Control of Hyperglycaemia in Paediatric intensive care

PROTOCOL

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SUMMARY

There is increasing 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].

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.

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].on-randomised research in children includes a number of reports from general paediatric intensive care units [43-45, 47] and paediatric cardiac intensive care units [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 et al.[43] 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.[46] 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=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.[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 et al. [44] 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 [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 et al. [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 ≥ 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 / or the use of healthcare resources.

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).

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 probablistic 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[49] 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.

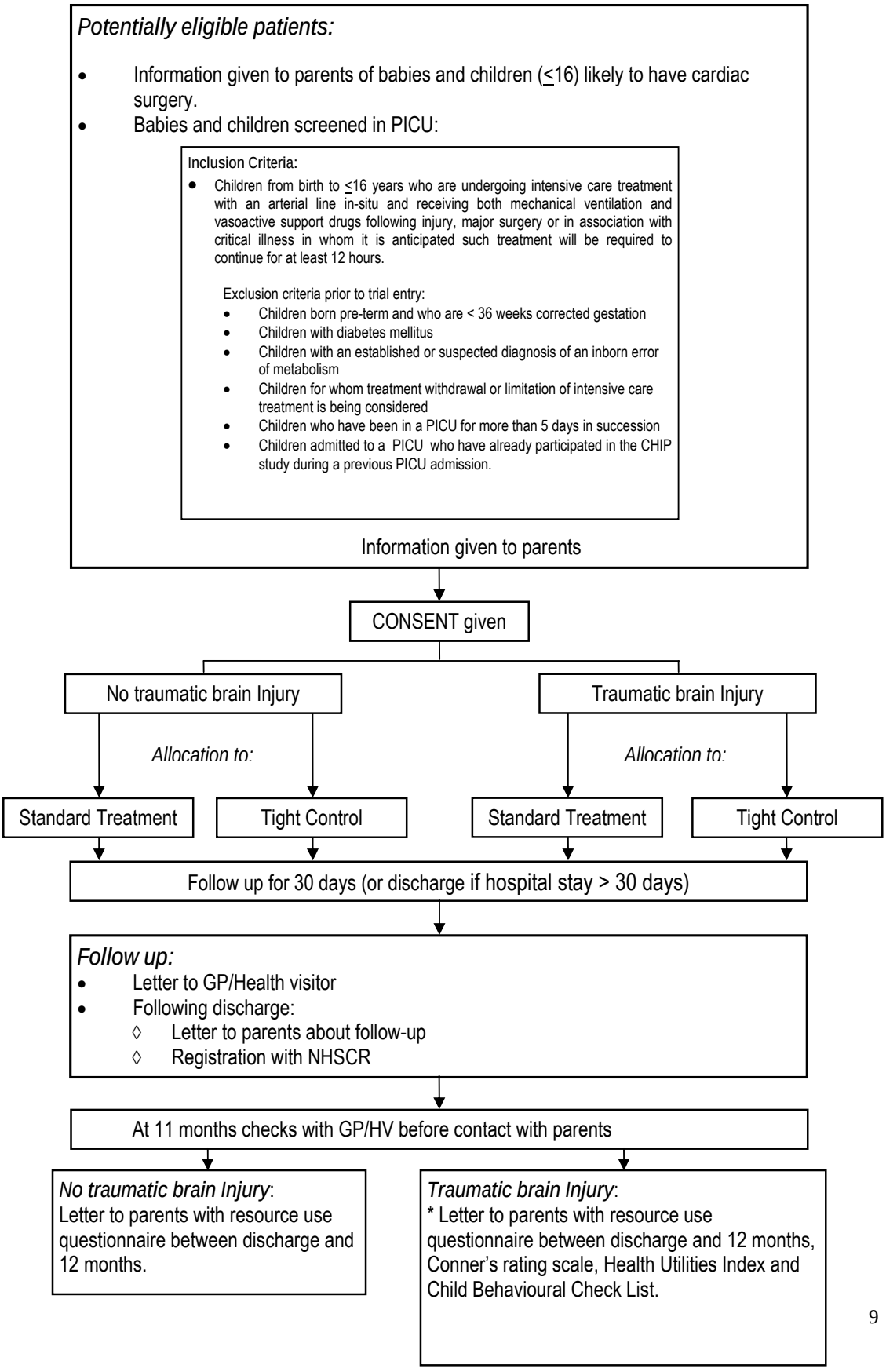
A protocol for glucose control in this group is attached as Appendix A.

