Protocol for the economic evaluation of a complex intervention to improve the mental health of maltreated infants and children in foster care in the UK (The BeST? services trial)

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ABSTRACT

Introduction  Children who have experienced abuse and neglect are at increased risk of mental and physical health problems throughout life. This places an enormous burden on individuals, families and society in terms of health services, education, social care and judiciary sectors. Evidence suggests that early intervention can mitigate the negative consequences of child maltreatment, exerting long-term positive effects on the health of maltreated children entering foster care. However, evidence on cost-effectiveness of such complex interventions is limited. This protocol describes the first economic evaluation of its kind in the UK.

Methods and analysis An economic evaluation alongside the Best Services Trial (BeST?) has been prospectively designed to identify, measure and value key resource and outcome impacts arising from the New Orleans intervention model (NIM) (an infant mental health service) compared with case management (CM) (enhanced social work services as usual). A within-trial economic evaluation and long-term model from a National Health Service/Personal Social Service and a broader societal perspective will be undertaken alongside the National Institute for Health Research (NIHR)-Public Health Research Unit (PHRU)-funded randomised multicentre BeST?. BeST? aims to evaluate NIM compared with CM for maltreated children entering foster care in a UK context. Collection of Paediatric Quality of Life Inventory (PedsQL) and the recent mapping of PedsQL to EuroQol-5-Dimensions (EQ-5D) will facilitate the estimation of quality-adjusted life years specific to the infant population for a cost–utility analysis. Other effectiveness outcomes will be incorporated into a cost-effectiveness analysis (CEA) and cost-consequences analysis (CCA). A long-term economic model and multiple economic evaluation frameworks will provide decision-makers with a comprehensive, multiperspective guide regarding cost-effectiveness of NIM. The long-term population health economic model will be developed to synthesise trial data with routine linked data and key government sector parameters informed by literature. Methods guidance for population health economic evaluation will be adopted (lifetime horizon, 1.5% discount rate for costs and benefits, CCA framework, multisector perspective).

Strengths and limitations of this study

- Prospectively designed economic evaluation alongside complex intervention trial.
- First economic evaluation of a complex, public health intervention directed towards improving abused children’s mental health in the UK setting.
- Preference-based (utility) outcome measures included to facilitate decision-making.
- Long-term economic model including linked data to other sectors, for example, crime/education.
- Challenges related to the complexity of this particular child services setting, with regard to the variability of the control arm (case management) in different sites across UK and to the different sources of data collection used.

INTRODUCTION

There is evidence that maltreated children are at greater risk for lifelong health and social problems, including mental illnesses, criminality, chronic diseases, disability and poorer quality of life. A history of child maltreatment is also associated with lower adult levels of economic well-being across a wide range of metrics, including higher levels of economic inactivity, lower occupational status, lower earnings and lower expected earnings. Existing research suggests a ripple effect caused by lower educational achievement, higher levels of truancy and expulsion reducing peak earning capacity by US$5000 a
early interventions to promote the health and well-being of children have been shown to help mitigate the negative consequences of child maltreatment and have long-term positive effects on the health of maltreated children. Services are required that provide support to families as soon as they need it, and provide early permanency decisions. Interventions that exhibit these characteristics are most likely to improve children’s mental health and well-being and reduce health and societal costs over the long term through increased likelihood that children will have higher educational achievements, successful lives and be less likely to be dependent on the state. In the short run, costs will be lowered by reducing social workers’ time, avoiding several repeated decisions due to multiple placements.

Several reports have highlighted the inadequacies of the UK’s care system and the high costs associated with implementing new services as well as the increasing costs that are associated with cycling placements or returns to care. Additionally, existing analyses have emphasised the challenges in conducting economic evaluations of interventions aimed at improving outcomes for maltreated children, which include the need for a long-term perspective, accounting for the context-specific nature of interventions, and overcoming obstacles of cross-comparison due to variations in methods, samples etc.

