The Best Services Trial (BeST$^{?}$): Effectiveness and cost-effectiveness of the New Orleans Intervention Model for Infant Mental Health.

BeST$^{?}$

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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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The Best Services Trial (BeST?): Effectiveness and cost-effectiveness of the New Orleans Intervention Model for Infant Mental Health. (BeST?)

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LIST OF ABBREVATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
CM	Case Management
DAI	Disturbances of Attachment Interview
DAWBA	Development and Wellbeing Assessment
FACS	Family Assessment and Contact Service
GIFT	Glasgow Infant and Family Team
ITSEA	Infant Toddler Social Emotional Assessment
NIM	New Orleans Intervention Model
NSPCC	National Society for the Prevention of Cruelty to Children
PEDS-QL	Pediatric Quality of Life Inventory
PIRGAS	Parent-Infant Relationship Global Assessment Scale
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDQ	Strengths and Difficulties Questionnaire
TIMB	This Is My Baby
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRO	Waiting Room Observation

STUDY SYNOPSIS

Title of Study	The Best Services Trial (BeST?): Effectiveness and cost-effectiveness of the New Orleans Intervention Model for Infant Mental Health
Study Centre	UK multicentre (lead site - NHS Greater Glasgow and Clyde/Glasgow City Council)
Duration of Study	60 months
Objectives	To evaluate the clinical and cost-effectiveness of the New Orleans Intervention Method (NIM) in relation to an enhanced services as usual model, Case Management (CM), for the management of maltreated infants and young children entering care in the UK.
Primary Objective	To establish whether NIM is effective in improving the mental health of maltreated infants and young children compared to CM.
Secondary Objective	To establish whether NIM, in relation to CM: - is effective in improving the relationship between maltreated infants and young children and their primary caregiver; - effects more timely permanent placement decisions for maltreated children; - is cost-effective in terms of the short term mental health of the child (as measured by SDQ and PEDS-QL at 2.5 years post-randomisation) and in terms of the lifetime analysis.
Primary Endpoint	Child mental health measured by the Total Difficulties scale of the Strengths and Difficulties Questionnaire (SDQ) 2.5 years after randomisation.
Rationale	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. Regardless of the severity of this abuse and neglect, these negative effects can largely be reversed if children are placed in secure, loving homes early enough in life. Placing children in nurturing foster placements can help them recover rapidly, but it is not known whether it is better for children's long term development to place them with substitute (foster or adoptive) families or return them to birth or extended families. Efforts to improve the mental health of maltreated children in birth families or foster placements have had mixed success and researchers have recommended that far more intensive approaches are required. We have carried out careful exploratory research, in Glasgow, on an intensive approach, which was developed in the United States. We have called this the New Orleans Intervention Model (NIM). NIM offers families who have a child who enters care due to abuse or neglect a structured assessment of family relationships followed by an intensive treatment that aims to improve family functioning and child mental health. If adequate change is achieved a recommendation is made for the child to return home but, if not, the recommendation is for adoption. Preliminary research from the US suggests that NIM might reduce future maltreatment of the child and other children in the family, and improve mental health in middle childhood. We are currently conducting a study in which, since December 2011, we

	have managed to recruit around two-thirds of all maltreated children aged 6 months to 5 years coming into an episode of care in Glasgow. Half of the families who are taking part receive NIM, which is delivered by a multidisciplinary team comprising health and social care professionals. The remaining half of families will receive usual services, which is delivered by social workers. Preliminary findings suggest that NIM is acceptable to parents, foster carers, social workers and legal professionals. We are currently conducting detailed exploratory work in an additional site, South London , with plans to launch the trial there in 2017. We now need to test whether NIM is effective, in terms of both clinical outcomes and cost, in the different legal systems across England and Scotland. We, therefore, propose a study of NIM involving a continuation of our current Glasgow work and including 1-2 additional sites. We plan to involve approximately 500 children (462 families) in total across the sites, including those recruited in our current Glasgow internal pilot study. This will allow us to determine whether or not NIM is effective in the UK and to follow up Glasgow children for five years to examine longer term effects on mental health.
Methodology	Cluster randomised controlled trial
Sample Size	462 families
Screening	On notification of a new entry onto the study housekeeping electronic system, the relevant recruitment co-ordinator will email the child's social worker and foster carer's social worker to confirm that the parent and foster carer have been informed about the study and have expressed interest in being contacted by the recruitment co-ordinator to discuss it further. Interested foster carers will be telephoned by one of the research assistants who will confirm receipt of the study information materials (copy of the relevant Participant Information Leaflet, Consent Form and Digital Video Disc), address questions and make arrangements for baseline research assessment at the study clinic. A letter confirming the agreed arrangement will be sent along with copies of the study information materials. The foster carer will be asked to complete and return the Consent Form in a prepaid, pre-addressed envelope to the study office. If the foster carer requests a face-to-face meeting to discuss the study before deciding whether or not to sign the Consent Form, the recruitment co-ordinator will visit their home prior to the study baseline assessment. Interested parents will be telephoned by the recruitment co-ordinator who will confirm that they have received the study information materials (copy of the relevant Participant Information Leaflet, Consent Form and Digital Video Disc/mp3 card), address questions and make arrangements for obtaining informed written consent and one of the baseline assessment measures (ie the section of the Development and Wellbeing Assessment (DAWBA) relating to the child's early development). This will involve a face-to-face meeting either in the participant's home or at a safe and mutually convenient location (e.g. social work premises). The recruitment co-ordinator will send a letter confirming the agreed arrangement for this appointment. This letter will include copies of the study information materials. A telephone reminder call or text will be sent to the parent carer within a few days of the appointment. This appointment takes around 30 minutes.

	If either the foster carer or parent indicates that they are not interested in participating, the child and family will still be eligible to receive social work services as usual, however, no data will be collected for the purposes of the research trial. If the foster carer has consented but it has not been possible to contact the parent to discuss consent during the 10 weeks following the child's entry into care, consent by the person with day to day care of the child (i.e. the foster carer) will be considered adequate. This strategy has been approved by the West of Scotland Ethics Committee 5. N.B. under a previous version of the protocol, randomisation was conducted prior to consent. This was largely because of concerns about trial-related delays to delivery of a service. It became clear, however, that randomisation-before-consent did not reduce the time between entry to care and receipt of a service. This procedure has therefore now changed and, in both London and Glasgow, randomisation will take place only after informed consent.
Randomisation	Families will be allocated 1:1 to NIM or CM via an online system, using a mixed minimisation/randomisation system, designed to ensure balance of allocations with respect to study site (Glasgow/London), the age of the youngest child coming into care at the point of randomisation (<2/≥2 years), the number of children coming into care at the point of randomisation (1/>1), and whether or not the birth family is fluent in English.
Inclusion Criteria	• Family with a child aged 0-60 months who enters care in the recruiting sites for reasons associated with maltreatment during the study recruitment period.
Exclusion Criteria	• Families will be excluded from the trial if the parent(s) is unavailable to take part in intervention (e.g. because of death, unknown whereabouts or long term imprisonment).
Intervention	The trial intervention is NIM. NIM fulfils the criteria for a Complex Intervention in that it comprises several interacting components i.e. there is a range of behaviours required by those delivering and receiving the intervention; a number of different groups and organisational levels require to be targeted by the intervention; there are a number- of different possible outcomes of the intervention; and the intervention itself entails a degree of flexibility and tailoring in its delivery. The children and families randomised to NIM will be asked to take part in a detailed attachment-based clinical assessment. This begins with an assessment of the quality of the foster placement which may result in a recommendation that the child is moved to a more appropriate foster placement. The process then goes on to include each member of the child's family, including non-biological partners who are likely to be directly involved in care-giving should the child be returned home. The assessment is manualised and standardised using structured interviews, self-report measures and observations. The assessment assists in identifying the child's developmental and emotional needs in the context of maltreatment. By these means, parallel areas are identified where intervention should occur between child and foster carer and between child and biological parents. An intervention is then tailored for each family drawing on a small "toolbox" of relationship-based therapeutic techniques, all of which comply with the recommendations of a meta-analysis that examined ways of improving parental sensitivity. In addition, the intervention addresses problems which

