CLINICAL TRIAL PROTOCOL for I2S2
EudraCT number 2008-001024-31
Sponsor protocol number 08/S0501/31
CTA number 21584/0251/001

GENERAL INFORMATION

Title
A randomised controlled trial of iodine supplementation in preterm infants with follow up at 2 years

Version 8.1, 15th November 2013

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BACKGROUND INFORMATION

Name of the investigational product, including pharmaceutical form
Sodium iodide

Summary of Clinical and Non-Clinical Studies

**Transient hypothyroxinaemia** Thyroid hormone is essential for normal development of the human brain in-utero and for the first two years of life. Damage through deficiency of the preferred iodothyronine, thyroxine (T4), is irreversible. Transient hypothyroxinaemia in preterm infants is common (evident in 41% of infants under 27 weeks gestation and in 23% of infants between 28-30 weeks gestation). Recent studies have linked low plasma T4 in preterm infants with later neurodevelopmental deficits in motor and cognitive function. The aetiology of transient hypothyroxinaemia is not clear and may have contributions from the withdrawal of maternal-placental thyroxine transfer, hypothalamic-pituitary-thyroid immaturity, developmental constraints on the synthesis and peripheral metabolism of iodothyronines, iodine deficiency, and non-thyroidal illness.

**Enteral nutrition** Iodine is essential for the synthesis of T4. Mild and moderate deficiencies of iodine are associated with neuropsychointellectual deficits in infants and children. In 1987 the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommendation for enteral iodine intake was 12 microgram/kg/day. However, subsequent iodine balance studies on enterally fed, healthy preterm infants at one month postnatal age concluded that an enteral intake was required of at least 30 to 40 microgram/kg/day. Iodine contents of a number of term and preterm formulae have since been increased and further increments, to 40-50 microgram/kg/day, have no effect on plasma thyroid hormone levels.

**Parenteral nutrition** Parenteral nutrition is routinely used immediately post delivery in all extreme preterm infants i.e. all infants less than 31 weeks gestation and thereafter enteral feeds are gradually introduced with the speed dependent on the clinical condition of the infant. The fetal thyroid is inordinately sensitive to the inhibitory effect of iodine with the subsequent development of goitre and hypothyroidism. Iodine contamination is the major cause of transient neonatal hypothyroidism. This can follow the application of maternal vaginal povidone-iodine solutions during the last trimester or in labour. Risk factors in the postnatal period are the injection of iodinated contrast dyes to visualise parenteral feeding lines or the topical application of povidone-iodine solution as an antiseptic to the skin of the newborn. These latter risk factors are more common in preterm infants and in response many neonatal intensive care units currently do not use povidone-iodine antiseptics, or non-radiopaque parenteral feeding lines. In the 1980’s when clinical exposure to exogenous and often excess iodine was common the American Society for Clinical Nutrition reduced the recommended iodine intake in parenteral nutrition regimens to 1 microgram/kg/day. Commercially available parenteral solutions for infants reflect these recommendations, and in the absence of other iodine sources, infants are now vulnerable to negative iodine balance and insufficiency, which contributes to transient hypothyroxinaemia.

There are no current studies indicating the iodine requirements of extreme preterm infants receiving parenteral or enteral nutrition. Iodine requirements in these infants are particularly difficult to assess as they have very limited iodine reserves but they are also susceptible to iodine toxicity and hypothyroidism if too much iodine is given.
Determining the iodine requirements of the extreme preterm infant must therefore be assessed through carefully controlled studies, which avoid iodine toxicity but also test the efficacy of iodine supplementation in reducing the severity of transient hypothyroxinaemia.

**Results of pilot studies** Analysis of our data from our completed European Union project (www.euthyroid.org) and CSO funded study confirms that hypothyroxinaemia is largely confined to infants ≤30 weeks gestation as in Dutch and USA studies. The full range of iodothyronines (FT4, T4, T3, rT3, T4S), TSH and TBG were analysed in our studies but only T4 levels were indicative of hypothyroxinaemia; T4 values decrease to a nadir at 7 postnatal days in 23-27 week gestation infants (figure).6,10

As part of our European collaboration we have started investigating the iodine status of extreme preterm infants. In a cohort of 13 extreme preterm infants (mean gestational age 26.8 weeks), we show that iodine intake and urinary iodine output increased with postnatal age, as enteral intakes increased and parenteral nutrition decreased.15 All enteral and parenteral fluids, including drugs, were analysed for iodine content and individually for each infant. All infants were in negative iodine balance on day 1, and 12 remained in negative balance at day 6. By day 13, six infants were in negative balance, and by day 28 three infants remained in negative balance. As a group, mean iodine balance became positive at day 13. Total parenteral nutrition at 150ml/kg/day, with no enteral component, supplied the infants with a mean iodine intake of 3 microgram/kg/day. The iodine supplementation used for infant parenteral nutrition regimens are similar in most European neonatal intensive care units and our analysis of their solutions confirms this extreme deficiency in parenteral supply. The recommended enteral intake of iodine for preterm infants based on balance studies is 30 microgram/kg/day.14,22 Enteral absorption of iodine in preterm infants appears to be at least 90%, based on stool iodine content and urinary iodine output.14,22 This suggests that there should be a near equivalence of dosage by the enteral and parenteral routes to prevent iodine deficiency in infants totally parenterally fed by current standard regimens.