**New Orleans intervention model for infant mental health in Glasgow and South London**

The New Orleans intervention model (NIM) (box 1) is based on the Tulane Infant Team programme and is being implemented in the UK through the collaboration between voluntary services National Society for the Prevention of Cruelty to Children (NSPCC), social (various City Councils including Glasgow and Croydon) and health services (including National Health Service (NHS) Greater Glasgow and Clyde and South London and Maudsley Trust) in the UK. A preliminary economic model exploring the likely costs and consequences of implementing the NIM in Glasgow concluded that NIM would be more costly, but the probability of repeated episodes is likely to fall significantly, as it involves both assessment and treatment phases as opposed to the assessment only nature of typical social services case management (CM).

**Box 1 The New Orleans intervention model (NIM) intervention**

NIM is an intervention which uses an infant mental health approach aiming to improve the quality of permanent placement decisions with the aim of improving outcomes for young children. The Tulane Infant Team, who developed NIM, assesses the mental health of every child under 5 years on reception into foster care and quality of the relationships between the child and their parents. A tailored intervention is then offered to each family aiming to improve parent–child relationships and child mental health. These assessments and the degree of change achieved through intervention inform recommendations to the legal system about the permanent future care of the child. Where change has been achieved which indicates it is safe, children are rehabilitated back to the birth family. If not, the recommendation is adoption or long-term care.

The NIM intervention will be delivered, in each site, by a multidisciplinary team comprising a child and adolescent psychiatrist, social workers therapists and administrative staff. Each member of clinical staff will receive specific training in assessment techniques and treatment delivery from the New Orleans and/or Glasgow teams.

Participants randomised to NIM will be asked to take part in a detailed attachment-informed assessment involving each actual and potential caregiver. The assessment is manualised, standardised and uses structured interviews, self-report measures and observations.

An intervention will then be tailored for every family, drawing on a small range of relationship-based therapeutic techniques all of which comply with the recommendations of a meta-analysis that examined ways of improving parental sensitivity. Parents will also be referred as required to other agencies for help with substance misuse, mental health issues or intrafamilial violence. The aim is to have the safest better outcome for the child, be this a recommendation of rehabilitation to birth family or adoption. Making well-informed permanent placement recommendations within 6–12 months could optimise physical, mental and social development, while also allowing parent the opportunity to make changes if possible.

randomised into receiving the NIM or enhanced CM.

The BeST? will continue as a definitive multicentre RCT expanding on the work currently taking place in Glasgow including an additional site in South London, England. Including a London site will increase generalisability of the findings which may have important policy implications for the UK. Details of the main trial study protocol are available elsewhere.

NIM has demonstrated preliminary evidence of effectiveness in USA, but its effectiveness and cost-effectiveness in terms of improving the mental health of children coming into care following maltreatment is unknown in a UK setting. The absence of any standardised mental health services for maltreated infants in the UK which favours a ‘social care’-oriented system, makes this an interesting case to analyse effectiveness

Enhanced care management is an enhanced service-as-usual in that a defined care pathway has been set and is being adhered to when a child comes into foster care.
and cost-effectiveness of the NIM intervention. Initial US
evidence suggests positive consequences of placement
stability and improvements in infant mental health, as
well as longer-term resulting benefits to academic perfor-
manence, employability, and reduction in teenage delin-
quency and crime.11

**Aim**
The BeST? trial aims to evaluate the effectiveness and
cost-effectiveness of NIM in improving the mental health
of maltreated infants and children in foster care, the
relationship between these children and their primary
caregivers, and the timeliness of permanent placement
decisions, compared with CM. The aim of the economic
evaluation alongside the BeST? RCT is to establish the
short-term and long-term cost-effectiveness of NIM
compared with CM from both a health and societal
perspective.

**METHODS AND ANALYSIS**
BeST? is a multisite RCT taking place in Glasgow and
London, UK. These sites are characterised by a high level
of deprivation and a large number of children coming
to foster care, thus representing an interesting location
to analyse effectiveness and cost-effectiveness of the NIM
intervention.

Families who have a child entering care at either site,
aged 0–60 months, will be randomised to receive NIM
or CM. Data collection captures information regarding
whoever the primary carer is at the time of follow-up
(whether that be birth parent(s), grandparents, foster
carers or adopted parents) and it will take place at base-
line and at follow-up (15 months and 2.5 years). The
primary outcome for the trial is the Strengths and Diffi-
culties Questionnaire (SDQ) at 2.5 years: a sample size of
462 will have 90% power to detect an effect size of 0.35,
allowing for 25% loss to follow-up in this intention-to-
treat analysis.12

The economic evaluation will involve a within-trial
economic analysis and a population health economic
model considering the long-term impact of the NIM
intervention on several government sectors where a
mental health intervention of this kind is likely to have
an impact.