	the parents may have, such as substance abuse, mental health issues and domestic violence, usually in liaison with other agencies. The New Orleans team has identified a number of factors which are related to a good outcome, amongst which accepting responsibility for the maltreatment of children is of central importance, with change represented by learning from interventions to become "a safe and effective parent". The aim of NIM is to have the best outcome possible for the child, be this recommendation for rehabilitation to birth family or for adoption. Two of features differentiate NIM from the typical approach to maltreated children and their families in the UK. First, the intensive relationship-focused assessment is offered in EVERY case, regardless of the nature of the maltreatment, with a view to maximising the chance of the child being able to be returned to the birth family. Second, strenuous attempts are made to offer clear, well evidenced yet timely recommendations to legal colleagues so that decisions regarding the child's permanent future placement can be made within timescales appropriate for optimal child development.
Duration of Treatment	12 weeks to 1 year
Statistical Analysis	All statistical analyses will be pre-specified in a detailed Statistical Analysis Plan, to be finalised prior to unblinding of intervention groups, and agreed by the Trial Steering Group. The primary analysis will use a generalized linear mixed effects regression model for the primary outcome measure to account for clustering of outcomes within families, and for repeated measures of the outcome over time. The residual variance within the model will be assessed in blinded analyses and an appropriate model will be used. The model will include fixed effects for randomised group, the minimisation/stratification factors, time points (baseline, 15 months, 2.5 years), treatment-by-time interaction, child's age at time of data collection, and version of questionnaire used, plus random effects for families and children, with a general covariance structure for the repeated measures. This model will be used to estimate the between-group differences at 15 months and 2.5 years from randomisation, with 95% confidence intervals and p-values. Missing outcome data will not be imputed in the first instance, but the characteristics of participants and families who fail to provide outcome data will be investigated, and the sensitivity of the primary analysis to alternative assumptions regarding missing outcomes will be assessed. This will include analyses based on multiple imputation of missing outcome data based on intermediate data, where available.

GLOSSARY OF TERMS

TERM/PHRASE	EXPLANATION
NIM	New Orleans Intervention Model – the trial intervention, developed by Charley Zeanah.
Case Management (CM)	Our control intervention – enhanced services as usual, based on a model trialled by Alicia Lieberman in the US.
Maltreatment	Physical abuse, sexual abuse, physical or emotional neglect or emotional abuse – or any combination of these.

SCHEDULE OF EVENTS

Study Procedure	Visit 1	Visit 2	Randomisation[1] automated system	Visit 3 (Baseline)[1] *10-14 weeks post entry care*	Visit 4 (Follow up)[2] *15 month post care entry*	Visit 5 (follow up)[3] *2.5 year post care entry*
Provision of study Information	✓	✓				
Consent		✓				
Randomisation			✓			
SDQ				✓	✓	✓
PIR-GAS				✓	✓	✓
ITSEA				✓	✓	
DAI				✓	✓	✓
DAWBA				✓	✓	✓
Service use questionnaire				✓	✓	✓
TIMB				✓	✓	✓
Observational Checklist for RAD				✓		
Cognitive assessment (WPPSI or WISC depending on age of child)						✓
PEDS-QL				✓	✓	✓
RPQ				✓	✓	✓
Data Linkage						✓

[1] *Baseline assessment (visit 3) can be performed up to 14 weeks after entering care if there is difficulty in making contact or for scheduling purposes*

[2] *15 month follow up (visit 4) assessment can be performed up to 6 months post the due date of the visit if there is difficulty in making contact or for scheduling purposes, attempts at contact will continue after this time to maintain contact with the families*

[3] *2.5 year follow up (visit 5) assessment can be performed up to 6 months post the due date of the visit if there is difficulty in making contact or for scheduling purposes, , attempts at contact will continue after this time to maintain contact with the families*

1 INTRODUCTION

1.1 BACKGROUND

Since December 2011, the New Orleans Intervention Model (NIM) has been piloted for children, aged between 6 and 60 months, who enter care in the Glasgow City Council catchment area for reasons associated with maltreatment. A randomised controlled trial (RCT) of NIM, is fully supported by Glasgow City Council and NHS Greater Glasgow and Clyde. The families of all eligible children will be invited to participate in the RCT of NIM; whereby a random sample of half will be offered the NIM intervention and half will be offered services as usual, which for the purposes of this study is Case Management (CM). Thus participating families will have a 1:1 chance of being randomly allocated to the NIM. Previous research with similar populations in both New Orleans and Glasgow has demonstrated high recruitment rates to intervention research.

Approximately 53,600 children are currently in care in England because of abuse and neglect. Only 11% will be adopted, while, of the 39% who return home, almost half will be abused again (1). There are currently no evidence based interventions aiding social work services and the legal profession in making the difficult decision about whether a child should be adopted or rehabilitated home.

We have only found one programme, NIM, using an infant mental health approach aiming to improve the quality of permanent placement decisions so that children can experience appropriate nurturing care as early in life as possible (15). The Tulane Infant Team, who developed NIM, assesses the mental health and relationship quality of every maltreated child under five years of age on reception into care. 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 significant change has been achieved, children are rehabilitated back to the birth family. If not, the recommendation is adoption. An evaluation of the four years prior to, compared with the four years after, the introduction of the NIM in the US suggested that the programme effects an increased rate of adoption and, for those returned to birth families, a relative risk reduction of more than 50% in repeated maltreatment for both that child and subsequent siblings (15). A follow-up of children several years after exposure to NIM in infancy has shown that on many mental health measures graduates of NIM, whether adopted or rehabilitated to birth families, differed only slightly from the general population (17). This is remarkable when the high rates of psychopathology in populations of children in care are considered (18). The extent to which these findings could be generalised to a UK context is not known. The US has nothing like the intensity of preventative social services that we have in the UK. This means that unlike US children, the families of children entering care in the UK are more likely to be already known by, and

have received interventions from, social services.

