Health Economics Analysis plan

CRAFFT – Children's Radius Acute Fracture Fixation Trial

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Health Economist: _____ date: __12/05/2021____

Senior Health Economist: _____ date: __12/05/2021__

Chief Investigator: _____date: __06/10/2021__

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2 Administrative information

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

3 Background

Approximately 20-30% of children in the United Kingdom (U.K.) attend accident and emergency (A&E) every year [1]. Of these, 9% constitute a fracture with up to 25% of these being a distal radius fracture [1]. A recent Cochrane review [2] highlighted the different approaches to treating a distal radius fracture, elements of which are also the focus of this randomised clinical trial (RCT). Most fractures are treated non-surgically [3] which typically involves splinting the wrist with cast immobilisation. In more severe cases of distal radius fracture, where the fracture is displaced, treatment usually involves manipulation of the fracture, with or without the insertion of wires or a plate to hold the bone together, followed by a plaster cast. Such procedures require sedation or general anaesthesia [3] as well as use of hospital operating theatre facilities. Surgical treatment carries risks and costs associated with admission, anaesthesia and surgical complications.

The distal radius has remodelling capacity, due to the presence of growth plates which support bone growth [4]. In younger children with more growth remaining, the bone is able to self-correct considerable deformity from a fracture as the bone grows. There is therefore uncertainty if a fracture with a deformity can be treated in a cast, and allowed to grow straight, or if manipulation of the fracture should routinely occur.

The Cochrane review [2] evaluated a number of interventions, assessing evidence for the effectiveness of different treatment methods for distal fractures in children. The NICE guidelines suggested that, per year, distal fractures accounted for 500,000 A&E visits in the UK [5]. Given the costs of admission and surgery, NHS Digital estimates the annual secondary care costs for these injuries amongst children up to 10-years-old is around £4 million. Furthermore, HES data is likely to underestimate costs of care due to under-reporting of hospital day-case admissions; some hospitals performing procedures under sedation - a resource-intense procedure for Emergency Departments.

Further consequences of distal fractures in children can also include parents taking time off work and increased burden of parental care. This may impact upon child and parent quality of life (QOL) and have financial implications for parents [6].

The Cochrane review [7] and NICE guidance [5] concur that there is little evidence to choose between various forms of treatments for distal fracture. The quality of the RCTs conducted were either low or very low [7].

Given the large number of distal fractures that occur nationally in the UK there remains considerable uncertainty about optimal treatment. In particularly, resolving whether non-surgical casting is non-inferior to surgical fixation would spare children surgical risks and reduce the burden on trauma

operating theatre capacity; particularly in the 'peak' childhood fracture season during summer months [8].

4 Trial Design

CRAFFT is a UK two parallel arm, multi-centre randomised controlled trial seeking to collect primary outcomes on at least 694 children (estimated recruitment 750 children accounting for 10% loss to follow up (LTFU)) with a displaced fracture of the distal radius, from a minimum of 32 centres. Randomisation is stratified by centre, fracture type at presentation (completely off-ended or incompletely off-ended), fracture location (metaphyseal or physeal) and age group (4-6 years or 7-10 years) and provided online by the Oxford Clinical Trials Research Unit (OCTRU). Each participant will be randomly allocated (1:1) to either non-surgical casting or surgical reduction. The control arm will receive cast immobilisation without any attempt to alter their level of consciousness, while the intervention arm receives surgical reduction, involving manipulation under general anaesthesia or sedation. The method used to hold the bones in place will be at the discretion of the clinician; i.e. plaster cast alone, plaster cast and wires, plaster cast and plate.

The primary objective is to compare the PROMIS Upper Extremity Score at three months post-treatment for each treatment arm. 'PROMIS scores' are a collection of non-disease-specific patient-reported health status tools available for children and adults, developed in collaboration with the US National Institute for Health. The PROMIS Upper Extremity Score for children is a validated childhood measure of upper-limb function. The PROMIS tools offer multiple methods of measurement. The computer adaptive test 'CAT' will be the method used for this trial (average 8-questions). A CAT enables the answer from one question to inform the choice of the next and so each participant could answer a distinct set of questions to arrive at their score.

Secondary measures, comparing non-surgical casting and surgical reduction in the first-year post-treatment, are:

1) Function using the PROMIS Upper Extremity Score
2) Pain scores using the Wong-Baker Faces Pain Score
3) Quality of life using EQ-5D-Y
4) Complication rates, including re-fracture, the need for further operative fixation and the absence of radiographic remodelling
5) Cost-effectiveness from an NHS and broader societal perspective
6) Parental satisfaction with the cosmetic appearance of the arm (VAS Cosmesis)
7) Patient Satisfaction Score

Measurements will be taken at baseline, 6 weeks, 3 months, 6 months and 12 months after randomisation. Long term outcomes for PROMIS, Wong-Baker Faces Pain Score, EQ-5D-Y, VAS Cosmesis and Complications will be reported separately up to 3 years post treatment.