**Within-trial analysis**
The within-trial analysis will investigate the cost-effective-
ness of NIM compared with CM through a number of
different analyses. The primary within-trial analysis will
be a cost–utility analysis (CUA) which will estimate the
incremental cost per quality-adjusted life year (QALY)
of NIM compared with CM. QALYs will be generated via
measurement of utility values using the Paediatric Qual-
ity of Life Inventory (PedsQL)13, child health-related quality
of life (HRQoL) instrument mapped to the EQ-5D (ie,
a widely used instrument to assess HRQoL) to generate
utility values.15 Furthermore, the same authors who
mapped the PedsQL to the EQ-5D are currently develop-
ing a preference-based index for the PedsQL. As this is
ongoing research, the inclusion of this preference-based
index will be explored at time of analysis, if available. This
mapping of the PedsQL to QALY represents a strength of
this project, since it will allow the estimation of child-spe-
cific health utilities.15 Additionally, the incremental cost
per unit improvement using the effectiveness outcome
SDQ16 will be explored. Within such a technical effi-
ciency framework, there is no accepted threshold value
for unit changes in the SDQ, however, the costs required
to reduce total difficulties scores (and remove altogether)
will be reported.

Increasingly, in complex public health evaluation
research, there are questions about whether all relevant
benefits can be captured in a single summary outcome
measure such as QALY or unit of ‘effectiveness’ or net
benefit approach17 which is why the use of a cost-conse-
quence analysis (CCA) framework is being recommended
for such economic evaluations.18 Other outcomes from
the trial such as the Parent–Infant Relationship Global
Assessment Scale (an observational measure that is inde-
dependently rated blind to group allocation) will be included
in the CCA so that all costs and outcomes from the trial
can be displayed transparently for decision-makers to
consider trade-offs themselves. This format can be partic-
ularly useful in capturing broader intervention effects
not contained within the psychometric properties of the
PedsQL or SDQ.

These analyses will adhere to good practice guidelines
for conducting economic evaluations alongside clinical
trials, reporting standards and the most recent National
Institute for Health and Care Excellence (NICE) public
health reference case.18–20 The within-trial analysis will
adopt the perspective of the NHS and Personal Social
Services (PSS) and examine the costs to these sectors
specifically. Additionally, a wider public sector perspec-
tive will be explored which will include societal resources
such as contacts with the police, residential or respite
care, and costs to the family in terms of additional child
care.

**Resource use**
**Identification of resource use**
The identification of the resources used within such a
complex intervention relates to the identification of
multiple components involved in the delivery of NIM and
CM interventions, as well as identification of the costs
incurred and cost savings arising as a consequence of the
intervention and the control.

The costs borne by the health and social care (NHS/
PSS) to deliver the NIM and the CM interventions
include the time spent by individuals delivering the
NIM and CM services, such as medical professionals and
service management (administrators, team leaders, team
members, area social workers, psychologists and psychi-
atrists). In addition, the consequential health and social
services used by participants (mental health services,
admissions to hospital, addiction/domestic violence services etc) will be also taken into account.

The time spent by birth parents and other primary caregivers’ involvement in NIM or CM as well as police contacts, day care, school or nursery usage will be incorporated into the calculation of scenario analyses to provide a broader societal perspective of the costs of these services.

Measurement of resource use

Data on the time spent by various practitioners (eg, social workers, administrators, psychologists etc) in providing each service will be measured from the services directly. Both NIM and CM collect information about each contact the service has with each child. This information includes the purpose, place, length of contacts and all individuals present at the meeting. The services also collect information about other services that the child and their birth parents or other primary caregivers were recommended to attend (eg, addictions support, women’s support etc).

