Infant deaths in the UK community following successful cardiac surgery - building the evidence base for optimal surveillance

Aims

To use a mixed methods approach including quantitative analyses of national audit data and qualitative approaches to gather information from key individuals, in order to establish an evidence based and realistic guideline for community based surveillance of fragile infants with congenital heart disease.

Research Objectives

1. To perform a literature review, exploring risk factors for death in infancy following cardiac surgery (rather than early post operative death in hospital), to identify examples of successful surveillance or intervention programs for infants with congenital heart disease (CHD) and explore evidence for social, ethnic and economic factors, which may reduce access to health care for children with complex medical disorders.
2. To perform a quantitative analysis of risk factors, including both medical and social variables available from routine data sources, that may be related to the outcome measures: late death or unplanned re admission to intensive care, in infants that have undergone surgery for CHD. This analysis will use national audit data from Central Cardiac Audit Database (CCAD) and Paediatric Intensive Care Audit Network (PICANET).
3. To perform a qualitative study drawing on a series of sources for information, including: an online discussion forum through the main user group's 'Facebook' site, the user group's help line staff, professionals caring for infants with CHD, and parents from high risk groups or of children that experienced one of the outcome measures. Qualitative data from the last three sources will be gathered via semi structured interviews. The objective here is to indentify actual barriers to health care for infants with CHD with particular focus on socio economic challenges and to inform subsequent intervention development. Two focus groups will review and discuss the proposed intervention designs.
4. To combine the data and information acquired in the first three objectives to generate the evidence based protocol or guideline for surveillance of infants with CHD, including the 'who' 'when' and 'how' this should best be delivered. The ultimate objective is to produce a workable and effective follow up surveillance protocol for infants discharged into the community after cardiac surgery, with appropriate targeting of higher risk patients and consideration of measures that will be acceptable and useful to parents and community based health care professionals. Intervention development will include consideration of measures of success.

Study Questions

1. Can a suitable surveillance program or complex intervention be designed with the objective of decreasing mortality associated with infant cardiac surgery, by averting unexpected deaths in the community, subsequent to discharge after 'successful' surgery?
2. Can linkage of individual data from existing routine sources including both clinical and social information, CCAD and PICANET, improve our understanding of why some infants die or collapse at home following cardiac surgery?
3. Can the parents of infants with heart disease and professionals involved in post discharge care better inform the follow up and surveillance processes for infants in the community who have undergone cardiac surgery and help to indentify barriers, which may be impairing their access to health care?

Health care need - Importance of the proposed research:

Congenital heart defects affect 5 to 8 per1000 UK live births [1] and contribute significantly to infant mortality accounting for 3% of all UK deaths in infancy [2]. Around 2500 operations for CHDs are undertaken annually in the UK for children under 1 year old [3]: UK CCAD data from 2000 to 2001 indicated that although 91% of neonates (babies under 1 month of age) survived to 30 days after surgery, only 86% were alive at 1 year and for infants (babies more than 1 month but less than 1 year of age), 95% survived 30 days after surgery, but only 89% were alive 1 year later [4]. Young babies are the most vulnerable group in terms of mortality risk from CHD: 20% of UK CHD deaths in 2003 were reported in children less than 1 year old [2] with a higher proportion of 48% of CHD deaths between 1999 and 2006 reported in children less than 1 year old in the USA [5]. Children who survive past the first year are much less likely to die later in childhood [2].

All cause mortality for CHD has fallen dramatically in recent years, reflecting improvements to cardiac surgery and in-hospital care [2,5], but less attention has been paid to post-hospital events. UK audit data from two units for the years 2000 to 2009 found that 11% of neonates operated died within 30 days of surgery, but a further 7% died later after apparently 'successful' surgery, around half of these deaths occurred in the community or after unexpected emergency readmission [6]. This audit also suggests that 'out of hospital' deaths may be related to ethnicity and deprivation but the mechanisms are unclear. Increased risk of CHD death was recently reported in non white ethnic groups in the USA [5,7], especially infants. Young children from more deprived backgrounds are more likely to require emergency admission to hospital for other reasons [8] and to be admitted to paediatric intensive care units in the UK [9]. The evidence suggests that infants who are more deprived

or from certain minority ethnic groups may be at a particular disadvantage in terms of accessing crucial health services at a particularly vulnerable time in their lives.
We hypothesise that a proportion of community CHD deaths might be preventable if their antecedents, individual, social and healthcare-related, were better understood and addressed. The evolving paediatric cardiac service networks could target community provision to support children at highest risk and provide a significant dividend in decreasing overall mortality and emergency readmissions. Datasets examining CHD outcomes are routinely but independently collected through CCAD and PICANET. Record linkage of individual data could vastly increase their value in providing evidence to support health improvement. Qualitative information regarding the views of parents and others involved in the community care of these high risk infants is lacking: we propose that this data is a vital piece of the jigsaw and suggest that a 'mixed methods' research study is required in order to adequately address this topic. Although this piece of work will not encompass evaluation of the effectiveness of the proposed intervention, measures of success will be identified that could be subject to audit either locally or nationally going forwards.

Summary of the current evidence:

CHD-related infant deaths

Mortality related to CHD surgery has fallen dramatically with improvements in hospital-based care [2,5], and a large proportion of research studies and publications have focused on surgical and intensive care advances, which have been beneficial. Nonetheless, UK CCAD data suggests that significant numbers of additional deaths occur beyond 30 days but within the first postoperative year [3,4]. During 2007-9, 1210 UK children underwent neonatal cardiac surgery of whom 64 died within 30 days and at least a further 63 died within one year [3]. It is well recognised that the first year of life is a particularly high risk time for children with CHD, and that those who survive past their first birthday are subsequently at lower risk during the rest of childhood [2,5]. To clarify the circumstances of death in neonatal surgery patients, case note reviews were conducted at Great Ormond Street and Royal Brompton Hospitals [6]. These identified 1018 neonates operated over the nine-year period to 2009; 116 (11%) died in hospital. Of 902 discharged, 60 (7%) subsequently died before their first birthday. Of deaths after initial discharge, 11 were associated with further intervention, 10 occurred following a decision to preclude further surgery, but the remaining 37 were unanticipated, often occurring after a short illness. Deaths occurred disproportionately in patients with complex cardiac anatomy or surgery, but also in individuals for whom favourable outcomes were expected. Analyses using a postcode-based index indicated that deaths occurred

disproportionately in babies in the highest quartile for deprivation and those of 'non White-British' ethnicity.

