DETAILED PROJECT DESCRIPTION

Selection, definition and evaluation of important early morbidities associated with paediatric cardiac surgery

SUMMARY OF RESEARCH

Background

Over 5000 paediatric cardiac surgery procedures are performed in the UK each year. Peri-operative mortality rates have steadily improved, with the efforts of clinical teams supported by world-leading collection and sharing of data on mortality. There is growing attention within the literature on the burden of surgical morbidity in this population but little account has been taken of patient and family perspectives. No systematic measurement of the incidence and impact of surgical morbidity on children, carers and health services is available and no routine monitoring is in place.

Aims and Objectives

We aim to identify the surgical morbidities that present the greatest burden on patients and health services and to develop and pilot routine monitoring and feedback of these key morbidities. Our objectives are to: identify key measures of surgical morbidity that can be used to capture the clinical and economic burden; validate a questionnaire designed for routine use in screening for neurological disability; measure the incidence of the selected morbidities; evaluate the clinical burden of these morbidities and their impact on quality of life and financial costs to the NHS and families; develop and pilot sustainable methods for collection and feedback of surgical morbidity data for use in quality assurance and continuous improvement.

Plan of Investigation

Our multidisciplinary study will take place over 42 months across 5 UK paediatric cardiac surgery centres that together serve over half of the patient population. We will:

Review existing literature and professional guidance and run focus groups to get the perspectives of patients and their carers on which morbidities are most important to them. A multi-disciplinary group with patient and carer involvement will then rank and select a shortlist of key morbidities, informed by clinical views on definitions and feasibility of routine monitoring;

Validate a new, nurse-administered questionnaire for assessing pre- and post-operative child development to screen for peri-operative brain injury;

Measure the incidence of the selected morbidities among 3000-3300 patients over 18 months and explore the relationship between these and potential risk factors including cardiac diagnosis, operation type and co-morbid conditions;

Recruit up to 500 patients with surgical morbidity as cases to a matched cohort study over 18 months to measure impact at 6 months on quality of life, clinical burden and costs to the NHS and families, with an equal number of controls recruited from similar patients with no surgical morbidity.

Develop and pilot methods suitable for routine in-house monitoring of morbidity in the context of multi-disciplinary mortality and morbidity conferences. These methods will be designed through repeated prototyping and engagement with clinicians, patient representatives and other stakeholders;

Propose which morbidities should be routinely monitored and how these complex data can be clearly presented. Overall incidence of morbidities will be fed back to patient and carer groups via the Children's Heart Federation.

BACKGROUND AND RATIONALE

Whilst there has been considerable research on measuring, understanding and reducing peri-operative mortality (1-4) there has been less attention on surgical morbidities. Surgical morbidities are health problems acquired around the time of surgery that are considered potentially avoidable or reducible: the most severe include brain injury, deep-seated surgical site infection and injuries to structures in the thorax such as the cardiac conduction system and the phrenic nerve. Such events can have long term impact on child development, lead to prolonged hospital stays and / or necessitate additional health interventions.

Measurement of morbidity, in particular neurological damage

A wide variety of complications arise during paediatric cardiac surgery and the risk of a challenging post-operative course is associated with patient related factors. (5) The Society of Thoracic Surgery (STS) in the US recently published 'National Quality Measures' based on professional views, including a list of selected morbidities. In the STS database, major complication rates varied from 1 to 38% depending on procedure complexity (6). One recent single centre study showed that prospective monitoring may lead to greater case ascertainment (7) and another that 14% of patients had multiple morbidities. (5)

Although routine audit of mortality outcomes is well established in the UK, underpinned by the Congenital Database at the National Institute of Cardiovascular Outcomes (NICOR) (8) morbidities are not routinely audited. There is no national consensus on the morbidities that should be monitored or their precise definitions. To make progress, robust agreed definitions and clear feasible measurement protocols need to be implemented.

Neurological damage following cardiac surgery is considered crucial by patients, families and clinical staff. Systematic evaluation of infants undergoing common congenital heart repairs in the USA with a ‘gold standard’ assessment indicated that neurological difficulties occurred in up to 25% of patients. (9) UK National Audit reports deterioration in cerebral performance category (10) in 1.2% of children following surgery (personal communication from NICOR 2012). This is almost certainly an underestimate, with data quality undermined by lack of expertise among cardiac specialists in assessing neurological development, exacerbated by the medical complexity and age mix of the patients. The importance of improving these assessments goes beyond audit and quality assurance; early detection of neuro-developmental deficits can prompt timely intervention and improve outcomes.

The 'Brief Developmental Assessment' (BDA) tool is a new questionnaire covering different age bands (0-4 months, 4-8 months, 9-14 months, 15 months – 2.9 yrs, 3 – 4.9 yrs and 5-17 yrs) to account for the different stages of development. Designed for neuro-developmental surveillance by nurse practitioners rather than specialists, the BDA has the following promising features for this context: it assesses the key domains of neuro-development at risk in paediatric critical illness; includes direct observations and history (both are required as parents of surgical patients may be stressed or their assessment impaired by their child’s general condition); is designed for non-specialists, facilitating routine collection and audit; provides prompts for further developmental evaluation and treatment.

Current information on validity and reliability of the BDA:

Face validity – The BDA tool was designed by a multi-disciplinary group including: paediatric neurologists, developmental experts, paediatricians, psychologists, nurses and a statistical expert. The BDA development group consulted the published literature on long-term outcomes of children with cardiac disease and critical illness in order to identify the optimal domains to incorporate within the measure, these being *gross motor skills,(11-15) fine motor skills, (11, 12, 16, 17) daily living skills, (16-18) receptive and expressive communication, (11-13, 17, 18) socialisation, (19, 20) behaviour and coping skills. (21-24)*

Content validity – In selecting item content, a full range of available measures were reviewed, whilst considering the following proposed goals or criteria for the BDA measure:
1) Suitability for neuro-developmental *surveillance* (audit of new injuries occurring during surgery) and

screening (detection of injuries that would have otherwise remained undetected or unacknowledged).
2) Coverage of the pertinent domains of child neurology and development, across the relevant patient age range (term neonates to children aged 17 years).
3) Testing conditions (no special equipment, non-specialist users, time allowed 10 to 20 minutes).
4) Elements of direct observation in addition to elements of parental report.

The measures reviewed are tabulated in the appendix, with comments outlining their pertinent features and limitations given the BDA remit and include: *Mullen Scales of Early Learning, Battelle Developmental Inventory, Denver Developmental Screening Test II, Bayley III Screener test, Bayley III Scales of Infant and Toddler Development, Bayley Infant Neurodevelopmental Screen, Ages and Stages Questionnaire (ASQ), Developmental Neuropsychological Assessment (NEPSY-II), Wechsler Individual Achievement Test (WIAT-II - academic), Wechsler Abbreviated Scale of Intelligence (WASI-II), Children's Memory Scales, Behaviour Rating Inventory of Executive Function (BRIEF), Wechsler Intelligence Scale for Children, The Behavioural Assessment of the Dysexecutive Syndrome (BADS), Parents Evaluations of Developmental Status (PEDS) and Battelle Developmental Inventory Screen.*

Within each age band of the BDA individual items were selected by the expert panel based on review of the measures listed, each item group pertaining to a specific important neuro-developmental domain as listed above. Individual items have an answer yes / no or a graded answer with three options as appropriate. Items have been revised in an iterative fashion based on pilot data.

Construct validity – Discrimination by the BDA of known groups of children with developmental problems has been borne out in pilot data collection by lower scores in these children. This area will be explored further as part of objective 3, for which we provide further sample size data below.

Internal consistency – Pilot data indicate an acceptable level of consistency between individual items within a domain generating Cronbach's Alpha in the range 0.8 to 0.9.

Test retest and Inter rater reliability – These aspects form part of objective 3, for which we provide power calculations and levels of acceptability required in order to validate the BDA measure. Based on pilot data intra class correlation coefficients for inter rater reliability are above 0.8.

Two independent collaborators will work with the study team with a specific remit of advising on the BDA validation. Professor John Rust, director of the Psychometrics Centre at the University of Cambridge and Professor Monica Lakhanpaul, Professor of Integrated Community Child Health at University College London, will both critically appraise the BDA tool and the related pilot data, prior to the start of the validation work.

<u>Impact of morbidity</u>

Much of the current research on surgical morbidities has focused on establishing their links with longer stays in hospital and establishing that children that experience prolonged hospitalisation and complications are also at greater risk of death. (5, 25) Over the long-term, children with specific heart conditions who experienced prolonged stays in hospital following surgery developed higher levels of neurological disability, (17, 26) with children experiencing the most difficult post-operative courses involving a period of mechanical circulatory support developing neurological disability in around 50% of cases (27). This can impact upon long-term quality of life for children and carers and can incur significant short and long-term health care costs. Other morbidities among these patients can also be very expensive to manage, with mechanical circulatory support costing over £10,000 per day (28, 29).