New Orleans intervention model

Total costs for NIM will comprise the cost of delivering NIM plus resources used during the trial period. To determine the cost of the intervention an approximate care pathway was defined with the help of key social care and infant mental health experts. This includes: (1) a standardised assessment taking approximately 12 weeks; (2) treatment which could consist of up to six different types of intervention; (3) post-treatment meetings; (4) debriefing and (5) any other substantial activity such as a court hearing or court attendance. Data on the use of this service are collected by the NSPCC’s data collection system. This system routinely collects data on each contact for each child including the practitioner providing the service, all the individuals who were in attendance and the duration of the contact. This system is reliant on the routine input from NSPCC staff members and also collects information about other services that were recommended by practitioners for the birth parents/other primary caregivers. An example of the data that is extracted is given in online supplementary appendix 1.

The NSPCC’s data collection system does not collect the key resource use items of preparation and administrative staff time for each contact with or for the child in question. An informal Delphi technique will be used to estimate the likely average, minimum, and maximums of the preparation and administrative time that goes into each contact, precontact and postcontact. NIM team members in Glasgow and London will be surveyed individually to provide their estimates, and those estimates will be combined to provide averages with uncertainty estimates on either side. The team will then be consulted again with these estimates to come to a final consensus.

Case management

CM provides social work service as usual, enhanced through the standardisation that comes with the RCT. This includes regular multiagency meetings that troubleshoot problems with services and individual cases. Information on date, the nature of the contact, duration, attendees, and if they were referred to an outside service are all collected electronically and held on a shared drive as multiple people may work on existing cases. Duration includes time spent before (preparing and setting up the meeting), during and after (writing up notes, updating case files and report writing) the contact. In Glasgow, there are typically eight observed contacts and six individual interviews over approximately 4 months and the intensity of contacts remains to be seen in London. However, the case may remain open for some time after the initial contacts, for example, to attend court dates or other judicial meetings. Therefore, any further contacts for each case will be recorded at their 15-month and 2.5-year follow-ups. The form used in collecting resource use from contacts is provided in online supplementary appendix 2.

Additional service use

Additional service use (ASU) data will be collected with questionnaires at baseline and at each point of follow-up. The ASU questionnaire (see online supplementary appendix 3) aims to obtain an estimate about the usage of services beyond those provided directly by NIM and CM.

This questionnaire asks birth parents and other primary caregivers about the number of attendances, contacts and hours for several different services (eg, hospital admissions, police contacts, day care or nursery usage etc) for both the child and themselves. These additional services are important resource use items to capture as CM and NIM both sometime refer patients out to these additional services, so the ASU provides a method that attempts to capture these.

The ASU Questionnaires will be compared with service use at baseline and used in conjunction with data from the NIM and CM services about recommended service uptake to identify what services were used resulting from involvement in either the CM or NIM services.

Valuation of resource use

Unit costs

Unit costs for each component of resource use will be expressed in pounds sterling (£) for a base cost year 2020/2021, unit costs will be obtained from routine sources (ie, NHS Agenda for Change Pay scales, the Personal Social Services Resource Unit, NHS reference costs) or will be collected from the trial directly where they are not available in routine sources. The Hospital and Community Health Services pay and price index will be used to for any inflation.

Outcomes

A number of different outcomes will be collected by the trial. The primary outcome measures of interest for the economic evaluation are the PedsQL and the SDQ scores, both of which will be used in the economic evaluation.
The PedsQL questionnaire is used to measure HRQoL in children aged 2–18. The PedsQL is a validated measure of child quality of life which has recently been mapped to utility values for use in health economic evaluations. The PedsQL has demonstrated responsiveness, construct validity and predictive validity in paediatric patients. The PedsQL scores can be mapped to generic EQ-5D utilities, facilitating calculation of QALYs, thus meeting most recent NICE guidance for public health interventions.

The SDQ is a short behavioural screening questionnaire that is completed by parents, guardians or teachers of children aged 2–16 which records any emotional and behavioural difficulties and any impairment experienced by the child or family. Children can self-complete from ages 11 to 17. The SDQ is one of the most widely used validated measure of mental health in children and is sensitive to change; in intervention studies, effect sizes have been shown to be moderate to large.

Tables 1 and 2 provide a summary list of the economic evaluation measures, their schedule collection and the framework for analysis each will be used in. As recruitment is rolling, there is no set time for baseline, 15-month and 2.5-year data collection.