Following the balance study we piloted an iodine supplementation RCT on a further 17 infants, ≤30 weeks gestation with iodine balance studies at 1, 7, 14 and 28 days postpartum and with infant and maternal iodothyronines T4, FT4, T3, Tg, TSH, TBG measured at delivery and in infants at 7, 14 and 28 days. The two parenteral solutions (potassium iodide and potassium chloride) were made up and labelled either A or B solutions at 20 µg /ml (anion concentration) by our supplier, who also held the code to the labels, whereby ensuring triple blindness of the study. A protocol for administration of the solutions was devised with solutions given over a six hour period; no adverse affects were seen during this stage. The six hour period of infusion ensures that no bolus doses of iodide are given that could suppress thyroid function. The normal daily parenteral requirement of potassium ions for preterm infants is 2,000,000

**Figure** Mean and twice the SEM T4 by gestational group, in cord blood and at postnatal days 7, 14 and 28. The grey lines show the x2 SEM boundaries for T4 in cord blood for individual gestations.10

**Blue line = 23-27 weeks**
**Pink line = 28-30 weeks**
**Green line = 31-34 weeks**
**Purple = term infants**
Potential Risks and Benefits
We have piloted carefully various iodide supplementation approaches and the recommended daily allowance of iodide was well below the threshold limit in all infants. Even an infant on full enteral nutrition with the highest commercially available iodide content (Cow and Gate range) containing 20 microgram iodide/100ml and with a volume intake of 150ml/kg/day, and receiving 30 microgram iodide/kg/day from the intervention arm of I2S2, will have a total intake of 60 microgram/kg/day which is well below the maximal allowance for infants of 100 microgram/kg/day.

I2S2 is an inherently low risk trial. The main opportunity for risk is a prescription error for the supplement of sodium iodide. To avoid the delivery of excess daily iodide, vials are restricted in volume and concentration so that even if a full vial was given no infant, over 1.8kg, would be above the recommended daily amount of iodide of 100 microgram/kg. In such a case a routine incident reporting form, NHS IR1 form, will be completed, copied to the PI, and the cause of the error investigated locally. If such a prescription error occurs in infants below 1.8 kg, an I2S2 serious (unexpected) adverse event form will be completed as soon as the error is noticed; the reverse of this form will detail a clinical protocol, which should be followed. Infants below 1.8kg will not have further supplementation; thyroid function will be monitored for clinical and trial purposes.

If I2S2 shows that iodide supplementation improves neurodevelopmental outcome there will be worldwide clinical support for iodide supplemented parenteral nutrition for preterm infants. In addition, the current iodine recommendation of 1mcg/kg/day extends to term infants and indeed children up to 15 kg (3-4 years of age) and they are also likely to benefit. The pragmatic means to achieve iodine sufficiency in parenterally fed infants is to ensure that the parenteral nutrition is adequate.

Description of, and Justification of Routes of, Administration, Dosage and Treatment Periods
The I2S2 trial interventions will be administered parenterally while that route is available, and thereafter by the nasogastric or oral route as appropriate.
**I2S2 Trial solutions** The active arm is sodium iodide diluted to a total iodide content of 75 microgram/ml. The placebo is sodium chloride diluted to a total chloride content 75 microgram/ml; the volumes given of each will be equivalent at 0.4 ml/kg/day. Infants will receive daily placebo or iodide supplements from within 42 hours of birth until 34 corrected weeks. The active solution and placebo will be made up and labelled (unique number) by the supplier (an example of the label is attached as a JPEG file); NPEU will generate and be responsible for the randomisation code, and a copy will be held by the supplier. NPEU will ensure that I2S2 trial staff, and neonatal unit staff are blind to the trials solutions. I2S2 trial solutions will be manufactured in 3 batches during the trial; boxed and labelled by the supplier; each infant will have a personalised 30-day supply pack and will be issued with repeat supplies as required. NPEU will initiate resupply of trial solutions from the supplier. The Neonatal units will hold 5 packs of trial solutions for emergency cover when hospital pharmacies are on limited cover such as week-ends and public holidays. The trigger for re-ordering trial solutions will be determined by the shelf-life of the trial solutions and the actual/anticipated recruitment of infants per hospital. The trial solutions may be stored safely at room temperature. A guidance sheet outlines pharmacy procedures for receiving, storing, re-ordering and supplying the neonatal unit with the trial solutions.

**Monitoring of investigational medicinal products** The supplier is responsible for monitoring the quality of the investigational medicinal product and placebo. Destruction of remaining trial solutions at the end of the study will be the responsibility of hospital pharmacies. Pharmacies within each of the participating I2S2 hospitals will monitor the movement and use of I2S2 investigational medicinal product and placebo within their hospitals and NICUs. The Clinical Trials Unit, NPEU, will monitor the movement of I2S2 trial solutions between the supplier and the I2S2 hospital pharmacies.

**Statement of compliance**
The trial will be conducted in accordance with the protocol, GCP and applicable regulatory requirements.

**Population to be studied**
Extreme preterm infants less than 31 weeks gestation admitted to the Neonatal Intensive Care Units of the participating I2S2 hospitals.

**TRIAL OBJECTIVES**

**Primary research question**
Does iodine supplementation of extreme preterm infants improve neurodevelopment outcome at 2 years corrected age?

**TRIAL DESIGN**

**Primary outcomes**
Appreciable neurodevelopmental impairment at 2 years corrected age.

The primary outcome will be the three main domains of the Bayley III\textsuperscript{38,40} score: i.e. cognitive score, language composite score and motor composite score. \( P \leq 0.05 \) will be the level used to indicate statistical significance. If the infant dies before neurodevelopmental assessment, they will be recorded as a Bayley III score of 55. The
Primary outcome will be ordered as cognitive score, motor composite score and language composite score in all results presented.

**Secondary outcomes**

Blood levels of T4, TSH and TBG on day 7, 14, 28 and 34 weeks corrected age. The nadir of T4 levels in infants <31 weeks gestation occurs at day 7, the other days are needed so that the interplay can be determined between iodothyronine levels, iodide status and illness type and severity: necrotising enterocolitis, persistent ductus arteriosus, respiratory distress (days of endotracheal intubation, days of continuous positive airways pressure); chronic lung disease (need for oxygen at 36 weeks corrected age), cranial ultrasound changes, acquired infection; hearing and vision impairment; postnatal drug use (e.g. diamorphine, dexamethasone, dopamine, caffeine and indomethacin); nutritional status; BAPM level of care; highest recorded bilirubin levels; and death – immediate and underlying causes.

Blood levels are required on days other than day 7 as some infants will have suppression of the hypothalamic-pituitary-thyroid axis by illness or drugs and although iodine replete will not be able to respond until resolution of the condition. Levels of T4, TSH and TBG are needed to confirm the efficacy of iodide supplementation; and to distinguish between transient hypothyroxinaemia, transient hypothyroidism and transient hyperthyrotropinaemia.

