical (significant problem)
61-65	Mildly atypical (possible significant problem)
56-60	Slightly atypical (borderline)
45-55	Average (no concern)
≤ 44	Good

the TCG arm of the study which is aiming to control BG within the range 4 - 7 mmol/l which is well above the 2 mmol/l threshold for clinically important hypoglycaemia [55]. The principal measure to avoid clinically important hypoglycaemia will be hourly measurement of BG when insulin is first administered. The insulin administration protocols aim to achieve glucose control with the lowest possible incidence of hypoglycaemia and the avoidance of neuroglycopenia. Hypoglycaemic events will be reported to the Clinical Co-coordinating Centre and if necessary, the BG control protocols will be revised, whilst still aiming to achieve BG levels within the target ranges.

Insulin is reported to occasionally cause a rash which may be associated with itching.

Data collection

To minimise the data collection load for busy units, the trial will collaborate with the Paediatric Intensive Care Audit Network (PICANet <http://www.picanet.org.uk>) to make best use of the established data collection infrastructure which exists in all PICUs in the UK. The PICANet dataset includes most of the items being used in the trial and these data will be transmitted from the participating centres to the Data Co-ordinating Centre electronically using strong encryption. The remaining short term data items will be collected locally by the research nurses, and those for the longer term follow-up will be collected separately by telephone and postal questionnaires. These data will be double entered onto electronic database storage systems at the Data Co-ordinating Centre.

Economic evaluation

Cost-consequence and cost-effectiveness analyses will be undertaken as part of the proposed study. These economic evaluations will assess whether the costs of achieving tight BG control are justified by subsequent reductions in hospitalisation costs and/or by improvements in patient outcomes. The evaluations will be conducted in two phases, in the first phase all hospital costs at 30 days post randomisation will be compared across

treatment groups alongside 30-day outcomes, in the second phase cost and outcomes at 12-months will be compared across the groups.

For the first phase evaluations, detailed resource use data will be collected for each patient enrolled in CHIP using the Paediatric Critical Care Minimum Dataset (PCCMDS)[56] which will be collected by each PICANet unit. Where information on resource use required in CHIP is not available from these sources datasheets similar to those developed as part of the INNOVO study will be used [57]. Information will also be collected on the resources required to achieve tight BG control, in particular all medication use and the staff time involved in monitoring the patients and managing adverse events (e.g. hypoglycaemia) will be noted.

Unit costs for hospital services will be taken from the NHS 'payment by results' database[58]. Where more detailed unit costs are required, for example those associated with staff time and the use of insulin infusion, these will be collected on site visits to centres. Hospital costs up to 30 days will be estimated by valuing each resource use item by the appropriate unit cost.

In the second phase of the study the time horizon of the economic evaluation will be extended to 12 months, and resource use data for hospital re-admissions, outpatient visits and the use of community health services will be collected for all cases. For the sub-sample of patients diagnosed as having traumatic brain injury at study entry, information on the patient's disability at one-year will be collected during telephone interviews with the patients' relatives based on previously developed interview schedules [57]. All community service use will be valued using national unit costs[59]. Total costs for each patient will be calculated by summing the costs of all hospital and community health services used.

All the economic analyses will be based on the treatment groups as randomly allocated ('intention to treat'). The initial analysis will include a cost-consequence analysis and will report mean differences (95% CI) between treatment groups in resource use (e.g. length of hospital stay) and total hospital costs per patient, alongside the primary clinical endpoint. The initial analysis will also combine costs and outcomes at 30 days post-randomisation in a cost-effectiveness analysis, which will report cost per death averted and cost per adverse event averted. The subsequent analysis will use 12-month cost and outcome data to report the cost per death averted for all patients. For the sub-sample of patients diagnosed as having brain injury at study entry, the cost-effectiveness analysis will also report the cost per death or disabled case averted.

The sensitivity analysis will test whether the results are robust to key assumptions made, for example to the choice of unit costs and the time horizon of the analysis.

The cost and outcome data collected at one-year will be used to project the impact of the intervention on longer-term costs and outcomes.

Sample size

A difference of 2 days in the number of ventilator-free days (VFD) within the first 30 days post-randomisation between the two groups has been chosen as the primary outcome measure for the trial. Information from PICANet using data from UK PICUs for 2003-4 estimates that the mean number of VFDs in cardiac patients is 26.7, with a standard deviation (SD) of 4.2. Corresponding figures for non-cardiac patients are a mean of 22.7 days, with a standard deviation (SD) of 6.8 days. As the SD is estimated with error, to be conservative we have assumed the SD is nearer 5.5 days for the cardiac and 8 days for the non-cardiac patients. There are likely to be more non-cardiac than cardiac patients eligible for the trial. We have therefore assumed an overall SD across both cardiac and non-cardiac strata of 7 days. Assuming this is the same in both trial arms, and taking a type I error of 1% (with a 2-sided test), a total sample size of 750 patients would have 90% power to detect this difference. Whereas we can assume minimal loss to follow up to 30 days, there may be some non-compliance (some patients allocated to tight control not receiving this, and some allocated to usual care being managed with tight control). The target size will therefore be inflated to 1000 to take account of possible dilution of effect.

As information from PICANet indicates that there are differences in outcome between cardiac and non-cardiac patients not merely in VFDs but also in 30 day mortality rate (3.4% vs. 20%) and mean duration of time on a ventilator (3.7 vs. 8.0 days, survivors and non-survivors combined), we also wish to be able to detect whether any effect of tight glucose control differs between the cardiac and non-cardiac strata. To have 80% power for an interaction test to be able to detect a difference of two days in the effect of intervention between the strata at the 5% level of statistical significance, we would need to increase the sample size to 1500. If the interaction test was positive this size would allow us to assess the effect of tight glucose control separately in the two strata.

Recruitment rate

There are approximately 1300 cardiac and 1550 non-cardiac eligible patients per year in the collaborating PICUs. If half of those eligible are recruited into the trial, it should be feasible to recruit the overall total sample size of 1500 within the 24 months recruitment period.

Type of analysis

Analysis will be by intention to treat. The following subgroup analyses will be conducted; age (Age \leq 1 year versus between 1 year and \leq 16 years), severity of illness,

traumatic brain injury or not, cardiac surgical versus non-cardiac cases, RACHS1 (cardiac cases) (Groups 1-4 versus 5 and 6), PIM2 group (non-cardiac cases) (categorised by probabilities of death of $<5\%$, $5\% - <15\%$ and $\geq 15\%$), run in cases v. non-run in cases.

Frequency of analysis

An independent Data Monitoring and Ethics Committee (DMEC) will review, in strict confidence, data from the trial approximately half way through the recruitment period. The Chair of the DMEC may also request additional meeting/analyses. In the light of these data and other evidence from relevant studies, the DMEC will inform the Steering Committee if in their view:

- i. There is proof that the data indicate that any part of the protocol under investigation is either clearly indicated or clearly contra-indicated either for all patients or a particular subgroup of patients. using the Peto and Haybittle rule [60,61]
- ii. It is evident that no clear outcome will be obtained with the current trial design.
- iii. That they have a major ethical or safety concern

Ancillary studies

In addition to the main study, some collaborators may wish to conduct other more detailed or complementary studies. The grant holders welcome this provided that proposals are discussed in advance with the Trial Steering Committee and appropriate additional Research Ethics approval is sought.

Organisation

The Trial Steering Committee (TSC) responsibilities are to approve the main study protocol and any amendments, monitor and supervise the trial towards its interim and overall objectives, review relevant information from other sources, consider the recommendations of the DMEC, and resolve problems brought by the trial co-coordinating centres. Day to day management of the trial will be overseen by a Trial Management Group (TMG) comprising the grant holders and project staff from the Clinical Co-coordinating Centre at the Royal Brompton Hospital NHS Trust and the Data Co-coordinating Centre (DCC) at the LSHTM.

Publication policy

To safeguard the integrity of the trial, data from this study will not be presented in public or submitted for publication without requesting comments and receiving agreement from the Trial Steering Committee. The primary results of the trial will be published by the group as a whole with local investigators acknowledged. The success of the trial depends on the collaboration of many people. The results will be presented first to the

trial local investigators. A summary of the results of the trial will be sent to parents of participating children on request and also made available on the trial website.

Confidentiality

Patients will be identified by their trial number to ensure confidentiality. However, as the patients in the trial will be followed up to 12 months following randomisation, it is essential that the team at the Data Co-ordinating Centre has the names and addresses of the trial participants recorded on the data collection forms in addition to the allocated trial number. Stringent precautions will be taken to ensure confidentiality of names and addresses at the Data Co-ordinating Centre.

The Chief Investigator and local investigators will ensure conservation of records in areas to which access is restricted.

Audit

To ensure that the trial is conducted according to ICH GCP guidelines, site audits will be carried out on a random basis. The local investigator will be required to demonstrate knowledge of the trial protocol and procedures and Good Clinical Practice. The accessibility of the site file to trial staff and its contents will be checked to ensure all trial records are being properly maintained. Adherence to local requirements for consent will be examined.

If the site has full compliance the Site Visit Form will be signed by the Trial Manager. In the event of non-compliance the Data Coordinating Centre will address the specific issues to ensure that relevant training and instruction is given.

Termination of the study

At the termination of planned recruitment the Data Co-ordinating Centre will contact all sites by telephone, email or fax in order to terminate all patient recruitment as quickly as possible. If the study is terminated prematurely by the Steering Committee all sites will be informed immediately. When all recruited patients have been followed until 30 days post randomisation (or hospital discharge if stay longer than 30 days) a declaration of the end of trial form will be sent to EurdraCT and the MREC. The following documents: original consent forms, original data forms, trial related documents and correspondence will be archived in each Site File and kept for at least five years. At the end of the analysis and reporting phase, the Trial Master Files at the Clinical and Data Co-ordinating Centres will be archived for 15 years.