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.


Potentially eligible patients:
Information given to parents of babies and children (≤16) likely to have cardiac surgery.
Babies and children screened in PICU:
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.
Information given to parents
CONSENT given
No traumatic brain Injury
Traumatic brain Injury
Allocation to:
Allocation to:
Standard Treatment
Tight Control
Standard Treatment
Tight Control
Follow up for 30 days (or discharge if hospital stay > 30 days)
Follow up:
Letter to GP/Health visitor
Following discharge:
◊ Letter to parents about follow-up
◊ Registration with NHSCR
At 11 months checks with GP/HV before contact with parents
No traumatic brain Injury:
Letter to parents with resource use questionnaire between discharge and 12 months.
Traumatic brain Injury:
* Letter to parents with resource use questionnaire between discharge and 12 months, Conner's rating scale, Health Utilities Index and Child Behavioural Check List.

Outcome measures

Primary:

Following the influential ARDSNET study [50] 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 (Vedas) brings together these two outcomes. Schoenfeld et al [51] define ventilator free days (VFDs) as: VFD=0 if the child dies before 30 days; VDF=(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 [52].

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)[52-54],
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 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 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:

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 sides 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[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 neuroglycopaenia. 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) 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 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)[56] 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 [57]. 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[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 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 [57].

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 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 within the 24 months recruitment period.

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 [59, 60]
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 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.
- 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

Professor Michael Preece (Chair)	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	Centre for Family Research, University of Cambridge.

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	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
Professor Diana Elbourne	Professor of Healthcare Evaluation, Medical Statistics Unit, London School of Hygiene and Tropical Medicine (LSHTM)
Dr Richard Grieve	Lecturer in Health Economics, Health Services Research Unit, LSHTM
Dr. Kevin Morris	Consultant in Paediatric Intensive Care, Birmingham Children's Hospital
Mr. Roger Parslow	Senior research fellow, University of Leeds
Dr. Robert Tasker	Clinical Senior Lecturer, Department of Paediatrics, University of Cambridge
Mrs Ann Truesdale	Trials Advisor, 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

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
Dr Jon Smith (from Sept. 2009)	Consultant Cardiothoracic Anaethetist, Newcastle General Hospital
Mr. Giles Peek (till Sept. 2009)	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.
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 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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LIST OF APPENDICES

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.

- 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 ≥ 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 ≥ 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

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 ≥ 50 % in which case stop the infusion. if fall has been 25-49% reduce infusion by 50%)

If BG ≤ 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.

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.

Lead Study Nurse Royal Brompton Hospital 020 7351 8546 chiptrial@rbht.nhs.uk	Dr Duncan Macrae Chief Investigator CHIP Trial Royal Brompton Hospital 020 7351 8546 d.macrae@rbht.nhs.uk

Definitions

Adverse 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

Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

- post-study SUSARs that occur after the patient has completed a trial
- a new event, related to the conduct of the trial or the development of insulin that is likely to affect the safety of subjects, such as:
    - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial
    - a significant hazard to the subject population such as lack of efficacy of the insulin used for the treatment of a life threatening disease

Contacts

Following a serious adverse event, site investigators must inform the Study Nurse and Chief Investigator at the Royal Brompton Hospital immediately or within 24 hours of being made aware of the event.

Lead Study Nurse Royal Brompton Hospital 020 7351 8546 chiptrial@rbht.nhs.uk	Dr Duncan Macrae Chief Investigator CHIP Trial Royal Brompton Hospital 020 7351 8546 d.macrae@rbht.nhs.uk

It will then be the responsibility of the Chief Investigator to inform the Research and Development Department at the Royal Brompton & Harefield NHS Trust Hospital.

MHRA, Pharmacovigilance Unit:	0207 084 2000 0207 210 3000	Weekdays (9am-5pm) all other times
MREC	Brighton East Research Ethics Brighton & Hove City Teaching PCT 1st Floor, Prestamex House 171-173 Preston Road Brighton BN1 6AG	

Forms

SUSAR should be reported on the following standard forms and sent to the appropriate address.

