REACT Health Economics Analysis Plan

Objective of analysis plan

The goal of the economic evaluation is to estimate the incremental cost-effectiveness of real-time continuous glucose monitoring in neonatal intensive care. Incremental cost-effectiveness will primarily be expressed as the incremental cost per additional case of adequate glucose control. The economic evaluation will be conducted prospectively alongside the Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (REACT) randomised controlled trial (RCT). The purpose of this health economics analysis plan is to outline an explicit framework of methods that will be used to analyse the health economic data in a robust manner.

1. Introduction

The REACT trial aims to evaluate the efficacy, safety and utility of real time continuous glucose monitoring (CGM) for newborn babies cared for in neonatal intensive care units (NICUs). This is a multicentre randomised controlled trial (RCT) of real time continuous glucose monitoring (CGM) with a paper based algorithm compared to standard management. The experimental intervention involves real time continuous glucose monitoring (CGM) whereas usual care (control group) involves standard clinical management with continuous glucose monitoring data blinded to the clinical team. The study will be carried out in 200 preterm infants ≤1200 g and ≤24 hours of age through a minimum of five level three neonatal intensive care units (NICUs) in Europe. The primary clinical outcome is the percentage of time sensor glucose (SG) falls within the target range of 2.6-10mmol/l during the first 6 days of life. Secondary outcomes include efficacy relating to glucose control, utility including staff acceptability, safety outcomes relating to incidence and prevalence of hypoglycaemia. Clinical data will be collected until 36 weeks corrected gestational age.

1.1 General principles for economic evaluation

1.1.1. Perspective

Following recent National Institute for Health and Care Excellence (NICE) recommendations [1], the primary analysis will adopt a National Health Service (NHS) and personal social services (PSS) perspective.

1.1.2. Time horizon and follow-up

Clinical data will be collected until 36 weeks corrected gestational age. Study participants will be hospitalised in a NICU and it is expected that the majority of participants will still be in the hospital at the 36 week gestation assessment. Long term decision modelling will be considered if the study interventions are expected to impact on longer term costs and outcomes.

1.1.3. Discounting

For the trial-based analysis, as the trial is following up patients for less than one year, there is no need to discount costs or measures of health outcome. If longer-term decision modelling is performed, then costs and outcome measures will be discounted at 3.5% per annum beyond the first year of life [2].

1.1.4. Potential hierarchical data structure

Although participants are randomised at the individual level, each individual belongs to a centre (hospital unit). Patient costs and outcomes may vary according to the centre they belong to. To reduce the impact of this, the randomisation procedure stratifies for clinical centre. Despite that, an inherent correlation in costs and outcomes in individuals in the same centre may exist, which may not be present in individuals across centres. In other words, observations may be clustered within centres.

The implication of clustering in data in multicentre RCTs is that cost-effectiveness estimates may vary between centres [3]. In the presence of clustering, the trial data will acquire a hierarchical structure. This makes standard ordinary least squares (OLS) regression methods inappropriate for the analysis due to violations in their assumptions. The extent to which OLS methodology will provide inappropriate inferences depends on the level of clustering in the data, which can be measured using the intra-class, or intra-cluster, correlation coefficient (ICC) [4]. ICC is measured as the proportion of between-cluster variance divided by the total variance (between- and within- cluster variance). The values that the ICC takes ranges from zero to one, with values approximately more than 10% suggesting a high degree of clustering [4].

For the purposes of our analyses, the ICC will be estimated. If ICC is estimated at 10% or more [3], a hierarchical model will be used for the cost-effectiveness analysis (CEA). If not, standard regression methods will be employed.

1.2. Missing data

Missing data will be addressed within the health economics analysis. Missing data are a common occurrence within RCTs and it is necessary to address them in a standardised principled manner. Within the health economic literature, RCTs have been subject to particular criticism for failing to use appropriate methods to address missing data [5]. Descriptive analyses of missing data will be carried out (missing data patterns using graphical tools, association between missing data and baseline variables, association between missing data and outcomes). The results of the descriptive analysis will be discussed by the trial team to infer possible reasons for missing data and inform the assumption about the missing data mechanism.

Multiple imputation will be used to impute missing data and avoid biases associated with complete case analysis. Missing data may be a particular issue for costs and the health outcome measures of interest. Multiple imputation using Markov chain Monte Carlo (MCMC) and predicted mean matching (PMM) will be carried out on the main outcome measure. PMM is a semi-parametric imputation approach, and generally performs better than linear regression despite the similarities in method.