Indemnity

If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person

harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation.

Discussion

Data from level 2 trials have driven the adult intensive care clinicians to adopt treatment regimes that favour tight glycaemic control. Equipoise presently exists in the paediatric intensive care community and this allows us a very important opportunity to conduct an adequately powered randomised controlled trial in this setting.

Data monitoring committee

Professor David Dunger (CHAIR), Department of Paediatrics, University of Cambridge; Dr David Harrison, Statistician, Intensive Care Audit and Research Network (ICNARC); Professor David Hatch, Emeritus Professor of Paediatric Anaesthesia and Intensive Care, Great Ormond Street Hospital; Mr. Giles Peek, Consultant Cardiac Surgeon, Glenfield Hospital, Leicester (until 2009);

Dr Jon Smith, Consultant Paediatric Cardiothoracic Anaesthetist, Freeman Hospital, Newcastle (from 2009).

Abbreviations

AE: Adverse Event; AR: Adverse Reaction; BG: Blood glucose; CBCL: Child Behavioural Check List; CHIP: Control of Hyperglycaemia in Paediatric Intensive Care; DCC: Data Co-ordinating Centre; CI: Confidence interval; CRS-RS: Connor's Rating Scales revised - short version; DMEC: Data Monitoring and Ethics Committee; GCP: Good Clinical Practice; HTA: Health Technology Assessment; HUI: Health Utilities Index; ICNARC: Intensive Care Audit and Research Network; JACHO: Joint Commission on Accreditation of Healthcare Organization; KOSCHI: Kings Outcome Scale for Childhood Head Injury; LSHTM: London School of Hygiene and Tropical Medicine; NEC: Necrotising enterocolitis; ONS: Office of National Statistics; PCCMDS: Paediatric Critical Care Minimum Dataset; PELOD: Paediatric logistic organ dysfunction; PDEIII: Phosphodiesterase type III; PI: Principal investigator; PICANet: Paediatric Intensive Care Audit Network; PICU: Paediatric intensive care unit; PIM2: Paediatric index of mortality version 2; RACHS1: Risk adjusted classification for Congenital Heart Surgery 1; RR: Relative risk; SD: Standard deviation; SPC: Summary of Product Characteristics; SSAR: Suspected Serious Adverse Reaction; SUSAR: Suspected, unexpected, serious adverse reaction; TBI: Traumatic brain injury; TGC: Tight glucose control; TMG: Trial Management Group; TSC: Trial Steering Committee; VFD: Ventilator free days

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Authors' contributions

All authors have read and approved the final manuscript. DM came up with original concept; RT on behalf of the Paediatric Intensive Care Society Study Group endorsed the proposal; DM, RT, RG, RP and DE wrote the grant application and original protocol, JP has written this submission; All other authors played important parts in final protocol development.

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 (In attendance: Mr. Michael Loveridge Royal Brompton Hospital (Trial sponsor))

Competing interests

The authors declare that they have no competing interests.

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Appendix 5 Diary on use of health services

CHiP Control of Hyperglycaemia in Paediatric intensive care

Diary on use of health services

Hospital stay

If your child stays in hospital overnight, please note the date when they arrive and the date they leave the hospital. Use one line for each hospital stay.

Date admitted to hospital	Date discharged from hospital	Hospital name	Which hospital ward(s)?*	
			Same PICU?	Different PICU? Other?
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>

* Which type of ward(s) did your child stay on? Did he/she stay on the same Paediatric Intensive Care Unit (PICU) as when they joined CHiP, a different Paediatric Intensive Care Unit (different PICU), or any other ward (other)? If your child stayed on more than 1 different type of ward (e.g. same PICU then other ward), then you can tick more than 1 box.

Hospital outpatient visit

If you child visits hospital outpatients please note the name of the hospital and the date of each visit. Use one line for each visit.

Hospital name	Date of visit	Where did the visit take place?		Date of the visit
		At home	GP surgery	
		<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	
		<input type="checkbox"/>	<input type="checkbox"/>	

GP visit

If your child sees a GP please tick the box showing whether this was at home or at the GP surgery. Please also give the date. Use one line for each visit.

To add more visits please turn the page...

Appendix 6 Follow-up: traumatic brain injury subgroup

The subgroup of children with TBI is more likely to have longer-term morbidity and parents of children (aged ≥ 4 years) in this subgroup will be asked to provide additional information at 12 months (for patients recruited until September 2010). We will specifically include assessments of attention and behaviour as patients with TBI are commonly left with deficits in these areas.

Definition of traumatic brain injury

Accidental trauma to the head resulting in need for intubation and mechanical ventilation.

Population

Seven hundred and fifty ICU admissions per year in UK. Estimate of 150 recruited to the trial.

Outcomes assessment

This will comprise four components:

Overall health status: measured by the Health Utilities Index (HUI-3) [HUI-3. Copyright 2002 Health Utilities Inc. (HUInc), 88 Sydenham Street, Dundas ON, Canada L9H 2V3. www.healthutilities.com].

Global neurological outcome: measured by the Kings Outcome Scale for Childhood Head Injury (KOSCHI).⁴⁶

Attention and behavioural assessment: measured by the CBCL (CBCL. Copyright 2000 Achenbach T and Rescorla L. ASEBA, University of Vermont, 1 South Prospect Street, Burlington, VT 05401-3456. www.ASEBA.org).

The CRS-R:S.⁴⁷

The HUI, CBCL and CRS-R:S are written questionnaires that will be posted out to the families. They take approximately 30 minutes to complete.

Health Utilities Index is a multi-attribute health status classification system. Seven attributes (sensation, mobility, emotion, cognition, self-care, pain, fertility) are categorised according to one of 4 or 5 levels. In this population fertility will be excluded. The algorithm (from death to perfect health scale) provides a single numerical value.

KOSCHI is a 5-point categorical scale, ranging from death to normal neurological function, and is similar in structure to the Glasgow Outcome Scale, which is widely used in adult studies. In addition the KOSCHI is further subdivided into two subcategories at points 4 and 5 on the scale (moderate outcome and good outcome). Patient outcomes will be dichotomised between patients in categories 1, 2, 3 and 4A, and those in 4B, 5A and 5B.

Child behaviour checklist (CBCL/4–18), problem scales

The CBCL is based on parent's report and assesses problematic child behaviour that is summarised in internalising behaviour (anxious/depressed, withdrawn/depressed, somatic complaints), externalising behaviour (rule-breaking, aggressive) and other (social problems, thought problems, attention problems).

In reference to 1991 normative data:

T-score (whole)	Guideline	T-score (individual scale)	Guideline
< 60	Normal	< 65	Normal
60–63	Borderline	65–69	Borderline
> 63	Clinical	> 69	Clinical

Patient outcome can be summarised according to placement within one of the three groups, or according to the T-score.

Conners' rating scales revised – short version

The CRS-R:S assesses symptoms of attention-deficit/hyperactivity disorder and related problem behaviour in children and adolescents based on parent's report.

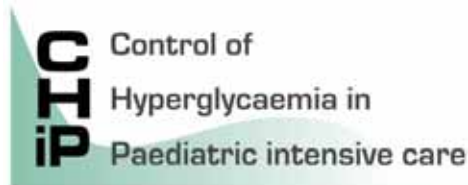
In reference to 1993 normative data:

T-score	Guideline
≥ 70	Markedly atypical (significant problem)
66–69	Moderately atypical (significant problem)
61–65	Mildly atypical (possible significant problem)
56–60	Slightly atypical (borderline)
45–55	Average (no concern)
≤ 44	Good

Patient outcome can be summarised according to placement within one of the three groups (marked + moderate, mild + slight, average + good), or according to the T-score.

Appendix 7 Post-discharge letters to patients and general practitioners, follow-up forms and case report form

Appendix 7a



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

<Date>

«Parent_title» «Parent_Forename» «Parent_Surname»
 «Address_Line1»
 «Address_Line2»
 «Address_Line3», «Address_Line4»
 «Postcode»

Dear «Parent_title» «Parent_Surname»,

We are pleased that «Patients_Forename» has now been discharged from hospital. We are writing to thank you for taking part in the CHIP Study so far. In case you didn't keep the information leaflet you read when «Patients_Forename» was in intensive care, we enclose another copy as a reminder.

This letter is to summarise what happens next.

- We will be writing to «GP_Name», your child's GP, to inform them that «Patients_Forename» is in the study.
- About 11 months after «Patients_Forename» joined the study, we will contact you again and send a questionnaire about use of health services for you to fill in at home and send back to us.

You may wonder why we need to contact you again with extra questions now that «Patients_Forename» is home. These questions are because families and researchers feel strongly that it is very important not just to look at the short-term, but also to compare the longer-term health of children who had tight glucose control with those who had the more usual care. It is very important that we follow up as many children as possible as it is only by doing this that we will be able to tell which approach is better.

We will keep you informed about the progress of the study unless you say that you do not want this information. When the study finishes we will ask if you would like to have a summary of the study results.

We attach the contact details we have for you. Please can you confirm these details by completing and returning the enclosed reply slip. Also, if you are going to change your address between now and the time we will be contacting you next, please send us the enclosed change of address card in the freepost envelope. You don't need a stamp.

If you have any questions about «Patients_Forename»'s health, you should go to your own doctor. But if there is anything further you would like to know about the study, please do not hesitate to contact us at the study office at the address above.

Thank you again for your participation. The results of the CHIP study will help other parents in the future.