Neurodevelopment impairment will also be assessed as a composite of death or a Bayley III score of <85 in any of the score’s three main subsets domains: cognitive, language and motor composites.

Neurodevelopmental impairment will be assessed also as a difference between the iodine supplemented and placebo groups in each of the four subset scores of the Bayley III i.e. receptive communication, expressive communication, fine motor or gross motor.

**Trial Type**

A randomised, controlled, parallel-group trial of iodine supplementation versus placebo and neurodevelopmental status at 2 years corrected (for prematurity) age.
**Figure 1:** Flow chart of I2S2 trial

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**Exclusion Criteria**
- Maternal exposure to excess iodine during pregnancy or labour e.g. povidone iodine use for skin disinfection

**Eligibility Criteria**
- < 31 weeks gestation
- < 42 hours old
- Written informed consent

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**Randomisation by NPEU Clinical Trials Unit**

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**Active Intervention Group**

**Sodium Iodide**
- Daily until 34 corrected weeks gestation
- Prescribed on drug kardex*
- If parenteral route – infused over a period not less than 6 hours
- If enteral route – nasogastric or oral over a period not less than 4 hours

**Placebo/Control Group**

**Sodium Chloride**
- Daily until 34 corrected weeks gestation
- Prescribed on drug kardex*
- If parenteral route – infused over a period not less than 6 hours
- If enteral route – nasogastric or oral over a period not less than 4 hours

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- Case report form completed continuously until discharge from NICU
- Guthrie card completed day 7, 14, 28 and 34 completed weeks gestation

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**2 year follow-up**

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* both parenteral and enteral solutions are prescribed drugs and recorded on the drug Kardex or equivalent
Guidance Sheets for clinical aspects and local trial procedures within participating I2S2 hospitals
Guidance sheets are available to guide each stage of the I2S2 trial and will be available in the trial documentation in all hospitals participating in I2S2.

Randomisation
Web-based randomisation will be performed by the NPEU Clinical Trials Unit, Oxford, using a bespoke minimisation algorithm to ensure balance on important prognostic factors, one of which is gestational age. Randomisation is via a secure web site www.npeu.ox.ac.uk/I2S2 with a telephone back-up available 24 hours a day. Infants will be randomised within 42 hours of birth.

Masking
Masking will be used so that the study participants and parents, the research team, and the participating neonatal units and local pharmacy will be blind to the contents of the trial solutions. The randomisation codes will be held by core programming staff of the NPEU Clinical Trials Unit, Oxford. The packaging of the products will be identical, in boxes with supplies sufficient for 28 days.

I2S2 trial solutions
The active arm is sodium iodide diluted to a total iodide content of 75 microgram/ml. The placebo is sodium chloride diluted to 75 microgram/ml; the volumes given of each will be equivalent at 0.4 ml/kg/day. Infants will receive daily placebo or iodide trial solutions until 34 corrected weeks. The active solution and placebo will be made up and labelled by the supplier.

Duration of Trial
I2S2 has two distinct phases: an intervention phase and a non-intervention phase. During the intervention phase the infants receive a daily trial solution until 34 corrected weeks gestation. The end of the intervention phase is defined as two weeks after the last infant recruited finishes the intervention.

In the non-intervention phase the infants will be followed up at 2 years corrected age. The end of the non-intervention phase is when the last infant recruited has received their 2 year assessment.

Procedures for emergency unblinding of the treatment codes
The randomisation codes will be held by the NPEU Clinical Trials Unit, Oxford. If a code requires breaking this will be undertaken by the NPEU Clinical Trials Unit, Oxford at the request of the Chief Investigator; emergency unblinding is the responsibility of the Chief Investigator with medical advice as required and is available 24/7.

Monitoring of patient safety
The amount of 30 micrograms/kg/day of iodine in the active arm of this trial has been derived from studies of preterm infants with a mean gestational age of 32 weeks gestation and who were well and being enterally fed with breast milk or formula. The current fluids available for parenteral feeds are severely iodine deficient. In a pilot study, we applied this level of iodine supplementation to parenterally fed extreme preterm infants <31 weeks gestation and all infants on this regimen were in iodine balance and without toxicity effects. In the I2S2 trial all infants in both arms of the trial will have routine UK thyroid hormone screening at postnatal day 6 and a further TSH screen at 36 corrected weeks gestation. I2S2 trial hormone screening will be done on postnatal days 7, 14, and 28, and 34 corrected weeks gestation. The results of both
the clinical blood and I2S2 trial blood tests will be analysed in the UK and Dutch screening services respectively, both will detect infants with congenital hypothyroidism or hypothyroidism secondary to iodine toxicity, and both report their findings immediately to enable timely clinical diagnostic testing (figure 3). NICU’s will report all infants with TSH of ≥6mU/L (as indicated by Amsterdam Screening Centre) as an SAE, this will ensure each infant is further investigated and any necessary action is documented.

Infants will be receiving active trial solutions until they are 34 corrected weeks gestation. During this period all infants will be in a Neonatal Intensive Care Unit and will be reviewed thoroughly at least daily by specialist staff who will be aware of this trial and the consequences of potential iodine toxicity. There will be a low threshold for instigating thyroid hormone investigations should there be any clinical features suggestive of hypothyroidism. These clinical parameters constitute our prime safety features and will be recorded formally in the infant’s case report form and clinical case notes. Any infant with confirmed hypothyroidism will immediately stop receiving the trial solutions and will be closely monitored clinically. Such infants will continue to have thyroid hormones levels monitored as per I2S2 trial protocol; information recorded on their case report forms and will be assessed at 2 years corrected age.