An important outstanding question is therefore whether an infant mental health approach to early intervention with maltreated children can improve their health outcomes in a UK context.

Infant mental health services are virtually non-existent in the UK and we are not aware of any aimed specifically at maltreated infants other than the one we are currently trialling in Glasgow. Early identification and intervention are crucial for improving health outcomes, especially for our most vulnerable children (19). Maltreated children are at greatly increased risk of mental health problems such as conduct disorder and Attention Deficit/Hyperactivity Disorder (ADHD) (20) with effects amplifying across the lifespan. Children with the poor self-control associated with these disorders are more likely to be involved in crime as adults (21) and adults who were aggressive as children commit more than 50% of violent offences (22). Maltreated children are at increased risk of a range of adverse mental and physical health outcomes including cardiovascular disease (23), substance misuse and suicide (24), possibly as a result of early changes in the brain (25) and stress response systems (20). Children with ADHD are more likely to have poor physical health in adulthood (21) while adolescents with conduct disorder have a 9-fold increase in all-cause mortality (26). Early childhood adversity and associated disorders impose a massive financial burden on individuals, families and society (27). Improving the mental health of young maltreated children is likely to yield substantial rewards in terms of the health and productivity of the population as a whole (28). Maltreatment-associated mental health problems, e.g. conduct disorder and ADHD are treatable (29) (30).

The most cost-effective way to improve the mental health of the youngest children is to improve existing relationships (31) and medium to large effect sizes (0.5 - 0.9) on a range of outcomes have been noted with these strategies (32, 33). For maltreated children, the most important intervention may be the provision of a safer and more nurturing home environment: research on sensitive periods in neural development suggests that addressing inadequate care in the early months and years of life may improve neural circuits underpinning emotional regulation (34) and allow maltreated children to reach their full developmental potential (35). Recovery from the effects of early maltreatment can be rapid and remarkable if safe nurturing care is achieved early enough, ideally in the first year of life (36) and one of the most robust predictors of poor outcome for maltreated children is placement instability and “drift” in care (37) (38). A Glasgow audit in 2010 showed that many children “revolve” between maltreating birth families and temporary foster placements (39). This disrupts attachments and is detrimental to child wellbeing (39). In the UK, adoption does not take place on average until 4 years of age (40, 41), despite the presence of adversity in most cases since birth. There is much current debate about the ethics of permanent care (i.e. adoption) for maltreated children and the timescales involved in making these decisions(42).

1.2 RATIONALE

Because of the very poor outcomes for maltreated infants in our current system, there is an urgent need for new technologies to be tested that have the potential to provide safe, nurturing care in timescales that allow benefits in terms of optimal brain development. We are not aware of any previous or current RCT addressing this need. We have conducted a number of linked studies within the MRC Complex Interventions Framework (43) including extensive mapping and modelling work. We are now in the final year of a feasibility RCT and funding from NSPCC has allowed us to continue recruitment up to the date when funding for the start of the definitive trial is being sought. The families recruited in the feasibility study (currently 108) and during the extended recruitment period (an anticipated additional 54) will contribute to the overall study population of the definitive trial (anticipated 462). Our criteria for deciding that progression to a definitive trial is timely and justified include the existence of enough eligible potential participants in Glasgow and other sites; the demonstrable willingness of participants to be randomised to services; the full support of the local health and social services; suitable primary outcome measures; our ability to conduct in-depth assessments that are acceptable to families and excellent recruitment and retention rates in our feasibility trial.

In the pre-feasibility trial phase, we carried out 20 qualitative interviews and focus groups with clinicians, social workers and legal professionals in New Orleans and Scotland, and two audits of NHS and social services for maltreated children. A preliminary economic model exploring the possible consequences of potentially introducing NIM in Glasgow concluded that the additional costs of implementing NIM could be offset within five years by positive consequences such as placement stability and improvements in child mental health with likely longer term impacts on academic performance, employability and reduction in teenage delinquency and crime (44). Our pre-feasibility phase led to the development of the team delivering NIM – Glasgow Infant and Families Team (GIFT). In addition, it allowed standardisation of the comparison intervention, Case Management (CM) (see section 7 below).

In our feasibility trial, the research questions addressed included:

- Is a definitive multicentre UK RCT feasible, acceptable and necessary?
- What would be the required size of a definitive RCT?
- What would be the optimal outcome measures for a definitive trial?

The feasibility trial/internal pilot (completed) was conducted to determine whether a definitive multicentre UK RCT was feasible, acceptable and necessary.

From December 2011 to April 2015, each month an average of 6 children aged between 6 and 60 months entered care in Glasgow for reasons associated with maltreatment. Our recruitment rateduring this phase was consistent at 63%. The mean (SD) age of our child participants in the feasibility phase

was 31.5 (15.5) months and the large majority (81%) were White British. At the time of referral to the trial, just under one-third (31%) of the children's' parents were still together, around two-thirds (63%) came into care from the parental home and, for most (75%), this was their first care episode. The most common reasons for a child coming into care were "parenting issues" (86%) and/or neglect (72%). The majority of the children (80%) had siblings.

At 1 year follow-up, 59% were still with their first foster carer, 22% were in a second foster placement, 9% were in a third foster placement, 4% were in parental care and 1% was in kinship care. Forty–seven per cent of the under-5s coming into care in Glasgow were aged 0-6 months and we plan began including this population in main multicentre trial in April 2014 . The reasons for coming into care in the 0-6 month age group are similar to the children already in the study.

An exploratory economic analysis was undertaken alongside the feasibility trial to look at the potential incremental difference in costs and outcomes (improved mental health) of NIM compared to CM. This exploratory work has allowed us to identify the resources required for an economic analysis of NIM and CM and, as such, we have developed and set up data collection systems and tools such as service-use questionnaires to collect data from both foster carers and birth families on behalf of themselves and the child.

Our detailed qualitative process evaluation in Glasgow has included individual interviews with 18 foster carers and 7 birth parents, 8 focus groups with social workers, and 2 focus groups (each) with the teams delivering NIM and CM. Interviews and focus groups with legal professionals are about to begin.

Our consultations with foster carers and social workers have shown that the research processes and assessments in the trial are largely acceptable and concerns raised have been addressed by streamlining procedures. For example, it has taken, on average, 8 weeks to achieve consent to the trial (mean 48days; SD 27.6 days), often because families are hard to find in the community. This was why we initially decided that a randomisation before consent system, as agreed by West of Scotland Multicentre Ethics Committee 5, would be most appropriate for the trial participants. On-going work over the 18 months since we implemented this system raised a different set of problems for the trial and the delivery of the NIM intervention. The randomisation before consent led to an increase in the number of families that are listed as open cases with the GIFT team in Glasgow, and much more resource was required by the team to ensure that the families are engaging and contactable before they can appoint the family for the initial assessment, which resulted in a waiting list for the families randomised to the GIFT service. Work to address this has reduced the times the families are now waiting: continued work towards an increase in GIFT capacity has resulted in the trial team deciding that reverting back to the more classical consent before randomisation would benefit the trial in achieving recruitment targets by increasing the capacity of the GIFT team. Our process evaluation over the last 18 months has shown that, with this population, there is an inevitable delay of two to three months before a service can be instituted, while families are engaged. This is also the case in New Orleans. Our consultations with the

GIFT team have shown that there has been an increase in the efficiency of their processes and an increase in confidence in their decisions earlier in the treatment process with families. Mapping of NIM timescales, and work with our partners in Croydon local authority, has demonstrated that these timescales are compatible with the new timescales for care proceedings in the English legal system. Our consultations with the CM team have shown that CM remains embedded within usual social work processes. While this has apparent advantages in terms of cohesion between CM and social work reporting systems, CM is also vulnerable to the usual stresses and staffing difficulties of a busy social work service.