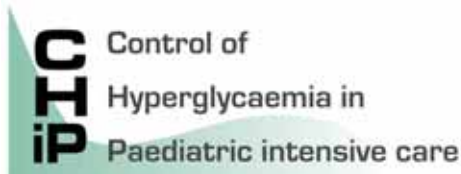
Yours sincerely

Laura Van Dyck / Korotimi Diallo
 Study Manager

Enc:

Original information sheet
 Change of address card

Contact details
 Freepost envelopes



CHIP Data Co-ordinating Centre
Medical Statistics Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

Study Number: «Study_Number»

Reply Slip

Please can you check whether the below details are correct and amend any incorrect information.

Your Contact Details

Home address:

«Parent_title» «Parent_Forename» «Parent_Surname»
«Address_Line1»
«Address_Line2»
«Address_Line3» «Address_Line4»
«Postcode»

Telephone number: «Telephone_Number»

Mobile number: «Mobile_Number»

Email address: «Email»

GP Contact Details

«GP_Name»
«GP_Address1»
«GP_Address2»
«GP_Address3» «GP_Address4»
«GP_Postcode»

I would like to receive updates about the CHiP Trial (please tick)

Yes No

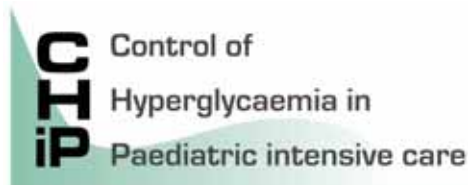
I would like to receive a copy of the CHiP Trial results when available (please tick)

Yes No

Thank you. Please now return this reply slip in the FREEPOST envelope provided to:

**The CHIP Trial Data Co-ordinating Centre, Medical Statistics Unit
London School of Hygiene and Tropical Medicine
FREEPOST, Keppel Street, LONDON**

Appendix 7b



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

<Date>

«Parent_title» «Parent_Forename» «Parent_Surname»
 «Address_Line1»
 «Address_Line2»
 «Address_Line3», «Address_Line4»
 «Postcode»

Dear «Parent_title» «Parent_Surname»,

We are pleased that «Patients_Forename» has now been discharged from hospital. We are writing to thank you for taking part in the CHIP Study so far. In case you didn't keep the information leaflet you read when «Patients_Forename» was in intensive care, we enclose another copy as a reminder.

This letter is to summarise what happens next.

- We will be writing to «GP_Name», your child's GP, to inform them that «Patients_Forename» is in the study.

We will keep you informed about the progress of the study unless you say that you do not want this information. When the study finishes we will ask if you would like to have a summary of the study results.

We attach the contact details we have for you. Please can you confirm these details by completing and returning the enclosed reply slip. Also, if you are going to change your address between now and the time we will be contacting you next, please send us the enclosed change of address card in the freepost envelope. You don't need a stamp.

If you have any questions about «Patients_Forename»'s health, you should go to your own doctor. But if there is anything further you would like to know about the study, please do not hesitate to contact us at the study office at the address above.

Thank you again for your participation. The results of the CHIP study will help other parents in the future.

Yours sincerely

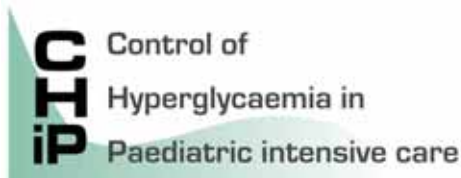
Laura Van Dyck / Korotimi Diallo
 Study Manager

Enc:

Original information sheet
 Change of address card

Contact details
 Freepost envelopes

Letter at discharge, version 2, Aug 2010



CHIP Data Co-ordinating Centre
Medical Statistics Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

Study Number: «Study_Number»

Reply Slip

Please can you check whether the below details are correct and amend any incorrect information.

Your Contact Details

Home address:

«Parent_title» «Parent_Forename» «Parent_Surname»
«Address_Line1»
«Address_Line2»
«Address_Line3» «Address_Line4»
«Postcode»

Telephone number: «Telephone_Number»

Mobile number: «Mobile_Number»

Email address: «Email»

GP Contact Details

«GP_Name»
«GP_Address1»
«GP_Address2»
«GP_Address3» «GP_Address4»
«GP_Postcode»

I would like to receive updates about the CHiP Trial (please tick)

Yes No

I would like to receive a copy of the CHiP Trial results when available (please tick)

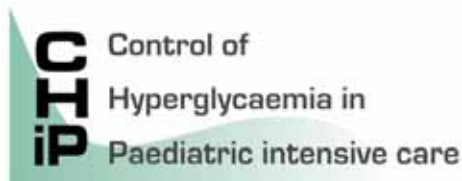
Yes No

Thank you. Please now return this reply slip in the FREEPOST envelope provided to:

**The CHIP Trial Data Co-ordinating Centre, Medical Statistics Unit
London School of Hygiene and Tropical Medicine
FREEPOST, Keppel Street, LONDON**

Letter at discharge, version 2, Aug 2010

Appendix 7c



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

<Date>

«Parent_title» «Parent_Forename» «Parent_Surname»
 «Address_Line1»
 «Address_Line2»
 «Address_Line3», «Address_Line4»
 «Postcode»

Dear «Parent_title» «Parent_Surname»,

We are pleased that «Patients_Forename» has now been discharged from hospital. We are writing to thank you for taking part in the CHIP Study so far. In case you didn't keep the information leaflet you read when «Patients_Forename» was in intensive care, we enclose another copy as a reminder.

This letter is to summarise what happens next.

- We will be writing to «GP_Name», your child's GP, to inform them that «Patients_Forename» is in the study.

We will keep you informed about the progress of the study unless you say that you do not want this information. When the study finishes we will ask if you would like to have a summary of the study results.

We attach the contact details we have for you. Please can you confirm these details by completing and returning the enclosed reply slip. Also, if you are going to change your address between now and the time we will be contacting you next, please send us the enclosed change of address card in the freepost envelope. You don't need a stamp.

If you have any questions about «Patients_Forename»'s health, you should go to your own doctor. But if there is anything further you would like to know about the study, please do not hesitate to contact us at the study office at the address above.

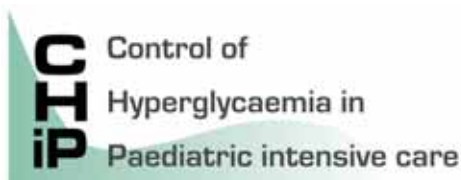
Thank you again for your participation. The results of the CHIP study will help other parents in the future.

Yours sincerely

Laura Van Dyck / Korotimi Diallo
 Study Manager

Enc:
 Original information sheet Contact details
 Change of address card Freepost envelopes

Letter at discharge, >1yr I/P, version 1 18Mar2010



CHIP Data Co-ordinating Centre
Medical Statistics Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

Study Number: «Study_Number»

Reply Slip

Please can you check whether the below details are correct and amend any incorrect information.

Your Contact Details

Home address:

«Parent_title» «Parent_Forename» «Parent_Surname»
«Address_Line1»
«Address_Line2»
«Address_Line3» «Address_Line4»
«Postcode»

Telephone number: «Telephone_Number»

Mobile number: «Mobile_Number»

Email address: «Email»

GP Contact Details

«GP_Name»
«GP_Address1»
«GP_Address2»
«GP_Address3» «GP_Address4»
«GP_Postcode»

I would like to receive updates about the CHiP Trial (please tick)

Yes No

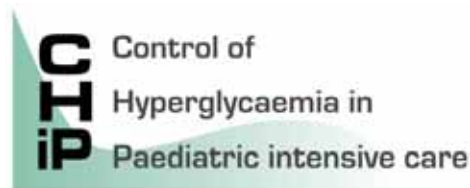
I would like to receive a copy of the CHiP Trial results when available (please tick)

Yes No

Thank you. Please now return this reply slip in the FREEPOST envelope provided to:

**The CHIP Trial Data Co-ordinating Centre, Medical Statistics Unit
London School of Hygiene and Tropical Medicine
FREEPOST, Keppel Street, LONDON**

Appendix 7d



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

Date

Parent Name

Address

Dear *Parent Name*,

On behalf of everyone involved with the CHIP study, I am writing to say how sorry we were to hear of the death of your *son/ daughter [Child's first name]*.

Your *son/ daughter* has played a really valuable part in this study and we would like to thank you for your help. It is through the contributions of children and parents like yourselves that we will eventually be able to find the best way to control blood sugar levels in very ill children in the future.

I am the study manager for CHIP, and I am writing to you to ask whether or not you would like to have any further contact with CHIP. Some bereaved parents wish to be kept informed about the progress of the study; other bereaved parents might prefer not to be sent any further details. We want to make sure that we give everyone the chance to stay in touch, but we fully understand if you would prefer us not to send anything more to you.

There is a reply slip with this letter to let us know if you would like to receive the newsletters that other CHIP parents are sent, and/or the final results of the study. The results should be available sometime in 2012.

The reply slip can be sent to me in the FREEPOST envelope provided. If we do not hear from you we will not contact you again; but even if you do not reply now, but later change your mind and would like to see the newsletters or results, do not hesitate to contact me.

We in the CHIP team are very grateful for your help so far and do hope that this letter has not caused you any distress. If it has done, I do apologise.

Thank you again.