Known risk factors for CHD deaths

Risk factors for early postoperative death and prolonged hospital stay after infant CHD surgery are well understood; certain more complex underlying cardiac diagnoses and the presence of non-cardiac co-morbidities are important determinants [10,11]. Very small premature babies that undergo surgery and those who are particularly unwell before the operation are also at greater risk [11,12].

Deprivation, ethnicity, ICU admission and mortality in childhood

Parslow et al 2008 examining rates of admission to PICUs using PICANET data, documented that South Asian children were disproportionately admitted relative to non south-Asian and the age-sex standardised admission rate for children in the highest quintile of deprivation was twice that for the lowest quintile, using an area-based index [9]. Freemantle et al 2009 documented an 8-fold difference in infant mortality between England's 300 Primary Care Trusts (PCTs); a model including social deprivation, ethnicity and maternal age accounted for 70% of heterogeneity in outcomes between PCTs [13]. Kyle et al in 2010 examining emergency admissions of children to hospital in London, found that this was significantly more likely in those from lower index of multiple deprivation [8]. There is no research on community-based factors potentially predictive of death after hospital discharge of babies in the cardiac context, although there is recent data from the USA which indicates that infants from ethnic minority communities [5,7] and those with very complex heart defects living in more deprived neighbourhoods [14] are at greater risk of death and that children with cardiac transplants from ethnic minority families and those with greater levels of deprivation are at higher risk of graft loss [15].

Impacting deaths

Evidence from single-institution American studies strongly suggests that intensive post-discharge surveillance can avert deaths in the community for patients on staged-palliation management plans, e.g. a study of 139 babies with Hypoplastic Left Heart Syndrome [16]. Inclusion in these protocols relies entirely on 'cardiac' criteria and the data is from highly selected small groups of patients. There have been no corresponding publications from UK centres, and none, which take the views of parents or socio economic factors into consideration. An intervention that is likely to be effective in this context is 'complex', since a whole range of effects are likely to be in play, all of which need to be considered going forwards. Furthermore, it will be important to understand how any proposed intervention is likely to work practically at various levels: for professionals, parents, disease complexity of patients, in order to get the best and most efficient solution.

Service implications

The Children's Heart Federation (CHF), preparing for the NHS 'Safe and Sustainable Report 2010' [17] commissioned a survey (Ipsos MORI 2009). Exploring equity issues, evidence of difficulties for low income families emerged. Also the families' strong valuation of the role of specialist cardiac liaison nurses, was highlighted, who have a role in post discharge care. There is little formal qualitative research documenting families' view of their own needs. Information about issues of language and comprehension, understanding how health services operate and practicalities of accessing help if a baby becomes sick is anecdotal and would benefit from qualitative research.

Summary for the Non-Expert:

Over recent years, the outcomes of children's cardiac surgery have improved, largely related to better management in hospital. Death rates within 30 days of operation for UK children are publicly available on the internet in the form of national audit data. Perhaps surprisingly, for babies under 1 year of age, almost as many die later on, between 30 days and 1 year after their surgery, as die in the immediate 30 day postoperative period. A further proportion of babies experience readmissions to intensive care after deteriorating at home. These later deaths and readmissions, which may happen quite unexpectedly, are less well understood than deaths in hospital and it is possible that some of them could be prevented by different approaches to monitoring of babies in the community. A local audit of 1019 babies, performed at two London paediatric cardiac centres, suggested that certain babies were at higher risk of dying after discharge home: those with more complex disease and those from more deprived environments. Previous research in children does suggest that those from more deprived backgrounds and from certain ethnic minority groups are at greater risk of very serious illness requiring admission to intensive care, suffering accidents and dying in hospital. We hypothesise that similar mechanisms may put certain vulnerable babies with heart disease at particular risk of dying after their cardiac surgery has been completed.

There is data from a single centre in the USA involving around 150 patients, indicating that babies are more likely to survive infancy after particularly complex heart surgery, if extra home monitoring measures are put in place. This study did not evaluate social or ethnic factors. We would like to obtain more information about which UK babies are particularly at risk and therefore which would benefit most from special 'surveillance' and intervention. This work could be done by studying UK audit datasets that were collected for all children that undergo cardiac surgery (Central Cardiac Audit Database, CCAD) and admissions to intensive care (Paediatric Intensive Care Audit Network, PICANET). These databases contain verified information about deaths as well as a wealth of other medical and demographic data: analysis of linked information could provide valuable insights into which

babies were at higher risk of dying in the community, and therefore which families need extra help watching over their vulnerable infants with congenital heart disease (CHD).

The paediatric cardiac programs in the UK have undergone a 'Safe and Sustainable Review' in 2009-10, which prompted the concept of networks of practice outside specialist centres, that link to the specialist centres and provide follow up care to children with CHD. For this model of healthcare to work effectively, with best use of available resources, follow-up and surveillance procedures should be optimal and where feasible, evidence based. We aim to evaluate the relationship between different follow up regimes (including the use of liaison nurses) and the study outcome measures (community deaths and ICU readmissions) by surveying all the UK paediatric cardiac centres, interviewing a nurse and a doctor involved in the network from each specialist centre.

As family circumstances may vary considerably in terms of language, resources and cultural factors, we aim to interview a set of 20 to 25 families with children that have CHDs from 3 different cardiac centres in the UK (Birmingham, Great Ormond Street and Royal Brompton Hospitals). Selection of families will focus on infants who clinicians indentify as having been re-admitted unexpectedly to intensive care after ‘successful’ surgery and families identified as ‘higher risk’ through our proposed analyses of the data collected nationally about all children undergoing surgery. We will also seek ethical approval to interview some families who have lost an infant with CHD unexpectedly in the community. These family interviews will be carried out in the parent’s home by a psychologist and where necessary with the help of an interpreter. The aims of this qualitative enquiry will be to establish more in-depth information about issues influencing families' ability to recognise the need for and access health care and information about their child's condition, since this may in turn have an effect on the chances of an infant dying unexpectedly. For this stage of the project, we have consulted the parent representatives of the Children's Heart Federation (CHF), a group in contact with 12,000 parents and patients with CHD. We will use prior stages of information gathering in order to indentifying appropriate families to meet, the most informative topics to cover and ideas for intervention approaches. These steps are: the initial analysis of which children were at risk based on the analysis of national audit data, interviews with the individuals running the parent help line and an online discussion forum using the CHF Facebook site.