Overall, our consultations have revealed much support for the trial and perceived advantages of both NIM (e.g. more thorough intervention) and CM (e.g. shorter time to decision-making). We continue to be in a position of equipoise.

We have carefully considered whether or not we should simply extend our feasibility trial and whether it might be possible to judge effectiveness from an extended pilot. Firstly, although the recruitment rate in Glasgow has been ideal for us to carefully explore trial systems, it would not be sufficient to allow us to answer our primary research question within a feasible timescale (see next section). Evidence from our previous RCT with Scottish children in foster care has shown that even involving many Scottish Local Authorities (all of which are much smaller than Glasgow) would fail to achieve the required numbers (45). Even if the size of an effect of NIM was apparently very large, so that it was statistically significant within the Scottish population, such a result would not be credible without going on to confirm this in a larger trial involving other geographical populations. Secondly, we now require a definitive multicentre trial involving sites in both England and Scotland as the legal systems in these two countries are very different. It will be essential to demonstrate effectiveness across these different jurisdictions for generalisability and relevance within the UK NHS and if the study is to have implications for policy internationally.

We are currently mapping and modelling the landscape of services-as-usual and the level of acceptance of a trial of NIM in our proposed additional sites to understand site-specific contextual issues and practical details such as team composition and routes of referral into the trial. Legal changes come into force this year in England (Children and Families Bill, 2013) which will provide a context more similar to that of New Orleans, placing a tighter legally enforced timescale within which decisions about permanent placements need to be made for children in care. Our research is timely in that the new framework will focus our work, and our findings will feed into discussions about how the changes to the legal framework in England can be used to ensure the most effective support for children entering care. London data collection has included three focus groups and five telephone interviews with multi-agency professionals. This has resulted in refinement of our recruitment procedure and the operational model of NIM in order to comply with this new framework.

Combined, our findings to date indicate that the feasibility, acceptability and necessity of a definitive trial

have been established.

What would be the required size of a definitive RCT?

Sample size calculations (see Section 8) suggest that we require a total sample size of 462 families in order to have 90% power to detect an effect size of 0.35, allowing for 25% loss to follow-up. By the time this proposed study begins in London we will have already recruited162 families and will require to recruit a further 300 families across Glasgow and London At a rate of 6 families/month in both sites, this will be achieved in 2.5 years.

What would be the optimal outcome measures for a definitive trial?

Our primary outcome is child mental health. Based on the findings of our feasibility trial and our review of the literature, our primary outcome measure will be the Strengths and Difficulties Questionnaire (SDQ), the most widely used and well validated measure of mental health in children. Because of the complexity of, and inter-relationship between, different aspects of mental health in infancy (59), we have included a range of other outcome measures of relationship functioning, attachment disorders and cognition. See Section 4.2 for more details.

1.3 PRIOR EXPERIENCE

We have systematically reviewed the literature on interventions for maltreated in foster care (2). Programmes generally focus either on improving parenting by foster carers or on improving the functioning of the birth family while the child remains at home. Two previous reviews focussing on interventions with foster carers (3, 4) concluded that these are complex and costly (4) and have limited impact on the behavioural problems, placement stability and emotional health and wellbeing of the children (3). A Cochrane review of short-term individual and group-based parenting programmes for the treatment of physical child abuse and neglect concluded that there was insufficient evidence to support the use of these interventions in this population (5). Longer term home-visiting programmes have had more success in reducing maltreatment by young first-time mothers, with effect sizes increasing over time (6). Randomised Controlled Trials (RCTs) of home-based programmes that target individual families have shown improvements in maternal sensitivity, infant cooperativeness (7) and child mental health (8, 9), better identification of child protection concerns (7) and a reduction in child abuse potential (8). However, these programmes were aimed at parents deemed *at risk* of maltreating their child and usually did not target families in which a child had already been maltreated. In contrast, a high quality RCT of an intensive home-visiting programme for families where abuse or neglect had already occurred found no reduction in subsequent maltreatment (10).

A handful of trials have used fostering or adoption as an intervention in itself (11-13). In older children previously living in birth families, reductions in delinquent and externalising behaviour have been demonstrated (12, 13) and in previously institutionalised infants, there were improvements in cognition (11), language (14) and mental health (15). A Cochrane review concluded that children in extended family ("kinship") care experience better behavioural development, mental health functioning, and placement stability than children in non-kinship foster care but, of the 62 studies included in this review, none was a RCT (16).

1.4 STUDY HYPOTHESIS

We hypothesise that introducing an infant mental health approach to working with maltreated pre-school children coming into care will be a cost-effective way of improving their mental health.

2 STUDY OBJECTIVES

There are four main study objectives

Primary objective

- Is NIM effective in improving the mental health (as measured by SDQ at 2.5 years post-randomisation) of maltreated infants and young children, compared to enhanced services as usual, Case Management (CM)?

Secondary Objectives

- Is NIM effective in improving the relationship between maltreated infants and young children and their primary caregiver (as measured by PIR-GAS at 2.5 years post randomisation), compared to enhanced services as usual, Case Management (CM)?
- Does NIM effect more timely permanent placement decisions (see 2.2 below) for maltreated children at 2.5 years post-randomisation?
- Is NIM cost-effective in terms ofthe short term mental health of the child (as measured by SDQ and PEDS-QL at 2.5 years post-randomisation)and in terms of the lifetime analysis ?

Appendix A contains a table with additional information on outcome measures.

2.1 PRIMARY ENDPOINT

- Strengths and Difficulties Questionnaire at 2.5 years post randomisation.

2.2 SECONDARY ENDPOINT(S)

- Observational Schedule for Reactive Attachment Disorder also known as the Waiting Room Observation (WRO)
- This Is My Baby (TIMB)
- Disturbances of Attachment Interview (DAI)
- Infant-Toddler Social-Emotional Assessment (ITSEA)
- Pediatric Quality of Life PEDS- QL
- Development and Wellbeing Assessment (DAWBA)
- Parent-Infant Relationship Global Assessment Scale (PIRGAS)
- The WPPSI.
- Service Use Questionnaire
- Relationship Problems Questionnaire
- Time to Permanent Placement defined as placed from care in the family intended to be permanent. This could be the a. rehabilitated birth family or kinship care, b. adoptive family or c. longterm

foster placement (

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3 STUDY DESIGN

This multi-site definitive cluster randomised controlled trial (RCT) compares two services, NIM and CM, for infants and young children who enter a period of foster care for reasons associated with maltreatment. The unit of randomisation is the family. BeST[?] will be performed to Research Governance Framework for Health and Community Care (Second edition, 2006).