Mothers will be aware, at the time of giving written informed consent, that they may withdraw their infant from the trial at any point without the need to give any explanation and that such action will not in any way effect the medical treatment that they or their infant will receive. Throughout the trial the I2S2 research nurse and later the research psychologists will ensure that mothers are still happy that their child is part of the I2S2 trial.
Figure 3: Management of an infant whose I2S2 trial Guthrie Cards TSH level ≥ 6 mU/L

TSH ≥ 6 mU/L

YES

- Exposure to excess iodine (e.g. iodinated contrast media / skin)
  - Withdraw infant from I2S2 supplement immediately
  - Continue Guthrie Card bloods and complete I2S2 case report forms and SAE notification form

NO

- No known exposure to excess iodine
  - Principal investigator should refer to paediatric endocrinologist for management
  - Diagnostic tests for hypothyroidism initially TSH and FT4
  - Urine sample for iodine estimation
  - Treated with thyroxine
    - Withdraw infant from I2S2 supplement
    - Continue Guthrie Card bloods and complete I2S2 case report forms and SAE notification form
  - Not treated with thyroxine
    - Continue in I2S2 and complete SAE notification form

Continue I2S2
Source data/Epidemiological data
An extensive range of data describing the social and clinical background of the infant and mother will be collected from the infant and mother’s clinical notes while the infant is in NICU and recorded on a specific case report form. The range of data is the same as that collected for our previous work.1,6,8,10,17 and includes: basic demographic information, events of the intrapartum and postpartum, neonatal illnesses and drug prescription. Additional data about hospital utilisation between discharge from the NICU and the two year follow-up will be recorded on a bespoke I2S2 form. At the two year follow-up forms will be completed which records neurodevelopmental assessment and potential confounding factors. Data derived from Guthrie Cards will be made available electronically.

Ethical approval and other approvals
1. Multi-centre ethics 08/S0501/31
2. MHRA – CTA number 21584/0251/001
3. EudraCT number 2008-001024-31
4. Trial Sponsor Number 08/S0501/31
5. Data registration Number DP02/488
6. Clinical Trials No NCT00638092

SELECTION AND WITHDRAWAL OF I2S2 TRIAL PARTICIPANTS
Setting
Neonatal Units selected from the pool of twenty-one I2S2 hospitals

Recruitment
Mothers will be recruited primarily by a trained and dedicated research neonatal nurse; some recruitment will be by attending clinicians and other neonatal nurses. The research nurse, or someone designated by her, will talk to potential mothers about I2S2 and the possible inclusion of her infant in I2S2. Written information will be given at this time. After a period for question and reflection the nurse will speak again to the mothers, providing an opportunity for further discussion, and obtaining written consent if participation in the trial is confirmed. The local clinical leads (principal investigators) and I2S2 investigators will also be available to respond to queries. Copies of written consent will be held by: the mother, the principal investigators, the NPEU, CTU (on behalf of the Sponsor) and a copy placed in the infant’s clinical case notes.

Inclusion criteria
All infants born <31 weeks gestation, up to 42 hours old and with written informed consent.

Exclusion criteria
Infants transferred into an I2S2 unit will be ineligible if they or their mother were exposed to povidone-iodine as a skin disinfectant or mother to other sources of excess iodine during pregnancy. Infants who have no realistic chance of survival will not be recruited.

Participant withdrawal criteria
The algorithm (figure 3) will apply to any infant whose TSH level is equal to or above 8.0 mU/L.
I2S2 infants will be routinely screened for congenital hypothyroidism as part of the UK screening programme, on postnatal days 5-6 (incidence approximately 1:3500).
Thereafter the most likely cause of hypothyroidism detected by the Amsterdam Screening Centre in infants recruited to I2S2 will be iodine toxicity caused by exposure to iodinated contrast media or through iodinated skin disinfection prior to surgery. Infants who are diagnosed with hypothyroidism, irrespective of cause, will be treated with thyroxine and will have the trial solution withdrawn and reported as an SAE. Such infants will continue in all other aspects of the trial, i.e. to have study bloods taken on days 7, 14, 28 and 34 corrected weeks gestation as appropriate; the case report form fully completed; their data analysed under intention to treat; and assessed at the 2 year follow-up. Withdrawn participants will not be replaced.

There are 16 screening laboratories in the UK; three use a cut-off TSH level of 5 mU/l, four use 6 mU/l, three use 8 mU/l and six use 10 mU/l. We will use a TSH threshold of 6.0 mU/L (which is also the criteria of the Amsterdam Screening Centre) as the criteria for alerting NICU of the possibility of hypothyroidism (figure 3). Such infants will be further investigated by formal diagnostic tests of thyroid function as appropriate to the relevant NICU. Relevant NICU’s will report all infants with TSH of ≥≥≥≥6 mU/L (as indicated by Amsterdam Screening Centre) as an SAE, this will ensure each infant is further investigated and any necessary action is documented.

TREATMENT OF PARTICIPANTS

Investigational medicinal product and placebo
Sodium iodide and sodium chloride

Dose
(As appropriate for iodide or chloride) 30 micrograms/kg/day; the volumes given of each will be equivalent at 0.4 ml/kg/day

Dosing schedule
Parenteral route: daily over a period not less than 6 hours e.g. midnight to 06.00hrs.
Enteral route: daily over a period not less than 4 hours.

Route of administration
The route of administration will be parenteral or enteral as appropriate. All infants <31 weeks gestation are initially parenterally fed, and as their clinical condition stabilizes are slowly weaned onto enteral feeds. The trial solutions may be given by both routes although while the infant is receiving any parenteral feeding, this is the preferred route of administration. The enteral solution will be administered via the nasogastric tube or orally.

Treatment period
From within 42 hours of birth until 34 weeks corrected gestation.

Follow-up
Infants will be reviewed formally and clinically at least daily while in the NICU; most infants will be followed up post discharge from the NICU until 2 years of age or for as long as clinically necessary.

Infant blood will be taken at 7, 14, 28 postnatal days and 34 corrected weeks gestation. Blood will be spotted onto Guthrie card and sent to the Amsterdam Neonatal Screening laboratory for the estimation of thyroid hormones and proteins (T4, TSH and TBG). All infants recruited to the I2S2 trial will be followed up at 2 years corrected age and be assessed primarily using the Bayley Scales III38; this is an established test for assessing global development and is routinely used in neonatal follow up e.g. Epicure;39 several studies have demonstrated poorer development on the Bayley Scales.
Mental Development Index (MDI) in children who had abnormal thyroid hormone levels. The clinical rationale for iodine supplementation is a benefit to subsequent neurodevelopment.