We have enlisted the help of a primary care specialist, a general paediatrician involved in the care of children with complex needs and parent group representatives to assist us in reviewing the study information, and using it to inform the design of an intervention suitable

for preventing community deaths in infants with CHD. Surveillance and intervention would be targeted at infants who have been discharged after undergoing 'successful' cardiac surgery and are indentified as being at greatest risk of dying in the community based on our proposed analysis of risk factors at the time of discharge. Costs of the proposed intervention will be considered. The proposed intervention types will be reviewed by a focus group of parents and at a national meeting of professionals. When designing the new follow up guideline we will consider things that could be measured going forwards to assess whether the guideline is successful. We believe that the right type of intervention in this situation is likely to be 'complex' since several different factors are in play, including health care system issues, parental and family factors and considerations related to the severity of the diagnosis. We propose that a mixture of approaches combined together is the best method for obtaining the key information about this topic, since the relevant information does not fall under one simple umbrella.

Methods

1) LITERATURE REVIEW

The aims of the literature review will be:

1) to identify risk factors for death in infants and young children discharged home well following infant cardiac surgery (excluding early post-operative death in hospital),
2) to explore evidence for social, ethnic and economic factors, which reduce access to health care for these children,
3) to identify examples of surveillance or intervention programs which have been successful in preventing post-discharge deaths in infants with complex medical disorders.

The literature review methodology will comprise the development of a comprehensive search strategy of relevant medical and nursing electronic databases (Cochrane, Medline, EMBASE, PsycINFO & CINAHL) using clearly defined criteria for the inclusion and exclusion of retrieved abstracts (including time period, language, study design and age-range of subjects). Subjects will include children under the age of 16 years with heart disease, the intervention of interest will be post discharge care and the outcome of interest will be death or critical illness late after treatment for heart disease. A proportion of all retrieved abstracts will be screened by two members of the study team and inter-rater agreement calculated (kappa statistic). Original published papers will be obtained and reviewed, for any abstracts which meet the inclusion criteria, using a data review and extraction proforma to identify factors relating to the quality of the reported study and of the findings relevant to the stated

objectives of the literature review. Each paper will be assigned a quality score based on the study design and adapted from previous scores reported by Khan[18] and Wells[19] . A narrative synthesis of the evidence addressing each of the objectives will be presented descriptively with higher priority given to studies with higher quality scores. Evidence tables including brief details of all excluded and included abstracts identified by literature search strategies will be provided as appendices.

2) QUANTITATIVE ANALYSES

Inclusion criteria, outcome specification and data sources

- The inclusion criteria will be children under the age of 1 year having cardiac surgery or interventional catheterisation for CHD in the UK.
- Inclusion dates will be between 1/4/2005 and 31/3/2011: this is an era during which data quality has been optimised in CCAD.
- The list of patients will be obtained from CCAD, which has complete capture of UK cardiac procedures for CHD in children between these dates and tracks mortality via the Office of National Statistics (ONS).
- Included patients will be subdivided into those undergoing the primary intervention in the neonatal period (less than 30 days of age) and the primary intervention in infancy (more than 30 days but less than 1 year of age), since different procedure types and risk profiles apply to the two groups, which may impact on follow up procedures.
- Exclusions will be patients from overseas that cannot be subjected to follow up, and premature babies who had ligation of patent ductus arteriosus since the majority of these are a different population of premature infants and subject to different discharge and follow up processes run mainly from neonatal intensive care units.

The outcome measures of interest will be:

Primary Outcome:

All deaths between the date of discharge to home following surgery and 1 year after the primary intervention date.

Secondary Outcome:

All unplanned re admissions to a UK paediatric intensive care unit (ICU) between the date of discharge to home following surgery and 1 year after the primary intervention date. These unplanned readmissions to ICU will be tracked using the patient NHS number in the PICANET database.

Comment on Outcome Measures:

It is difficult to disentangle the causal antecedents of either late deaths or PICU readmissions in 'cardiac babies' – the intubation, ventilation and feeding problems associated with cardiac surgery all increase the risk of aspiration and late respiratory vulnerability. While late 'sudden' death may in principle relate exclusively to the heart, arrhythmias or coronary problems are very rare in this age group. More likely, most PICU readmissions are in the same spectrum of complications as the 'sudden deaths' at home and could be treated as 'near misses' – a surrogate in terms of event rates and contributing risk factors. Our hypothesis is that a proportion of such readmission events may reflect issues relating to care access, and ideally in the longer term an intervention that could reduce the likelihood of this happening would be beneficial, perhaps by intervening at an earlier stage. There is some evidence referenced in our protocol that children from more deprived environments and from South Asian heritage are at increased risk of critical illness from all causations[9]. This issue has not as yet (as far as we know) been evaluated specifically in the high-risk group of young infants with congenital heart disease.

Sample Size

The sample size is based on 5 years data but we have extended the inclusion dates by 1 year allowing for an additional 20% of data to be used for the analyses bringing the estimated total number of cases up from 8000 to 9600.We plan to include as our sample, all UK infants and neonates, discharged after cardiac surgery during the first year of life, over a 6 year period.

Sample Size Calculations (based on 5 years data):

Based on public CCAD data [3], we anticipate that there will be 8000 infant operations and 2200 infant catheters for CHD and 4250 neonatal operations and 1400 neonatal catheters during this time period. Since around 75% of patients undergo one procedure and 25% undergo more than one (personal communication, Sonya Crowe, Clinical Operational Research Unit, UCL), we estimate this will involve approximately 9190 patients for surgery and 2700 for catheters: 35% neonates and 65% infants. Considering exclusions (isolated PDA procedures and overseas patients, plus early post operative deaths[3]) we anticipate there will be 2900 neonates (post surgery death rate assumption 10%[3,4,6]) and 5250 infants (post op death rate assumption 5%[3,4]) after exclusions and early deaths (total eligible patients 8150). Assuming the national late death rate for neonates is similar to the GOSH and Brompton rate of 7% [6], then we could have up to 203 late deaths for neonates. Assuming the infant late death rate is between 2 and 6% (based on published data[3,4] and unpublished local audit) there would be 105 to 315 late deaths for infants. Of course we

expect to have a certain amount of missing data and cases for which we are unable to provide a match, so in reality the number of deaths for which we have prognostic data is likely to be less than this.