The missing data mechanism will fall under one of the following: categories missing completely at random (MCAR), covariate-dependent missing completely at random (CD-MCAR), missing at random (MAR) or missing not at random (MNAR) [6]. In general, multiple imputation is not recommended when data are MNAR.

It is recommended to include all the variables used in the analysis model for multiple imputation [7]. Inclusion of explanatory variables enables the analyst to use multiple imputation by chained equations (MICE). Missing values in variable x are replaced by draws from the posterior predictive distribution of x and imputed using the values of other explanatory variables [7].

2. Outcomes

2.1. Primary outcome

The primary clinical outcome measure for this study is percentage of time sensor glucose falls in the target range of 2.6-10mmol/l within the first 6 days of life in the trial participants. For the purposes of the economic evaluation, cost-effectiveness will primarily be expressed in terms of incremental cost per additional case of adequate glucose control during the first six days of life. Given the data from the REACT feasibility study and external clinical evidence, adequate glucose control based on multiple glucose readings for a baby is not straightforward to define. For the purpose of the primary cost-effectiveness analysis, adequate glucose control will be defined as 80% of readings within the target range. However, a number of sensitivity analyses will also be performed that will vary the threshold for number of readings falling within the target range of 2.6–10 mmol/L; adequate glucose control will therefore be re-estimated at alternative thresholds of 60%, 70%, 90% and 100% of readings falling within the target range. Cost-utility analysis using a preference-based measure, for example quality-adjusted life years (QALYs), will not be performed because of the methodological constraints surrounding utility measurement in newborn babies.

2.2. Secondary outcomes

The secondary clinical outcome measures for this study are exploratory outcomes such as death, necrotising enterocolitis (NEC), and bronchopulmonary dysplasia (BPD). Cost-effectiveness analyses using these secondary clinical outcome measures will also be presented within the incremental cost-effectiveness ratio (ICER) and expressed in terms of incremental cost per death averted, incremental cost per case of NEC averted, and incremental cost per case of BPD averted, using imputed costs and valued over a time horizon extending to 36 weeks corrected gestation.

3. Resource use and costing

The purpose of this section is to outline how all resource inputs and costs will be captured, measured and valued. The primary analysis will focus on direct intervention and broader healthcare and PSS costs.

3.1. Direct intervention costs

Direct intervention costs are the costs associated with the application of the two comparator interventions, namely CGM with paper algorithm and standard care with blinded CGM data collection. In the intervention arm, babies will have glucose sensors inserted, Enlite® (Medtronic) that will be linked to a Medtronic MiniMed® 640G system and will be calibrated with point of care blood glucose levels, and data will be collected using CGM. The management of glucose control will be guided by the monitor's CGM display. As a result, the costs of the intervention include the cost of the Enlite sensor (MiniMed system), the cost associated with fitting the device to patients (hospital staff time), and the costs associated with any changes required to Enlite sensors (e.g. removal of sensor). The resource use associated with the direct intervention costs will be captured prospectively. Table 1 presents an outline of the types of resource use that will be measured, how resource use will be captured and the source from which unit costs will be obtained.

Table 1: Direct intervention costs

Resource type	**Resource use**	**Unit cost source**
Glucose monitoring		
Enlite sensor (MiniMed system)	Cost of Enlite sensor	Manufacturers
Enlite sensor insertion and set up of MiniMed	Staff time	Personal and Social Services Unit (PSSRU) Cost Compendium, University of Kent
Sensor Glucose Monitoring	Staff time	PSSRU Cost Compendium

Removal of sensor	Staff time	PSSRU Cost Compendium
Standard care		
Standard care (Nova StatStrip® & Nova meters)	Cost of Nova Biomed devices	Manufacturers
Standard care monitoring	Staff time	PSSRU Cost Compendium

3.2 Broader healthcare and PSS costs

In addition, we will prospectively measure length of stay by intensity of hospital care during the trial follow-up period, as well as additional investigations, procedures, surgical interventions, medications, and hospital transfers. Healthcare resource use will be stratified by period of follow-up and will primarily be captured through the trial case report forms completed daily during the first week of life and then at 36 weeks corrected gestation. The different types of resource categories for broader healthcare costs and their respective sources of unit costs are presented in Table 2.

