Health Economics Analysis Plan (HEAP)
Version 1.0

Induction of labour for predicted macrosomia 'The Big Baby Trial'	
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HEAP Amendments

Amendment No.	Date of Amendment	Date of Approval

Roles and Responsibilities:

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Table of Contents

1. Administrative information

This document describes the planned analysis of economic data within the Big Baby Trial (ISRCTN18229892). This Health Economics Analysis Plan (HEAP) should be read in conjunction with the Big Baby Statistical Analysis Plan and the Trial Protocol which provide in detail: the trial design and methods, amendments, documentation, oversight, roles and responsibilities, and the statistical plan of analysis of clinical and patient outcome measures.

2. Introduction

Shoulder dystocia is a complication of vaginal delivery where the fetal shoulder is stuck behind the mother's pubic bone delaying the birth of the body. Large-for-gestational age fetuses are at a greater risk of shoulder dystocia than smaller babies. Shoulder dystocia can lead to long-term complications for the baby such as permanent brachial plexus injury, hypoxic ischaemic encephalopathy and neonatal death, as well as complications for the mother, such as haemorrhage and third and fourth-degree tears and cervical/vaginal laceration. Apart from adverse maternal and perinatal effects, shoulder dystocia is also one of the most common reasons for litigation, with settlement of 250 cases from 2000 to 2010 having cost over £100 million, or approx. £400,000 per case.

3. Trial design

The aim of the Big Baby Trial is to investigate the potential benefits and harms of induction of labour in suspected large for gestational age fetuses at $38+^{0}$ to $38+^{4}$ weeks gestation and to see whether this mitigates the risk of shoulder dystocia as the fetus weighs less than at 40 weeks gestation. The Big Baby Trial is a prospective, individually randomised, multicentre trial of induction of labour at 38^{+0} to 38^{+4} weeks gestation versus standard care in women who have a fetus with an estimated fetal weight >90^{th} customised centile according to ultrasound scan at 35^{+0} to 38^{+0} weeks gestation. The recruitment for the trial was stopped on the 25^{th} November 2022 as recommended by the Data Monitoring Committee (DMC), as further recruitment was not expected to affect the outcome. A total of 2,895 participants were recruited.

There is a parallel cohort study for women who decline randomisation. The objective of this cohort group is to confirm generalisability of both the baseline data and the incidence of shoulder dystocia and will comprise of two sub-groups. One sub-group will be for women requesting a planned caesarean section, and one sub-group is for women not planning a caesarean section.

The primary objective is to determine the effectiveness of induction at $38+^{0}$ to $38+^{4}$ weeks gestation in reducing the incidence of shoulder dystocia.

The secondary objectives are to evaluate whether: standard care increases the risk of neonatal birth injury, induction increases the risk of infant complications related to prematurity and induction increases the risk of birth injury to the mother.

4. Health Economics Objectives

The objective of the health economic evaluation is to estimate the cost-effectiveness of labour induction at $38+^{0}$ to $38+^{4}$ weeks gestation versus standard care in women with large for gestational age fetuses using resource use, outcomes and health-related quality-of-life data from baseline to 6 months. The within-trial economic analysis will be conducted under the intention-to-treat (ITT)

principle (in line with the main trial, the very few non-eligible randomised women due to incorrect readings of the estimated fetal weight centile, and using the ultrasound scan report prior to 35+0 days will be included in the base-case analysis), presenting resource use, cost, outcome and health-related quality-of-life findings by trial arm. This requires that study participants are analysed according to their treatment assignment regardless of actual treatment received. Attention will be paid to levels of completeness of data, identifying issues and potential remedies.

5. Analysis

In accordance with this HEAP, a prospective economic evaluation of the Big Baby Trial will be conducted from a National Health Service (NHS) and personal social services (PSS) perspective for the base-case analysis. Costs and resource use will be collected for both arms for the 6-month follow-up period of the trial. An incremental cost-effectiveness analysis will be performed. In the baseline analysis, the economic evaluation will be expressed as the incremental cost per case of shoulder dystocia prevented and in a secondary analysis, the economic evaluation will be expressed as the incremental cost per quality adjusted life year (QALY) gained. The findings of this economic evaluation will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of health economic evaluations.[1]

5.1 Resource use and costs

Within trial data will be collected on the health service resources used in the treatment of each woman and infant during the period between randomisation and hospital discharge. The trial data collection instruments and data extracted from routine health systems will record the duration and intensity of intrapartum, postnatal and neonatal care, based on standard criteria for level of care, as well as maternal and neonatal complications. Details of the resources associated with induction of labour and normal or alternative modes of delivery, as well as staff time, tests, procedures, drugs and equipment will be recorded.