5 Objective

The health economic objective is to estimate the comparative cost-effectiveness of the two trial treatment groups using resource use and quality of life data from baseline to 12 months follow-up. Analysis is by intention-to-treat, presenting resource use, cost and quality of life findings by trial arm. Attention will be paid to completeness of data, identifying issues and potential remedies.

6 Economic Evaluation

In accordance with this HEAP, a prospective economic evaluation of the CRAFFT trial will be conducted from a NHS and personal social services perspective [9] following intention-to-treat principles. A broader social perspective will include out-of-pocket expenses and parental absence from work. Using data from the CRAFFT trial, a within-trial patient cost-effectiveness analysis will be conducted comparing non-surgical cast to surgical reduction. Treatment effects will be summarised at the patient level as overall cost and quality adjusted life years (QALYs). As follow-up continues for 1 year only, costs and benefits will be undiscounted.

6.1 Resource use and costs

Resource use in each arm of the trial will be captured with the case report forms (CRFs) at scheduled clinical visits and contacts. Data will be collected on health and social service use, parental time off work and out of pocket expenses during the period between randomisation and 12 months after randomisation. Resource use data will be collected at each follow-up time point.

The cost of hospital care for a non-surgical cast and the cost of surgical reduction will be identified from National Reference costs via the HRG4+ Grouper and procedure codes (OPCS) for paediatric distal radius fractures.

Individual patient costs will be estimated in UK pounds sterling as the sum of resources used weighted by their reference costs, reflated to the latest common year base available. Costs of outpatient visits will be estimated using the National Schedule of Reference Costs (NSRC) [10]. Community health contacts will be costed using unit costs provided by PSSRU [11]. Parental lost earnings will be estimated from published national average weekly earnings [12]. Medication will be costed using national Prescription Cost Analysis (PCA) averages by therapeutic [13]. Aids and adaptations will be costed using statistics from the PSSRU [11].

Additional data derived through clinical and complication reports will be used in the health economic analysis. These include questionnaires related to patient complications, serious adverse events (SAE) or unplanned care.

6.2 Outcomes

Generic health-related quality-of-life (QoL) will be assessed using the EuroQol questionnaire: a patient-completed two-page questionnaire consisting of the EQ-5D-Y descriptive system and the EQ visual analogue scale (EQ VAS) [14, 15]. The EQ-5D-Y includes 5 questions addressing mobility, looking

after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy, with each dimension assessed at 3 levels: no problems, some problems and a lot of problems.

EQ-5D-Y responses will be valued using the most appropriate valuation set available for the trial population at the time of analysis. If necessary, the adult EQ-5D-3L will be applied, in which case we will undertake sensitivity analysis to make sure that trial findings are not sensitive to the valuation set chosen [16].

Quality of life measures are captured within trial CRFs during clinic visits or contacts at baseline, 6 weeks, 3 months, 6 months, and 12 months. Using the trapezoidal rule, the area-under-the-curve (AUC) of health status scores will be calculated, providing patient-level QALY estimates for the cost-effectiveness analysis. Similarly, EQ-VAS will be integrated discretely over time. 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.

6.3 Analysis

Follow-up of trial participants is problematic particularly over long periods and some incompleteness of data is anticipated. Consequently, the base case analysis will use multiple imputation, to account for missing data. The base case analysis will present the imputed within trial incremental cost and QALY quality-adjusted life years (QALYs) gained, adjusted for trial covariates. Supportive sensitivity analyses will include participants with complete data and explore the impact of imputation.

Imputation will be conducted according to good practice guidance [17] if overall missingness of complete case data exceeds 5% [18]. Multiple imputation 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 and QALYs against baseline variables [19]. A regression model will be used to generate multiple imputed datasets (or 'draws') for individual treatment groups, where missing values are predicted. The imputation model will use fully conditional (MCMC) methods (multiple imputation by chained equations), which are appropriate when missing and correlated data occur in more than one variable. Burn-in traces for imputation variables will be visualised to assess convergence. Outcome measures and costs (at each time point) will contribute as predictors and imputed variables. Each draw provides a complete dataset, which reflects the distributions and correlations between variables. Predictive mean matching drawn from the five nearest neighbours (knn=5) will be used to enhance the plausibility and robustness of imputed values, as normality may not be assumed. Within the imputation, missing costs and EQ-5D-Y scores will be imputed for each period of follow-up and aggregated to overall patient costs and QALYs for each draw. Analysis of multiple draws will be conducted using bivariate regression (see below) within Stata's MI framework, providing mean and variance estimates of costs and QALYs adjusted for Rubin's rule [20]. To minimise the information loss of finite imputation sampling the numbers of draws will be taken will exceed the percentage fraction of missing information. The distribution of imputed and observed values will be compared visually and statistically to establish the consequences of estimation. If overall missingness is less than 5%, then a complete case analysis will be conducted instead.