With kind regards,

Laura Van Dyck
 CHIP Study Manager

Enc:
 Reply slip
 Freepost envelope



Further Contact Reply Slip

Study no.: *Study number*

I/We would like to receive the CHIP Newsletters which are sent periodically to families participating in CHIP (please tick):

Yes No

I/We wish to be informed of the final results of the CHIP Study when they are available around 2012 (please tick):

Yes No

Name: *Parent Name*

Address: *Address*

Telephone: *Telephone number*

Mobile: *Mobile number*

Email: *Email address*
(If you would prefer us to contact you this way)

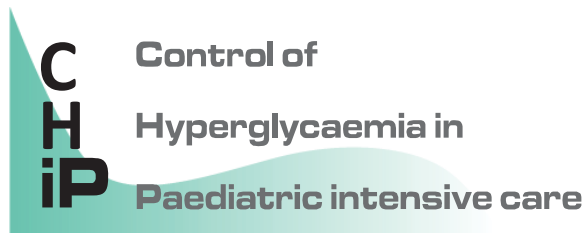
Please correct any of the above details if they are incorrect.

If you have any further comments, please let us know:

Please return this form in the postage paid, pre-addressed envelope provided.

Thank you.

Appendix 7e



From: Laura Van Dyck/Lucy Brooks
 Phone: 020 7927 2075
 Fax: 020 7927 2189
 Company Name: CHiP Data Coordinating centre, LSHTM

To: «GP_Name»
 Fax: «GP_Fax»
 GP Surgery: «GP_Address1»

Dear «GP_Name»

RE: Patient Name: «Patients_Forename» «Patients_Middlename» «Patients_Surname»
DOB: «DOB» **Study Number:** «Study_Number»

We wrote to you recently regarding the above patient who is taking part in the CHiP trial and we thank you for your reply. We are now ready to send the parents the one year follow up questionnaire to which they gave consent for when the child entered the study. We would just like to confirm with you that the child is still registered with your practice and that there is no reason why we should not contact the family.

- The child is still registered with the practice and it is ok to contact the family.
- The child is no longer registered with this practice.
- I think it is unsuitable to make contact with this family at this time.

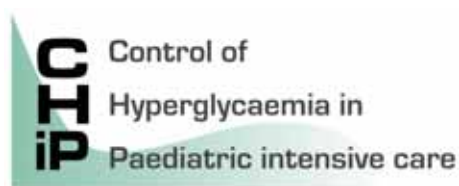
Please indicate above and fax back to **020 7927 2189**.

Thank you for your time.

Yours Sincerely,

Laura Van Dyck/Lucy Brooks

Appendix 7f



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

<Date>

«GP_Name»
 «GP_Address1»
 «GP_Address2»
 «GP_Address3», «GP_Address4»
 «GP_Postcode»

Dear «GP_Name»,

Re: «Patients_Forename» «Patients_Middlename» «Patients_Surname», DOB: «DOB», CHIP study number: «Study_Number»

«Patients_Forename» was recruited into The CHIP Study on «Date_of_Randomisation». A copy of the information sheet which was given to «Patients_Forename»'s parents prior to trial entry is enclosed. The parent's consent included agreement to random allocation and to being contacted by researchers at around 12 months from trial entry. I am also enclosing a copy of the letter which has been sent to «Patients_Forename»'s parents following «his/her» discharge home on «Discharge_date».

If the parent(s) are still willing to take part I will fax you two months before making contact with the parents to confirm that «Patients_Forename» is alive, is still registered with you and that there is no reason that you know of why we should not contact «Patients_Forename»'s parents about follow-up.

Non-TBI patients

Nearer the time I will follow-up the fax with a phone call to check that there have been no changes before I contact the parents to make arrangements to send them a questionnaire about resource use.

TBI patients

Nearer the time I will follow-up the fax with a phone call to check that there have been no changes before I contact the parents to make arrangements to send them questionnaires about resource use, the child's overall health status, behaviour and attention.

As many families with young children move addresses several times, to keep track of «Patients_Forename»'s family and to facilitate this we will be asking «Patients_Forename»'s parent(s) for «his/her» NHS number. However we would be very grateful if you would provide this on the reply slip in case they cannot easily find it. Please would you also check that we have the correct contact details.

We will also be registering «Patients_Forename» on the NHS central register for possible later follow-up. «Patients_Forename»'s parents have already given their permission for this.

Please return the reply slip using the enclosed freepost envelope. Alternatively you can fax it on 020 7637 2853, or send an email message to Laura.VanDyck@lshtm.ac.uk.

If you wish, we will send you the results of the study when it is completed – please indicate on the reply slip if this would be of interest to you. If you have any questions about the enclosed, or would like any further information, please do not hesitate to get in touch with me.

With many thanks for your time and assistance.

Yours sincerely

GPlettertbi, version2, 19 Feb 10

Laura Van Dyck / Korotimi Diallo
Trial Manager

Enc: Reply slip, Copy of letter to parents, Information sheet for parents
Freepost envelope

GPslettertbi, version2, 19 Feb 10



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

Reply slip

«GP_Name»
 «GP_Address1»
 «GP_Address2»
 «GP_Address3», «GP_Address4»
 «GP_Postcode»

**Re: «Patients_Forename» «Patients_Middlename» «Patients_Surname», DOB:
 «DOB», CHIP study number: «Study_Number»**

1. I am the GP for above named child

- Yes (go to question 3)
 No (go to question 2)

2. The GP responsible for this child/baby is:

Name: _____

Address: _____

Postcode: _____ Telephone: _____

3. The following parent's home address for «Patients_Forename» is correct/incorrect (please delete as applicable and amend if required).

«Parent_Forename» «Parent_Surname»
 «Address_Line1»
 «Address_Line2»
 «Address_Line3», «Address_Line4»
 «Postcode»

4. «Patients_Forename»'s NHS number is: «NHS_number»

5. I would like to receive a copy of the CHIP newsletter Yes No

6. I would like to receive a copy of the CHIP Trial results when available
 Yes No

Thank you. Please now return this reply slip in the FREEPOST envelope provided to:

**The CHIP Trial Data Co-ordinating Centre, Medical Statistics Unit
 London School of Hygiene and Tropical Medicine
 FREEPOST, Keppel Street, LONDON**

GPslettertbi, version2, 19 Feb 10

Appendix 7g



CHIP Data Co-ordinating Centre
 Medical Statistics Unit
 London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

<Date>

«Parent_title» «Parent_Forename» «Parent_Surname»
 «Address_Line1»
 «Address_Line2»
 «Address_Line3», «Address_Line4»
 «Postcode»

Dear «Parent_title» «Parent_Surname»,

We are pleased that «Patients_Forename» has now been discharged from hospital. We are writing to thank you for taking part in the CHIP Study so far. In case you didn't keep the information leaflet you read when «Patients_Forename» was in intensive care, we enclose another copy as a reminder.

This letter is to summarise what happens next.

- We will be writing to «GP_Name», your child's GP, to inform them that «Patients_Forename» is in the study.
- About 11 months after «Patients_Forename» joined the study, we will contact you again to find out how «heshe» is doing.
- We will send some questionnaires for you to fill in at home and send back to us.

You may wonder why we need to contact you again with extra questions now that «Patients_Forename» is home. These questions are because families and researchers feel strongly that it is very important not just to look at the short-term, but also to compare the longer-term health of children who had tight glucose control with those who had the more usual care. It is very important that we follow up as many children as possible as it is only by doing this that we will be able to tell which approach is better.

We will keep you informed about the progress of the study unless you say that you do not want this information. When the study finishes we will ask if you would like to have a summary of the study results.

We attach the contact details we have for you. If any of these are incorrect, please would you amend them and send them back to us. Also, if you are going to change your address between now and the time we will be contacting you next, please send us the enclosed change of address card in the freepost envelope. You don't need a stamp.

TBI letter at discharge version 2, 19 Feb 10

If you have any questions about «Patients_Forename»'s health, you should go to your own doctor. But if there is anything further you would like to know about the study, please do not hesitate to contact us at the study office at the address above.

Thank you again for your participation. The results of the CHiP study will help other parents in the future.

Yours sincerely

Laura Van Dyck / Korotimi Diallo
Study Manager

Enc:
Original information sheet
Contact details
Change of address card
Freepost envelopes

TBI letter at discharge version 2, 19 Feb 10



CHIP Data Co-ordinating Centre
Medical Statistics Unit
London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

ISRCTN61735247

tel: 020 7927 2376/2075 fax: 020 7637 2853 www.chip-trial.org.uk

Study Number: «Study_Number»

Reply Slip

Please can you check whether the below details are correct and amend any incorrect information.

Your Contact Details

Home address:

«Parent_title» «Parent_Forename» «Parent_Surname»
«Address_Line1»
«Address_Line2»
«Address_Line3» «Address_Line4»
«Postcode»

Telephone number: «Telephone_Number»

Mobile number: «Mobile_Number»

Email address: «Email»

GP Contact Details

«GP_Name»
«GP_Address1»
«GP_Address2»
«GP_Address3» «GP_Address4»
«GP_Postcode»

I would like to receive updates about the CHiP Trial (please tick)

Yes No

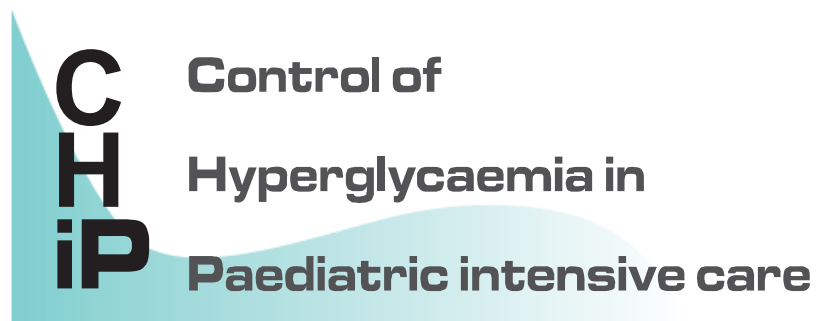
I would like to receive a copy of the CHiP Trial results when available (please tick)

Yes No

Thank you. Please now return this reply slip in the FREEPOST envelope provided to:

**The CHIP Trial Data Co-ordinating Centre, Medical Statistics Unit
London School of Hygiene and Tropical Medicine
FREEPOST, Keppel Street, LONDON**

Appendix 7h



Case Report Form (CRF)

Once this CRF is completed (i.e. 30 days after randomisation or upon patient death) please photocopy all data sheets and store in completed CRF file.