Infants’ names and addresses will be sent to the NHS Information Centre and the NHS Central Register to be used for flagging to help contact mothers and provide information about the infants’ health status.

Other treatments not permitted during the trial
There are no restrictions to the clinical medications or treatments permitted during I2S2 except that infant exposure to iodine is not permitted during I2S2; for example the use of povidone iodine for skin disinfection or from the use of iodinated contrast media for the visualisation of central venous catheters.

Procedures for monitoring compliance
A dedicated nurse coordinator and psychologist coordinator will have responsibility for maximising compliance (at appropriate stages of the I2S2 trial) and for giving specific training to all participants to ensure compliance with the protocol. Compliance will be reinforced through regular meetings and communication with participating units, newsletters, and a dedicated web site. The prescription of the investigational medicinal product and placebo will be written daily in the infant’s drug Kardex (or equivalent). Compliance will be monitored in a variety of ways. For example, during data entry checks can be made to ensure that the number of consent forms matches the randomisation list, and that the Guthrie Card returns matches the expected number of cards per infant. The nurse coordinator will check unannounced the accuracy of completed Case Report Forms against medical notes; ensure that a signed consent form and participant information sheet are included in each I2S2 trial participant’s medical notes; and will review the drug Kardex’s to ensure appropriate prescribing.

ASSESSMENT OF EFFICACY
The primary outcome of the I2S2 trial is neurodevelopment at two years corrected age, thus the primary assessment of efficacy is a significant difference in mean Bayley–III cognitive score, language or motor composite scores between the arms of the trial assessed at the two year follow-up.

ASSESSMENT OF SAFETY
I2S2 is an inherently low risk trial and the sole consequence of iodine overdose is thyroid dysfunction. The main opportunity for risk is a prescription error for the supplement of sodium iodide. To avoid the delivery of excess daily iodide, ampoules are restricted in volume and concentration so that even if a full ampoule was given no infant, over 1.8kg, would be above the recommended daily amount of iodide of 100mcg/kg. In such a case a routine incident reporting form, NHS IR1 form, will be completed, copied to the Clinical Trials Unit, NPEU, and the cause of the error investigated locally. If such a prescription error occurs in infants below 1.8 kg, an I2S2 Serious Adverse Event/Suspected Unexpected Serious Adverse Reaction Form will be completed as soon as the error is noticed; guidance will be available on the subsequent action which should be followed. Infants below 1.8kg will not receive further trial solution. In both instances thyroid function will be monitored for clinical and trial purposes.

There are no other safety issues specific to I2S2. However it is possible that some infants (under 5%) may be exposed to excess iodine from sources outwith the control of the I2S2 trial, such as during surgery or if gastrografin is required. This
information will be recorded on the case report form and guidance will be available for
the local clinician on subsequent management. Such infants will not receive further
I2S2 trial solutions and will have their thyroid function monitored 10-14 days post
exposure. Thereafter infants will be managed according to clinical need following local
clinical protocols.

Pharmacovigilance and safety monitoring
The I2S2 trial will be conducted in accordance with the Pharmacovigilance
requirements set out in the Medicines for Human Use (Clinical Trials) Regulations 2004,
in response to Directive 2001/20/EC and the European Medicines Agency Clinical Safety
Data Management: Definitions and Standards for Expediting Reporting 1995 (revised
2006).

Safety will be monitored continuously while the infant is in the neonatal unit. The
following definitions and arrangements will apply to the coding and reporting of adverse
events (AEs), adverse reactions (ARs), serious adverse events (SAEs), serious adverse
reactions (SARs), and suspected unexpected serious adverse reactions (SUSARs).

**Adverse Event (AE)** is defined as any **untoward** medical occurrence affecting a trial
participant whilst receiving a medicinal product (investigational medicinal product or
placebo), whether or not it is considered to be related to the medicinal product.

The setting for I2S2 is Neonatal Intensive Care Units and all infants in I2S2 will
be initially extremely premature. This group of infants are expected to have many
anticipated adverse events before their discharge; these will not be recorded in the
case report form.

**Adverse Reaction (AR)** is defined as an AR that is suspected to be causally linked to
the investigational medicinal product or placebo. At the concentration and volume of
the trial interventions there are no known side effects if prescribed according to the
I2S2 protocol.

**Serious Adverse Event (SAE)** is defined as the occurrence of an AE where the death
of the participant resulted or was otherwise threatened or where the participant
required prolonged hospital stay; or resulted in persistent or significant disability or
incapacity; or was a congenital anomaly/birth defect. Medical judgement may consider
other adverse events fall also in this category.

The group of infants in the I2S2 trial will have many serious adverse events and
these will be recorded in the case report form. We anticipate the following SAEs in our
infant population: death (for instance current death rates in infants born under 27
weeks gestation is 29% in the first month following delivery and 11% in infants born
between 28-30 weeks gestation); septicaemia, meningitis, bacteraemia, pneumonia,
congenital anomaly, respiratory distress syndrome, pneumothorax, pulmonary
interstitial emphysema, pulmonary haemorrhage, intraventricular and other cerebral
haemorrhages, cerebral pathology, periventricular leucomalacia, persistent ductus
arteriosus, necrotising enterocolitis, chronic lung disease, retinopathy of prematurity,
hypoglycaemia, hyperglycaemia and hyperbilirubinaemia. At the two year follow up we
anticipate: motor and cognitive disability, sight and hearing dysfunction including
blindness and deafness. Amsterdam Screening Centre use a TSH threshold of ≥6mU/L
as the criteria for alerting NICU of the possibility of hypothyroidism. NICU’s will report
infants with TSH of 6mU/L or above as an SAE, this will ensure each are further
investigated as appropriate to the relevant NICU.