There is currently no audit data available on the rate of unexpected readmission to PICU in cardiac babies, and evidence for this is anecdotal. Therefore the sample size calculation for this is more challenging. In the largest UK cardiac centre (one of 12 current tertiary paediatric cardiac centres nationally) the rate of unexpected readmission to PICU in cardiac babies in the years 2008 to 2010 was very similar to the late unexpected death rate in the same population, however we do not currently know if the rate will be similar nationally, since this may have been influenced by local case mix and practice patterns to that centre.

For developing prognostic models, Harrell [20] suggests as a rule of thumb to have no more than m/10 potential predictors, where for binary data (late death) m is equivalent to the number of deaths in the data set on which the model is derived. This increases the chances of obtaining a reliable model and allows predictive discrimination that validates on a new future sample. We expect to consider no more than 12 predictors although of course may consider additional transformations for some of these. So in terms of the likely number of deaths we feel it is reasonable to consider the predictors we have described.

The development of a risk model from this dataset is proposed with the aim of informing an algorithm for follow up and re intervention in vulnerable infants with CHD. Our aim is to design a new and refined follow up process including when to intervene, which is based on available evidence and may serve more effectively than the current approaches used. The quantitative and qualitative data we propose to gather all informs this end. In terms of the expected number of patients available for this analysis, we can demonstrate the expected precision of the sensitivity of the resulting models. The calculations below are based on a range of plausible values for sensitivity.

The total number of patients (Neonates +Infants) = 8000. We propose to discriminate neonates and infants by using patient age at operation as a covariate.

Number of positives (deaths) range from 300 – 600 i.e. prevalence for the primary outcome varies from approximately 3.5 to 7%. We estimate that prevalence of the secondary outcome is similar, but do not have the same level of evidence for the primary outcome to back this up.

For an anticipated sensitivity of 75%, with a sample size of 8000 patients we will be able to estimate sensitivity with a precision of +/- 5%, for an overall prevalence of 4%, i.e. 95% CI

for sensitivity would be (70%, 80%). For a lower sensitivity, 65% say, we would have a precision of +/-6%. If the overall prevalence is higher, then we would expect greater precision. As the prevalence of deaths is small, then the estimation of the specificity will not be a problem.

In terms of the predictors in the models, we demonstrate below the power of our study for two important predictors of interest, deprivation and ethnicity, basing these estimates from the sample of data from the two cardiac centres referred to earlier in the protocol on page 3.

For logistic regression analysis using several continuous, Normally distributed variables, to detect a change in the probability of an adverse event of 0.02 when all predictors are at their mean level, to a probability of 0.04, when predictor of interest, deprivation score for example is increased to one standard deviation above the mean, we would require a sample size of 1511. This change corresponds to an odds ratio of 2.04. As there is likely to be correlation between predictors, we have assumed a high squared multiple correlation coefficient of 0.6. The above calculation assumes a power of 80% and a significance level of 5%. Similarly to detect a change in adverse event from 0.04 to 0.06 (OR of 1.53) would require 2270 patients.

For the predictor ethnicity, we anticipate investigating the odds ratio for late death for non whites versus whites, and aim to detect an odds ratio of 1.4 as being statistically significant. Assuming our sample will contain twice as many whites compared to other ethnicities in total and with an 80% power and a 5% significance level, we will need 6000 patients to pick up this effect, which is well within our sample size.

List of potential predictors

Sex

Weight at operation

Age at operation

Deprivation Index (Index of multiple deprivations)

Ethnicity (details below)

Table showing the standard NHS ethnic categories & codes:

Ethnic Categories		Codes
a. White	British	A
	Irish	B
	Any other White background	C
b. Mixed	White and Black Caribbean	D
	White and Black African	E
	White and Asian	F
	Any other mixed background	G
c. Asian or Asian British	Indian	H
	Pakistani	J
	Bangladeshi	K
	Any other Asian background	L
d. Black or Black British	Caribbean	M
	African	N
	Any other Black background	P
e. Other ethnic Groups	Chinese	R
	Any other ethnic group	S
f. Not Stated	Not stated	Z

Diagnosis Category (Complexity of underlying heart defect[21])

Co-morbidity (additional congenital abnormalities and acquired health problems not involving the heart)

Procedure type (Complexity of cardiac intervention[22])

Duration of hospital stay (This is a reflection of medical complexity and morbidity events[23])

Duration of ventilation (This is a reflection of medical complexity and morbidity events[11])

Birth weight

Gestational age

Statistical Methods

We will undertake initial descriptive analyses of the data set, followed by univariate analyses of the relationships between the risk factors mentioned and the two outcome measures separately. Once these results have been reviewed and discussed by the study team, further multivariable analyses will be performed.

For the 2 main outcomes, death after hospital discharge and unplanned ICU readmission within 1 year, prognostic models will be developed to identify important medical and social predictors. For the late death model, a random effects logistic regression model will be used, adjusting for clustering both within an anonymised PCT code and within an anonymised centre code. Odds ratios with 95% confidence intervals will be presented for each of the significant predictors. A random effects Poisson regression model will be used for the readmission data, using the number of admissions as an outcome and log of time since

discharge as a likely offset. Again, clustering within PCT and within centre will be considered and rate ratios, with 95% confidence intervals will be presented for the predictors of interest.

We anticipate the relationship between some of the predictors and outcome may not be linear (age for example) and we will investigate such relationships through fractional polynomials or cubic spline models, as appropriate. In addition, we will explore interaction terms based on findings in the literature, e.g. Parslow explored the interaction between deprivation and ethnicity. Akaike Information Criteria (AIC) will be used to compare the various models.