For example, some of the resources used which will be recorded include:

a) For the woman:

1. Any unscheduled hospital visits prior to delivery,
2. Induction of labour,
3. Normal or alternative modes of delivery including ventouse, forceps and caesarean section (planned or emergency),
4. Date and time when the woman was admitted to hospital, including time spent on labour ward, and the date and time when the woman was discharged from hospital,
5. Drugs such as pain relief and/or antibiotic use, and
6. Complications of labour or any adverse events.

b) For the baby:

1. Type of care received such as intensive care, high dependency, or special care,
2. Transfer of baby to another hospital,
3. Any neonatal procedures or tests, and
4. Any adverse events or medications.

In addition, questionnaires completed by study participants at two and six months will provide profiles of the woman's and baby's hospital readmissions, hospital outpatient visits, accident and emergency attendances, medication use, and community health and social service resource use.

Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. We will use appropriate national sources such as the Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) annually, NHS reference costs and the British National Formulary.[2-4]

5.2 Outcomes

The within trial analysis will report separate outcomes for the woman and the baby.

For the baby, the primary outcome of the within-trial economic evaluation will be cases of shoulder dystocia prevented (measured during birth admission).

For the woman, the primary outcome of the within-trial economic evaluation will be the QALY (measured up to six months) as recommended in the National Institute of Health and Care Excellence (NICE) reference case.[5] This will allow an incremental cost-effectiveness ratio for labour induction versus standard care in women with large for gestational age fetuses to be generated in the form of incremental cost per QALY gained. The QALY is a measure that combines quantity and health-related quality of life lived into a single metric, with one QALY notionally equating to one year of full health. QALY estimates will be generated by combining length (survival) and health-related quality of life data from participants for the period covering the trial time horizon. The QALY estimates will be derived using the area-under-the-curve (AUC) approach and linear extrapolation of health utilities.[6] Since AUC estimates are predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates will be adjusted for baseline scores within regression analyses. Health-related quality of life outcomes delineated by the EQ-5D-5L descriptive system will be converted into health-state utilities indexed at 0 and 1, where 0 represents death and 1 represents full health.

To calculate QALYs, women will be asked to complete the EuroQol (EQ) questionnaire: a patient-completed two-page questionnaire consisting of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS) at baseline, 2 months and 6 months. The descriptive system includes five questions addressing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each dimension assessed at five levels: from no to extreme problems. The EQ-5D-5L responses will be converted into health utilities using the NICE recommended value set for England. The current NICE position as it stands is to use the Hernández Alava et al algorithm where EQ-5D-5L responses should be mapped or cross-walked onto the EQ-5D-3L.[7]

5.3 Data quality and cleaning

All data relevant to the health economics analysis will examined for data quality. All questionnaires are being checked on return to the trial office. Any questionable data will be queried with trial staff. Descriptive statistics will be calculated for each value with outliers being critiqued. Missing data will be examined and tabulated for each economic component.

5.4 Analysis

5.4.1 Missing data

Missing data will be examined and tabulated for each economic component. We will use multiple imputation (MI), to account for missing data. MI provides unbiased estimates of treatment effect if data are missing at random: this assumption will be explored in the data, for example by using logistic regression for missingness of costs, outcomes and QALYs against baseline variables.[8] MI generates a series of datasets with each dataset replacing missing values with sampled values. For example, MI replaces each missing observation with a set of plausible imputed values, taken from the predictive distribution of the missing data given the observed data.[9] Supportive sensitivity analyses will include participants with complete data and explore the impact of imputation.

5.4.2 Base-case analysis

Cost-effectiveness results for the base-case analysis will be obtained by using regression methods such as bivariate regression using seemingly unrelated regression equations appropriate for the trial data. The requirement of regression methods is justified by the likely imbalance of baseline values between the two trial arms, which needs to be accounted for in the estimation process.[10] Failure to account for such an imbalance with inevitably lead to biased cost-effectiveness estimates. Non-parametric bootstrap methods provide unbiased cost-effectiveness estimates only if baseline covariates are balanced between the trial arms.[11] Bootstrapping jointly resamples costs and outcomes from the original data with replacement (maintaining the sample correlation structure) to create a new bootstrap sample from which a change in costs and outcomes are estimated.