All of these conditions will be recorded on the case report form but none require
immediate reporting to the sponsor.
**Serious Adverse Reaction (SAR)** is defined as a serious adverse reaction that is suspected to be causally linked to the study investigational medicinal product or placebo. The only adverse reaction known to be associated with iodine is associated with excess iodine and is transient hypothyroidism. This will only occur if there is a prescription error with the investigational medicinal product; which we anticipate will be very rare. Vials are restricted in volume and concentration so that even if a full vial was given no infant, over 1.8kg, would be above the recommended daily amount of iodide of 100 microgram/kg. If such a case occurred a routine incident reporting form, NHS IR1 form, will be completed, copied to the PI, and the cause of the error investigated locally. If a prescription error occurs in infants below 1.8 kg, an I2S2 serious adverse event form will be completed as soon as the error is noticed; the reverse of this form details a clinical protocol, which should be followed. Infants below 1.8kg will not have further supplementation; thyroid function will be monitored for clinical and trial purposes.

We estimate that about 5% of infants might be exposed to excess iodine which is not prescribed for the I2S2 trial. For instance, if the infant receives excess iodine for a competing medical need e.g. via iodinated contrast media to visualise long-lines, or during cardiac catheterisation, or through the use of gastrointestinal gastrografin studies etc; or via exposure to iodinated skin disinfectants.

We appreciate that at the stage of initially submitting a Serious Adverse Event/Suspected Serious Unexpected Serious Adverse Reaction form it will not be known if the infant was in the investigative medicinal product (sodium iodide) or placebo (sodium chloride) arm of the trial. Similarly the infant may or may not develop the features of transient hypothyroidism even though exposed to excess sodium iodide solution through prescription error. In addition the onset of the features of transient hypothyroidism may be delayed after acute exposure to excess iodine.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)** is defined as any suspected unexpected adverse reaction to the investigational medicinal product or placebo that is unexpected or serious; i.e. its nature and severity are not consistent with the information described in the Investigator’s Brochure.

**Reporting procedures of the PIs and CI**

- Any event or adverse reaction which is described in the Investigator’s Brochure will not be reported
- The CI will ensure that PIs are asked about any untoward SAEs / SARs occurring since the previous contact.
- The PIs will ensure that all anticipated SAEs and SARs are recorded in the infant’s case report form; these will be reviewed regularly by the DMC during the trial.
- The PIs will report SUSARs to the Clinical Trials Unit, NPEU by telephone/fax/email at the earliest opportunity and within one working day of them becoming aware of the occurrence.
- The PI will provide a written detailed report to the Clinical Trials Unit, NPEU within 3 days of first knowledge of a fatal SUSAR and within 7 days of a non-fatal SUSAR.
- The CI or person with delegated responsibility will review all SAR/SUSARs as reported on Form 1 within one working day hours of their receipt, and will consider causality and expectedness. Where there is any suspicion that an event is linked to the I2S2 trial intervention that event will be classified as a SUSAR and reported accordingly.
• All expected SAEs will be recorded on the case report form, and will be reviewed regularly by the Data Monitoring Committee during the trial. SUSARs will be sent to the chair of the DMC for regular review.

• The CI will notify the MHRA and Fife, Forth Valley and Tayside REC and Sponsor of all SUSARs reported to them by the PIs within 7 days if the SUSAR is linked to a death or considered life-threatening; with additional information sent within a further 8 days. All other SUSARs will be notified to the MHRA/REC within 15 days of first knowledge of the event.

• As soon as practicable, the CI will inform PIs in all participating Neonatal Intensive Care Units in I2S2 of the notified SUSAR.

• The CI will maintain a detailed record of all SAEs, SARs and SUSARs reported to them by the PIs. The record will be kept electronically in a secure computer file at the NPEU, with off-site back-up. The CI will send details of this record in the annual safety report to the MHRA and Fife, Forth Valley and Tayside REC and Sponsor. A copy will be made available to the MHRA at any time on receipt of a written request.

• SUSARs will be reported for each infant for the period of the trial supplementation plus two weeks or discharge from hospital (whichever is first).

STATISTICS
Sample size
Twenty-one hospitals form a pool of NICUs willing to participate in I2S2. The death rate varies according to prematurity. We are using the death rates found in our previous work as a guide: 29% ≤27 weeks and 11% 28-30 weeks with an overall mean death rate of 20% in infants born <31 weeks gestation. Recent population data are not available about the proportion of infants <31 weeks gestation who score under 2 sds in neurological assessment, but a recent EPICure paper42 (which is limited to infants <27 weeks gestation) found 21% of their tested children scored under 2 sd. I2S2 would expect to have a much smaller percentage than this and our observations from our previous work (unpublished) show that 9.3% of infants <31 weeks gestation are below 2 sd at 5.5 years.

To detect a clinically important difference in mean overall Bayley III score (defined as 0.4 of one standard deviation (sd) requires between 1100 and 1700 infants (Table 4) depending on the variability of the measurement encountered in trial participants.

Table 4 Sample size required to detect a mean difference in Bayley III score in survivors

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Intention–to-treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in mean Bayley Score of 0.4 sd</td>
<td>Difference in mean Bayley score (including deaths)</td>
</tr>
<tr>
<td>6</td>
<td>4.9 (81%* of 6)</td>
</tr>
<tr>
<td>6</td>
<td>4.9 (81%* of 6)</td>
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* 81% is the assumed survival rate based on pilot data

On this basis 17 units are needed to meet the target sample size. This number allows for a recruitment rate of 35% of eligible infants for the first 6 months of recruitment, followed by 50% for the remaining 18 months of the recruitment.
Analysis
The primary analysis is by intention-to-treat and therefore outcomes will be compared for all infants recruited regardless of whether, or for how long, they received the I2S2 intervention. The primary outcome will be the three main domains of the Bayley III score: i.e. cognitive score, language composite score and motor composite score. \( P \leq 0.05 \) will be the level used to indicate statistical significance. Deaths will be scored with an arbitrary low score of 55. The primary outcome will be ordered as cognitive score, motor composite score and language composite score in all results presented.

In the secondary analysis we shall explore the relationship between intervention group and specific categories of illness, levels of T4, TSH and TBG, and prescribed drug usage. Neurodevelopment impairment will also be assessed as a composite of death or a Bayley III score of <85 in any of the score’s three main subsets domains: cognitive, language and motor composites.

The treatment effect will be compared in different gestational age groups and other factors using F Tests.

The primary and secondary analyses will be presented under intention to treat as well as for survivors only. The rationale for this is to give a fair representation of the average ability of assessable children.