The **original** CRF (including instructions) should be stored in a secure location until the Data Co-ordinating Centre at the LSHTM can arrange collection by courier.

CHiP Site Number:	<input type="text"/>	PICU Admission Date:	<input type="text"/>
			<small>D D M M M Y Y Y Y</small>
Patient's Initials:	<input type="text"/>	Date of Birth:	<input type="text"/>
	<small>First Middle Last</small>		<small>D D M M M Y Y Y Y</small>
CHiP Study Number: (as assigned at randomisation)	<input type="text"/>		
Patient Hospital Number:	<input type="text"/>		

Consent Form

Please place a **COPY** of the patient's consent form here.

STUDY SCHEDULE, CHiP TRIAL				
Activity	Baseline	Days after enrolment into study	Days after enrolment into study	Follow up
	Pre-study entry	Day 1	Day 2 – Day 30	1 year
Informed consent signed	X			
PIM 2	X			
RACHS 1	Xa			
Insulin Infusion		X	X	
Weight		Xb		
Height		X		
Waist Circumference		X		
Primary diagnosis		X		
Blood glucose		X	Xc	
PELOD		X	X	
Inotrope score		X	X	
Cardiac, Respiratory & Renal, dysfunction		X	X	
Red cell transfusions		X	X	
Antibiotic therapy		X	X	
Enteral carbohydrate, enteral caloric, intravenous carbohydrate and intravenous caloric intake		X	X	
Local labs:				
Plasma creatinine	X	X	X	
Platelets	X	X	X	
WBC	X	X	X	
AST	X	X	X	
Blood cultures		X	X	
Lactate		X	X	
Adverse events		X	X	X
Transfer information			Xd	
Day 30 status			Xe	
Health care resource Questionnaire				Xf
HUI, KOSCHI, CBCL, CRS-R:S questionnaires				Xf

Abbreviations: CRF = case report form; PIM = paediatric index of mortality; RACHS2= Risk Adjusted outcomes for Congenital Heart disease; PELOD = Paediatric Logistic Organ Dysfunction score; WBC = White Blood Cell count; AST = Aspartate Aminotransferase test.

- Cardiac surgery patients only.
- Actual if within 10 days of admission, or otherwise give estimated.
- Record 12 hourly at 06:00 and 18:00
- Form to be completed upon initial transfer/discharge from study PICU/CICU or death if prior to day 30.
- To be assessed on Day 30 (by telephone if patient discharged prior to day 30) or on death if prior to day 30.
- Follow up by Data Co-ordinating Centre – LSHTM

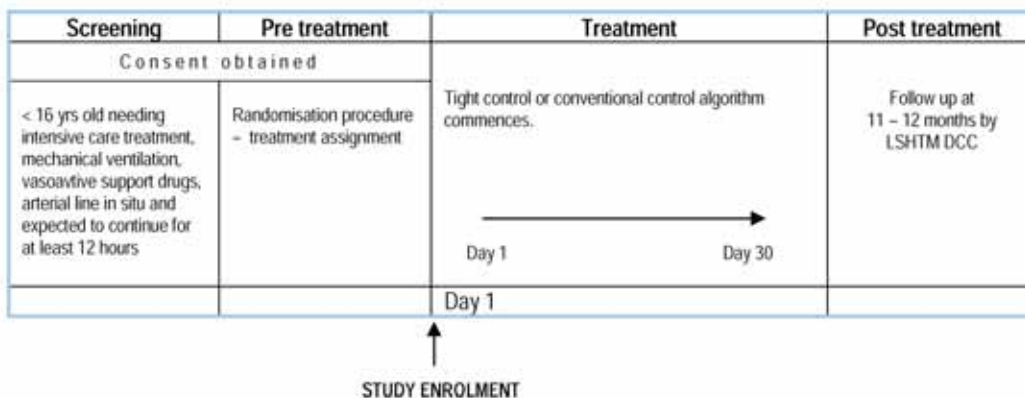
General instructions

Screening period

Potential patients will be screened based on available clinical and laboratory information. Informed consent will be obtained prior to the performance of any study-related procedures.

Patients eligible for enrolment into this study must meet **ALL** the inclusion criteria and **NONE** of the exclusion criteria immediately preceding the time of enrolment into the study.

Patients who do not meet all entry criteria may be continuously re-screened within 5 days of their admission to the PICU/CICU and if they meet **ALL** inclusion and **NONE** of the exclusion criteria at this time, can be entered into the study.



General instructions for completing the CRF

No field should be left blank.

Use permanent **black ink** when completing.

To make a change in the CRF:

- Cross through the incorrect data with a single line
- Write the new data alongside the old data
- Initial and date the change
- If the reason for the change is not obvious, write the reason for the change alongside it
- Never use correcting fluid

ND (not done) should be used if data are unavailable

NK* (not known) should be used if the data are unknown and every effort has been made to find the data (please justify).

NA (not applicable) should be used if a measure is not required at that time for that patient.

***NOTE:** The use of NK may be queried by LSHTM DCC.

Select option boxes with a tick Please do **NOT** use a cross .

The form should be signed by all site personnel completing the CRF.

Randomisation Form (Page 2)

Has the patient had cardiac surgery?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<hr/>		
If YES:		
Was surgery cardiopulmonary bypass?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
RACHS1 score:	<input type="checkbox"/> 1-4	<input type="checkbox"/> 5-6
<hr/>		
If NO:		
PIM2 (for calculation at randomisation—do not use PIM2 calculated earlier):		
Systolic blood pressure:	<input type="text"/> <input type="text"/> <input type="text"/>	mmHg
Both pupils fixed and dilated?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
FiO2:	<input type="text"/> <input type="text"/> <input type="text"/>	
PaO2 [arterial blood]:	<input type="text"/> <input type="text"/> <input type="text"/>	kPa
Base excess [capillary or arterial blood]:	<input type="text"/> <input type="text"/> <input type="text"/>	mmol/L <input type="checkbox"/>
Elective admission?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Recovery post procedure?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Does the child have a: High risk diagnosis?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Low risk diagnosis?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Calculated PIM2 score:	<input type="text"/> <input type="text"/>	%
Has patient been admitted due to traumatic brain injury?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Once the above data have been entered onto the web randomisation site please record the randomisation details below.

CHiP Study Number:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Allocation: Tight Control	<input type="checkbox"/>
		Conventional Control	<input type="checkbox"/>
Date of Randomisation:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>		
	<small>D D M M M Y Y Y Y</small>		
Time of Randomisation (24 hr clock):	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>		

Form completed by: _____	Date:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
		<small>D D M M M Y Y Y Y</small>

Please enter the data from this form onto the CHiP data entry software. For instructions on completed CRF procedure please see CRF cover sheet.

Randomisation – instructions

RACHS 1 categories:

LOW RISK CARDIAC SURGERY (categories 1 – 4)
<ul style="list-style-type: none"> All other cardiac operations
HIGH RISK CARDIAC SURGERY (categories 5 and 6)
<ul style="list-style-type: none"> Tricuspid valve repositioning for neonatal Ebstein anomaly at age <30 days Repair of truncus arteriosus with interrupted aortic arch All Norwood stage 1 operations

PIM2 score (Paediatric Index of Mortality)

For the purpose of this study the PIM2 score used should be calculated within an hour prior to randomisation, not on admission to the PICU even if that information is already available. The randomisation website has a built in calculator.

- Record the first systolic blood pressure measured nearest to the time of randomisation. If this information is missing record 120 mmHg
- Pupillary reactions to bright light >3mm and both fixed = yes other or unknown = no
- PaO₂, if unknown record 0
- Record the FIO₂ at the time of the PaO₂ if oxygen via ETT or headbox. If unknown record 0.
- Base excess in arterial or capillary blood only, mmol/l. If unknown record 0.

Recovery post procedure

Tick **Yes** if the main reason for the patient's admission to the PICU was to recover from surgery or a procedure (further clarification is given in the rules for PIM2 performance reliability in the trial site file).

LOW RISK DIAGNOSIS	
Asthma is the main reason for PICU admission	Bronchiolitis is the main reason for PICU admission
Croup is the main reason for PICU admission	Obstructive sleep apnoea is the main reason for PICU admission
Diabetic keto-acidosis is the main reason for PICU admission	
HIGH RISK DIAGNOSIS	
Cardiomyopathy or myocarditis	Cardiac arrest preceding PICU admission
Hypoplastic left heart syndrome	Severe combined immune deficiency
HIV infection	Leukaemia or lymphoma after first induction
Liver failure is the main reason for PICU admission	Spontaneous cerebral haemorrhage
Neuro-degenerative disorder	

- Tick **No** if the patient does not have any of the low risk or high risk diagnosis.
- For further information on rules for PIM2 performance reliability please refer to trial site file.

Traumatic Brain Injury

Tick **Yes** if patient was admitted with an accidental or non-accidental traumatic brain injury.

Please tick **No** if there is no traumatic brain injury or if brain injury was a pre-existing condition

Baseline Data

These data are to be collected **AFTER** the patient has been randomised.