Table 2: Broader healthcare and PSS costs

Resource type	Resource use	Unit cost source
Length of stay by level of care (e.g. intensive care, special care)	Staff salaries, on-costs, equipment, consumables and revenue and capital overheads	NHS Reference Costs
Medications	Cost of medications	BNF
Investigations	Staff time to deliver the investigations, associated costs	NHS Reference Costs
Medical (surgical) treatment	Staff time to deliver treatment, associated costs	NHS Reference Costs
Blood transfusion products	Cost of blood transfusion products	NHS Blood and transplant price list
Surgical procedures	Staff time to deliver the interventions, associated costs	NHS Reference Costs, PSSRU Cost Compendium
Mode of discharge	Mode and distance of transfer or discharge to home	NHS Reference Costs, PSSRU Cost Compendium, and the Automobile Association

4. Statistical analysis

4.1. Base case analysis

Cost-effectiveness results for the base case analysis will be obtained by using regression methods appropriate for the trial data. A generalised linear model (GLM) will be used to estimate total costs and the primary outcome. The GLM method helps overcome problems associated with skewed data [9] and is widely used in paediatric clinical trials [10]. After conducting statistical tests, such as the Pregibon link test and Pearson correlation test, on cost data, relevant family and link functions will be chosen as appropriate for the GLM estimator for the trial data. Such models consider a range of alternative distributions for the outcomes of interest (e.g. normal, lognormal, gamma and beta) so that distributions more closely reflecting the trial data can be chosen. We will apply such methods and consider different measures of model fit (Akaike Information Criterion, Bayesian Information Criterion) and diagnostics plots to identify the regression model that best reflects the REACT trial data. Mean costs and outcomes for each trial group will be estimated, together with the mean incremental cost-effectiveness ratio (ICER). Cost-effectiveness will be estimated using a bootstrap method to minimize sampling uncertainty. Nonparametric bootstrap methods

generate multiple replications of the statistic of interest by sampling replications from the original data [9, 11]. In order to express uncertainty around ICERs, and to show results across a range of cost-effectiveness thresholds, cost effectiveness acceptability curves (CEACs) generated on the basis of bootstrapped sample data will be used [12, 13]. These curves show the probability that a particular intervention is cost-effective at different levels of the cost-effectiveness threshold based upon modelled variation in patient outcomes observed [14].

Current methodological guidance suggests cost-effectiveness thresholds for treatments of between £20,000 and £30,000 per quality adjusted life year (QALY) [15]. There are currently no published cost-effectiveness thresholds for the primary and secondary clinical outcomes of the REACT trial. Hence, we will search the stated and revealed preference literature to identify any external evidence with respect to population preferences for health changes associated with adequate glucose control and for health changes associated with the secondary clinical outcomes, and use this evidence to inform a range of threshold values in our assessment of decision uncertainty.

4.2 Sensitivity and subgroup analyses

A range of sensitivity analyses surrounding aspects of the economic evaluation will be used to explore the effects of uncertainty on the estimates of cost-effectiveness. These will include re-estimating incremental cost-effectiveness using alternative thresholds of 60%, 70%, 90% and 100% of glucose readings falling within the target range of 2.6–10 mmol/L. Heterogeneity in cost-effectiveness estimates will be explored by including baseline variables considered as potential effect modifiers in the cost-effectiveness model. The sub group analysis will be carried out for a treatment interaction effect with the following baseline variables: centre, and gestational age (<26 weeks, ≥26 weeks).

4.3 Long term economic modelling

The costs and benefits of the comparator interventions may extend beyond the follow up period of the trial. If this is the case in the REACT trial, a long term economic model will be adopted. The health economists will work with the clinical team to develop a long term clinical pathway for patients. This pathway will be used to highlight the evidence requirements in order to populate the cost-effectiveness model. The decision model will utilise within trial data in conjunction with external data to inform parameters. Costs and outcomes arising after the first year of life will be discounted at 3.5% per annum. A full probabilistic sensitivity

analysis will be conducted to assess the effects of parameter uncertainty and CEACs will be generated to characterise decision uncertainty, i.e. uncertainty surrounding the value of the cost-effectiveness threshold.

5. Dummy tables

Table 3 illustrates the reporting of completeness of health economic data; Table 4 illustrates the presentation of final estimates of resource use data by trial arm and follow-up period; Table 5 summarises the unit cost values for resource inputs; Table 6 summarises cost differences between trial arms by follow-up period and resource input; Table 7 summarises cost differences between trial arms by follow-up period and overall cost category; and Table 8 summarises how the final cost-effectiveness analysis will be presented.