MHRA – CIOMS 1 form (available at http://www.cioms.ch/cioms.pdf)
MHRA

P.O Box 20, Mitcheldean, GL17 0WQ

Ethics Committee – CTIMP Safety Report to main ethics committee (available at

http://www.corec.org.uk/applicants/apply/docs/Safety_Report_Form_(CTIMPs)v2.0.doc)

Brighton East Research Ethics
Brighton & Hove City Teaching PCT
1st Floor, Prestamex House
171-173 Preston Road
Brighton
BN1 6AG

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

All SAE s 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

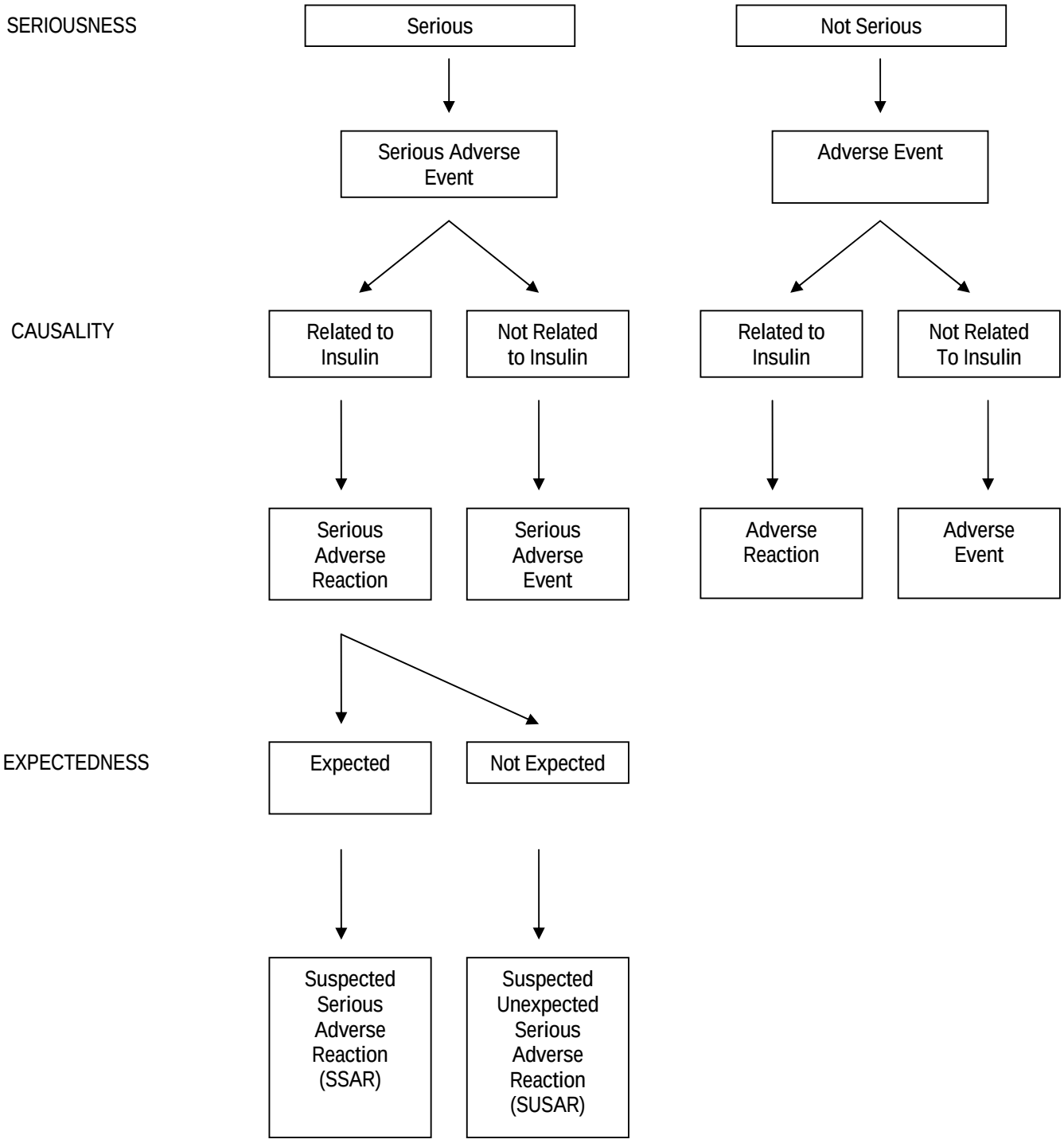
Clinical Trials Unit, MHRA, Market Towers, 1 Nine Elms Lane, London SW8 5NQ

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 vist.

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.

Adverse Events



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 Connor'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-braking, 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 (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 [61].

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.

Information Sheets

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.

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

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.