3.1 STUDY POPULATION

The study will enrol 462 families who have a child aged between 0-60 months who have entered a period of foster care for reasons associated with maltreatment. Foster carers and birth parents will provide written informed consent.

The study settings are the geographical areas served by social services in the recruiting areas. The interventions in all sites will be managed, in partnership, by the NHS, social services and the National Society for Prevention of Cruelty for Children (NSPCC). These sites were selected for two reasons. First, each uses a centralised social work service to determine the foster carer allocation for each child. Second, social work services and their partners in each site have implemented, or have agreed to implement, a policy to offer either NIM or CM to all children meeting the study inclusion criteria. The decision as to which partnership to take forward will depend on which neighbouring local authority has the qualities mentioned above and can also provide, similar numbers of eligible families as the Glasgow site.

In this definitive trial, NIM will be delivered by the Glasgow Infant and Family Team (GIFT). GIFT is already established through the feasibility study for this proposed trial. A detailed project plan for other NIM teams is under development and training will soon begin led by staff from both New Orleans and the GIFT team. We are currently conducting extensive mapping and modelling in new sites which will facilitate implementation.

CM will be delivered by the Family Assessment and Contact Service (FACS) in Glasgow, an enhanced service-as-usual. In other sites these services-as-usual also fit with the description of CM (see Section 7) and are of a similar level of standardisation and quality as FACS.

Families will be eligible for the trial if they have a child aged 0 to 60 months who enters care in the recruiting sites, for reasons associated with maltreatment, during the study recruitment period.

When a child meeting study inclusion criteria enters foster care, the usual social work service placement provider will enter on the study “housekeeping” electronic system: the date of entry to care; age of child; name of the child’s social worker; name of the foster carer’s social worker and the study ID of any siblings already enrolled.

Entry of these data will prompt the system to: record the date of the entry onto the system; allocate a

provisional study ID to the new entry and send an email alert of the new entry to the relevant study recruitment co-ordinator and project manager.

3.2 INCLUSION CRITERIA

- Families will be eligible for the trial if they have a child aged 0 to 60 months who enters care in the recruiting sites, for reasons associated with maltreatment, during the study recruitment period.
- Written informed consent from the birth family and/or the child's foster family.

3.3 EXCLUSION CRITERIA

- Families will be excluded from the trial if the parent(s) is unavailable to take part in intervention (e.g. because of death, unknown whereabouts or long term imprisonment).
    - "Families will not be randomised if they have previously been randomised and exposed to one of the study interventions as part of the trial. If a family has been randomised previously, but became ineligible (e.g. if the children are returned to the birth family), without being exposed to either of the study interventions, then the family may be randomised again, should they become eligible at a later date."

3.4 IDENTIFICATION OF PARTICIPANTS AND CONSENT

When a child meeting the study inclusion criteria enters an episode of foster care, the usual social work service placement provider or study recruitment co-ordinator (a member of the social work service) will enrol the child on the trial automated electronic system. Enrolment is managed via the RCB, https://www.glasgowctu.org/BEST/Login.aspx?ReturnUrl=%2fBEST%2fdefault.aspx
and will require a log in and password to access the system. Log in and passwords are arranged by BeST^2 trial team, and should be allocated to relevant staff, those listed on the trial delegation log, in advance of the enrolment procedure. The details required to enrol the child are as follows:

- date the child entered care,
- age of child (in months) on care entry,
- name of the child's social worker and area team (ie those involved in the decision for the current episode of care entry),
- name of the foster carer's social worker (ie those responsible for the carer with whom the child has been placed), and
- the study ID of all siblings already enrolled

(NB no personalised details about the child, family or foster carers are entered on the system at this time)

Entry of these data will prompt the system to:

1. record the date of the entry onto the system,
2. allocate a provisional study ID to the new entry,
3. send an email alert of the new entry to the relevant study recruitment co-ordinator and project manager

On notification of a new entry onto the study RCB electronic system, the recruitment co-ordinator will email the child's social worker and foster carer's social worker to confirm that the parent and foster carer have been informed about the study and have expressed interest in being contacted by the research team to discuss the study further. The child's social worker will also be asked to confirm whether or not there are any issues that may pose a risk to the recruitment officer as a sole worker visiting the family. In the event that there is, this will be reviewed on a case by case basis and appropriate arrangements will be put in place to minimise risk (e.g. arranging to meet in social work premises or arranging joint home visits with the child's social worker).

Interested parents will be telephoned by the recruitment co-ordinator who will confirm that they have received the study information materials (copy of the relevant Participant Information Leaflet, Consent Form and Digital Video Disc), address questions and make arrangements for obtaining informed written consent and one of the baseline assessment measures (Development and Wellbeing

Assessment (DAWBA) relating to the child's early development). This will involve a face-to-face meeting either in the participant's home or at a safe and mutually convenient location (social work premises). The research co-ordinator will send a letter confirming the agreed arrangement for this appointment. This letter will include copies of the study information materials (identical to those they should already have received). A telephone reminder call or text will be sent to the parent a few days prior the appointment.

Interested foster carers will be telephoned by the study recruitment co-ordinator or one of the research assistants who will confirm receipt of the study information materials (copy of the relevant Participant Information Leaflet, Consent Form and Digital Video Disc) and address questions. If the parent has not declined the invitation to participate in the study, arrangements will be made with the foster carer for the baseline research assessment. A letter confirming the agreed arrangement will be sent with copies of the study information materials (identical to those they should already have received). The foster carer will be asked to complete and return the Consent Form in a prepaid, pre-addressed envelope to the study office. The consent form must be received before the assessment but can be completed on the day if necessary – as long as the foster carer has had 24 hours to consider the information leaflet. If foster carers request a face-to-face meeting to discuss the study before deciding whether or not to sign the Consent Form, the recruitment co-ordinator will visit their homes prior to the study baseline assessment.

In the event that it proves impossible to contact a parent during the 10 week period following the child's entry to care, the foster carer, as the person designated with the responsibility for the day to day care of the child, will be considered to have parental responsibility for the decision. However if either the foster carer or parent decline the invitation to participate in the study, the family will receive social workservices as usualand no data will be collected about them for research purposes.

The children recruited to the study are aged between 0-60 months therefore no age appropriate information sheets/consent forms will be required.

3.5 RANDOMISATION

Randomisation is also managed via the RCB, which is access via https://www.glasgowctu.org/BEST/Login.aspx?ReturnUrl=%2fBEST%2fdefault.aspx and will require a log in and password to access the system. Log in and passwords are arranged by BeST$^{?}$ trial team,

and should be allocated to relevant staff, those listed on the trial delegation log, in advance of the randomisation procedure.