### Analysis of cost and effects

Regression analysis will explore the effect that baseline variables have on the cost and effect (PedsQL and utility) of each intervention over a 2.5-years' time horizon. The incremental difference in cost and QALYs between groups at follow-up will be assessed while adjusting for baseline characteristics such as site, language, gender, baseline PedsQL and deprivation. Appropriate methodologies will be used in order to deal with the potential clustering of costs and outcomes by household and intervention site (eg, multilevel models) and with non-normality and correlation of cost and outcome data.

Two incremental cost-effectiveness ratio (ICER) will be calculated to evaluate the incremental cost per QALY (calculated from PedsQL scores) and the incremental cost per improvement in SDQ.

The ICER formula is given below:

\[
\text{ICER} = \frac{\text{Cost}_{\text{NIM}} - \text{Cost}_{\text{CM}}}{\text{Effect}_{\text{NIM}} - \text{Effect}_{\text{CM}}} 
\]  

A CCA will be presented in tabular format with costs collected from the resource used in the trial presented on one side (table 1) and all outcomes listed along the other side (table 2).

Subgroup analysis will explore heterogeneity of the cost-effectiveness results by age group and intervention site.

To reduce bias and increase statistical power, missing information for the key variables used in the BeST trial will be imputed separately for each of the two arms of the trial using multiple imputation by chained equations. Costs and outcomes will be discounted at 1.5% as recommended for public health economic evaluations.

### Handling uncertainty

The uncertainty surrounding the estimate of incremental costs, QALYs and ICERs will be investigated by use of a non-parametric bootstrap of the cost and effect pairs for 1000 iterations. This uncertainty will then be presented on the cost-effectiveness plane with a 95% CI of the bootstrapped ICER estimated. Results will be summarised using a cost-effectiveness acceptability
curve to reflect the probability of NIM being cost-effective at various willingness-to-pay thresholds, including the £20 000 to £30 000/QALY threshold.24

Heterogeneity will be explored and subgroup analyses undertaken, for example, based on study site, age groups and other relevant subgroups which may impact on cost-effectiveness. Scenario analyses will be conducted to examine the effect of the costs and consequences of the services to the immediate family of the child in care. To this end, ICERs will be recalculated including the costs and effects to the birth families and other primary caregivers (largely the time spent by these individuals during the period over which the service was provided).

### Long-term population health economic model

While the within-trial economic evaluation assumes a relevant time horizon of 2.5 years, modelling the long-term cost-effectiveness of the NIM intervention will consider the wide spectrum of cross-sectoral impacts and costs to society of the intervention34 35 over the lifetime.

While several studies have evaluated interventions aiming at improving children’s mental health in terms of effectiveness36 and cost-effectiveness,37–39 evidence over a lifetime horizon is limited40 41 and non-health costs and consequences are rarely considered.9

However, improvements in child mental health are likely to have broad societal (health and non-health related) and long-lasting impacts on the child, including reducing the risk of poor physical health, problems with substance abuse, suicide or other mental health risks, involvement in crime.1 2 29 39 42 43

Furthermore, in line with the theory of ‘Investing in Child Health’,44 the social rate of return of more resource-consuming interventions directed to improve child mental health is likely to be potentially high, thus justifying the additional costs sustained by the decision-maker.8 39

The aforementioned multisector lifetime decision model will be based on the theory of ‘Investing in Child Health’44 and will be adapted to model the long-term cost and outcomes from NIM and CM in four key sectors in society: education system, child welfare system, criminal justice, NHS and PSS as informed by this theory.

Online supplementary appendix 4 illustrates the economic logic model developed for this study which will inform the basic structure of the model.

Pending within-trial results, a Markov model (a mathematical model used to model randomly changing
systems where it is assumed that future states depend only on the current state not on the events that occurred before it) will be used to predict the multisector lifetime cost-effectiveness. Several studies have used this framework to evaluate interventions directed towards the improvement of mental health in both adult and infant population.

The economic evaluation of NIM over a long-term horizon will use the trial data and outcome measures at 15-month and 2.5-year follow-up as predictors for parameter estimates in the lifetime model, and will be further supported by evidence from a systematic literature review and available record routine linkage data.