It is likely there will be some missing data and we will employ suitable methods to account for this. Depending on the nature of the missing data, it may be appropriate to use formal multiple imputation methods, or sensitivity analysis.

In order to validate the final models, we plan to use the bootstrap algorithm described by Harrell [24], to estimate potential optimism of the model, as a consequence of possible over fitting. We aim to derive a model that allows us to rank likely outcome, although not necessarily to present an absolute risk score for each outcome.

To determine the discriminatory power of the final models, i.e. the ability to differentiate between death/survivor and readmission yes/no, we will evaluate the receiver operating characteristic (ROC) curves for each model and report the area under the curve (AUC). Calibration of the models will be assessed using the Hosmer-Lemeshow goodness of fit $\chi 2$ test, based on estimated percentiles of risk.

In addition to the derivation of the above two prognostic models, we will fit a further model for each outcome, including centre effects as a fixed effect, through the use of a series of dummy variables. This will allow us to describe any differences in outcomes between centres, adjusting for all other factors.

3) **QUALITATIVE ANALYSES**

The qualitative study aims to explore whether parents experience or perceive barriers to accessing care for a range of social, economic or medical reasons, and will particularly focus on barriers to care that are amenable to modification. We propose to use the framework approach to the analysis of our qualitative research data [25], which will include transcripts of interviews with families and health professionals, as well as data collection from focus groups and electronic media. The framework approach was specifically developed for

applied qualitative research and designed to allow appraisal of research findings by others in addition to the primary qualitative researcher. This approach is particularly well-suited to our proposed study, as it facilitates linkage between qualitative analyses and quantitative findings. A framework approach has the additional benefit of allowing *a priori* objectives to inform the qualitative analyses; interpretation of the qualitative data is thus influenced by the themes emerging from these data, the original research aims and relevant quantitative analyses.

Information will be gathered from the following sources:

Online forum

An online forum will be established with the CHF as a link from their website and Facebook page. The advantage of an online forum is that a wider range of parents can be asked to contribute their experience of living with an infant who has been discharged after cardiac surgery. The breadth of services may vary between regions and tertiary centres, as well as between rural and urban areas, and interventions may need to be adapted to these varying situations. The Facebook forum will seek to obtain information from a national sample of parents to inform the study but will be restricted to a more limited range of questions suited to a survey and written medium. We recognize that access to online media will vary between socio-economic, age and ethnic groups so the forum will supplement data from interviews. The use of online forums is increasing, however these forums are considered a relatively novel method for qualitative research, evidence about managing these is limited but emerging [26] for example in women with breast cancer. However, we would expect to manage the forum as a short written survey with a request to parents to also submit a narrative of a specific health-seeking experience if appropriate. The predefined and limited set of questions will ask about the services they receive, how they value these, any barriers to access that they have identified and what additional support they would find helpful. If appropriate, they can submit a short narrative describing seeking healthcare for a post-operative child in the community at a time of illness. We will clearly inform participants when they sign up to the forum that they are participating in a survey and we will obtain demographic details although not including identifiable information. The qualitative researcher will collate survey responses and undertake a thematic analysis of the narratives. Results of these analyses will inform the interview topics and possibly development of the intervention.

Professionals

Professional participants will be identified via CHUKRA (Children's Heart UK Research Association), which will publicise the study with the specialist centres and identify two members of staff from different disciplines, involved in the network for each of the 12 UK centres to participate. These interviews will explore experiences that professionals may recall related to the outcomes of interest, as well as processes that are in place to deal with follow up needs of infants with CHD at their centre and professionals rating of these. If feasible based on the quality of data collected, variability in community deaths between units will also be clarified by linking the quantitative outcome data with the health care process data from the specialist centres, for example using clear quantitative variables such as the ratio of liaison nurses to patients, presence or absence of written information for parents and follow up protocols. Interview transcripts will be reviewed in order to identify themes. Process problems identified and barriers to care noted by the professionals interviewed will be presented in stage 4 (Intervention design).

Children's Heart Federation (CHF)

Following a period of training, the CHF will assist with the qualitative study as co researchers, contributing to the qualitative study in the following ways: they will use their website in terms of the online forum described above, recruit members of their telephone help line for interviews and dedicate a section of their regional user group meetings to recruit participants for focus groups as described below. Their involvement will assist with the exploration of social, practical and economic factors underlying access to specialist services and support when an infant with CHD is at home, as well as different intervention approaches (examples: telephone, text, webcam, home visit, clinic visits), from the perspective of parents and families: these data will be used later for intervention design.

Parents and families

Interviews will be undertaken with approximately 25 parents from 3 cardiac centres (GOSH, Brompton, Birmingham); participants will be recruited by the clinical team in each of the three participating centres. Families who express an interest or wish to take part will be sent further information about the study, and where appropriate will proceed to written informed consent. We have included individuals in the study team that have experience of counselling distressed parents in case this should arise during the course of the study. Interviews will be carried out in the parent's home with a second person present who may be an interpreter where this is indicated. Parents currently managing a child post-surgery in the community are the focus of the qualitative investigation, as this is the group that will be targeted by the intervention. In particular, parents who are from high risk groups based on the quantitative

analyses will be targeted. The second group of parents to be targeted for interview will be those who have experienced the outcomes. We will seek ethical approval to interview bereaved parents and will ask consent to include any who are willing to report their experiences. Parents of a child that was readmitted as an emergency will be interviewed. Themes for inclusion in the interview plans will be taken from earlier stages of data collection, including comments from professionals, online forum and help line staff. The interviews aim to explore parents' concerns about their child's health, current and anticipated use of support services and ability to recognize, anticipate and appropriately respond to future illness or emergency situations.

Interviews

Comments on interview plans for each group of interviews:

- *Semi-structured interviews with nurses/health professionals* will ask them to review and critique the processes in place at their centre to address the follow up needs of infants with CHD, and the circumstances of specific instances when they have been involved in the unexpected readmission of a child to hospital ICU or a community death and explore
    - The factors that precipitated this admission
    - Support services being provided or used by families – and the relative value of these
    - Any factors relating to the family or health care contacts prior to admission which may have contributed to readmission
    - Timing and types of additional support which might have been offered to prevent readmission – specific examples of these will be suggested and discussed.
- *Semi-structured interviews with CHF helpline staff* will ask them to describe parent use of the helpline to obtain advice about accessing support services day-to-day and in the emergency situation. The focus of these interviews will be on understanding
    - The range and frequency of different types of advice sought by parents from the helpline
    - Parents knowledge and understanding of services available and how to access these
    - Barriers to accessing support services – as perceived by the helpline staff
    - What advice and help parents seek from the helpline at times of emergency (if any).