While some information is available, the impact of individual morbidities on quality of life, health care use and NHS costs are unclear and have not been reported in the literature. Validated patient reported outcome measures exist for use in this patient group (30, 31) and so the impact of morbidity on quality of life can be measured. The measured impact of morbidities should influence the selection of morbidities for future monitoring, audit and bench marking purposes.

Eliciting patient perspectives and determining group priorities

Focus groups and formal consensus methods have been used to elicit patient and carer perspectives and determine group priorities in many contexts. (32) The nominal group technique was successfully used among GPs to identify prioritised lists of quality markers for the management of children in general practice (33) and by kidney transplant patients in ranking outcomes by importance. (34) A recent NIHR funded study showed differing perceptions and priorities between clinicians and patients regarding chronic obstructive pulmonary disease services and outcomes. (35)

Reporting of morbidity

To enable routine monitoring of morbidities, approaches to data analysis and display must be developed alongside defining suitable measures. Analytical and graphical methods for the timely reporting of risk adjusted mortality outcomes for the purposes of quality improvement are well established in adult cardiac surgery practice (36) and have been developed by members of our research group for paediatric cardiac surgery. (37) Two single centre studies have attempted to generate an aggregate 'Morbidity Index' by assigning subjective weights to post-operative complications (38, 39) and the STS has attempted a similar 'Morbidity Score'. (6) Condensing diverse morbidities into a single score loses information and recent work on using graphical methods to routinely monitor a range of morbidities (7) highlighted the complexity of graphically summarising multiple morbidities (see also commentary by Utley, Brown and Tsang (40)).

What our proposed research adds

The incidence and impact of surgical morbidities is not clear to patients, families or clinicians. The best approach to select, define, measure and track surgical morbidities in routine practice is unknown, case mix considerations are unresolved and patient and family perspectives on which morbidities are the most important have not been incorporated.

Our proposal addresses these major gaps in current knowledge. We will incorporate patient and carer priorities into the selection of morbidities for audit, test a way that enables better routine measurement of neurological deficit following surgery and establish robust definitions for, and the current incidence of, major morbidities and their impact in the UK paediatric population following heart surgery. Additionally, we will develop new graphical methods for reporting morbidity, both for in-house routine monitoring but also for feedback to patients and families.

EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW

Morbidity, disability and quality of life are increasingly viewed as key outcomes by patients, families and clinical teams who are looking to deliver further improvements in service quality, partly due to decreasing mortality rates. Although they've not involved patient perspectives and are based on clinical opinion of what is important rather than the measured impact of morbidities, recent initiatives in the US (6) and Canada (7) are illustrative of growing attention worldwide on the issue of surgical morbidity in this population. In the UK, a recent major review of the specialty highlighted the need to monitor outcomes in a timely and meaningful fashion (41) and commissioners of services are appropriately seeking evidence on outcomes and quality assurance from providers.

Increased focus on measuring and reporting outcomes and incorporating patient perspectives in the choice of such metrics is not limited to paediatric cardiac surgery. Our research will inform the development of outcome monitoring in other specialties in a number of ways:

- Our experience of combining patient and carers' perspectives with those of professional groups in defining a prioritised list of outcomes for audit may be valuable to other specialties;
- Generic methods for monitoring, benchmarking and displaying morbidity outcome metrics are highly likely to be translatable to other fields of specialist practice;

- The definitions and measurement protocols we develop for non-disease specific morbidities such as neurological damage and infection will have wide applicability in paediatrics.

To illustrate the latter point, around 19,000 children are admitted to paediatric intensive care in the UK, the majority suffering an emergency critical illness or undergoing non-cardiac surgery. Currently there is no national audit of morbidity since measures are not available in a useable form. The CPC score of neuro-developmental outcome is used in some settings (42, 43) but there is vast potential for the widespread, beneficial deployment of the BDA if validated in this study.

AIMS AND OBJECTIVES

Our aims are to identify which surgical morbidities present the greatest burden on patients and health services following paediatric cardiac surgery and to establish how they should be routinely monitored.

The objectives required to achieve these aims are:

1) Identify the key surgical morbidities following paediatric heart surgery, taking into account views from patients, carers, psychologists, nurses and clinicians, that together capture important aspects of the clinical and health-economic burden;

2) Develop objective definitions and measurement protocols for the identified morbidities and further determine which morbidities for routine monitoring and amenable to service improvement;

3) Validate a tool suitable for routine screening of neurological disability peri-operatively;

4) Measure the incidence of defined morbidities in the UK patient population and in subgroups defined by case complexity;

5) Evaluate the impact of defined morbidities on quality of life and estimate their clinical and health economic burden;

6) Develop and pilot sustainable methods for collection and feedback of surgical morbidity data for use in future quality assurance and patient/carer information.

RESEARCH PLAN / METHODS

In this interdisciplinary project involving 5 UK paediatric cardiac surgery units, we shall achieve objectives (1) – (6) as follows.

Objective (1): to identify the key surgical morbidities following paediatric heart surgery

(1.i) Systematic review:

We will conduct a systematic review of the literature and professional guidance to identify a list of surgical morbidities for consideration. The search strategy will be designed to identify published literature from MEDLINE, EMBASE and CINAHL that describes complications and morbidities related to paediatric cardiac surgery. Given the recent rapid changes in the speciality, we will include papers from the last 12 years only. Search terms are listed in the main application form (RESEARCH PLAN) and include paediatrics, cardiac surgery and complications.

Abstracts will be screened by two clinical co-applicants and included in the structured review phase if they are papers written in English relating to surgery for congenital heart disease, in children under the age of 16 years, are randomised trials, other types of trial, cohort studies, case series with greater than 20 patients and are studies reporting ‘non death outcomes’ including post-operative complications, hospital acquired infections, salvage mechanical circulatory support or neurological damage. Where the separate reviewer assessments on a paper differ, they will come to a decision on discussion, consulting a third member of the team if necessary.

Independent structured review of the included studies by two clinical co-applicants will capture information pertaining to: the study type, the geographical location, the case mix and types of operation discussed, the duration of follow up, the morbidities reported and how these were defined and measured and the nature of any patient reported outcomes or health economic assessment included. Analysis will include tabulation, graphical summaries and qualitative commentary rather than meta-analysis, given the known paucity of randomised data. Further detail on the systematic review is given in the main application form.

(1.ii) Focus groups:

We will run three focus group meetings in London, the Midlands and Glasgow with patient and family representatives recruited via the Children's Heart Federation to identify those morbidities considered key from their perspective. Focus groups will be recorded and transcribed and the content subjected to thematic analysis in order to identify key issues and domains of outcome that are important to parents and patients. The Children's Heart Federation will also host an online forum around this topic where parents and patients from all round the country can contribute their views. The outputs of this patient and parent involvement will feed into the broader selection panel meetings in (1.iii) below.

(1.iii) Selection panel meetings:

We will convene three meetings of a panel of family representatives, surgeons, liaison nurses and other health professionals to shortlist and then select surgical morbidities for routine monitoring.

The shortlist of surgical morbidities, the incidence and impact of which will be measured as part of this research, will be selected by the panel using a modified nominal group technique (NGT) (44, 45) informed by the systematic review (1.i) and the focus groups (1.ii). It will be professionally facilitated and recorded. The question addressed by the panel will be "What are the important surgical morbidities to monitor routinely following paediatric cardiac surgery?" We will assess group preferences between options using the robust secret voting process developed by Utley et al. (46)

At the first meeting of the panel, the emphasis will be on shortlisting the morbidities considered important and potentially reducible, with participants encouraged not to self-censor due to issues of definition and measurement. The output of this meeting will be a prioritised list of 10 to 15 candidate morbidities with other, less favoured options discarded at this stage. At the second meeting, informed by the definition group (see 2.i), the panel will have a short discussion on any issues raised by the definition group before again individually ranking remaining options in a secret vote, with a view to shortlisting 6-10 morbidities for the incidence and matched cohort studies (objectives 4 and 5).

A third and final round of discussion and voting will take place following completion of the incidence and matched cohort studies (at the end of Year 3). The objective here will be to discuss the findings of these studies, re-rank the shortlisted options via a secret vote as above and then select the final set of surgical morbidities recommended for monitoring in routine practice.