When the recruitment coordinator confirms that a family of an eligible child meets study eligibility criteria and written informed consent has been obtained the recruitment coordinator will be required to access the electronic system using the trial ID, allocated at enrolment, to perform the central randomisation. The randomisation system will:

- allocate the family to either the CM or NIM service within the relevant site;
- record and store the date of randomisation onto the system;
- send an email alert of the new allocation with the trial IDs to the relevant study recruitment co-ordinator, project manager and appropriate allocated CM and NIM service manager

A guidance document outlining the enrolment and randomisation requirements has been developed and can be obtained by contacting the BeST$^{?}$ project manager, Lynn McMahon via email on lynn.mcmahon@glasgow.ac.uk

Random allocation of families will be performed using a mixed minimisation/randomisation method, stratified within study site. A randomisation schedule will be prepared for each site, in blocks of 10: in each block, 8 allocations will be decided by minimisation, and two at random (one to each group). For those to be minimised, the schedule will indicate which group to allocate to in the case of "no preference" according to the algorithm (4 to each group, at random).

3.6 ASSESSMENT VISITS / COHORT MAINTAINENCE

When consent has been obtained the participant is required to attend for 3 assessment visits, as follows:

- Time 1 Baseline approximately 10-14weeks post entry to care
- Time 2 at approximately 15 months post entry to care
- Time 3 at approximately 2.5 years post randomisation

The details of the assessment requirements are listed on the study schedule on page 17 of this protocol

Where possible, assessment visits should be undertaken at the study site. As these families can have very chaotic living arrangements up to date contact information should be taken at each visit in order to maintain contact and ensure that as many assessments as possible can be completed. In order for the study to maintain the cohort of participants there is provision for home visits to maintain the study cohort and the details on when these should be performed are noted below.

1. For participants, that have given written informed consent, contacted to arrange an assessment visit that request the assessment at home, as the family are unable or unwilling to

travel, by the study team. This will be a pre-arranged visit agreed at a time convenient to the participant.

2. For participants, that have given written informed consent, where attempts to contact by calling and lettering to arrange an assessment visit have failed, over the 4 month period from when the date the assessment is due, may be visited at home to complete a less intensive assessment visit (targeting the primary outcome measures), to re-arrange a visit at a more convenient time, or to confirm that they do not want to participate further with the study. These visits will be un-scheduled with the participant but should be proceeded with a contact letter which states that the study team may drop into see them.

Risk assessment of a home visit must be undertaken and any concerns with the families should be discussed with the study team prior to any staff undertaking a visit at a participants home. If there are any concerns of note home visits should not be performed for these families. Standard NHS home visit policy applies.

We will also maintain contact with families who have consented to participate via social media, using tried and tested research methods to ensure that participant confidentiality is not breached and no correspondence is visible between members of the group.

3.7 WITHDRAWAL

Participants will be withdrawn from the trial in the following circumstances:

- At their own request
- At the request of the court or Children's Hearing System
- At the request of the Data Monitoring Committee

Participants have the right to withdraw from the trial at any point for any reason. The investigator can also withdraw participants from the study intervention in the event of safety concerns, protocol violations or any other relevant reasons.

If a participant is to be withdrawn, a discussion will take place with the participant – and if necessary with his/her legal representative and/or the data monitoring committee. The data collected till the point of withdrawal will be retained and this will be clearly documented in participant information sheet and consent form.

Withdrawal due to adverse events is unlikely as our feasibility study has not identified any risks to

participants from either of the trial interventions. However, should this occur, the participants social worker and/or general practitioner (depending on whether the adverse event is a social or health one) would be asked to follow the participant up.

4 TRIAL PROCEDURES

4.1 STUDY SCHEDULE

4.1.1 VISIT 1: Initial approach

- Discussion with birth family social worker about if and how to approach birth parent(s)
- Visit to birth family at home or another convenient location such as social work department
- Reading through of study information leaflet and provision of information leaflet and DVD

Eligible children will be enrolled onto the trial database by the recruitment coordinator or delegated staff as per section 3.4 of this protocol

4.1.2 VISIT 2: Obtain informed consent

- Discuss study information
- Ask parent to decide about consent and sign consent form accordingly

N.B. For foster carers, this can occur at baseline visit whereas for birth parents (who usually need longer to consider study information) it is likely to be conducted in a separate visit.

Parents that sign consent will then be randomised to the appropriate service by the recruitment coordinator as per section 3.6 of this protocol.

4.1.3 VISIT 3: Baseline assessment

N.B. Initially, during the feasibility study the procedure for baseline assessment was as follows:
>Consent; baseline assessment; randomisation.
Due to concerns about delays to service delivery this was changed to the following:
>Randomisation; consent; baseline assessment.
Now, due to a realisation that randomisation-before-consent does not reduce delays to participants receiving a service and to ensure that delays are not brought in due to participants awaiting baseline assessment we are following this procedure:
>Consent; randomisation; baseline assessment

- Strengths and Difficulties Questionnaire
- Parent-Infant Relationship Global Assessment of Functioning (video recording of meal and play time, independently rated)
- Infant Toddler Social-Emotional Assessment

- Development and Wellbeing Assessment
- Disturbances of Attachment Interview
- PEDS-QL (questionnaire measure of child quality of life)
- This is My Baby interview
- Observational checklist for Reactive Attachment Disorder
- Relationship Problems Questionnaire

4.1.4 VISIT 4: 15 months post entry to care, (approx..1 year post randomisation)follow-up

- Strengths and Difficulties Questionnaire
- Parent-Infant Relationship Global Assessment of Functioning
- Infant Toddler Social-Emotional Assessment
- Disturbances of Attachment Interview
- Service use questionnaire
- PEDS-QL (questionnaire measure of child quality of life)
- This is My Baby interview
- Relationship Problems Questionnaire

4.1.5 VISIT 5: 2.5 year post randomisation follow-up

- Strengths and Difficulties Questionnaire
- Parent-Infant Relationship Global Assessment of Functioning
- WPPSI (child cognitive assessment)
- Disturbances of Attachment Interview
- Service use questionnaire
- PEDS-QL (questionnaire measure of child quality of life)
- This is My Baby interview
- Time to permanent placement (routine data)
- Routine data on mental and physical health
- Relationship Problems Questionnaire
-

4.2 STUDY OUTCOME MEASURES

4.2.1 PRIMARY OUTCOME MEASURE(S)

Our primary outcome is child mental health and our primary outcome measure is the Strengths and Difficulties Questionnaire (SDQ) measured 2.5 years post randomisation . This is a brief behavioural screening questionnaire for 2-16 year olds, completed by the primary caregiver, with 25 items in 5 subscales; emotional symptoms; conducts problems; hyperactivity/inattention; peer relationship problems and prosocial behaviour (54). It is sensitive to change: in intervention studies, effect sizes are moderate to large (55-57). Our review of the literature suggests that SDQ is the most widely used and well validated measure of mental health in children.

4.2.2 SECONDARY OUTCOME MEASURE(S)

1. Parent- or carer-child relationship. This will be measured using the Parent-Infant Global Assessment Scale (PIR-GAS) (58) at 2.5 years post-randomisation.
2. PEDS-QL at 2.5 years post-randomisation

There is no risk of unblinding with PIR-GAS as it is rated/entered independently from the research team.