- *Semi-structured interviews with parents* will explore the following issues by asking first about actual experiences of their child becoming unwell in the past and then about anticipating future events. Topics for use with bereaved parents in particular will be scrutinised by parent co researchers and psychologist:
    - Parent concerns about their child's health in day-to-day activities, such as feeding, sleeping, attending nursery, playing with friends or other family members
    - Parents' ability to recognise signs of illness in their child and their response to illness in the past, as well as their anticipation, knowledge and confidence in their ability to address situations in the future
    - Who parents would (or did) consult in the event of a child becoming unwell and why
    - Whether they have previously had difficulties accessing care, or would anticipate future difficulties
    - What additional support services they would value (or would have valued)
    - Ways in which support might be offered (or could have been offered) – specific examples of these will be suggested and discussed (e.g. text, home visits) with parents if appropriate.

- Although the structure of the semi-structured interviews will be based on the above, each interview will be developed with the interviewee to explore the issues that are most relevant to them.

Focus groups with parents

Recruitment to participate in the focus groups will be performed by the CHF team with some assistance from the professionals involved in the study: each will have 8 to 10 participants. A detailed focus group moderator guide will be informed by the data analysis from quantitative, interview and online forum sources and will therefore be developed with regard to these. One researcher will moderate the focus group and at least one other will act as an observer and recorder of the discussion and non-verbal interactions in addition to the digital recording/transcription.

- The aim of the focus groups is for parents to influence the design and development of the intervention, and to ensure its acceptability to parents.

- Focus groups will be structured to ensure that participant characteristics are sufficiently representative of parents of children at higher risk who would be receiving the intervention.
- Detailed focus group schedules will be informed by the data analysis from quantitative, interview and online forum sources and will therefore be developed with regard to these.
- Two focus groups will be undertaken, and the discussions recorded digitally and transcribed. One researcher will facilitate the focus group and at least one other will act as an observer and recorder of the discussion in addition to the digital recording/transcription.
- A thematic analysis will be undertaken.

4) **INTERVENTION DEVELOPMENT**

An intervention development panel will consist of: 2 parent representative co researchers (recruited through CHF), a primary care specialist, a general paediatrician from a district hospital, a psychologist, two liaison nurses, a quality improvement expert, an NHS manager and two medical representatives from a tertiary centre. It is anticipated that this workshop panel will meet 6 to 8 times over the latter 18 months of the study period, most intensively during the final 6 months for intervention design, and will be facilitated by members of the research team / advisory group. This is essentially an 'expert panel' which will review and critique the outputs of the earlier phases of the study, in order to explore the best option for a new guideline for infant heart disease going forwards.

Key themes from the first three sections of the study will be presented and discussed at meetings of this group, including the results of 1) the literature review, 2) the risk model analysis from national audit data with identified risk factors for poor outcome, and 3) concepts emerging from qualitative data including perceived barriers to care access from the standpoint of both professionals and parents / families and new options for complex intervention design. User responses to proposed intervention approaches will be considered. Options for complex intervention will be developed by the research team and subsequently presented to this group for appraisal and comment. Costs of proposed interventions will be considered. Currently follow up processes are in place for these infants, but the pilot study performed indicates that these may not be effective and in particular may put certain ethnic minority or more deprived families at a disadvantage. Furthermore, the current follow up pathways may vary nationally or may be inconsistent from centre to centre. A hospital manager with quality improvement training has been included on the intervention development group in order to explore the relative costs of intervention options. Costs of

current processes and resources such as staff that are already in place will be considered in the evaluation of intervention options.

A national workshop will be convened alongside a professional society gathering (British Congenital Cardiac Association) to critically discuss and appraise the study findings and proposed intervention options; this workshop will involve the intervention development panel, project management group, professionals from different national centres affiliated to CHUKRA and CHF representatives. The purpose of the national workshop is to ensure that a proposed intervention is acceptable to professionals and to optimise uptake of the intervention. This approach has been tried and tested by the Central Cardiac Audit Database (CCAD) with their annual national stakeholder meeting which provides a forum for two way communication of key information with individuals from the various cardiac centres. This will contribute to the development of a final report defining the evidence available and the proposed intervention pathway. Development of the intervention will include consideration of indicators of success that would be practicable to collect locally or nationally, such as clinical measures (for example, mortality rates) and possible patient experience measures (PREMS).

Contribution to collective research effort

The study team intends to identify professional participants at the 12 UK cardiac centres (1 recently stopped doing cardiac surgery but still running outpatient services) using the Children's Heart Research Network (CHUKRA) in order to contact the relevant doctors and nurses involved in the follow up care of patients discharged home following cardiac surgery. Any evidence based protocol for the follow up of infants with heart disease developed during this study, including information identifying high risk patient groups and special surveillance measures applicable to them will be disseminated to the specialised centres via the CHUKRA network at the end of the study period. This information could then be fed back and potentially implemented within the follow up networks administered by each of the 12 specialist cardiac centres, in order to give greatest impact on patients. There would also be the option of introducing a new complex intervention in the form of a trial or intervention study at a later stage.

Plan and investigation timetable

See Flow diagram and Gantt chart.

Approval by ethics committee

The study will require full ethical approval by a research ethics committee.

Quantitative section: Linkage between CCAD and PICANET will require use of NHS numbers and is needed in order to permit counting of patients readmitted to intensive care as an emergency after hospital discharge (in PICANET). This will require approval from the Ethics and Confidentiality Committee of the National Information Governance Board (NIGB), which has governance oversight of the national audits and will be carried out by PICANET after receipt by them of a list of NHS numbers from CCAD. Deprivation scoring will be performed within CCAD so that patient identifiers can be removed from the data before it is released to the research team for statistical analysis. Individual cardiac units will be coded by number in the released data such that they cannot be identified. Release of the national audit data to the research team will be on the basis of appropriate information governance and data security arrangements and we will seek formal approval for these through the National Information Governance Board (NIGB). Data will be analysed and managed at Great Ormond Street Hospital / Institute of Child Health..