Objective (2): To develop operational definitions for routine morbidity monitoring

(2.i) Definition meetings

We will convene meetings of a surgical morbidity definition group including representatives from all 5 participating centres. The work product of this group will be: 1) establish the diagnostic criteria that constitute the definition of each 'individual morbidity' selected at (1.iii); 2) define the measurement protocol for each individual morbidity, including any aspects that require additional specialist input or alternatively surveillance outside the tertiary centre; and 3) outline the clinical pathway and necessary referrals and treatment for children who experience each individual morbidity over the first 6 months post-operation. This section of work will draw upon information forthcoming from the literature review, and any relevant established guideline will be incorporated (example: Health Protection Agency 2008 Surgical Site Infection Surveillance).

The group will be led by Mr Mclean, who has worked extensively on this area with the North American and European audit databases in his role as surgical lead for the Congenital NICOR audit in the UK. In its first

phase of work, which will be conducted through an initial face to face meeting followed by email correspondence, the group will provide the selection panel with views as to whether each candidate morbidity nominated by the first meeting of the selection panel is definable, measureable and feasible to measure in routine practice, highlighting any additional issues identified in relation to each morbidity. A clinical lead will be identified to take forward each of the individual shortlisted morbidities, utilising both email and web based interactions to develop each protocol, eventually reporting back at the second meeting of the definition group with an agreed package to sign off. The protocols for identification, measurement and management of shortlisted morbidities, including the timings of measurements, will be designed for use in the incidence and cohort studies (objectives 4 and 5) but with suitability for routine use a key requirement. The group will reconvene prior to the pilot study in year 4 (methods 6.iii) to make any adjustments prompted by the incidence study or logistical considerations raised during framework development (methods 6.i).

The morbidity definition group will draw upon the skilled input of senior surgeons, specialist nurses and cardiac intensivists involved in the study, and will further call upon the expertise of collaborators including cardiologists, paediatricians, a GP, members of the group that developed the BDA and an infection control specialist. Neurological morbidity is almost certain to be included in the final shortlist as it is often cited as a priority by both parents and clinicians and the definition group will decide, based on the validation study, whether to use the BDA method for monitoring neurological injury.

Objective (3): To validate the BDA tool for identifying neurological disability

(3.i) Evaluation of validity and reliability

We will evaluate internal consistency of the items within each domain of the BDA and assess reliability in terms of inter-rater and test-retest performance.

In the absence of a single "gold standard" test that covers all the relevant aspects of neurological development, we will assess concurrent validity of the BDA against an amalgam of well-established tests, an approach used in validating a psychometric measure in children with heart disease (21, 22). Given the relative rarity of neurological damage, it would be infeasible to prospectively validate the BDA specifically for sensitivity to change within individual patients.

In the 5 age bands for children under 5 we will use as gold standard the Mullen Scales of Early Learning (MSEL) (47) (a well-validated measure for early developmental assessment in the context of children with heart disease. (48)) This will be augmented by the Ages & Stages Questionnaire-3 (ASQ-3) (49) to capture the Cognitive, Adaptive, and Social & Emotional domains not covered by the MSEL.

For the older age band (over 5 years) the gold standard will comprise: the Wechsler Abbreviated Intelligence Test (WASI) consisting of 4 subtests measuring non-verbal abilities, visuo-motor coordination skills and verbal abilities (50) and two subtests of the Children's Memory Scale (CMS), (51), the short form of the Bruininks-Oseretsky Test of Motor Proficiency (52) and the Child Behaviour Checklist (CBCL)(53) which assesses behavioural and emotional problems as well as social competence and progress at school.

We will assess construct validity by determining the ability of the BDA to detect known groups of children with developmental abnormalities. This will involve assessing the sensitivity and specificity of the BDA in detection of known abnormalities based on Mullen/WASI scores in children with established syndromic or developmental diagnoses (Cerebral palsy, Down, Di George, CHARGE and other chromosomal defects) including receiver operator curves.

(3.ii) Recruitment

Patients will be recruited at Great Ormond Street and Evelina Children's hospitals in London using a team of three psychology assistants (PA) under the supervision of Dr Wray and Dr Hoskote, with the close proximity of centres enhancing the management and supervision of this work stream.

A convenience sample of 200 patients within each age band will be recruited from preadmission and outpatient clinics at the two centres. Children and carers will be invited to participate by letter sent ahead of their appointment, which will include an information leaflet with the contact details of the study team in case there are questions. Clinicians will ask parents at clinic if they would like to receive more information from the research team.

In order to evaluate construct validity of the BDA by discrimination of known groups of children with abnormalities we propose to over sample children with syndromic diagnoses (who are known to have significant neuro developmental problems), (54) aiming for a proportion of 25% for the top 5 age bands. The figure of 25% incudes 15% of severe cases (Gold standard score >2 standard deviations (SD) below the mean or less than 70) and 10% moderate cases (Gold standard score 1-2 SD below the mean or a score of 71 to 84). This is likely to be feasible in the older 4 age bands of the BDA because of the high proportion of children with known syndromes / known deficits in the population. (9) We will exclude the youngest age band (age less than 4 months), since at this age the impact of a known diagnosis on development may as yet be undeclared.

(3.iii) Data collection

After obtaining consent, the psychology assistant (in conjunction with the parents) will administer the BDA, the gold standard for the child's age and complete a demographic information sheet. Parents will be asked to complete the ASQ whilst the PA is administering the other tests. Blinded to the results obtained by the first assessor, a second PA will administer the BDA. It will not be possible to blind the assessors to some characteristics associated with known developmental difficulties, such as Down syndrome. We anticipate that the BDA and gold standard tests will take up to 45 minutes to complete, depending on the age of the child.

One of the assessors will perform a retest 2-4 weeks later on a convenience sample of 56 children in each age band recruited in outpatient clinics to measure intra-rater reliability for all age bands other than 0-4 months (excluded because the rate of medical interventions at this age precludes a stable period).

Any patients in whom any of the tests raise concern will be referred for specialist help and their parents supported by hospital psychology services.

(3.iv) Data analysis

For each of the 6 age bands, BDA inter-rater and intra-rater reliability and BDA agreement with the relevant gold standard will be measured by the intra-class correlation (ICC) coefficient, with 95% confidence intervals.

An interim analysis will be performed using data from the first 100 patients in each age band and the study abandoned for any age band where the ICC coefficient for agreement between the BDA and the relevant gold standard is below 0.6.

Successful validation will be defined as the lower 95% confidence limit (CL) for the ICC exceeding 0.85 for BDA intra-rater reliability, 0.75 for BDA inter-rater reliability and 0.75 for BDA agreement with all components of the relevant gold standard other than the ASQ, for which we set the lower threshold of 0.63 (see sample size calculation) since the ASQ incorporates a smaller proportion of the BDA items. Adequate construct validity will be defined as a sensitivity of at least 80% in detecting all known abnormalities.

The definition group (2.i) will make the final decision on using the BDA in the incidence study (objective 4).

(3.v) Sample size calculation

We require 56 patients in 5 age bands to detect an intra-class correlation of 0.9 with 5% precision for **intra-rater** reliability, so 280 patients will have repeat BDA measurements.

To estimate an expected **inter-rater** intra-class correlation of 0.8 with 5% precision, we need 200 patients per age band (1200 patients in total). This number of patients would be sufficient to allow us to estimate the

agreement between BDA and gold-standard metrics with 5% precision. We require the BDA and the ASQ to match less well, and an ICC of 0.7 would be acceptable. We will have a precision of approximately 7% for this estimate, hence the threshold for the lower CL of 0.63 in the analysis plan above.

Within each of the age bands (excluding the youngest babies), a sample size of 200 (approximately 50 children with known abnormalities and 150 children presumed to be normal, for an assumed prevalence of 25%) will provide sufficient numbers to detect a 0.5 SD difference in mean BDA scores between known groups, with 80% power and 5% significance. When assessing the ability of the BDA to discriminate between children with and without abnormalities, we will be able to detect an abnormality with 12% precision, for an assumed **sensitivity** of 80%. We anticipate the use of the BDA will result in a lower **specificity**, possibly 65% and for this our sample will provide 8% precision for this estimate. We are less concerned about the level of specificity since false positives where a child is subjected to medical review are unlikely to be harmful. Furthermore we expect the BDA to have a higher sensitivity of 90% for detecting severe abnormalities, so for a conservative estimate of prevalence for severe cases of 10%, our sample size of 200 would provide a precision of 14%.

Following completion of objectives 1-3, we will be in a position to measure the incidence and impact of shortlisted morbidities in each of the 5 participating centres.

Objective (4): To measure the incidence of defined morbidities in the UK patient population

(4.i) Recruitment and Data Collection

All children under 16 years of age undergoing cardiac surgery in each of the five participating centres will be monitored for the presence of the morbidities selected at (1.iii) and defined at (2.i) by the clinical team who will liaise with the dedicated research nurses and the consultant surgeon.