An incremental cost-effectiveness ratio (ICER) will be estimated as the difference between treatments in mean total costs divided by the difference in mean total QALYs. Value-for-money will be determined by comparing the ICER with a threshold value, typically the NICE threshold for British studies, of £20k-30k/QALY.[5] This represents the willingness to pay for an additional QALY, and lower values than the threshold could be considered cost-effective for use in the NHS. In the baseline analysis, the economic evaluation will be expressed as the incremental cost per case of shoulder dystocia prevented, and in a secondary analysis, the economic evaluation will be expressed in terms of an incremental cost per QALY gained using the maternal health-related quality of life assessments. For both analyses, the imputed within trial incremental cost and outcomes, will be adjusted for trial baseline covariates.

5.4.3 Sensitivity and subgroup analyses

We will also undertake several sensitivity analyses to explore uncertainties around key parameters in the economic analyses. These sensitivity analyses may include:

1. Basing the economic estimates on complete cases;
2. Exploring utility estimation using the van Hout crosswalk algorithm;[12]
3. Using alternative cost assumptions in the analysis;
4. Adopting a societal perspective (if relevant information is available).

Any subgroup analyses will be those mirrored in the SAP, for example, using a modified ITT approach.

5.4.4 Longer-term analysis – use of economic modelling

Should costs and outcomes not converge within the six-months, economic modelling will be undertaken to project the lifetime clinical and economic consequences of induction of labour at $38+^{0}$-$38+^{4}$ weeks' gestation of fetuses that are suspected to be large for gestational age and will be expressed as the incremental cost per QALY gained. The long-term economic evaluation will require the application of decision-analytic methods and estimation of subsequent health status and health care costs over the lifetime of an adversely affected compared to a healthy mother and infant (combined mother-child dyad).

The decision-analytic model will be framed by the potential sequelae of induction of labour in this clinical context, the appropriate model type (e.g. Markov model, discrete-event simulation) and the appropriate analytical framework (e.g. cohort analysis, individual-level simulation). The decision-analytic model will be populated, in part, using data collated by economic questionnaires completed by the trial participants at two months and six months postpartum, and supplemented where necessary using the best available information from the published literature, expert opinion together with stakeholder consultations. Given the methodological limitations surrounding preference-based outcomes measurement in young children, it will be necessary to model the relationship between developmental outcomes in the children and multi-attribute utility measures. This will draw, where available, upon longitudinal datasets containing economic measures that are held by the co-applicant team.

Long-term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom.[5] We will use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for incremental cost-effectiveness ratios. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. In addition, cost-effectiveness acceptability curves will be constructed using the net-benefit approach.

5.4.4 Cohort analysis

In a separate economic analysis that will be based on individual-level observations of costs and outcomes collected within the context of the RCT and the parallel cohort study, we will also aim to compare the costs and effects of the trial interventions with a policy of elective caesarean section in women that meet the trial inclusion criteria.

6. References

1. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *International Journal of Technology Assessment in Health Care* 2022; 38.
2. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary No. 81, March-September 2021*. London: BMA and PRS, 2021.
3. Jones K and Burns A. *Unit Costs of Health and Social Care 2021*. University of Kent, Canterbury: Personal Social Services Research Unit, 2021.
4. Department of Health. NHS reference costs 2020 to 2021, https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (2021, accessed 15/11/2022 2022).
5. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, https://www.nice.org.uk/process/pmg36 (2022, accessed 15/11/2022 2022).
6. Glick HA, Doshi JA, Sonnad SS, et al. *Economic evaluation in clinical trials*. OUP Oxford, 2014.
7. Alava MH, Pudney S and Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. *Policy Research Unit in Economic Evaluation of Health and Care Interventions: Universities of Sheffield and York* 2020.
8. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II—an ISPOR Good Research Practices Task Force report. *Value in Health* 2015; 18: 161-172.
9. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* 2009; 338: b2393.
10. Manca A, Hawkins N and Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health economics* 2005; 14: 487-496.
11. Gomes M, Ng ES-W, Grieve R, et al. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Medical Decision Making* 2012; 32: 350-361.
12. Van Hout B, Janssen M, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health* 2012; 15: 708-715.

7. Dummy tables

Table 1 illustrates the presentation of completeness of data; Table 2 and 3 illustrates the presentation of quality-of-life, resource and cost data for complete cases and complete cases with imputed data for missing/withdrawals, respectively; Table 4 cost-effectiveness results.