Qualitative section: Professional interviewees will be approached by the CHUKRA lead. Focus group participants will be sought via the CHF group meetings and Facebook site. Those who agree to participate will be given an information leaflet and consent form, including information about date and location. Names and contact details of these interested participants will be held in an encrypted file on a password protected computer. Participation will be voluntary. Once consent to participate has been provided in written form the forms will be stored in a locked cabinet only available to the researcher. Professional interviews may be conducted by telephone. Focus groups and interviews 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.

Ethical approval is not required for online social science research. Although the online world is formally a public space, as researchers we still need to ensure that we are conforming to ethical standards specific to online populations.

Suitable parents for interview will be identified from the databases at the three participating cardiac centres in consultation with the lead clinician for the study at each centre. Selected parents will be sent a letter of introduction with information about the study by the clinical care team. If families express an interest in participating to the research team either by telephone, or in writing or via their clinician, they will be sent information about the study to consider further. Participation will be voluntary. Written consent will be taken at the time of the interview. Interviews will be conducted in the family home or another location of the parent's choosing. The research fellow will be accompanied by a second person who may be an interpreter where this is indicated. Once consent to participate has been provided in written form the forms will be stored in a locked cabinet and interviews will be recorded.

Transcripts will be made, in which participants will not be identified by name, but by a code ID. Recordings will be destroyed after transcripts have been taken. Data will be stored electronically in encrypted files on the secure study computer at Great Ormond Street Hospital.

Project Management

The project will be managed by an advisory board consisting of the principal investigator (Kate Brown, the named project manager), research fellow, qualitative research expert, health psychologist, statistical expert, quality improvement expert, 'CHUKRA' lead clinician, CCAD vice chair, cardiac surgeon and family liaison officer. Members of the advisory group will meet bi monthly either in person or via telephone conference.

Service users and public involvement

Patient and public representatives are involved in the study at various levels as listed below. The Children's Heart Federation is an umbrella organisation for the various parent and family groups connected to children with heart disease, and has contact with 12,000 parents and patients. Representatives of the CHF have been involved in the design of the study with respect to section 3b) of the methodology. One of these representatives is a co investigator on the application. Section 3b) of the methodology includes seeking the views of parents and patients via Face Book, meeting with representatives of the CHF patient help line to debrief them and recruiting to focus groups via the CHF organisation which holds around 4 open meetings per year for parents all over the UK. Two focus groups and 20 to 25 interviews will be held with family members, particularly targeting representatives of patient types that are a greater risk of poor outcome in infancy. The study incorporates an intervention development group that will comment on output at various stages of the study (literature review, statistical analysis of risk factors for late death and qualitative research) and work on a proposed intervention program in phase 4). Two parent co researchers will be part of that group, along with other members from various disciplines. The results of the study after completion will be made available to the CHF for feedback via their various public outlets including Facebook and national user meetings.

Abstract:

Background

In-hospital mortality rates have improved for infants undergoing cardiac surgery: much less is known about events after discharge of these infants into the community. Available national

audit data indicates that a similar proportion of young babies may die after leaving hospital but before the end of their first year of follow up as are lost in the immediate postoperative period; others have 'near miss' emergency readmissions to intensive care units (ICU), though data about numbers is very limited. Information from local audits already conducted by the study team suggests that medically complex babies and those from more deprived environments may be at greatest risk of death. This association with deprivation is concordant with other sources of evidence regarding paediatric ICU admissions for different reasons. Importantly, there is some evidence from a US context that out of hospital surveillance measures can lead to improved outcomes for certain high risk infants.

Aims and Methods

The ultimate goal of the study is to provide research evidence to inform surveillance and intervention processes for vulnerable infants discharged after cardiac surgery.

1) Literature review

   A structured review of available literature will seek previous evidence of risk factors poor outcome in vulnerable infants with heart disease, including the role of ethnicity and deprivation as well as any previous examples of successful interventions in this context.

2) Quantitative research

   A primary objective is to ascertain, using linkage and statistical analysis of routine data, which infants are at most risk of death or ICU readmission in their first year at home. We aim to use routinely collected data from CCAD and PICANET. Medical and social factors (primarily ethnicity and deprivation inferred from post-code mapping) are documented in these datasets; these will inform analyses to estimate risk at the time of hospital discharge, permitting prioritisation of resources.

3) Qualitative research

   The aim of this section will be to explore perceived barriers to accessing health care in particular for disadvantaged families and to evaluate potential feasibility and acceptability of potential intervention types. Semi structures interviews with patient families, professionals and Children's Heart Federation Helpline staff will be performed. An online discussion forum using CHF Facebook and two focus groups will further inform the results.

4) Intervention design

   A multi disciplinary group will review the research output at stages 1 to 3 and critique intervention program options for infants discharged from hospital with CHD including the relative costs. Intervention development will include consideration of measures of success going forwards.

Product:

- Identification of high risk infants based on factors available to clinicians at the time of discharge home.
- Information about parental and professional views: focus on barriers and difficulties in accessing health care, after discharge into the community.
- Evidence based and achievable intervention program for infants with CHD discharged in to the community following intervention, designed to reduce rates of unexpected death and readmission.

Team Expertise

Co Investigators

1. Kate Brown (KB) is a consultant in paediatric cardiac intensive care and has Masters' in Public Health, Health Services Research from London School of Hygiene and Tropical Medicine (LSHTM). KB has experience of health services research and is a Co-I and project manager for a current NIHR HSR grant (The Application of a Mortality Risk Model to Adjust for Case Mix in Paediatric Cardiac Surgery for the United Kingdom using CCAD). KB has experience of validating and analysing CCAD and PICANET data and liaison with both organisations over the last 8 years.
2. Rachel Knowles (RK) is a Senior Research Fellow (Paediatric Epidemiology) at the MRC Centre for Epidemiology of Child Health, UCL Institute of Child Health. She trained in public health medicine (honorary NHS appointment) and has Masters' in Public Health (LSHTM) and Medical Anthropology. RK's doctoral thesis was a national study of predictors of survival of children with congenital heart defects (CHDs); this involved multiple imputation to address missing data in a multilevel model. RK gained experience of record linkage of routine data sources within a secure data environment through national studies of CHDs (as co-PI) and congenital adrenal hyperplasia (as PI).
3. Rodney Franklin (RF) is a consultant paediatric cardiologist and the guardian and a chief developer of the International Paediatric and Congenital Cardiac Code (IPCCC), RF has co-led the creation, development, and expansion of this comprehensive international, coding-nomenclature system (with over 10,000 terms) for paediatric and congenital cardiology and related procedures over the last two decades. RF is a member of the Cardiology Expert Working Group for the UK Department of Health Information Centre, developing new Healthcare Resource Groups and national procedural codes (OPCS 4) and Vice-Chair of the Steering

Group of CCAD, which monitors the outcomes of Paediatric and Congenital Heart Disease interventions.