Incidence data on the morbidity events selected at (1.iii) will be collected in line with the protocols defined at (2.i) alongside nationally mandated audit data including sex, postcode, pre procedure diagnoses, pre procedure co-morbid conditions, weight, age and procedure information. The data collected will be fully anonymised before it is provided to the research team: all names, numbers, dates and places will be removed (see ethical issues section for details) and very rare conditions will be grouped.

(4.ii) Data analysis

The incidence of each selected morbidity, both alone and in combination with others, will be estimated with 95% confidence intervals using multilevel multinomial regression. We will similarly estimate the incidence of specific combinations of morbidities and explore any patterns in the order in which morbidities become manifest to identify any “sentinel” morbidities particularly worth monitoring.

Similar regression techniques will be used to explore the role of pre-operative, patient-level case mix factors on morbidity. The case mix factors considered will be those listed above with the addition of a calculated weight-for-age z-score and risk of 30-day mortality as estimated using the PRAiS risk model. (5) As a preparatory step, we will group diagnostic (55), procedural and co-morbidity data. (5)

Univariate and multivariable models will be fitted and the estimated effects presented along with 95% confidence intervals. The differing associations between case mix and different morbidities will be explored through interactions. Clinical insight and findings from the literature will guide us in defining important interactions to explore. (5, 26) We will investigate non-linearity between covariates and outcome using fractional polynomials. If we are unsure about the parametric assumptions of our underlying model then we will use bootstrap confidence intervals to validate our results. If appropriate and necessary we will impute missing data using multiple imputation by chained equations.

This investigation of the role of case mix will initially consider “multiple morbidity” as a separate entity alongside the lone morbidities. Further analysis may include taking this approach with the most common combinations or analysing separately patients with multiple morbidities to model the number of morbidities as an ordinal outcome, again taking into account the above methodological issues.

(4.iii) Sample size

We anticipate between 3000 and 3300 surgical patients at participating sites over the 18 months. This is a sufficient sample to estimate accurately the incidence of each morbidity (e.g. an observed incidence of 3% would have confidence interval [2.4% - 3.6%]) and to identify sufficient cases for the matched cohort study of impact (objective 5).

Objective (5): To evaluate the impact of morbidities

We will conduct a prospective matched cohort study designed to measure the impact of morbidities on patients, families and the health service.

(5.i) Recruitment

Cases (patients with at least one of the shortlisted morbidities) and potential controls (those with none) will be identified through the 18-month incidence study (4.i) and the clinical team at each site will make the initial approach to eligible patients and families. The research nurse at each site will then approach families who have expressed an interest in the study and will have responsibility for recruitment and consent.

We aim to recruit 36 case-control pairs for each of the individual morbidities selected. Depending on the morbidities shortlisted (1.iii), we anticipate up to 10 different sets of 36 pairs (up to 720 children). Children with multiple morbidities will be recruited as a separate group, with the goal being to recruit as many of these children as possible, and matched to controls with no morbidity. Based on reported rates of multiple morbidity (5) we anticipate recruiting around 120 such pairs and possibly more depending on the morbidities selected.

Patients undergoing transplant or tracheal surgery and neonates undergoing the hybrid procedure will be excluded to remove patient groups treated at just one centre and in small numbers. Premature babies undergoing ligation of patent ductus arteriosus will be excluded as they experience major morbidities before and after a procedure due to their extreme prematurity.

A proportion of cases will die in intensive care. Clearly this an emotive subject, and outcome evaluation including longer term quality of life in these children will not be feasible, however we will seek consent to include available data related to the hospital course of these patients in the analysis as cases.

(5.ii) Matching of controls to cases

Cases and controls will be matched within individual centres. Each case will be paired to the next available control based on following criteria:

1. Age (matched within 3 months for children under 1 year, within 1 year in children under 5 years and within 2 years in children over 5 years)
2. Single or double-ventricle status. (56)
3. Surgical procedure type matched by the broad RACHS-1 category (2) or where there is a choice by the finer CCAD procedure classification. (8)

If a match based on all three criteria does not arise within 2 months, a control will be approached based on the first two.

The research nurses at each site will follow up with each patient to collect quality of life data four times over a 6 month period: at (first) discharge from hospital, at 6 weeks, 3 months and 6 months following the primary procedure.

(5.iii) Outcome data collection

We plan to assess the impact of morbidity using three different outcome measures:

A. Quality of life and psychological burden on children and parents using age specific measures;
B. NHS costs, including further interventions and hospitalizations, and costs borne by families;
C. Days at home (as an additional measure of disruption to family life).

Outcome A: Quality of Life

We will use the following measures (details of each measure are provided in Table 1):

Health-related quality of life for cases and controls will be assessed using the PedsQL4.0 core scales, which are generic measures for children of 0-18 years. (57, 58) For patients under 5 years of age there are parent-proxy versions only; for those over 5 years of age there are self-completed versions and parent-proxy versions. Normative data exist for all forms of the PedsQL and the measures have been widely used with healthy and ill children, including those with heart disease.

Although we will preferentially collect self-reported data where possible, the majority of patients will be under 5 years of age and parent-proxy reporting will thus be unavoidable. Proxy reporting of a child's quality of life can be influenced by **parental mental health** and **quality of life**. We will measure these factors using the PHQ-4 (59) and the WHOQoL-BREF (60) respectively to explore their potential role as moderators or mediators of the impact of morbidity on the child's quality of life reported by parent-proxy .

A child's illness and subsequent treatment can also have a **broader impact on the family** and this will be assessed with the PedsQL Family Impact module. (61)

These questionnaires typically ask respondents to consider the past one-month. As we do not want to reflect the hospital experience, we will administer questionnaires at 6 weeks and 6 months post-procedure (more than a month after discharge for most), either face-to-face or by telephone interview. We will not use postal completion because of the poor response rates. The burden to parents will not be significant, with questionnaire completion expected to take no more than 20-30 minutes on each occasion. For those patients or parents who do not speak English, translations are available in a number of different languages (although we acknowledge the limitations of assessing cultural influences on quality of life).

QALYs: We will also take an 'area under the curve' approach to measuring quality of life, measuring quality adjusted life years (QALYs) over the 6 months post operation. Baseline QALY data attributable to each morbidity will be an important measure for future interventions aimed at reducing the burden of morbidity. The research nurses will collect child quality of life scores using the HUI-2 questionnaire (62) at 6 weeks, 3 months and 6 months (by parent proxy for children under 8 years old). Deaths will be assigned a score of zero, recorded at the date of death. Child-specific QALY profiles will be constructed assuming both a straight line and a smoothed relation between each of the quality of life scores at each follow-up point. The QALYs experienced by each child from baseline to 6 months will be calculated as the area underneath this profile.

A summary of the questionnaires to be used for Outcome A are included below:

Questionnaire	Discharge	6 weeks	3 month	6 month	Time taken
PedsQL4.0 generic core battery: assesses child's QOL in physical, emotional and school (where appropriate) domains. (57, 58)	X	✓	X	✓	5 min
HUI2 – a preference based multi-attribute health related QOL tool which delivers a single utility score; completed by parents (62)	X	✓	✓	✓	5 min
WHOQoL-BREF – a 26 item measure of health status comprising 4 subscales completed by parents about themselves (63)	X	✓	X	✓	10 min
PHQ-4 – a 4 item scale measuring parental anxiety and depression (59)	✓	✓	✓	✓	2 mins
PedsQL family impact module – a 36 item questionnaire completed by parents to assess impact of child's health on parental functioning, family relationships and activities of daily living (61)	X	✓	X	✓	10 min
Diary - non-tertiary NHS contacts, costs borne by families, days at home	✓	✓	✓	✓	–

Outcome B: NHS resource use and costs, and costs borne by families

We aim to estimate the health economic impact of morbidity in two ways: on the family of the child and on the health service. We will gauge the costs incurred by families in terms of the following items (*measures*):

- Transport to hospital/primary care (*method of transport, distance, number of times*);
- Accommodation required in order to visit hospital (*number of nights, cost per night*);
- Hospital café food, take-out foods eaten during visiting times (*expenditure*);
- Prescription and non-prescription medicines (*expenditure*);
- Extra telephone calls (*expenditure*);
- Childcare for other children in family, including babysitters (*expenditure*);
- Domestic help such as home help, laundry etc (*expenditure*);
- Financial services (*benefits claimed, information seeking about benefits*);
- Time off work (*days*).

This information will be collected using three prospective resource use diaries to cover the periods: up to 6 weeks from procedure, 6 weeks to 3 months and finally 3 months to 6 months following first procedure.

Unit costs for transport to hospital/primary care, accommodation required in order to visit hospital and time off work will come from market prices and published sources where available, allowing us to calculate the costs for each component for each child. These will be summed to calculate the total family cost per child.