OTHER OUTCOME MEASURES

The range of measures we have included reflect the fact that mental health in infancy is multi-faceted and the various aspects (relationship, psychiatric diagnoses, cognition and language) overlap with one another (59).

- The Infant-toddler social-emotional assessment (ITSEA) is a well validated parent/carer-completed questionnaire covering a wide range of social and emotional behaviours in infants and preschool children (60). It has been shown to be sensitive to change in previous intervention research with maltreated children with medium to large effect sizes (61) and has good longitudinal stability.
- Because mental health in pre-schoolers is so linked to cognitive functioning, we have included a full-scale IQ measure (see Table 1, below), WPPSI (62), measured from age 2.5 years. WPPSI is the most commonly used and best-validate measure for this age-group and covers both performance and language aspects of cognition.
- Psychiatric diagnoses will be assessed using the Development and Wellbeing Assessment (DAWBA) - a validated semi-structured interview generating ICD and DSM diagnoses (63).
- The Relationship Problems Questionnaire (64) and the Disturbances of Attachment Interview

(DAI) (65) will be used to investigate Reactive Attachment Disorder (RAD) symptoms. The Observational checklist for RAD (66) will be used, alongside these measures, to establish diagnoses of RAD.

- Because the commitment of carers to their child has been shown to be related to the quality of the relationship (67) we will use the This is My Baby (TIMB) questionnaire – a brief questionnaire investigating carers' long-term view of their relationship with the child (68).
- In order to adhere to the recommended methods for economic evaluation of public health interventions by the National Institute for Health and Clinical Excellence (NICE) (69) the PedsQL, a validated measure of child Quality of Life (70), will be included with the intent to map outcomes to EQ-5D utility so as to estimate Quality Adjusted Life Years (QALYs). Recent work by Khan et al (71) has mapped EQ-5D utility scores from the PedsQL generic core scales hence these algorithms will provide an empirical basis for estimating health utilities in this population.
- Linkage with routine data will allow us to measure repeat episodes of maltreatment and validated physical and mental health diagnoses. Consent for this is sought at recruitment.
- Time between first care episode and permanent placement decision (adoption, permanent foster care or rehabilitation). This will be determined through scrutiny of routinely held social work data.

5 ASSESSMENT OF SAFETY

During our feasibility trial, we have maintained good communication with the GIFT and FACs teams so as to find out quickly about any adverse events. There was one serious adverse event in the feasibility trial (a parental death) that was associated with an incident unrelated to the trial. We have also, through our qualitative interviews with foster carers, social workers and birth families, been made aware of any concerns regarding the trial. The most serious of these has been concerns about delay to children achieving permanent placement.

Our experience from the feasibility trial suggests that risks to children are, in fact, reduced considerably for participants because there is now far greater scrutiny of the health and safety of child participants by clinicians and social workers than before the trial started.

We have now instituted a system of routine monthly scrutiny of any major changes in the birth family situation through the social work and health data systems in order that we are aware of any adverse events or major changes in care situation in our participants. We also plan to test the feasibility and cost of asking the FARR Institute to scrutinise mortality data on our dataset intermittently throughout the trial. While we do not consider it necessary to pre-specify Stopping Rules as the feasibility trial has not suggested any harm, data monitoring is the responsibility of Data Monitoring and Ethics Committee (see Section 11) which can examine unblinded data and recommend stopping the trial if thought necessary at any point during the study.

6 STUDY INTERVENTION

6.1 NIM

The NIM intervention will be delivered, in each site, by a multidisciplinary team comprised of a child and adolescent psychiatrist, psychologists, social workers a psychotherapist and administrative staff. In addition, family transport will be provided by a dedicated team of 2 trained drivers who are an essential part of the team. In other sites, each member of clinical staff will receive specific training in assessment techniques and treatment delivery from the New Orleans and/or Glasgow team.

Participants randomised to NIM will be asked to take part in a detailed attachment-based assessment involving each actual and potential caregiver. The assessment is manualised, standardised and uses structured interviews, self-report measures and observations (15). 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 (49). 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 best outcome possible for [the] particular child" (Zeanah, personal communication, 2014), be this a recommendation of rehabilitation to birth family or adoption (15). Making well informed permanent placement recommendations within 6-12 months could optimise physical, mental and social development.

Maintenance of fidelity to NIM has been supported, in Glasgow, by fortnightly videoconferences between the GIFT team and Professors Charley Zeanah and Julie Larrieu in New Orleans who scrutinise and comment on videotaped material from GIFT assessments and treatments. In addition, during the feasibility trial, Professors Zeanah and Larrieu have agreed to rate 10 randomly selected reports from the GIFT team using a checklist prepared for the study. These data will be shared only with the research team. We plan and have costed for this process of report-rating to continue in the definitive trial. Other NIM teams will receive a similar level of clinical support, again by teleconference, from experienced NIM clinicians but this will be shared between the New Orleans and Glasgow teams.

6.2 CM

Families not randomised to NIM will receive Case Management (CM). CM was successfully used in a US RCT (32) and provides additional monitoring of social work provision and signposting of families towards existing services.

Although "*local authorities have a duty to safeguard…children … and…[provide] a range and level of services appropriate to the children's needs*" (50, 51) the delivery of early intervention services has historically been *"varied and diffuse"* and hard to quantify (52). CM therefore represents a significant enhancement over current "services as usual". In accordance with the CM model, social workers will assess the family and help to engage them with support/clinical services.

CM –(in Glasgow called the Family Assessment and Contact Service (FACS)) – is an ideal attention control for NIM because it also offers a relationship-based assessment of the parental capacity to care for the child, but has a social work ethos, including more naturalistic observations of the family and unstructured assessments of case files. It does not contain an infant mental health treatment component. Current services-as-usual (SAU) in other sites are relatively sophisticated compared to many areas of the UK. Although we are confident that SAU conform in general terms to the Case Management model, further exploration of the detailed nature of SAU in other sites is a key objective of qualitative mapping and modelling we are currently undertaking.

7 SAFETY REPORTING

7.1 DEFINITIONS OF ADVERSE EVENTS

Adverse Event (AE) – Any untoward medical occurrence in a subject to whom a trial intervention has been offered, including occurrences which are not necessarily caused by or related to that product.

7.2 SERIOUS ADVERSE EVENT (SAE)

Serious Adverse Event (SAE) - An untoward occurrence that:

a) Results in death
b) Is life threatening
c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability or incapacity
e) Consists of a congenital anomaly or birth defect
f) Is otherwise considered medically significant by the investigator

N.B. See section 5 “Assessment of Safety” for methods of determining whether a Serious Adverse Event has occurred.

7.3 RECORDING AND REPORTING OF ADVERSE EVENTS

Any SAE occurring to a research participant will be reported to the main REC (i.e. the REC that gave a favourable opinion of the study) where in the opinion of the Chief Investigator (CI), the event was:

• "Related" – that is, it resulted from administration of any of the research procedures, **and**

• "Unexpected" – that is, the type of event is not an expected occurrence.