CHiP Site Number: <input type="text"/> <input type="text"/>	CHiP Study Number: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Patient's Initials: <input type="text"/> <input type="text"/> <input type="text"/> <small>First Middle Last</small>	Date of Birth: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>D D M M M Y Y Y Y</small>

Weight: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Kg	Actual	<input type="checkbox"/>	Estimated	<input type="checkbox"/>
Height: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cm		<input type="checkbox"/>		<input type="checkbox"/>
Waist circumference: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> cm		<input type="checkbox"/>		<input type="checkbox"/>

The following values should be taken from the data collected closest to the time of randomisation:

Inotrope score:

Plasma creatinine: $\mu\text{mol/L}$

Blood glucose: mmol/L

PELOD Score:

Did the patient receive insulin prior to randomisation? Yes No

If YES:

Date of first insulin infusion: 2 0
D D M M M Y Y Y Y

Time of first insulin infusion: : (24 hr)

Data required by those randomised via RACHS1 score only:

Length of time of Cardiac bypass (if applicable): Minutes

Length of time of Cross Clamp (if applicable): Minutes

Form completed by: _____ **Date:** 2 0
D D M M M Y Y Y Y

**Please enter the data from this form onto the CHiP data entry software.
For instructions on completed CRF procedure please see CRF cover sheet.**

Baseline Data - instructions

After informed consent has been obtained and the patient has been randomly assigned to receive either conventional treatment or tight control, complete the baseline data as close as possible to the time of randomisation.

WEIGHT AND HEIGHT MEASUREMENTS

An **actual** weight or height can only be recorded if it has been measured within 10 days of the PICU / CICU admission. Otherwise tick **estimated**.

INOTROPE SCORE

Using the table below calculate a score for each inotrope the patient is receiving at the time of randomisation. If a patient is receiving more than one inotrope add all the scores together and record a total inotrope score. (see example)

Dopamine / Dobutamine	1mcg / kg / min = 1
Milrinone	0.1 mcg /kg / min = 1
Adrenaline / Noradrenaline	0.01 mcg / kg / min =1
Total inotrope score =	
Dopamine / Dobutamine = mcg / kg / min X 1	For example: At a single time point a patient is receiving Dopamine 5mcg / kg / min and Adrenaline 0.06 mcg / kg /min 5mcg/kg/min x 1 = 5 0.06mcg/kg/min x 100 = 6 Total inotrope score = 11
Milrinone = mcg / kg min X 10	
Adrenaline / Noradrenaline = mcg / kg / min X 100	

PLASMA CREATININE

Try to collect data as soon as possible AFTER the time of randomisation. However if the nearest data collection point (after randomization) is more than 12 hours after randomisation, record the data point as ND (Not Done), Unless data are available within the 6 hour period preceding randomisation, in which case it would be acceptable to use this information.

PELOD SCORE

Paediatric Logistic Organ Dysfunction Score (PELOD)

At the closest time point to randomisation, record the values for the PELOD variables and then using the PELOD calculator that has been incorporated into the CHiP data entry software, record the PELOD score.

PELOD Scoring

Baseline data and Hospital data

Cardiovascular

Heart rate:			
> or = 12 years	< or = 150	> 150	
< 12 years	< or = 195	>195	
Systolic blood pressure (mmHg):			
< 1 month	> 65	35 - 65	< 35
1 month - < 1 year	> 75	35 - 75	< 35
1 year - < 12 years	> 85	45 - 85	< 45
> or = 12 years	> 95	55 - 95	< 55

Neurologic

Glasgow coma score:			
12 - 15	7 - 11	4 - 6	3
Pupillary reactions:			
Both reactive		Both fixed	

Hepatic

ALT	
< 950 UI / L	> or = 950 UI / L
PT	
< 20 secs	> or = 20 secs

Pulmonary

PaO ₂ /FiO ₂ :	
> 9.3 kpa	< or = 9.3 kpa
PaCO ₂ :	
< or = 11.7 kpa	> 11.7 kpa
Mechanical ventilation:	
No ventilation	Ventilation

Haematologic

WBC:		
> or = 4.5	1.5 - 4.4	< 1.5
Platelets:		
> or = 35	< 35	

Renal

Creatinine:		
< 7 days	< 140 µmol / L	> or = 140 µmol / L
7 days - < 1 year	< 55 µmol / L	> or = 55 µmol / L
1 year - < 12 years	< 100 µmol / L	> or = 100 µmol / L
> or = 12 years	< 140 µmol / L	> or = 140 µmol / L

Contact DetailsCHiP Site Number: CHiP Study Number: Patient's Initials:
First Middle LastDate of Birth:
D D M M M Y Y Y Y

Patient's Surname:	
Patient's Forename:	
Sex (Please tick):	<input type="checkbox"/> Male <input type="checkbox"/> Female
Patient's Hospital Number:	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Patient's NHS Number: (If available)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
Parent / Guardian Details	
Title:	
Surname:	
Forename:	
Relationship to Patient:	
Home Address:	
Post Code:	
Telephone Number Home:	
Mobile:	
Email:	
GP Details	
GP Name:	
Surgery Address:	
Post Code:	
Telephone Number:	
GP Code (if available):	

Form completed by: _____ Date:
D D M M M Y Y Y Y

**Please enter the data from this form onto the CHiP data entry software.
For instructions on completed CRF procedure please see CRF cover sheet.**

Hospital Data – instructions

DAY 1 is the day that the patient is enrolled into the study (not all patients will start insulin on day 1).

NOTE: Please be aware that this data collection sheet of the CRF is 3 pages long (sheet 1a, b and c) and covers days 1 – 15. If the patient is still in PICU/CICU after day 15, the data collection sheets for days 16 – 30 can be found at the back of the completed CRFs file.

INSULIN START TIME

Record the time the first insulin infusion is commenced following randomisation on the appropriate calendar day.

INSULIN INFUSION RATE – 06:00 hrs and 18:00 hrs

If a patient is receiving insulin, record the rate it is being administered at exactly 06:00 hrs and 18:00 hrs for that calendar day.

AVERAGE INSULIN INFUSION RATE – (average 00:00 – 23:59)

Calculate the average infusion rate over the 24 hour period from 00:00 to 23:59 hrs for that calendar day.

DOCUMENTATION OF INSULIN INFUSION RATE AND AVERAGE INSULIN INFUSION RATE

If a patient never received insulin please use NA. For patients who did receive insulin use NA prior to the time insulin was started, and then from the time the insulin infusion was started use the appropriate rates or zero

MECHANICAL VENTILATION

Mechanical ventilation is defined as: A patient receiving intermittent positive pressure ventilation via an Endotracheal tube (ETT) or tracheostomy tube. Record Yes if the patient received this therapy at any point during that calendar day.

Record No on any calendar day that no positive pressure ventilation via an ETT tube or tracheostomy tube is given. (The patient does not necessarily need to be extubated).

VASOACTIVE DRUGS

Record Yes if a patient receives any dose of dopamine, dobutamine, epinephrine (adrenaline), norepinephrine (noradrenaline), Milrinone, Vasopressin and Phenylephrine for any process during that calendar day.

Record No on any calendar day that no vasoactive drugs were given, this includes anti-arrhythmics, vasodilators, anti-hypertensives and prostaglandin.

RENAL REPLACEMENT THERAPY

Renal replacement therapy is defined as: A patient who receives dialysis, peritoneal or haemofiltration.

Record Yes if a patient receives this therapy at any point during that calendar day.

Record No on any calendar day that no renal replacement therapy was given. Note that the patient does not need to have all catheters for renal replacement therapy removed.

Hospital Data – instructions cont.

BLOOD STREAM INFECTION

Record **Yes** if a positive culture is documented in association with two or more features of systemic inflammation or on any positive blood culture for fungus.

FEATURES OF SYSTEMIC INFLAMMATION : SIRS Criteria
Core temperature of > 38.5 °C or < 36°C
Tachycardia defined as a mean hear rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5 – 4 hour time period OR for children < 1 year old: bradycardia, defined as a mean heart rate < 10 th percentile for age in the absence of external vagal stimulus, β blocker drugs, or a congenital heart disease; or otherwise persistent depression over a 0.5 hour time period.
Mean respiratory rate > 2 SD above normal for age or mechanical ventilation for an acute process not related to an underlying neuromuscular disease or the receipt of general anesthesia
Leukocyte count elevated or depressed for age not secondary to chemotherapy induced leucopenia or > 10% immature neutrophils.

Reference: Goldstein, B; Giroir B; Randolph A; Members of the International Consensus Conference on Pediatric Sepsis. *Pediatric Critical care Medicine*, Vol 6 (1). January 2005. 2-8.

ANTIBIOTICS

Record **Yes** if the patient is receiving antibiotics for any process.
Record **No** on any calendar day that no antibiotic was given

NUMBER OF HYPOGLYCAEMIC EPISODES - MODERATE (< 2.5 mmols) and SEVERE (< 2.0 mmols)

Record the number of hypoglycaemic episodes that occur during that calendar day. If these occur, follow the Serious Adverse Event reporting procedure (SAE).

Each episode should only be recorded once, for example if a patient had a blood glucose of 1.8 mmols this would **only** be recorded as SEVERE (< 2.0 mmols).

SEIZURES

Record whether the patient had a seizure but only if it required pharmacological treatment during that calendar day. If it is considered to be related to the administration of the study drug insulin, follow the Serious Adverse Event reporting procedures (SAE)

ENTERAL CARBOHYDRATE, TOTAL ENTERAL CALORIFIC INTAKE, INTRAVENOUS CARBOHYDRATE and TOTAL INTRAVENOUS CALORIFIC INTAKE

Using the total energy guide for paediatric feeds, calculate the amount of enteral carbohydrate, total enteral calorific intake, intravenous carbohydrate and total intravenous calorific intake the patient received during that calendar day.