Criteria for determining termination of the trial
Two factors will determine early termination of I2S2: an unacceptable increase in death rate and an unacceptable increase in the incidence of hypothyroidism. What constitutes unacceptable is difficult to quantify. The current death rate in the first month of life in infants born \( \leq 27 \) weeks gestation is 29%, and 11% for infants between 28-30 weeks gestation. The incidence of hypothyroidism is 1:3500, but the incidence of iatrogenic hypothyroidism is unknown. The Data Monitoring Committee will discuss/inform the Trial Steering Group if they believe the rates of either have increased appreciably and whether or not the increase is likely to be caused by participation in I2S2. The final decision is likely to be a judgement that is part statistical and part clinical opinion.

Procedure for accounting for missing, unused or spurious data
Missing data will be minimal as all incoming case report forms will be reviewed by the Clinical Trials Unit (NPEU) and copies of the incomplete forms will be returned to the local I2S2 hospital for amendment. Any information that is still missing at the time of statistical analysis will be categorised as such and described in the final analyses. Data checks and cleaning will be performed and questionable data checked at source. All the data collected will be used in the analyses as we have restricted data collection to key information only.

Procedures for reporting any deviations from original statistical plan
Deviations from the original statistical plan are unlikely; however, if any need arises it will be discussed with approval sought from the Data Monitoring Committee and the Trial Steering Group. Any approved change will be recorded in the final report and clinical protocol as appropriate.

Participants included in the analysis
All randomised infants will be included in the statistical analysis.

Data Monitoring Committee An independent Data Monitoring Committee (DMC) is appointed with the remit to review the trials progress. The DMC is independent of the I2S2 trial organisers. There is one planned interim analysis at half way through the
intervention phase of the trial, but others can be arranged at the request of the DMC chair. A DMC charter will be formulated following the recommendations of the DAMOCLES study. I2S2 investigators, collaborators, administrative staff and the Trial Steering Committee will not have any knowledge of the results of the interim analysis, unless modification or cessation of the trial is recommended by the DMC. DMC members are Professor Henry Halliday (Chair), Professor Gordon Murray, and Professor Christopher Kelnar.

RESEARCH GOVERNANCE

LEVELS OF CLINICAL RESPONSIBILITY
During their postnatal stay, about 50% of infants are likely to be transferred from their recruiting hospital to a Continuing Care Site for surgery, for specialist opinion or to be closer to home. Some infants participating in I2S2 are therefore likely to be moved from their recruiting hospital to another hospital whilst still requiring daily trial solutions and possibly the collection of blood samples on a Guthrie card. Infants may be transferred multiple times between sites and often these transfers happen quickly and with little warning. Although, under the trial protocol the study intervention will need to be given at the receiving hospital, the level of clinical trial responsibility at that site is lower than at the Recruiting Site. For instance receiving hospitals will not be required to obtain initial consent for entry to the trial. There will in fact be three different levels of hospital involvement in the I2S2 trial:

1. **Recruiting Sites** – where mothers/infants are recruited, daily trial solutions given, blood spots cards completed and data collection forms completed
2. **Continuing Care Sites** – where infants requiring daily trial solutions, perhaps blood spot cards and data collection forms completed
3. **Date Collection Sites** - where data collection forms completed

This arrangement was discussed with R&D Forum, MHRA, MREC and MRC.

The responsibilities for each level vary as do the approvals required to comply with the regulatory authorities. The information below takes account of the transfer of Site-Specific Assessment to NHS R&D since 1 April 2009. Requirements are as follows:

**RECRUITION SITES**
Each Recruiting Site will have a nominated Principal Investigator (PI) and a funded I2S2 nurse. The PI will be responsible for overseeing recruitment of eligible infants to the trial, the administration of the daily trial solutions and completion of Guthrie card blood spot samples on day 7, 14, and 28 postnatal and at 34 corrected weeks gestation. The procedures for prescribing, recording, giving and calculating the dosage of the trial solutions and taking blood samples on Guthrie cards constitute routine clinical practice for neonatal staff.

All members of staff involved within the trial at each recruiting site must be competent and confident in:
1. Their knowledge of the study and their ability to answer questions raised
2. Their competence in obtaining informed consent from the families
3. And, they must be adequately trained by experience or have received training in GCP
A log of delegated responsibilities will list members of staff involved within the I2S2 trial and will be maintained in the Study Site File.

Each Recruiting Site requires NHS permission for research, a contract between the study Sponsor (Oxford University) and the Trust, and a financial contract between University of Dundee (clinical coordinating centre) and the Trust. All recruiting sites have been notified to the MHRA and REC.

CONTINUING CARE SITE
The Continuing Care Site will not be involved in any decisions about entering patients into the study or seeking consent. They are defined as a research site for the purpose of clinical trial regulations as they will be administering trial solutions to those infants less than 34 corrected weeks gestation.

If an infant is transferred from a Recruiting Site to a Continuing Care Site whilst still requiring daily trial solutions, a transfer pack will accompany the infant; this contains a sufficient supply of I2S2 trial solutions up until 34 corrected weeks gestation, data collection forms and essential training material in order to carry out study procedures. The I2S2 nurse from the transferring hospital will inform the coordinating centre (NPEU,CTU) and the I2S2 nurse coordinator (University of Dundee) about the transfer to a Continuing Care Site or Data Collection Site. The I2S2 nurse will be responsible for liaising with the receiving site, establishing and maintaining an audit trail for the movement of each transferring infant.

A Principal Investigator will be identified at each of these sites who is prepared to accept responsibility for overseeing the care of the infant under the I2S2 trial protocol. All potential continuing care site’s will be notified to the MHRA and REC as part of the notice of substantial amendment explaining the arrangements for continuing care sites. The level of responsibility taken on by the Continuing Care Site is, therefore, lower than at a Recruiting Site and the level of approval required should reflect this. NHS permission for research is required as the sites are responsible for undertaking research activities. However, the extent and content of the review by R&D offices would take into account the activities being undertaken at the continuing care site. All study procedures such as recording, giving and calculating the dosage of the trial solutions and blood samples on Guthrie cards constitute routine clinical practice for neonatal staff. Trial specific training material, to a level appropriate to the work, will be provided to all continuing care sites including training in the reporting of SAE’s and SUSAR’s. The I2S2 nurse at the Recruiting Site will be responsible for following up the outcomes of infants transferred to Continuing Care Site to ensure that: (i) on-going training is provided if required; (ii) staff are familiar with the study protocol; (iii) SAE’s and SUSAR’s are reported in a timely manner.