We will undertake a detailed analysis of the costs incurred by cases and controls from both an NHS and personal social services perspective (as recommended by NICE). Data will be obtained from the hospital record for events at the tertiary centre, and a combination of diaries and the hospital record for events outside the tertiary centre. The cost components included in the analysis will include the following items (*measures*):

- ECMO (*number of times, number of days each time*);
- ICU stays (*number of stays in each level of care, number of days for each stay*);
- Inpatient stay for index hospital procedure (*number of nights*);
- Secondary hospital stays (*number of stays, number of nights for each stay*);
- Outpatient visits (*number*);
- A&E visits (*number*);
- Day case attendances (*number*);
- GP contacts (*at practice, at home, via telephone*);
- Primary care or community nurse contact (*at practice, at home, via telephone*);
- Prescribed medications (*name, dosage, number of doses per day, number of days*);
- Contacts with any other health services (*type of service, number of contacts*);
- Financial services (*benefits claimed, information seeking about benefits*);
- Cleaning service (*number of contacts*);
- Domestic help (*e.g. home help, laundry*).

Outcome C: Hospital-free days

Another objective measure of the impact of morbidity is the number of hospital-free days a child experiences within 6 months of the primary procedure. Using the data collected above, the research nurses will collate all relevant data about hospital stays in secondary as well specialist centres, A&E visits and outpatient appointments. Patients who died will score zero on this scale (even if they did spend time at home) to reflect that this is the worst outcome.

(5.iv) Data Analysis:

For each outcome (A to C) multilevel modelling will be used to make comparisons within case control pairs, taking into account the nesting with centres, ensuring model assumptions are satisfied and using appropriate transformations where necessary. Depending on the nature of multiple morbidities, children within this group might be analysed in separate subgroups.

The hospital-free days outcome is likely to be negatively skewed, as the measure is right censored with maximum follow-up of 6 months (180 days), therefore we will investigate various different distributions and modelling approaches. A single model will be fitted for each outcome (A to C), combining data for all individual morbidities and the multiple morbidity pairs as a group. We will employ the same modelling approach described above for the incidence data (4.iii) with fractional polynomials and bootstrap confidence intervals employed as appropriate. We will adjust for confounding effects of pre-operative co-morbid conditions and any important confounders not included in matching. We anticipate complete data but will use multiple imputation if necessary.

For presentation to the selection panel (1iii), we will present and rank the estimated effects and 95% confidence intervals for each morbidity and the multiple morbidity cases for each of the 3 outcomes. For the quality of life data we will consider the 6 week and 6 month data separately and present results for both short term and longer-term impact.

(5.v) Sample size:

A clinically relevant difference in quality of life between pairs corresponds to a mean difference of at least 0.5 standard deviations (52). To detect such a difference at 5% significance with 80% requires a minimum of 32 matched pairs. Allowing for a 10% loss to follow-up rate, we will recruit 36 matched pairs for each morbidity. With 3000-3300 patients anticipated, we will have 80% power to detect a significant effect for any morbidity with a prevalence of at least 1.5%. Based on analysis of one year of cardiac surgery cases from GOSH (5), several major morbidities are anticipated to have lone incidence rates of 1-3% and a multiple morbidity rate of 4-7% so we are confident that there will be sufficient cases from which to recruit 6-10 sets of 36 matched pairs and around 120 matched pairs for multiple morbidities (a total of 672 to 960 children depending on the number of morbidities included) from the estimated 3000-3300 patients in the incidence study (objective 4).

Note on patient and parental attitudes to data collection

Experience from work carried out at GOSH is that parents and children engage positively with completion of quality of life questionnaires and other non-clinical assessments. Families want professionals to understand the impact of their child's heart condition on all aspects of their life and want the opportunity to discuss this. Patients and parents also recognise that collection of QOL and other non-clinical data facilitates improved communication with health care providers, allows for monitoring of changes over time (particularly after specific medical, interventional or surgical therapies) and enables child and parent preferences and perspectives to be included in the prioritisation of problems or treatments. Furthermore, the early identification of associated non-cardiac problems (psychological, emotional, financial etc) allows for early referral and implementation of appropriate interventions.

Results and learning from objectives 4 and 5 will feed into the final meetings of the consensus (1.iii) and definition groups (2.i) in year 4.

Objective (6): To develop and pilot sustainable methods for collection and feedback of surgical morbidity data for use in future quality assurance and patient/carer information

(6.i) Developing a framework for monitoring morbidities

This aspect of the study will involve discussions between clinical staff, analysts and data managers to identify logistical processes for collecting and storing data on morbidities in routine practice. As well as defining a practicable data-trail we will identify training needs and any modification to measurement protocols that emerge from the incidence study as being important to facilitate monitoring by staff that are available within existing resources. Although initially focused on participating centres, we will later engage other paediatric cardiac surgery centres in England and the NICOR stakeholder group. This will ensure that the framework developed to facilitate routine monitoring has the best possible chance of being rolled out effectively to other centres nationally.

(6.ii) Developing graphical summaries of surgical morbidity data

It will be an important challenge to develop innovative methods for reporting very different morbidities (across a programme) and presenting them in a way that is easy to produce and easy to understand. There will be two related activities here. One will be the development of graphical summaries to distil the findings of the incidence study (objective 4) for use in informing patients and families about the levels of different surgical morbidities experienced by patients following paediatric cardiac surgery. Where possible, separate data summaries will be prepared for different sub-groups of patients, with the data presented in a consistent format across groups. Initial designs for informing families of the incidence of single or multiple morbidities will be based on the use of isotypes, (64) building on experience within the project team. (65, 66)

The second activity will be the development of graphical data summaries and attendant software for use by clinical teams to monitor programme-level patterns of surgical morbidity, with an emphasis on putting recent morbidity outcomes in the context of national or institutional benchmarks derived from the incidence study. It is likely that the graphical methods developed will be bespoke for this project and the aim is to capture both frequency of morbidities and their relative impact (objective 5) in visually clear and engaging graphical formats. A key challenge will be to provide sufficient information in a format that is intuitively easy for clinical teams to grasp: there are large barriers to adoption of new monitoring tools, which should not be ignored. Members of the project team have experience of successfully developing and deploying graphical monitoring tools for mortality outcomes in multi-disciplinary teams.

In both strands of work, the analysts will go through a process of identifying options for data presentation, consulting with family representative and clinical co-applicants, and iterative refinement of graphical design. The iterative design process will be guided by the key concepts of the data-to-ink ratio, the use of graphical hierarchies to reflect information hierarchies and intuitive labelling promulgated by Tufte. (67)

(6.iii) Pilot routine monitoring of morbidity

Following the final group meetings in year 4 (see objectives 1-2), we will pilot the routine collection and monitoring of the final list of morbidities at the 5 participating centres over 3 months, using the framework developed at (6.i). This will allow us to explore the feasibility of adding the routine measurement of morbidity to existing workload with cardiac units. We will additionally present data on morbidities every month in the context of multi-disciplinary clinical meetings and incorporate feedback concerning the software tool before this is made available to other sites.

DISSEMINATION AND PROJECTED OUTPUTS

Knowledge Output:

Outputs will include:

- The incidence of those morbidities following paediatric cardiac surgery in the UK considered key by patients, families and clinical teams;
- The impact of these key morbidities on quality of life and the burden to families and the NHS;
- Evidence concerning the validity of the BDA tool intended for use by non-specialists in neuro-developmental surveillance before and after cardiac surgery;
- If validated, a training package will be developed for use of the BDA, which will require a particular skill set or competency to be acquired by those undertaking it.
- A list of morbidities recommended for routine monitoring along with measurement protocols and guidance for early management;
- Morbidity monitoring methods and graphical reporting tools for use in local and national audit.

Dissemination:

The work will be reported to the Children's Heart Federation and will be fed back through their various open meetings, newsletters and online (after approval from the funder). The patient and family summaries generated at (6.ii) will be offered for dissemination through these routes to augment existing patient information resources.

In addition to publications in peer-reviewed journals and presentations at academic conferences, the research output will be shared in detail with other centres conducting this surgery and with the national children's heart surgery audit (NICOR Congenital), which is supportive of the planned research.

Knowledge mobilisation opportunities:

This research project has been designed with effective knowledge mobilisation at the front of our minds. The work of the definition group in designing morbidity measurement protocols for routine use within existing resources, and the development of frameworks and tools to help practicing clinicians in the service make effective use of the empirical evidence generated, are intended to help bridge the gap between research and practice. Specifically:

There are very good prospects for the routine monitoring of morbidities begun as part of this project to continue beyond this study, spread to other sites and become an ongoing improvement process for the benefit of patients, families and the health service;

Through existing links and continued engagement with NICOR congenital it is likely that, if our research is successful, morbidity measures selected and defined in this research will be added to national audit.