Include fluids associated with the administration of continuous intravenous drug infusions.
Do not include fluids used in the preparation of single bolus drug administration.

NOTE: These values can also be calculated using a tool incorporated into the CHiP data entry software.

Hospital Data – instructions cont.

NUMBER OF RED CELL TRANSFUSIONS

Record the number of prescribed red cell transfusions that were administered on that calendar day.

PAEDIATRIC LOGISTIC ORGAN DYSFUNCTION SCORE (PELOD)

Record the worst values available for the PELOD variables between 00:00 hrs and 23:59 hrs of that calendar day. Use the PELOD calculator incorporated into the CHiP data entry software to calculate the PELOD score.

INOTROPE SCORE

Using the table below calculate a score for each inotrope the patient is receiving at 06:00 hrs. If a patient is receiving more than one inotrope add all the scores together and record a total inotrope score. (see example)

Dopamine / Dobutamine	1mcg / kg / min = 1
Milrinone	0.1 mcg /kg / min = 1
Adrenaline / Noradrenaline	0.01 mcg / kg / min =1

Total inotrope score =	For example: At a single time point a patient is receiving Dopamine 5mcg / kg / min and Adrenaline 0.06 mcg / kg /min $5\text{mcg/kg/min} \times 1 = 5$ $0.06\text{mcg/kg/min} \times 100 = 6$ Total inotrope score = 11
Dopamine / Dobutamine = mcg / kg / min X 1	
Milrinone = mcg / kg min X 10	
Adrenaline / Noradrenaline = mcg / kg / min X 100	

BLOOD GLUCOSE

Blood glucose levels should be recorded at 06:00 hrs and 18:00 hrs whether or not the patient is receiving insulin therapy and until discharge from the PICU/CICU.

Blood glucose levels should be measured using standard arterial or capillary point of care monitoring.

Samples analysed by hand held glucometers, a blood gas machine or a result from a laboratory sample can be used. All equipment used for measuring blood glucose samples should be checked for validity, according to normal local practice.

LACTATE

Record the lactate measurement only if it is collected using the same blood sample that was used for the blood glucose measurement. Otherwise record NA (Not Applicable).

Day 30 status / transfer summary

LOCATION OF PATIENT AT DAY 30

Tick the box that corresponds with where the patient is located at day 30

TRANSFER SUMMARY

Using the codes found in the table below, record all patient locations from the date the patient was enrolled into the study (day 1) until day 30

CODE		CODE	
1	Acute care hospital	5	PICU
2	General ward	6	Skilled nursing facility
3	HDU	7	Home
4	CICU	8	Other

Appendix 8 Questionnaire on use of health services



Questionnaire on use of health services

The questions refer to all services that [child's name] may have used since [he/she] left the hospital on [insert date], and before [insert date].

HOW TO FILL IN THE QUESTIONNAIRE

Most questions can be answered by ticking the box next to the answer that applies to you. Please tick one box only for each question.

AN EXAMPLE

Since [child's name] left hospital on [insert date] has [he/she] stayed overnight in hospital again?

1.1 No Yes

If [child's name] has stayed in hospital overnight we need to know how many nights this was for. If you can remember how many nights [he/she] stayed for then just write the number in the **box** (3 nights in the example below).

How many nights?
3

OR If you are unsure about your answer please provide your 'best guess'. For example if you cannot remember the exact number of nights [child's name] stayed in hospital for, please tick whichever box in the **second** column gives your best guess (2-7 nights in the example below).

OR If you cannot remember the exact number of nights, please tick one box for each hospital stay:			
1 night	2-7 nights	8-14 nights	15 or more
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Many thanks

The results of the CHIIP study will help us to compare the longer-term health of children who had tight glucose control with those who had the more usual care.

Part 1. Hospital stay

1.1 Since **[child's name]** left hospital on **[insert date]** has **[he/she]** stayed overnight in hospital?

No If **No** go to Part 2 **Yes**

1.2 **If yes**, please state how many times? _____

1.3 For **each time** **[child's name]** has stayed in hospital please answer the following

Hospital Stay	How many nights?	OR If you cannot remember the exact number of nights, please tick one box for each hospital stay:				Which hospital ward(s)? ¹ Please Tick the appropriate box(es)		
		1 night	2-7 nights	8-14	15 or more	Same PICU?	Different PICU?	Other?
1 st stay	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 nd stay	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 rd stay	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 th stay	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

¹Which type of ward(s) did **[child's name]** stay on? Did **[he/she]** stay on the same Paediatric Intensive Care Unit (PICU) as when they joined CHIP, a different Paediatric Intensive Care Unit (**Different PICU**), or any other ward (**Other**)? If your child stayed on more than 1 different type of ward (e.g. **Same PICU** then **Other** ward), then you can tick more than 1 box.

If **[child's name]** has stayed in hospital overnight more than 4 times since **[he/she]** left hospital on **[insert date]**, please could you provide information on these further hospital stays in Part 6 of the questionnaire.

Part 2. Hospital outpatient visits²

2.1 Since **[child's name]** left the hospital on **[insert date]** has **[he/she]** visited hospital outpatients about **any aspect** of **[his/her]** health?

No If **No** go to Part 3 **Yes**

2.2 **If yes**, please give details about the number of outpatient visits

Exact number of outpatient visits	OR If you cannot remember the exact number of visits, please tick one of the following boxes			
<input type="text"/>	<input type="checkbox"/> 1 visit	<input type="checkbox"/> 2-4 visits	<input type="checkbox"/> 5-9 visits	<input type="checkbox"/> 10 or more

²Outpatient visits are when a patient comes to the hospital to see a specialist (e.g. eye specialist) but does not stay overnight.

Part 3. Visits to health care providers

3.1 Since **[child's name]** left the hospital on **[insert date]** has **[he/she]** visited any of the following health care providers at the GP's surgery about **any aspect** of **[his/her]** health?

No If No go to Part 4 Yes

3.2 If **[child's name]** visited any of these providers, please indicate how many visits?

Health care provider	Did your child visit this provider?		Exact number of visits	OR If you cannot remember the exact number of visits, please tick one box for each provider [he/she] has visited.			
	No	Yes		1 visit	2-4 visits	5-9 visits	10 or more
GP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Practice Nurse ³	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health visitor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

³A practice nurse works in a GP surgery to provide a range of health and well being services.

Part 4. Visits to your home by health care providers

4.1 Since **[child's name]** left the hospital on **[insert date]** has **[he/she]** had **home visits** from any the following **health care providers** about **any aspect** of **[his/her]** health?

No If No go to Part 5 Yes

4.2 If **[child's name]** has been visited by any of these providers, please indicate how many visits?

Health care provider	Visit from this provider?		Exact number of visits	OR If you cannot remember the exact number of visits, please tick one box for each provider who has made a home visit			
	No	Yes		1 visit	2-4 visits	5-9 visits	10 or more
GP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Practice Nurse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health visitor Or District Nurse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 5. Contacts with other service providers

5.1 Since **[child's name]** left the hospital on **[insert date]** please indicate whether **[he/she]** has had **any** contact (either visits to the provider or home visits) with any of the following service providers about **any aspect** of **[his/her]** health?

No If No go to Part 6 Yes

5.2 If your child **has had contact with any of these providers**, please indicate the number of contacts?

Service provider:	Contact with this provider?		Exact number of contacts	OR If you cannot remember the exact number of contacts, please tick one of the following boxes:		
	No	Yes		1 contact	2-4 contacts	5 or more
Social worker	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Speech and language therapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Occupational therapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physiotherapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Children's disability team	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hospital discharge coordinator	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Child psychologist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dietician	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mental health service	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Specialist Paediatric Nurse ⁴	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
School nurse ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

⁴A Specialist paediatric nurse visits children in their own homes providing care for patients and supporting family members

⁵A School nurse works in partnership with a school to promote health and well being for children.

Part 6. Other services not listed so far

6.1 Since **[child's name]** left the hospital on **[insert date]** have they had further hospital stays or used **any** other health care services for **any aspect** of **[his/her]** health that you haven't included above?

No If **No** go to Part 7 **Yes**

6.2 **If yes**, please provide further information about each service

Type of service provider	Number of contacts (e.g visits)	Reason
<i>e.g. Audiologist</i>	<i>1 visit</i>	<i>Check-up</i>

Part 7. Comments

Please feel free to provide **any other** comments you have when completing the questionnaire, in the box below. **Your views are important to us.**

Many thanks for your help

If you would like to ask us any questions about completing the questionnaire please email or call:

Richard Grieve

Carla Guerriero

Email: Richard.Grieve@lshtm.ac.uk

Email: Carla.Guerriero@lshtm.ac.uk

Tel: 0207 927 2255

Tel: 0207 958 8292

Appendix 9 Trial Steering Committee: terms of reference and membership

The responsibilities of the TSC were to approve the main study protocol and any amendments, monitor and supervise the trial towards its interim and overall objectives, review relevant information from other sources, consider the recommendations of the DMEC, and resolve problems brought by the trial co-ordinating centres. The TSC therefore provided overall supervision for CHiP on behalf of the HTA and the Royal Brompton and Harefield NHS Trust (sponsor) to ensure that the trial was conducted to the rigorous standards set out in the MRC Guidelines for GCP. Face-to-face meetings were held at regular intervals determined by need and not less than once a year. Routine business was conducted by telephone, email and post.