4. Piers Daubeney (PD) is a consultant paediatric cardiologist and Reader at Imperial College with specialist expertise in international multi-institutional studies. He is the co-founder of the ongoing UK and Ireland study of pulmonary atresia, the UK, Ireland and Sweden study of total anomalous pulmonary venous connection and pulmonary vein stenosis, and the National Australian Childhood Cardiomyopathy Study. He is a member of the British Paediatric Surveillance Unit at the RCPCH, and the APICC section of the Medicine for Children Clinical Research Network. He is the joint founder of the Children's Heart UK Research Association (CHUKRA).
5. Jo Wray (JW) has a MSc in Evidence Based Healthcare and is an experienced health psychology researcher in the field of paediatric cardiology and has undertaken and supervised a range of qualitative and quantitative studies addressing psychological outcomes in children with congenital heart disease and their families. Dr Wray has extensive clinical psychology experience.
6. David Barron (DB) is a cardiothoracic surgeon and the clinical unit lead for the paediatric cardiothoracic centre at Birmingham Children's Hospital.
7. Kate Bull (KB1) is a Senior Lecturer in Cardiology and Medical Advisor: Family Policy at Great Ormond Street Hospital and has collaborated with RK on a HTA review on screening for CHD. Dr Bull is the family liaison officer for Great Ormond Street Hospital and has experience of counselling and liaising with bereaved parents in the aftermath of the organ retention scandal regarding events related to this topic.
8. The Children's Heart Federation has extensive experience with the telephone-based support of parents in the community. They also contributed to the benchmarking standards used in the recent Safe and Sustainable Review and have particular concerns about equity in access to services. They will inform and critique the questionnaire sent to Cardiac Units through CHUKRA. They will also contribute to the interview framework to be used by the Qualitative Researcher to elicit the family view of contingencies arising in the community and perceived obstacles to accessing help if a baby is unwell. They will offer two volunteer members to test out the interview script. They will participate in the write-up of the project, its dissemination and play a part in ensuring that the evidence the project provides is used in planning services.
9. Deborah Ridout is a Medical statistician with experience of research study design and data analysis.
10. Professor Faith Gibson: Clinical professor of children's cancer care, who has extensive experience of qualitative research studies and experience of working with lay co researchers.

Collaborators:

1. Unnamed Qualitative Researcher: A qualitative researcher will work independently to develop, conduct and analyse interview-based research with families. The qualitative researcher will be postdoctoral psychologist with experience of literature review, sampling for diversity, undertaking interviews, collating and thematic analysis of qualitative data appropriate to the paediatric health context.
2. Sally Hull: A general practitioner and primary care expert with research experience. Dr Hull is a Reader in primary care based at Queen Mary's University, London.
3. Nick Barnes: A general paediatrician working at Northampton General Hospital with experience in follow up care of children with complex medical needs.

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Appendix

Response to enquiry about child death review data

In the original proposal, we proposed to use data from child death reviews as a source of additional data about the risk factors influencing deaths in the community following infant cardiac surgery. We discussed the feasibility of this with a member of a CDOP, a staff member at the London Safeguarding Children Board and Sarah Wolstenholme, who has responsibility for child death data at the Department for Education. We also obtained copies of the forms completed for reviews.

Child Death Overview Panels (CDOPs) were established under the UK Government's Public Service Agreement 13 (PSA 13) and their duties are defined in Chapter 7 of Working Together to Safeguard Children (HM Government 2010).[1,2] Their key aim is to identify *"Events, actions or omissions contributing to the death of a child or to substandard care of a child who died, and which, by means of national or locally achievable interventions, can be modified".*[1]

Each case is reviewed by a local CDOP whose responsibility is for a limited area, and therefore one panel is unlikely to review more than one or two community deaths in children with repaired cardiac anomalies within a year.

The duties of Local Safeguarding Children Boards (LSCBs) are defined in Chapter 7 of Working Together to Safeguard Children (HM Government 2010).[2] LSCBs collect data from CDOPs about the number of preventable child deaths but not deaths assessed as 'not preventable'.[1] In 2009-2010, LSCBs were asked to collect additional optional information from CDOPs, e.g. the child's age, sex, ethnicity and registered cause of death.[2] However, these aggregated data do not code deaths in children with an underlying cardiac defect separately from congenital anomalies. No congenital anomaly deaths were coded as preventable.

In response to our enquiry about the collection of data at government level, Sarah Wolstenholme (Department for Education) informed us that *"Child Death Overview Panels (CDOPs) … are not required to provide their completed forms to the department. (Although we do collect a subset of information from the forms at aggregate level, which is published on our website http://www.education.gov.uk/rsgateway/DB/STR/d000943/index.shtml) The information you have requested may be available within CDOPs, but as not all panels have detailed datasets, this information may not be readily available or collected on a consistent basis."*

As there is no comprehensive routine recording of deaths due to cardiac causes and reviewed by CDOPs, we cannot know which individual CDOPs to approach to ask to share data. Moreover, as the data held by CDOPs is identifiable and sensitive, it would be necessary to seek individual consent to use these in research. We have therefore concluded that our original proposal to use child death reviews as a source of routine data to inform our investigation is not practicable.

[1]http://www.education.gov.uk/rsgateway/DB/STR/d000863/pcde-08v2.pdf

[2]http://www.education.gov.uk/rsgateway/DB/STR/d000943/osr17-2010v6.pd