In addition to the mobilisation of this research in the field of paediatric cardiac surgery, there are opportunities for this research to have significant impact in other areas of paediatric care:

If the BDA is validated, it could underpin the neuro-developmental surveillance of other paediatric populations such as those with critical illness and those undergoing other surgery. With current developmental surveillance in these populations considered to be very weak, there is thought to be significant unmet need for such a service. We will liaise with colleagues in the Paediatric Intensive Care Society to explore this opportunity once the BDA validation study is complete.

The morbidity definitions, measurement protocols and early follow up pathways adopted for this study may be applicable to other contexts for any non-cardiac morbidities.

Our experience of combining patient and carers' perspectives with those of professional groups in defining a prioritised list of outcomes for audit may be valuable to other specialties.

PLAN OF INVESTIGATION AND TIMETABLE

The project timetable is set out below.

Start: 1 January 2014 Finish: 30 June 2017

Activity	Month 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42
Methods (1.i) Systematic review	x x x x x x d d
Methods (1.ii) Focus groups meetings	m m
Methods (1.iii) Selection panel meetings	m m
Methods (2.i) Definition group work	x m x x x x m x x x x m
Methods 3. BDA validation study	x x x x x x x x x x x x d d d
Methods (3.iv) BDA analysis	x x x
Recruitment of research nurses and training	x x x
Methods (4) - Incidence study	x x x x x x x x x x x x x x x x x x x x x x x x d d d d
Methods (4.ii) Analysis of incidence study	x x x x x
Methods (5) Impact study	x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x d d d d
Methods (5.v) Analysis of impact study	x x x x x x x x
Methods (6.i) Developing routine monitoring framework	x x x x x x
Methods (6.ii) Information design and software development	x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x x d
Explore knowledge mobilisation to other specialties	x x x x x x x x x x
Methods (6.iii) Pilot implementation	x x x
Engagement with NICOR (national audit body)	x x x x x x x x x x x x x
Reporting to NIHR HS&DR	x x x x x x x x x x x x x

Legend
x - activity
m - meeting
d - dissemination

PROJECT MANAGEMENT

Data monitoring committee

An independent data monitoring committee will be in place to review measurement protocols and progress and data output at 6 monthly intervals. This DMC consists of: an independent cardiac surgeon as chair (Professor V Hjordhal), an independent intensive care specialist (Dr J Smith), an independent senior nurse (Ms L Tume), and ethics and patient affairs representative (Mrs B Teuton) and an independent statistical consultant (Dr C Rogers).

Steering committee

The study will have a steering committee (75% independent as per NIHR guidance) consisting of one of the co-chief investigators, Dr Christina Pagel (leading the academic partners), an independent chair a cardiologist from the national audit body (Dr R Franklin), Dr Kate Bull, an independent parent rep and three other independent members. The steering committee will oversee progress of the project, meeting at 6 month intervals. Lead surgeons from other centres will have an open invitation to attend steering group meetings.

Management and coordination of work streams

The project will be led by co-chief investigator Mr Tsang with clinical project management by the other co-chief investigator Dr Brown. Dr Pagel will manage the academic work stream. These three will meet fortnightly to: assess progress of the different work streams against the agreed project plan; discuss any

problems with delivery as they emerge, particularly focusing on the potential impact on other work streams; identify strategies for resolving problems; and escalate the response to any unresolved problems. Other individual applicants will join these project coordination meetings as and when necessary, made feasible with key academic partners based near to Great Ormond Street Hospital.

The main business of managing the separate work streams will be conducted though a number of subgroups, with the membership drawn from relevant applicants and collaborators and Drs Brown and Pagel members of every group to ensure oversight. A BDA validation sub-group will be led by Dr Jo Wray; a Selection and Definition subgroup by Mr McLean; the Incidence and Impact subgroup by Dr Brown; the Monitoring Framework group by Mr Thomas Witter and the Information Design group by Dr Pagel.

For the BDA subgroup, given that the two centres are in London and the importance of completing this sub-study in time to inform the incidence study, there will be frequent face-to-face meetings to monitor recruitment and respond to any problems to ensure timely delivery of this component. The work of other subgroups will largely be conducted electronically to facilitate full involvement from collaborators at all sites, using a project website to share material and host discussion forums.

Governance and mentorship at study sites

Responsibility for governance and the smooth running of the study at each site will reside with the lead applicant at that site, each an experienced consultant paediatric cardiac surgeon. In order to deliver this, in addition to the surgical lead, each centre will have a named collaborator who is a senior nurse with experience in advanced practice. This senior nurse collaborator will provide local mentorship to the band 7 research nurses based at each site. Given the specialist nature of the research topic, and the elements of advanced nurse practice involved in the research nurse role (identification of cases with morbidity, application of the brief developmental assessment and patient reported outcome tools with children and families), it is envisaged that the research nurses will require both specialised clinical and research mentorship and support in order for the project to succeed.

Research nurses engaged in data collection for the study will be supported by their local team consisting of the surgeon PI and line managed by the nurse collaborator. They will benefit from a central training program run from the sponsoring centre and support from the local comprehensive research network representatives.

Links with the Comprehensive Local Research Network (CLRN)

The study sponsor will be Great Ormond Street Hospital, where the main CLRN is Central & East London. The study team have consulted with chair of the CLRN paediatric subgroup (Prof Greenhough) and the Senior Manager of the sponsoring institution's CLRN (Mrs Barrett). The relevant CLRN does not have access to direct research nurse support, but does have data management support which the study team intends to draw upon for the data entry and some aspects of data management for the study. The senior manager for the CLRN noted that this study requires research nurses to have background knowledge of cardiac surgical procedures and post-operative morbidities in children with heart disease. She noted that securing funding for dedicated and experienced research nurses will be key to the success of the study. Dedicated research nurses will be able to focus on recruiting participants to the specified time points and other targets of the study. Neither the LCRN nor the Medicines for Children Network has research nurses with a background in cardiology (however the study collaborators at each site will provide this expertise). The LCRN has indicated it will support this study in other ways such as; recruitment of staff into posts, staff to support R&D approvals, training and education and professional development of research nurses.

ETHICAL ISSUES AND APPROVALS

The study will require Research Ethics Committee approval with site-specific Research and Development Office approval at each of the 5 study sites. These approvals will be sought as soon as funding is approved and ahead of the start of the contract for the study. The ethical issues are:

Data protection and consent

BDA validation: patients who are booked to attend a routine outpatient clinic or the preadmission ward, will be written to ahead of their appointment using a standard letter but sent from the clinical department where they are being seen, containing information about the study. They will be given the option to phone the coordinator and let the research team know ahead of the appointment, if they are interested in participating. When they attend the appointment the receptionist will check with them whether or not they wish to see the research team in order to participate further. Written informed consent will be taken for all participants. Age appropriate assent will be obtained with children after consent has been given by the parents.

Incidence of complications or morbidities: This section of the study involves the use of data that has been collected as part of the cardiac surgery mandatory national audit, as well as collection of a small number of additional data items (the selected complication events such as an infection or re operation as an additional yes or no field). This audit data will be fully anonymised before it is shared with the research team. The research team will not record identifying information such as actual names, addresses, numbers and dates. All times will be converted to ages (eg: age at operation, age at discharge, age at death if relevant). Very rare conditions will be grouped. The research team will not be given identifiers for this dataset at any time.

Families are consented at the time of heart surgery for the operation and also for the child's identifiable data to be kept for national audit. Many hospitals also collect certain other data items such as infection rates and other variable complications for internal audit. Further consent will not be sought from those patients whose anonymised data will be included only as part of the morbidity incidence evaluation. Where the parents decline to consent for data collection for national audit, the patient will be excluded from the incidence study. Of note, based on the experience of national audit over the last several years, this refusal of consent for use of data in audit of outcomes is extremely rare (personal communication NICOR 2012).

Impact of complications or morbidities: The local clinical team will be trained and informed about the study such that they are aware of the inclusion criteria and exclusion criteria. If a patient is noted that meets the inclusion criteria this family will be approached by a clinician, after the operation has been completed and the child is recovering in the ICU and asked if they are willing to hear more about the study from the research team. Families who express an interest will then be approached for full informed consent by the research nurses or other named members of study team such as the local PI who is a cardiac surgeon at each site.

Full written informed consent will be sought for all patients who are entered into this matched cohort study, which represents a subset of children undergoing surgery that have experienced a defined complication, and their controls. These patients will then have further follow up data collected which is part of research and goes beyond the usual level of care. There is no actual research intervention, but if any clinical issue is noted as part of the research follow up the patient will be referred appropriately for assessment and treatment by a clinician. Follow up data will be kept as part of the patient's pseudoanonymised study file.