Table 3: Completeness of data used for health economic evaluation

	Items	Intervention n (%)	Control n (%)	Total n (%)
Enlite sensor (MiniMed system)	MiniMed 640G Guardian™ Link transmitter Generation Enlite single sensor MMT-7008			
Glucose Monitoring	Enlite sensor insertion Enlite sensor Monitoring Enlite sensor Removal			
Point of care testing – used to calibrate MiniMed 640G	Nova StatStrip			
Length of stay	Intensive care High dependency care Special care Transitional care Other			
Medications	Inotropes Antibiotics Caffeine Morphine Corticosteroids Insulin			
Investigations	Cranial Ultrasound Scan Other Ultrasound Scan CT scan			

	X-ray EEG MRI ECHO ECG Other			
Blood transfusion products	Platelets Red Blood Cells Fresh Frozen Plasma Other			
Medical (surgical) treatment	Lumbar Punctures Ventricular Taps Long Lines Other			
Surgical procedures	VP shunts Surgical Procedures for Central Access Interventions for ROP Treatment Other			
Mode of discharge	Air ambulance Road			
Destination of discharge	NICU different hospital PICU Special care General Paediatrics Home Other			

Table 4: Mean resource use values by trial arm

	Unit	Items	Intervention Mean (SE)	Control Mean (SE)	Total Mean (SE)
Enlite sensor (MiniMed system)	**Quantity used**	MiniMed 640G Guardian Link transmitter Generation Enlite single sensor MMT-7008			
Glucose Monitoring	**Number of activities**	Enlite sensor insertion Enlite sensor monitoring Enlite sensor removal			
Point of care testing – used to calibrate MiniMed 640G	**Quantity used**	Nova StatStrip			
Length of stay	**Days**	Intensive care High dependency care Special care Transitional care Other			
Medications	**Quantity used**	Inotropes Antibiotics Caffeine Morphine			

		Corticosteroids Insulin			
Investigations	**Quantity used**	Cranial Ultrasound Scan Other Ultrasound Scan CT scan X-ray EEG MRI ECHO ECG Other			
Blood transfusion products	**Quantity used**	Platelets Red Blood Cells Fresh Frozen Plasma Other			
Medical (surgical) treatment	**Quantity used**	Lumbar Punctures Ventricular Taps Long Lines Other			
Surgical procedures	**Quantity used**	VP shunts Surgical Procedures for Central Access Interventions for ROP Treatment			

		Other			
Mode of discharge	**Quantity used**	Air ambulance Road			
Destination of discharge	**Quantity used**	NICU different hospital PICU Special care General Paediatrics Home Other			

Table 5: Unit costs of resource use items (£, 2017 prices)

	Items	Unit cost Sources
Enlite sensor (MiniMed system)	MiniMed 640G Guardian Link Generation Enlite single sensor MMT-7008	
Glucose Monitoring	Enlite sensor insertion Enlite sensor Monitoring Enlite sensor Removal Nova Strip Meter – for calibration of 640G device	
Length of stay	Intensive care High dependency care Special care Transitional care Other	
Medications	Inotropes Antibiotics Caffeine Morphine Corticosteroids Insulin	
Investigations	Cranial Ultrasound Scan Other Ultrasound Scan CT scan X-ray	

	EEG MRI ECHO ECG Other	
Blood transfusion products	Platelets Red Blood Cells Fresh Frozen Plasma Other	
Medical (surgical) treatment	Lumbar Punctures Ventricular Taps Long Lines Other	
Surgical procedures	VP shunts Surgical Procedures for Central Access Interventions for ROP Treatment Other	
Mode of discharge	Air ambulance Road	
Destination of discharge	NICU different hospital PICU Special care General Paediatrics Home Other	

Table 6: Cost differences between trial arms by follow-up period and resource input (£, 2017 prices)

Cost (intervention period - 1 to 7 days)	Items	Intervention Mean SE	Control Mean SE	Total Mean SE	Mean difference	Bootstrap 95% confidence interval
Enlite sensor (MiniMed system)	MiniMed™ 640G Guardian™ 2 Link Generation Enlite™ single sensor MMT-7008B					
Glucose Monitoring	Enlite sensor insertion Enlite sensor Monitoring Enlite sensor Removal Nova Strip Meter – for calibration of 640G device					
Length of stay	Intensive care High dependency care Special care Transitional care Other					
Medications	Inotropes Antibiotics Caffeine					

	Morphine Corticosteroids Insulin					
Investigations	Cranial Ultrasound Scan Other Ultrasound Scan CT scan X-ray EEG MRI ECHO ECG Other					
Blood transfusion products	Platelets Red Blood Cells Fresh Frozen Plasma Other					
Medical (surgical) treatment	Lumbar Punctures Ventricular Taps Long Lines Other					
Surgical procedures	VP shunts Surgical Procedures for Central Access Interventions for ROP					