Bivariate regression using seemingly unrelated regression equations will be used to model incremental changes in costs and QALYs. This method provides estimates in natural units, respecting the correlation of costs and outcomes within the data, and allows adjustment for a set of covariates, which can be explored and which improve precision [21]. Baseline QoL scores will be included within

models to allow for potential baseline imbalances [22]; trial randomisation covariates will also be included in the basecase model. Joint distributions of costs and outcomes will be generated using the (non-parametric) bootstrap method, with replicates used to populate a cost-effectiveness plane. Bootstrapping jointly resamples costs and outcomes from the original data with replacement (maintaining the sample correlation structure), from which incremental costs and QALYs can be re-estimated. Using bias-corrected non-parametric bootstrapping, 2000 bootstraps will be taken per model.

The incremental cost-effectiveness ratio (ICER) will be estimated as the difference between treatments in average total costs divided by the difference in average total QALYs. Value-for-money is determined by comparing the ICER with a threshold value, typically the NICE threshold for British studies, of £20k-30k/QALY [9]. 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. Base case assumptions will be explored using a range of supportive sensitivity analyses, providing an assessment of the robustness of findings. The ICER will be reported with its 95% confidence interval.

The net monetary benefit (NMB) of changing treatment will be reported as a recalculation of the ICER at a range of thresholds of willingness to pay for an additional QALY. The NMB succinctly describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at (up to) the same threshold. NMB estimates will be used to generate cost-effectiveness acceptability curves (CEACs). The CEAC describes the likelihood that treatments are cost-effective as the willingness to pay threshold varies [13].

The expected value of perfect information (EVPI) is the upper limit of the value to a healthcare system of further research to eliminate uncertainty [23]. Findings from cost-effectiveness analyses remain uncertain because of the imperfect information they use. If a wrong adoption decision (e.g. to make a treatment available) is made this will bring with it costs in terms of health benefit forgone: the NMB framework allows this opportunity loss to be determined and guide whether further research should be conducted to eliminate uncertainty. If EVPI findings indicate that further research may be valuable, the analysis will be augmented with an expected value of perfect information (EVSI) analysis, giving guidance on optimal sample size.

Analyses and modelling will be undertaken in Stata 16 SE (or later release if available). Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [24]

Should costs and quality-of-life not converge within one year, more extensive economic modelling using decision-analytic methods may be considered to extend the target population, time horizon and decision context, drawing on best available information from the literature and stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. If longer term decision modelling is undertaken, then costs and outcomes will be discounted at 3.5% after the first year of randomisation in line with NICE reference case [9]

7 Dummy tables

In accordance with the analysis plan, planned tables and figures are described below.

7.1 Table 1: Completeness of data by follow-up visit

	Control[1]		Intervention[2]		Total	
	n	(%, N)	n	(%, N)	n	(%, N)
Health status[3]						
EQ-5D – Y Baseline						
EQ-5D – Y 6 weeks						
EQ-5D – Y 3 months						
EQ-5D – Y 6 months						
EQ-5D – Y 12 months						
EQ-5D – Y All visits						
Resource use (by time period)[4]						
Intervention						
Post-intervention- 6 weeks						
6 weeks-3 months						
3-6 months						
6-12 months						
All periods						
Resource use (by item)[5]						
Inpatient						
Outpatient						
Community						
Work absence						
Childcare costs						
All items						

1 Non-surgical treatment
2 Surgical treatment
3 Using EQ-5D-3L index score
4 Overall resource completeness by follow-up period
5 Completeness by item during 12m follow-up

7.2 Table 2: Health status, resource use and cost (complete cases)

	Control			Intervention			Difference		
	mean	**SD**	**N**	**mean**	**SD**	**N**	**mean**	**95%CI**	**p**
Health status[1]									
EQ-5D -Y Baseline									
EQ-5D -Y 6 weeks									
EQ-5D -Y 3 months									
EQ-5D -Y 6 months									
EQ-5D -Y 12 months									
EQ-5D -Y AUC									
Resource use (all visits)									
Readmissions									
Orthopedics									
Other									
Emergency department visits									
Outpatient visits									
Orthopedics									
Hospital physiotherapy									
Other									
Community care									
GP surgery visits									
GP telephone contacts									
Other community contacts									
Medications									
Social costs[2]									
Work absence (days)									
Additional childcare (days)									
Cost									
Intervention									
Post-intervention- 6 weeks									
6 weeks-3 months									
3-6 months									
6-12 months									
Total (NHS+PSS)									
Total (Societal)									