The key for identifying study subjects will be kept securely at the hospitals participating in the study. Signed consent forms will also be kept at the individual participating hospitals. Data will be pseudoanonymised at all phases of the study. Data transfer of pseudoanonymised information for consented parts of the study will be conducted via NHS net using encrypted files.

Patient and public involvement

Focus group participants will be sought via the Children's Heart Federation (CHF) including the CHF website and Facebook site. Those people who agree to participate will be given an information leaflet and consent form, including information about date and location by the CHF. Participation will be voluntary and the recruitment of participants will be conducted by the CHF rather than the study team.

The study team will be represented and will assist with conduct of the focus group sessions, where participants will be asked to consent in writing prior to commencing the session. Once consent to participate

has been provided in written form the forms will be stored in a locked cabinet only available to the researcher. Focus groups will be recorded. Written transcripts will be made, in which participants will not be identified by name, but by a code ID. Data will be stored electronically in encrypted files on the secure study computer at Great Ormond Street Hospital.

Online discussion forum run by the parent and patient group (CHF): previous authors have stated that ethical approval is not required for online social science research. Although the online world is formally a public space, there are issues to consider in this regard. Drs Brown and Wray are currently drawing upon a Facebook discussion forum that is entirely run by the patient and family group the Children's Heart Federation (CHF) for another in-progress study (Infant deaths in the UK community following successful cardiac surgery, building the evidence base for optimal surveillance). This experience of working with the CHF on an online discussion forum run via Facebook is valuable in terms of alerting us to the ethical implications. As has been highlighted the most important ethical implications are data security or confidentiality and personal security or inappropriate content.

The proposed online discussion forum using Facebook will be held and organised by a party that is not part of the NHS (a user group). Therefore although the Research Ethics Committee will be made aware of the part it will play in the project, they are not being asked to formally approve it.

The following measures will be put in place in order to address the issues outlined above:
• The CHF currently maintains a Social Media Usage Guideline, for use by their staff as they monitor such discussion forums. This guideline covers areas that include respectful behaviour, seeking of permission, upholding confidentiality, removal of inappropriate or commercial content and draws upon the Data Protection Act 1998 and the Human Rights Act 1998.
• The identity of participants in the online forum will be unknown to the study team. The forum will be a separate online area for which users will need to register, sharing some basic demographic information with the CHF as they do so.
No identifying information of any kind will appear on line or be shown to the study team
• Once within the forum, discussants will appear under an alias, therefore they remain anonymous to other participants.
• CHF co-researchers will monitor all discussion content in order to ensure it conforms to the CHF Social Media Usage Guidelines.
. Participants will be told at the time of choosing to enter the forum that this relates to a research project, and that the content will be used to help the research team learn about what lay people consider to be important complications of children's heart surgery.

Harms or benefits to patients

Those patients and parents who consent to participate in the impact of morbidity case control section of the study will be expected to keep diaries and undergo more health care surveillance and questions than normal. Participation will be entirely voluntary and travel expenses for an additional patient visit will be met by the study. No research intervention is contemplated and no further harm is anticipated for these patients.

There may be some benefit to the patients and families who participate since they will have additional surveillance and support in the 6 months following cardiac surgery. Any health problems identified as part of the study will prompt a referral for further care. A standard operating procedure will be written with respect to this at objective 2 in the first year, including for neuro-developmental issues.

Audit and data monitoring issues

An independent data monitoring committee will be in place to review study progress and data output at 6 monthly intervals. The DMC has a representative from the national audit body (Dr R Franklin), whose advice will be sought should any matter related to audit of outcomes come to light during the course of the study. Furthermore, outputs of the study will be reported at to the national audit body.

PATIENT AND PUBLIC INVOLVEMENT

The patient or user perspective lies at the core of the study methodology. Specifically, a key goal of the study is to consider the views of patients and parents when measures of morbidity are selected for future audit and benchmarking, in particular since emphasis may potentially differ between professionals and parents / patients.

Patient and family representatives from the Children's Heart Federation (CHF) have been involved in aspects of the study design including determining where focus groups will be held and will recruit the participants to those focus groups and assist in running them. Focus group participants will be compensated for their travel and receive a meal voucher.

Representatives of the CHF will participate in the facilitated nominal group meetings to select morbidities for inclusion in the incidence and impact studies and ultimately those recommended for routine monitoring. These individuals will be recompensed at the INVOLVE rate of pay.

A member of the CHF and a parent representative will sit on the project steering group.

EXPERTISE AND JUSTIFICATION OF SUPPORT REQUIRED

The study team includes a cardiac surgeon co-applicant from each of the 5 participating centres:

PI Mr Victor Tsang (5% FTE), based at Great Ormond Street Hospital (GOSH), has a track record of quality improvement work and health services research. He recently led the successful development of a risk model for peri-operative mortality following paediatric cardiac surgery working with co-applicants Brown, Pagel and Utley. He will lead the project with the co-chief investigator Dr Kate Brown through the management group and additionally contribute clinical insight to the analysis of the role of case mix factors in the incidence of surgical morbidities.

Mr Serban Stoica (5% FTE, Bristol) has an active interest in outcomes research and quality improvement and previously designed a 'Morbidity Index' attempting to capture a range of clinically important burdens to patients following children's heart surgery. He will lead the study at Bristol and be one of the reviewers in the systematic review.

Mr Andrew Mclean (2.5% FTE, Glasgow) has considerable experience of achieving standard definitions for heart operations and morbidity outcomes nationally and worked with Brown, Pagel and Utley to implement a new risk model for mortality following paediatric cardiac surgery. He will lead the study in Glasgow.

Mr David Barron (2.5% FTE, Birmingham) has expertise in clinical outcomes research and has previously collaborated with co-applicants Wray and Brown in the successful validation of a paediatric cardiac disease specific measure for quality of life involving the recruitment of 800 children across 3 UK centres. Mr Barron will lead the study in Birmingham.

Professor David Anderson (2.5% FTE, Evelina) is an expert in the treatment of complex neonatal heart disease and has been a long-term active participant in both local and national audit of surgical outcomes. He will lead the study at Evelina Children's Hospital

Project Management: Dr Kate Brown (20% FTE, GOSH) has considerable experience of health services research and managed the project developing a risk adjustment model for paediatric cardiac surgery in the UK. In addition to managing the study as co-chief investigator with Mr Tsang, Dr Brown will lead the incidence and impact studies. Dr Brown will be assisted in project management by Dr Christina Pagel (30% FTE see below, CORU UCL) in terms of the data aspects.

Dr Aparna Hoskote (5% FTE, GOSH) is a paediatric cardiac intensive care specialist with an interest in neurological outcomes and a track record of research into neurological injury related to heart disease. She will co-supervise the psychology assistants in the BDA validation.

Clinician Collaborators: 5 further clinical collaborators including Mr Andrew Parry, a cardiac surgeon at Bristol, a paediatric cardiologist, a paediatrician, a senior nurse and a GP will contribute to the selection panel. Four further senior nurses will act as collaborators and mentor / support the research nurses at each centre. Two specialist collaborators with critical distance from the study will advise on the BDA validation study: Professor M Lakhanpaul, London and Professor J Rust, Cambridge.

Research Nurses (100% FTE, 2 years): the band 7 research nurse employed for this study at each of the 5 participating sites will perform a demanding role with elements of both research and advanced nurse practice. The advanced practice aspects will be a requirement to diagnose or correctly identify 'cases' or morbidities using the agreed definitions, with the support of the clinical mentors in their centre. These nurses will also need to administer quality of life measures and developmental measures in small children.

Psychology Assistants (100% FTE, 1 year): 3 band 5 psychology assistants will be employed for one year at GOSH and Evelina for the validation of the BDA tool.

Morbidity selection methods and information design: In addition to assisting the management of the project, Dr Christina Pagel, an operational researcher with experience of working on outcomes and improvement projects in paediatric cardiac surgery and in using graphical methods to presenting complex information, will lead the Information Design work stream. In this role she will help develop graphical monitoring tools and develop software for their implementation. Dr Pagel will also set up a project website to facilitate project management and collaboration. Professor Martin Utley (7% FTE) will assist in the development of graphical data summaries and monitoring tools and will also customise and operate robust voting software for use in the consensus meetings (for selecting morbidities).

Health Economics: Professor Steve Morris (2.5% FTE) has considerable experience of health economics, including evaluations of surgical treatments and will supervise the health economic analysis, which will be conducted by a research fellow in health economics (50% FTE for 1 year).