Table 1: Completeness of data

	Induction of labour		**Standard care**		**Total**	
	n	**(%, N)**	**n**	**(%, N)**	**n**	**(%, N)**
OUTCOMES						
EQ-5D-5L utility scores Baseline 2 months 6 months						
RESOURCE USE - MOTHER						
Hospital visits prior to delivery						
Labour ward triage/assessment area Maternity unit General ward						
During delivery and initial time spent in hospital						
Hospital admissions including admission date, time spent in labour ward and discharge date						
Induction of labour						
Mode of delivery Normal Ventouse Forceps Caesarean (planned) Caesarean (emergency)						
Medications Pain relief Antibiotic use						
Complications of labour Any adverse events						
Since discharge after birth						
Hospital admissions Outpatient visits Medications/drugs						
GP surgery appointment GP out of hours Walk-in-health care centre visit Practice nurse appointment Community nurse appointment Physiotherapy appointment Telephone calls to NHS 111 Social worker appointment						
RESOURCE USE - BABY						
Type of care received Intensive care High dependency						

Special care Transitional care Normal care			
Transfers Transfer to another hospital			
Neonatal procedures or tests			
Any adverse events or medications			
Since discharge after birth			
Hospital admissions General paediatric ward High dependency unit Neonatal unit Post-natal ward Outpatient visits Medications/drugs			
GP clinic visit GP out of hours Walk-in-health care centre visit Practice nurse appointment Midwife visit Health visitor contacts Community nurse appointment Physiotherapy appointment Community paediatrician appointment Telephone calls to NHS 111 Social worker visit			

Table 2 Health-related quality of life outcomes, resource use and cost (complete cases)

	Induction of labour		Standard care		Mean difference	p-value	Bootstrap 95% CI
	mean	(SD)	mean	(SD)			
OUTCOMES							
EQ-5D-5L utility scores Baseline 2 months 6 months							
RESOURCE USE - MOTHER							
Hospital visits prior to delivery							
Labour ward triage/assessment area Maternity unit General ward							
During delivery and initial time spent in hospital							
Hospital admissions including admission date, time spent in labour ward and discharge date							
Induction of labour							
Mode of delivery Normal Ventouse Forceps Caesarean (planned) Caesarean (emergency)							
Medications Pain relief Antibiotic use							
Complications of labour Any adverse events							
Since discharge after birth							
Hospital admissions Outpatient visits Medications/drugs							
GP surgery appointment GP out of hours Walk-in-health care centre visit Practice nurse appointment Community nurse appointment Physiotherapy appointment Telephone calls to NHS 111 Social worker appointment							
RESOURCE USE - BABY							
Type of care received Intensive care High dependency Special care Transitional care Normal care							
Transfers							

Transfer to another hospital					
Neonatal procedures or tests					
Since discharge after birth					
Hospital admissions General paediatric ward High dependency unit Neonatal unit Post-natal ward Outpatient visits Medications/drugs					
GP clinic visit GP out of hours Walk-in-health care centre visit Practice nurse appointment Midwife visit Health visitor contacts Community nurse appointment Physiotherapy appointment Community paediatrician appointment Telephone calls to NHS 111 Social worker visit					

Table 3 Health-related quality of life outcomes, resource use and cost (with imputed data)

	Induction of labour		Standard care		Mean difference	p-value	Bootstrap 95% CI
	mean	(SD)	mean	(SD)			
OUTCOMES							
EQ-5D-5L utility scores Baseline 2 months 6 months							
RESOURCE USE - MOTHER							
Hospital visits prior to delivery							
Labour ward triage/assessment area Maternity unit General ward							
During delivery and initial time spent in hospital							
Hospital admissions including admission date, time spent in labour ward and discharge date							
Induction of labour							
Mode of delivery Normal Ventouse Forceps Caesarean (planned) Caesarean (emergency)							
Medications Pain relief Antibiotic use							
Complications of labour Any adverse events							
Since discharge after birth							
Hospital admissions Outpatient visits Medications/drugs							
GP surgery appointment GP out of hours Walk-in-health care centre visit Practice nurse appointment Community nurse appointment Physiotherapy appointment Telephone calls to NHS 111 Social worker appointment							
RESOURCE USE - BABY							
Type of care received Intensive care High dependency Special care Transitional care Normal care							
Transfers							

Transfer to another hospital					
Neonatal procedures or tests					
Since discharge after birth					
Hospital admissions General paediatric ward High dependency unit Neonatal unit Post-natal ward Outpatient visits Medications/drugs					
GP clinic visit GP out of hours Walk-in-health care centre visit Practice nurse appointment Midwife visit Health visitor contacts Community nurse appointment Physiotherapy appointment Community paediatrician appointment Telephone calls to NHS 111 Social worker visit					

Table 4 Cost-effectiveness results

	Mean incremental costs, £ (95% CI)	**Mean incremental QALYs (95% CI)**	**ICER**	**Probability of cost-effectiveness**	**Incremental net monetary benefit**
Base case analysis					
Sensitivity analyses					
Unadjusted analysis					
Complete case analysis					