1 Using adult EQ-5D-3L index score

2 Broader social cost items, not included in base case NHS +PSS perspective

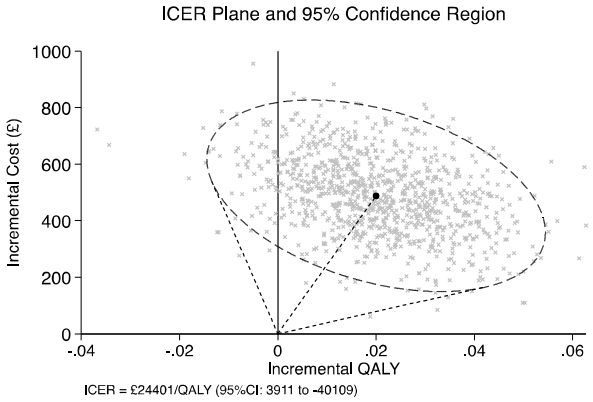
7.3 Table 3: Cost-effectiveness, cost/QALY (£20,000): non-surgical compared to surgical reduction

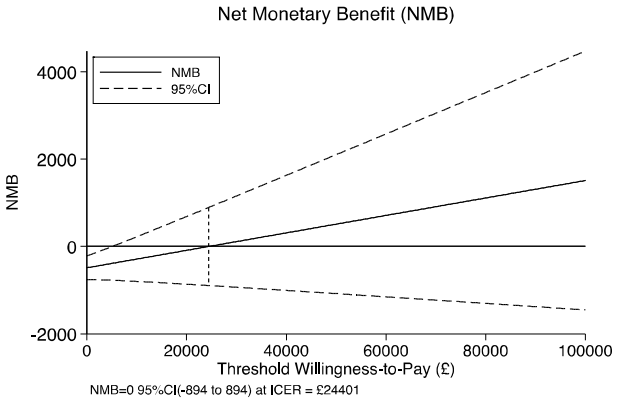
		Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p^1	p^2	NMB^1	NMB^2
Base case								
	Imputed costs and QALYs, covariate adjusted							
Sensitivity analyses								
1	Imputed costs and QALYs, baseline EQ-5D adjusted							
2	Complete case costs and QALYs, covariate adjusted							
Base case: trial strata sub-groups:								
3a	Presentation (completely off-ended or incompletely off-ended)							
3b	Fracture location (metaphyseal or physeal)							
3c	Age group (4-6 years or 7-10 years)							

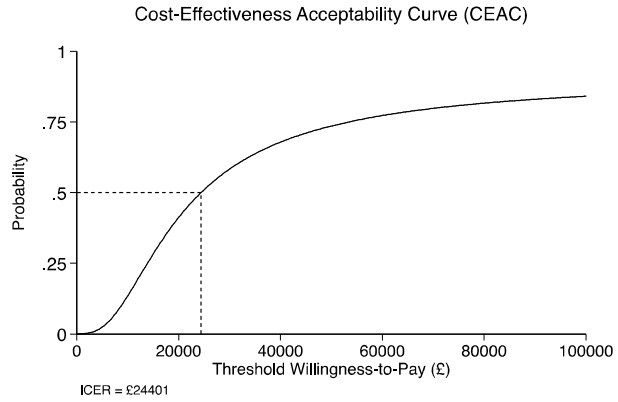
1 probability cost-effective or net monetary benefit if willing to pay £20,000/QALY

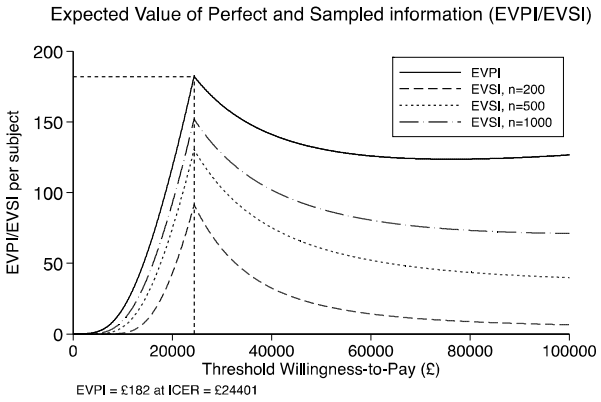
2 probability cost-effective or net monetary benefit if willing to pay £30,000/QALY

7.4 Figures 1-4 Presentation of base case economic analysis (illustrative example)









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