Considering the broad societal impacts and the multidisciplinary nature of many complex public health interventions affecting mental health, the model will calculate lifetime cost and sector-specific outcomes for each of the four key sectors (social care, informal care, production losses, crime and education), for the NIM intervention in comparison to CM including resource use; patient management and pathways; the cross-sectoral impact and implications of early intervention; quality of life; mortality and adverse events.

Specifically, routine data and a systematic literature review will inform specific parameters that will link early interventions on infant mental health—and related improvements in quality of life—with better health, educational and occupational outcomes, lower crime rates and cost savings for the health sector and the entire society.

Sensitivity analysis

Given that the assumptions about causal links from the trial into the future may not be valid over a long time frame (ie, over a child’s lifetime), extensive sensitivity analyses will be conducted to explore the effects of adjusting the underlying model parameter estimates and assumptions. Probabilistic sensitivity analysis around the longer-term estimates of costs, effects and cost-effectiveness of the NIM intervention versus CM will be performed using a 1000 iteration Monte Carlo simulation. Further, an alternative discount rate of 3.5% will be applied to costs and effects in line with NICE guidelines. Scenario analyses will explore altering some of the underlying model assumptions.

DISCUSSION

The economic evaluation alongside the BeST? has been prospectively designed to identify, measure, and value key resource and outcome impacts arising from the NIM compared with CM. This is the first economic evaluation of its kind in the UK and the addition of a long-term economic model, multiple economic evaluation frameworks and public health economic evaluation methods guidance, should provide decision-makers with a comprehensive guide as to the likely cost-effectiveness of NIM. Given the complexity of the economic evaluation, key practical steps assisted the design including the development of a health economics logic model and key stakeholder engagement to identify the full range of ASU impacts arising from the intervention.

The BeST? is comparing complex interventions within a complex social care environment. NIM is a tailored and resource intense intervention with contextual factors influencing the bespoke nature; this will make the findings less generalisable to contexts outside of the UK. Equally, even though CM ensures adherence to standardised procedure, certain cases may be much more resource intense affecting cost-effectiveness.

The planned economic evaluation does have some limiting factors. There is potentially a risk of bias due to measurement challenges. Different services delivered in the intervention and in the control arm required different systems to collect resource use information. Furthermore, while the data collected within the pilot study have been carried over to the BeST?, the data collection instruments which have been used differ slightly between the pilot and the main trial. Additionally, the control intervention is not standardised between the Glasgow and the London site. However, we have planned for this and where possible, steps (eg, preliminary checks of the data collected; informal contacts with professionals in charge of data collection) will be taken to minimise this risk.

The base case CUA relies on a utility measure that will not be directly measured by the children themselves, rather they will be mapped from the non-preference-based PedsQL to preference-based EQ-5D for adults. While this has its limitations, at the time of trial design (2011), there was not a validated paediatric preference-based quality of life measure.

Additionally, the Child Health Utility 9D (CHU9D) was validated for use in children in 2012 for ages 7–11 which is older than the targeted population of children. The very young children included in the study will also pose difficulties in terms of outcome measurement, because many of the paediatric outcomes included in the trial have not been validated for children under the age of 2 including the PedsQL although by the final trial assessment point, all children will have reached at least age 2.5 years. Despite these limitations, the recent mapping of the PedsQL to QALY does also represent a strength of current work, since it has allowed the estimation of children-specific health utilities. Further, the challenges mentioned above will be addressed through use of multiple economic evaluation frameworks, giving decision-makers transparent and comprehensive findings with which to improve resource allocation for this vulnerable population.

Given the broader and long-term consequences that inadequate responses to neglected and abused children has for the health sector and the society, investing in child health represents a key priority for the decision-maker. In this regard, the current study will provide evidence on the long-term value for money provided by a mental health individual-based intervention in the UK context.
Ethics and dissemination

Results of the main trial and economic evaluation will be submitted for publication in a peer-reviewed journal as well as published in the peer-reviewed National Institute for Health Research journals library (Public Health Research Programme).

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Contributors

MD drafted the economic evaluation protocol, KAB, NRSB and EM revised drafts. KAB and EM lead the design of the economic evaluation of the BeST? study. HM led the design of the BeST? study. EM, NRSB, HM, JD, KB and KAB commented on the final version.

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Competing interests

None declared.

Patient consent

Not required.

Ethics approval

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REFERENCES