Terms of reference

- The TSC should approve the protocol and trial documentation in a timely manner.
- In particular the TSC should concentrate on progress of the trial, adherence to the protocol, patient safety and consideration of new information of relevance to the research question.
- The safety and well-being of the trial participants are the most important consideration and should prevail over the interests of science and society.
- The TSC should provide advice, through its chair, to the chief investigator, the trial sponsor, the trial funder, on all appropriate aspects of the trial. Specifically, the TSC will:
 - Monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems.
 - Monitor completion of data sheets and comment on strategies from TMG to encourage satisfactory completion in the future.
 - Monitor follow-up rates and review strategies from TMG to deal with problems including sites that deviate from the protocol.
 - Approve any amendments to the protocol, where appropriate.
 - Approve any proposals by the TMG concerning any change to the design of the trial, including additional sub-studies.
 - Oversee the timely reporting of trial results.
 - Approve and comment on the statistical analysis plan.
 - Approve and comment on the publication policy.
 - Approve and comment on the main trial manuscript.
 - Approve and comment on any abstracts and presentations of any results *during* the running of the trial.
 - Approve external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples.
 - Receive reports from the DMEC.
 - The TSC will make decisions as to the future continuation (or otherwise) of the trial.
- Membership of the TSC should be limited and include an independent chair, at least two other independent members, two collaborators and two members of the public. The investigators and the trial project staff are *ex officio*.
- Representatives of the trial sponsor and the HTA should be invited to all TSC meetings.
- Responsibility for calling and organising the TSC meetings lies with the chief investigator. The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.
- There may be occasions when the trial sponsor or the HTA will wish to organise and administer these meetings in exceptional circumstances.

- The TSC will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.
- The TSC will maintain confidentiality of all trial information that is not already in the public domain.

Membership

Professor Michael Preece (chairperson) Consultant Paediatrician, Great Ormond Street Children's Hospital

Mrs Pamela Barnes Lay member

Ms Sian Edwards Paediatric Pharmacist, Royal Brompton Hospital

Professor David Field Neonatologist, Leicester Royal Infirmary and the University of Leicester

Dr James Hooper Consultant Clinical Biochemist, Royal Brompton Hospital

Mrs Tara Quick Lay member, parent

Dr Claire Snowdon Lecturer, Medical Statistics Department, LSHTM, and Centre for Family Research, University of Cambridge (until 2011)

Ms Lyvonne Tume Research Nurse, Royal Liverpool Children's Hospital

Dr Dirk Vlasselaers Consultant Paediatric Intensivist, Leuven, Belgium

Professor Paula Williamson Professor of Medical Statistics, University of Liverpool

In attendance

Mr Michael Loveridge (till March 2008) Royal Brompton Hospital (Trial sponsor)

HTA representative

Trial Management Group (see below)

Dr Duncan Macrae (Chief Investigator) Director of Paediatric Intensive Care, Royal Brompton Hospital

Dr Elizabeth Allen Senior Lecturer, Medical Statistics Department, LSHTM

Miss Helen Betts Lead Study Nurse, Royal Brompton Hospital

Professor Diana Elbourne Professor of Healthcare Evaluation, Medical Statistics Department, LSHTM

Dr Richard Grieve Senior Lecturer in Health Economics, Health Services Research Department, LSHTM

Dr Kevin Morris Consultant in Paediatric Intensive Care, Birmingham Children's Hospital

Dr Roger Parslow Senior research fellow, University of Leeds

Dr Robert Tasker Professor of Neurology and Anesthesia (Pediatric), Harvard Medical School and Children's Hospital Boston, Boston, MA, USA

Mrs Ann Truesdale (till 2008) Trials Advisor, Medical Statistics Department, LSHTM

Miss Laura Van Dyck (from August 2009) Study Manager, Medical Statistics Department, LSHTM

Appendix 10 Data Monitoring and Ethics Committee

Terms of reference

To safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the CHIP study.

The DMEC should receive and review information on the progress and accruing data of CHIP and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

The DMEC should inform the Chair of the TSC if, in their view the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.

Interim review of the trial's progress including updated figures on recruitment, data quality, adherence to protocol, follow-up, and main outcomes and safety data. Specifically, these roles include to:

- monitor evidence for treatment differences in the main efficacy outcome measures
- monitor evidence for treatment harm (e.g. toxicity, SAEs and SARs, treatment related deaths)
- assess the impact and relevance of external evidence
- decide whether to recommend that the trial continues to recruit participants or if recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- decide whether or not trial follow-up should be stopped earlier
- assess data quality, including completeness (and by so doing encourage collection of high quality data)
- maintain confidentiality of all trial information that is not in the public domain
- monitor recruitment figures and losses to follow-up
- monitor compliance with the protocol by participants and investigators
- consider the ethical implications of any recommendations made by the DMEC
 - monitor planned sample size assumptions, preferably with regards to
 - (i) a priori assumptions about the control arm outcome and/or
 - (ii) emerging differences in clinically relevant subgroups, rather than on emerging, unblinded differences between treatment groups, overall
- suggest additional data analyses if necessary
- advise on protocol modifications proposed by investigators or HTA (e.g. to inclusion criteria, trial endpoints, or sample size)
- monitor continuing appropriateness of patient information
- monitor compliance with previous DMEC recommendations.

Membership

Professor David Dunger (chairperson) Department of Paediatrics, University of Cambridge

Dr David Harrison Statistician, Intensive Care Audit and Research Network (ICNARC),
Professor David Hatch Emeritus Professor of Paediatric Anaesthesia and Intensive Care, Great Ormond
Street Hospital

Mr Giles Peek (till Sept. 2009) Consultant Cardiac Surgeon, Glenfield Hospital, Leicester

Dr Jon Smith (from Sept. 2009) Consultant Cardiothoracic Anaesthetist, Newcastle General Hospital

Appendix 11 Trial Management Group

A Trial Management Group was established and was responsible for the day-to-day management of the trial. The group comprised the grant holders and project staff from the clinical co-ordinating centre at the Royal Brompton Hospital NHS Trust and the data co-ordinating centre at the LSHTM. The group met regularly in person and by telephone.

The responsibilities of the TMG were:

- (a) to establish and monitor recruitment of participating centres
- (b) to distribute and supply of data collection forms and other appropriate documentation for the trial
- (c) data collection and management
- (d) data entry and cleaning
- (e) data analysis
- (f) organising and servicing the DMEC
- (g) assure data security and quality and observe data protection laws
- (h) ensure trial is conducted in accordance with ICH GCP.

Data co-ordinating centre responsibilities

- To ensure that all members of the study team are able by knowledge, training and experience to undertake the roles assigned to them and to comply with requirements as specified by the host organisation.
- To provide overall efficient day-to-day management of the trial ensuring compliance with GCP.
- To ensure each centre is put on-line with the randomisation service after Local Research Ethics Committee (LREC), research and development (R&D) approval and the signed local collaborator agreement have been received from the sponsor.
- To provide site folders and relevant documentation to each centre.
- To contribute to the development of the protocol, and all study documentation including data sheets.
- To design, produce and regularly update all trial materials and arrange printing and supply of documentation.
- To monitor recruitment and advise on remedial action if targets are not being met.
- To set up and maintain the website.
- To service the Project management Committee, Steering Committee and any other relevant advisory groups.
- To use all reasonable efforts to ensure that the data collected and reported are accurate, complete and identifiable at source; and that record keeping and data transfer procedures adhere to the Data Protection Act 1998.
- To undertake the interim and final analyses and report regularly to the DMEC in a timely way at their request.
- To supply documentation and reports as deemed necessary by the sponsors to fulfil their obligations.
- To co-ordinate the preparation and publication of data, reports and information, ensuring that these meet legislative, contractual and ethical requirements.
- To co-operate with audits or inspections undertaken by the host institution, the sponsors and regulatory authorities including the MHRA as required.
- To assist investigations into any alleged research misconduct undertaken by or on behalf of the co-sponsors.
- To ensure safe storage of data, including trial site file, data sheets and other records for a period of 15 years after the conclusion of the trial.
- To inform the chief investigator of any changes in the trial protocol that affect the conduct of the trial.

Appendix 12 Principal investigator's responsibilities

Each participating centre identified a paediatric intensivist as a PI. Each participating centre was allocated funding for research nursing time and expected to employ or second a Research Nurse to support all aspects of the trial at the local centre.

The responsibility of the PI will be to:

- (a) ensure local research ethics and R&D approval is obtained
- (b) discuss the trial with medical, and nursing staff who see eligible patients and ensure that they are updated on the current state of knowledge, the trial and its procedures
- (c) provide clinical support for the trial research nurse ensuring that relevant staff are trained in the trial procedures
- (d) ensure that potentially eligible patients are considered for the trial
- (e) report promptly to the clinical co-ordinating centre any problems in meeting recruitment targets so that support can be provided
- (f) maintain good contact with the paediatric cardiac unit to ensure that potentially eligible patients are given information about the trial
- (g) ensure that mechanisms for consent and recruitment are in place
- (h) ensure that data collection forms are completed and returned to the data co-ordinating centre promptly and to deal with any queries
- (i) inform and advise the relevant co-ordinating centre promptly
- (j) facilitate other aspects of co-ordination as relevant
- (k) make data available for verification, audit and inspection purposes as necessary
- (l) respond to requests for data from the Economics team
- (m) ensure that the confidentiality of all information about trial participants is respected by all persons and that records are kept in areas to which access is restricted
- (n) ensure the trial is conducted in accordance with ICH GCP
- (o) allow access to source data for audit and verification
- (p) ensure that adverse events are reported in line with statutory guidelines.

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME
HS&DR
HTA
PGfAR
PHR**

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