Children's Heart Federation (PPI) (20 days at the Involve rate of pay for co researchers): The Children's Heart Federation (CHF) has extensive experience of canvassing and collating the views of parents and supporters of children with heart disease, for example as part of the recent Safe and Sustainable review. The CHF is an umbrella organisation representing around 12,000 patients and families with heart disease. The CHF has been an active participant in the development of national audit of children's heart disease following on from the Bristol Inquiry and have a strong interest in outcomes that matter to patients and their families.

Medical Statistics: Ms Deborah Ridout (15% FTE) is a medical statistician with expertise in paediatric studies; she also contributes as a reviewer for journals and funding bodies and as a member of an NHS research ethics committee. She will design and conduct analysis for all aspects of the project.

Psychology (GOSH ICH): Dr Jo Wray (20% FTE for 1 year then 2.5% FTE) is a health psychology researcher who has designed and completed a range of qualitative and quantitative studies in paediatric health care. She will lead the BDA validation work stream (see above) and oversee the quality of life measures in the impact study.

Data Governance: Mr Thomas Witter (5%FTE), based at Evelina, has a nursing background and extensive experience of data management, training and governance from his work in local and national audit. He worked with Brown, Pagel and Utley to implement routine monitoring of risk-adjusted mortality at Evelina Children's Hospital. Mr Witter will organise the training for research nurses engaged in the study, alongside Ms Liz Smith (7 days as a collaborator) who is the lead advanced nurse practitioner in the cardiac unit GOSH

NHS costs – it is likely that the study will generate new referrals for further care, for example in children in whom a previously undiagnosed medical issue comes to light as part of the additional surveillance in the study. Therefore NHS costs have been calculated on the basis of an additional outpatient visit for cases in the cohort section of the work.

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Appendix: NEURODEVELOPMENTAL AND BEHAVIOURAL MEASURES CONSIDERED WHEN DEVELOPING THE BDA

Measure	Admin/Scoring	Screener/ full assessment	Age range	Description	How long does it take?	Price of Kit	Price of record form (pk 25)
Mullen Scales of Early Learning (MSEL)	Observer Rated- graduate and working with infants	full assessment	Birth to 68 months	Five scales: Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language	Time: 15 minutes (1 year); 25-35 minutes (3 years); 40-60 minutes (5 years)	£884 (+ VAT)	£40.50 (+vat)
Battelle Developmental Inventory, Second Edition (BDI-2)	Observer rated/	full assessment	Birth-7 years	Administration of the BDI-2 can begin in any of the 5 Domains (Peronal-Social Domain, Adaptive Domain, Motor Domain, Communication Domain, Cognitive Domain). The start points for each subdomain are clearly marked and are determined by the age or the estimated ability level of the child. Examiners proceed through each of the subdomains to determine the child level of development. Overall Developmental Quotient score (each with a standard score mean of 100, SD = 15, score range of 40-160).	1 to 2 hours	$1460.00	Scoring/work booklets $73.50 each (total $147, pk 15)
Denver Developmental Screening Test II (DDST-II), William K. Frankenburg & Josiah B. Dodds	Observer Rated- anyone who works with children	screen	1 month to 6 years of age	Performance-based and parent report items are used to screen children's development in four areas of functioning: fine motor-adaptive, gross motor, personal-social, and language skills.	Testing takes 10 to 20 minutes, on average	£154	£72.00 (pk 100)
Bayley-III Screener test	Observer Rated- trained technicians to administer. Psychologist to interpret	Screen	1 to 42 months	Cognitive, language and motor domains are tested, CaFeatures selected items from the full Bayley-III battery. To screens infant and toddlers at risk for developmental delays	15 to 25 minutes	£270.00	£47.40
Bayley Infant Neurodevelopmental Screen (BINS)	Observer Rated- trained technicians to administer. Psychologist to interpret	screen	3-24 months	The test administrator assesses neurological processes (reflexes, tone), neurodevelopmental skills (movement, symmetry), developmental accomplishments (object permanence, imitation, language	10-15 minutes	Not available in UK	£51.00
Bayley –III Scales of Infant and Toddler Development, 3rd Edition	Observer Rated- trained technicians to administer. Psychologist to interpret	full assessment	1 to 42 months	Cognitive, Language, Motor, Social-emotional, Adaptive behavior	30 to 90 minutes (depending upon age of child)	£1,246.80	£126.00 inc VAT

Ages and Stages Questionnaire (ASQ), Diane Bricker, Ph.D. & Jane Squires, Ph.D.	Parents complete questionnaires, clerical can score	screen	4-60 months	Questionnaire-To screen for developmental delays in the first 5 years of life. It covers 5 developmental areas: communication, gross motor, fine motor, problem solving, and personal-social. It includes 30-item questionnaires completed by the parent or caregiver at specific ages. The first questionnaire is completed when child is 4 months old and the last at 60 months of age. To each developmental item parent responds "yes", "sometimes", or "not yet".	Approximately 10-20 minutes for parent response.	£157	N/A (photocopy)
NEPSY-II (neuropsych battery)	professional scored	full	3-16 years	The *NEPSY–II* is the only single measure that allows the clinician to create a tailored assessment across six domains, specific to a child's situation in order to answer referral questions or diagnostic concerns. The results provide information relating to typical childhood disorders, which can lead to accurate diagnosis and intervention planning for success in school and at home. The six domains are: Social Perception (NEW), Executive Functioning/Attention, Language, Memory and Learning, Sensorimotor Functioning, Visuospatial Processing.	45 mins pre school 1 hour school age	avail in DPM	£58.20
WIAT-II (academic)	professional scored	full but could use 2 subests to screen (e.g. word reading/numerical ops)	4 years - 17 years 11 months	The *WIAT-II*^{UK} provides reliable assessment of reading, language and numerical attainment in one test. An expanded age range, more comprehensive items, and streamlined test materials	45-90 (or less 15 if using a couple of subtests)	avail in DPM	£75.60
WASI-II (IQ)	Administered by Grad student	screen	6-89 years	The WASI consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The four-subtest form can be administered in just 30 minutes and results in VIQ, PIQ, and FSIQ scores.	30 mins (4 subtests) 15 mins (2 subtests)	£342.00 (older version availl in DPM)	£72.00
CMS (memory)	professional scored	full	5 to 16 years	This battery comprehensively assesses the integrity of memory functions in children and enables comparison with measures of both ability and achievement.Its 6 core subtests load onto scales tapping: Immediate Verbal Memory, Delayed Verbal Memory, General Memory, Immediate Visual Memory, Delayed Visual Memory.	30 minutes	avail in DPM	£62.40

BRIEF (Exec function)	parent/child/ teacher rated professional scored.	screen	5-18 years	Each BRIEF questionnaire contains 86 items in eight nonoverlapping clinical scales and two validity scales. These theoretically and statistically derived scales form two broader Indexes: Behavioral Regulation (three scales) and Metacognition (five scales), as well as a Global Executive Composite score. Factor analytic studies and structural equation modeling provide support for the two-factor model of executive functioning as encompassed by the two Indexes. Validity scales measure Negativity and Inconsistency of responses	20 mins	avail in DPM	£44.00
WISC-IV (IQ)	Administered by Grad student	Full Assessment	6-16yr 11 mths	This fourth generation of the most widely used children's intellectual ability assessment meets your testing needs for the twenty-first century. While maintaining the integrity of the Wechsler® tradition, the *Wechsler Intelligence Scale for Children®—Fourth Edition (WISC–IV®)* builds on contemporary approaches in cognitive psychology and intellectual assessment, giving you a new, powerful and efficient tool to help develop and support your clinical judgments	60-90 minutes	avail in DPM	£91.20
BADS-C (Exec function)	grad psychology student	full assessment	7-16 years	The Behavioural Assessment of the Dysexecutive Syndrome (BADS) has been adapted for children (BADS-C) to examine a number of aspects of the dysexecutive syndrome (DES) such as: inflexibility and perseveration, novel problem solving , impulsivity, planning, the ability to utilise feedback and moderate one's, behaviour accordingly.	35-45 minutes	avail in DPM	£22.20
Parents Evaluations of Developmental Status (PEDS)	Parent rated/professional scores	screen	Birth - 8 years	This is a guidance system and triage tool used to elicit parents' concerns about the child's development. Ten questions are used to identify most appropriate response to parental concerns, from immediate referral for assessment, a second screening, developmental guidance for parents, to monitoring or reassurance. It is best used in situations where there is little time and children are followed longitudinally.	5 mins	manual $79	$36 (record and scoring form pk 50)
Battelle Developmental Inventory screen	observer rated/professional scores	screen	Birth-7 years	The BDI-2 Screening Test consists of a subset of test items from the full BDI-2 item pool. The scoring procedures are similar to those of the full BDI-2, but cutoff scores are provided to aid in identification of children who may need additional follow up	10 to 30 minutes	$445.00	$90.50 (pk 30)