Due to the different level of responsibility, a signed contract between the sponsor and Continuing Care Site is not required; the SSI and a letter outlining the responsibilities of each party will suffice. If the R&D office, after consideration of the above information, does not give permission for the research then the baby would have to be withdrawn from the trial, or transferred to another Continuing Care Site. Where there are potential issues to address, NHS organisation could consider issuing permission, pending completion of any such arrangements.

DATA COLLECTION SITES
Occasionally an infant will be transferred several times before it goes home. If an infant is transferred to a data Collection Site after it is 34 corrected weeks gestation, the Data
Collection Site would be asked to complete a short discharge form either when the infant is transferred from that hospital, is discharged home or dies. Parental consent to the transfer of these data to the coordinating centre will have been given as part of the initial consent process.

After 34 corrected weeks gestation the intervention phase of the study is complete; the infant will no longer require trial solutions or blood samples to be taken. The continuing Data Collection Site will be responsible for reporting of SAE’s and SUSAR’s up until 36 corrected weeks gestation but do not constitute a research site under the clinical trials regulations. Data collection does not require any agreement of responsibilities between the sponsor and the centre.

DIRECT ACCESS TO SOURCE DATA/DOCUMENTS
The Sponsor will ensure that the investigator will permit trial related monitoring, for example by I2S2 trial staff, the MHRA, Data Monitoring Committee and Trial Steering Group etc.
In addition, random, in trial monitoring/audit will be undertaken by the Nurse Coordinator and Neurodevelopmental Assessment Coordinator. For example a selection of case report forms will be verified from each of the participating I2S2 NICUs. Random audits of neurodevelopmental assessments will be undertaken by Peter Willatts, an international expert in this field.

QUALITY CONTROL AND QUALITY ASSURANCE
The laboratories measuring the thyroid hormones and urinary iodine comply with national and international criteria for quality control.

Staff training
Each participating centre with responsibility for recruitment will have a dedicated I2S2 research nurse and a nurse coordinator will be based with the co-ordinating investigator in Dundee. Fiona Williams and Robert Hume have already visited each participating I2S2 NICU at least once, and described the rationale and trial approach for I2S2. At the start of the trial (figure 4), the nurse coordinator will visit each unit and go through the I2S2 procedures. Training and adherence to the trial protocol will be monitored and enforced in many ways. The nurse coordinator will visit each NICU twice per annum; in addition to two nurse training days; Fiona Williams/Robert Hume have resources for 5 visits to each participating I2S2 unit; there will be two meetings for the principal investigators and annual meetings for the I2S2 trial applicants. The nurse and neurodevelopment coordinators will be hold weekly telephone ‘meetings’ with the nurses and psychologists involved in I2S2. The programmes web site (www.npeu.ox.ac.uk/I2S2 and www.euthyroid.org) will give access to I2S2 documents, protocols and procedures. All research nurses employed by I2S2 will receive ICH GCP training. For additional monitoring information see ‘Procedures for monitoring compliance’ page 14.
Data

All case report forms will be sent by mail to the Clinical Trials Unit (NPEU), where they will be entered, verified and checked for completeness. Incomplete or implausible entries will be returned to the local I2S2 unit for amendment. Regular audits of data quality will be undertaken by the Clinical Trials Unit (NPEU), the nurse coordinator and neurodevelopment coordinator.

An I2S2 trial programmer at the Clinical Trials Unit (NPEU) will undertake regular statistical monitoring and will evaluate parameters as specified by the chief investigator.

ETHICS

The trial sponsor will ensure that I2S2 is conducted in accordance with the principles of the Declaration of Helsinki.

Venepuncture of infants in skilled hands is usually swift and without hazard. Blood sampling for the project will be co-ordinated to coincide as far as possible with routine venepuncture necessary for clinical care. Blood volumes necessary for the estimation of the three thyroid related hormones is 0.25ml and whenever possible we will use that in excess of requirements taken for routine clinical investigation.

Pain of venepuncture can be reduced in term infants by the use of Emla cream (a local anaesthetic agent) but this product is not recommended for use in preterm infants as it may be excessively absorbed through the thin skin of these infants with toxic effects.

We are aware of the special position of infants and children in clinical research, and have followed the guidelines of the Royal College of Paediatrics and Child Health UK and the Medical Research Council (UK) in the preparation of the research protocols.

DATA HANDLING AND RECORD KEEPING

That a particular mother and infant are participating in the I2S2 trial will be recorded in the respective clinical notes. Results arising from the trial and which may be relevant to the management of the mother or infant will be recorded in the clinical notes and in addition the relevant consultant will be informed of abnormal results. Personal information will be stored in a separate database from the main I2S2 database, and the two will be linked by unique numeric infant identifier. The link is necessary to allow follow-up and matching of Guthrie Card data to Case Report Forms. All data relating to a particular infant will be stored on a secure network, access to the network is by
individual password, which is regularly changed. The project is registered under the Data Protection Act UK 1998, 2002.

FINANCE AND INSURANCE
The study is funded by the Medical Research Council and insurance is covered by the University of Oxford’s insurance scheme.

PUBLICATION POLICY
The research will be published in high impact, peer reviewed, scientific journals. More general dissemination of the results will be achieved through publication of summary findings on our dedicated programme web page: www.euthyroid.org. There are no commercial or intellectual rights issues that would delay publication of results. Local principal investigators, trial grant holders and trial coordinators will be named authors on the principle publications arising from the trial provided they meet the authorship criteria used by most high impact peer reviewed journals see http://www.icmje.org/. Principle investigators in non-recruiting centres and other trial personnel with significant input to the running of the trial will be acknowledged by name/address in all publications. The CI should nominate/agree as appropriate authorship on all publications.

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