	Treatment Other					
Mode of discharge	Air ambulance Road					
Total cost						
Cost (Follow-up - 8 days to 36weeks)		**Intervention**	**Control**	**Total**	**Mean difference**	**Bootstrap 95% confidence interval**
	Items	**Mean SE**	**Mean SE**	**Mean SE**		
Length of stay	Intensive care High dependency care Special care Transitional care Other					
Medications **Investigations**	Insulin Cranial Ultrasound Scan Other Ultrasound Scan CT scan X-ray EEG MRI ECHO ECG Other					
Blood transfusion products	Platelets Red Blood Cells					

	Fresh Frozen Plasma Other					
Medical (surgical) treatment	Lumbar Punctures Ventricular Taps Long Lines Other					
Surgical procedures	VP shunts Surgical Procedures for Central Access Interventions for ROP Treatment Other					
Mode of discharge	Air ambulance Road					
Total cost						
Cost (Entire follow-up period)		**Intervention**	**Control**	**Total**	**Mean difference**	**Bootstrap 95% confidence interval**
	Items	**Mean SE**	**Mean SE**	**Mean SE**		
Enlite sensor (MiniMed system)	MiniMed™ 640G Guardian™ 2 Link Generation Enlite™ single sensor MMT-7008B					
Glucose Monitoring	Enlite sensor insertion					

	Enlite sensor Monitoring Enlite sensor Removal Nova Strip Meter – for calibration of 640G device					
Length of stay (days)	Intensive care High dependency care Special care					

	Transitional care Other					
Medications	Inotropes Antibiotics Caffeine Morphine Corticosteroids Insulin					
Investigations	Cranial Ultrasound Scan Other Ultrasound Scan CT scan X-ray EEG MRI ECHO ECG Other					
Blood transfusion products	Platelets Red Blood Cells Fresh Frozen Plasma Other					
Medical (surgical) treatment	Lumbar Punctures Ventricular Taps Long Lines Other					

Surgical procedures	VP shunts Surgical Procedures for Central Access Interventions for ROP Treatment Other					
Mode of discharge	Air ambulance Road					
Total cost						

Table 7: Cost differences between trial arms by follow-up period and cost category (£, 2017 prices)

	Items	Intervention Mean SE	Control Mean SE	Total Mean SE	Mean difference	Bootstrap 95% confidence interval
Cost (intervention period - 1 to 7 days)						
Cost (Sensor) **Cost (Monitoring)** **Cost (Length of stay)** **Cost (Medications)** **Cost (Investigation)** **Cost (Blood transfusion products)** **Cost (Medical treatment)** **Cost (Surgical procedures)** **Cost (Mode of discharge)** **Total cost**						
Cost (Follow-up - 8 days to 36weeks)						
Cost (Length of stay) **Cost (Medications)** **Cost (Investigation)** **Cost (Blood transfusion products)** **Cost (Medical treatment)** **Cost (Surgical procedures)**						

Cost (Mode of discharge) **Total cost**						
Cost (Entire follow-up period)						
Cost (Sensor) **Cost (Monitoring)** **Cost (Length of stay)** **Cost (Medications)** **Cost (Investigation)** **Cost (Blood transfusion products)** **Cost (Medical treatment)** **Cost (Surgical procedures)** **Cost (Mode of discharge)** **Total cost**						

Table 8: Results of cost effectiveness analyses

	ICER* (95%CI)	NMB** (95%CI)
Base case (Incremental cost per additional case of adequate glucose control)		
Imputed costs and cases of adequate glucose control (80% threshold), covariate adjusted		
Sensitivity analyses		
Complete case attributable costs and cases of adequate glucose control (80% threshold)		
Imputed costs and cases of adequate glucose control (60% threshold), covariate adjusted		
Imputed costs and cases of adequate glucose control (70% threshold), covariate adjusted		
Imputed costs and cases of adequate glucose control (90% threshold), covariate adjusted		
Imputed costs and cases of adequate glucose control (100% threshold), covariate adjusted		
Sub-group analysis		
Stratification by centre		
Stratification by gestational age at birth		
Secondary analyses		
Imputed costs and cases of NEC averted, covariate adjusted		
Imputed costs and cases of death averted, covariate adjusted		
Imputed costs and cases of BPD averted, covariate adjusted		

*ICER denotes incremental cost-effectiveness ratio. **NMB denotes net monetary benefit.

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