Reports of related and unexpected SAEs should be submitted to the REC **within 15 days** of CI becoming aware of the event, using the 'report of serious adverse event form' for non-CTIMPs published on the National Research Ethics Service (NRES) website.

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

The form should be completed in typescript and signed by the CI (or designee). The PV Office will assist in the preparation and submission of the report.

The Data Monitoring and Ethics Committee will be notified of all such events whether considered to be related to the trial interventions or not. The co-ordinator of the main REC will acknowledge receipt of safety reports within 30 days.

7.4 ANNUAL SAFETY REPORTING

The CI is also responsible for providing an annual progress report to the REC using an NRES "Annual Progress Report form for all other research". This form is available at:
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

A section on the safety of participants is included in this report.

8 STATISTICS AND DATA ANALYSIS

8.1 STATISTICAL ANALYSIS PLAN

The study will have a comprehensive Statistical Analysis Plan (SAP), which will govern all statistical aspects of the study, and will be authored by the Trial Statistician and agreed by the Study Steering Committee (SSC) before any unblinded data is seen.

8.2 PRIMARY EFFICACY ANALYSIS

The primary outcome will be the Total Difficulties scale of the Strengths and Difficulties Questionnaire (SDQ) at 2.5 years after randomisation.

The primary analysis will use a generalized linear mixed effects regression model for the primary outcome measure to account for clustering of outcomes within families, and for repeated measures of the outcome over time. The residual variance within the model will be assessed in blinded analyses and an appropriate model will be used. The model will include fixed effects for randomised group, the minimisation/stratification factors, time points (baseline, 15 months, 2.5 years), treatment-by-time interaction, child's age at time of data collection, and version of questionnaire used, plus random effects for families and children, with a general covariance structure for the repeated measures. This model will be used to estimate the between-group differences at 15 months and 2.5 years from randomisation, with 95% confidence intervals and p-values. Should the regression model not converge, as specified here, then a simpler model will be applied; all modelling decisions will be fully justified in the SAP.

Data from all children in each family who enter the study at the point of randomisation will be included in the final analyses. Sensitivity analyses will be carried out using one child from each family (the youngest child at the point of randomisation). Missing outcome data will not be imputed in the first instance, but the characteristics of children and families who fail to provide outcome data will be investigated, and the sensitivity of the primary analysis to alternative assumptions regarding missing outcomes will be assessed. This will include analyses based on multiple imputation of missing outcome data based on intermediate data, where available.

8.3 SECONDARY EFFICACY ANALYSIS

Secondary and other outcomes will be:

- Parent-Infant Global Assessment Scale (PIR-GAS) – a measure of the parent- or carer-child relationship
- Time to permanent placement decision (see definition in section 2.2)
- Infant-toddler social-emotional assessment (ITSEA) – a measure of social and emotional behaviours
- Wechsler Preschool and Primary Scale of Intelligence (WPPSI) – a measure of IQ
- Development and Wellbeing Assessment (DAWBA) – a measure of psychiatric diagnoses
- Relationship Problems Questionnaire (RPQ) and Disturbances of Attachment Interview (DAI) – measures of Reactive Attachment Disorder symptoms
- This is My Baby (TIMB) questionnaire – a measure of carers' long-term view of their relationship with the child
- PedsQL - a measure of child Quality of Life to map to EQ-5D utility so as to estimate Quality Adjusted Life Years (QALYs)
- Repeat episodes of maltreatment and physical and mental health diagnoses, through routine data linkage.

Each continuous outcome measured at multiple assessment points will be analysed using methods similar to the primary outcome, using regression models appropriate for the outcome variable. Interaction models will assess whether intervention effects vary between subgroups.

Time to permanent placement (see definition section 2.2) will be analysed using survival analysis methods, including Cox Proportional Hazards regression models, adjusting for minimisation/stratification factors.

8.4 SAFETY ANALYSIS

Serious adverse events – both numbers of subjects and events – will be summarised by randomisation group and overall using descriptive statistics. No formal statistical tests comparing the randomised groups will be pre-specified.

8.5 SOFTWARE FOR STATISTICAL ANALYSIS

The statistical software to be used will be specified in the Statistical Analysis Plan.

8.6 SAMPLE SIZE

The principal outcome will be the SDQ at 2.5 years follow-up for all children. A sample size of 462 will have 90% power to detect an effect size of 0.35, allowing for 25% loss to follow-up. Due to practical

constraints, children from the same family cannot be randomised to different interventions, even if two children from the same family are referred at different times, therefore the study is effectively cluster randomised. The study will err on the side of caution and aim to recruit 462 families, though the analyses will be at the individual child level, with adjustment for clustering. Sensitivity analyses will look at analyses of one child per family, and still be well powered. This effect size equates to SDQ scores that are clinically significant.

8.7 MANAGEMENT AND DELIVERY

The Robertson Centre for Biostatistics, part of the Glasgow Clinical Trials Unit, a fully registered UK CRN Clinical Trials Unit, will manage and analyse trial data. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan.

9 HEALTH ECONOMIC ANALYSIS

The economic evaluation from a NHS/Personal Social Service perspective and a broader societal perspective will be undertaken in two stages, adhering to good practice guidelines (72) and (the NICE public health reference case (73).

The within-trial analysis will investigate the cost effectiveness of NIM compared to 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 QALY of NIM compared to CM. The CUA will calculate the incremental cost per QALY by using the Paediatric Quality of Life Inventory (PedsQL)[13] child health-related quality of life instrument mapped to EQ-5D to generate utility values.[14] Further, the incremental cost per unit improvement using the effectiveness outcome SDQ[15] will be explored.

The paediatric quality of life inventory (Peds QL TM) generic core scales is a validated measure of child quality of life (3, 43, 44) which has recently been mapped to utility values for use in health economic evaluations (71). Further work is also underway to explore mapping the PedsQL infant and toddler scores to utility. Incorporating this QALY aspect in the economic evaluation meets most recent NICE guidance for public health interventions (73).

Economic evaluation using a cost-consequence analysis framework – which would make possible to consider the wide battery of outcomes collected in the BeST trial- will be also implemented.

The within trial analysis will use the methods employed in previous early years economic studies (74). The costing component will focus on key cost drivers in the NIM and CM interventions. Patient level resource data will be measured, including the health and social care costs of the intervention.

In particular, the costs borne by the Primary care/community centre to deliver the NIM and the CM intervention 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 psychiatrists) and will be collected by and sourced from the services directly. In addition, the consequential health and social services utilised by participants (mental health services, admissions to hospital, addiction/domestic violence services etc.) will be also collected using the Additional Service Use (ASU) questionnaire.
The time spent by birth parents and fosters carers' involvement in NIM or CM as well as police contacts, day care or nursery usage will be also collected and incorporated into the calculation of scenario analyses to provide a broader societal perspective of the costs of these services.
Unit costs for each component of resource use expressed in pounds sterling (£) for cost year

2020/2021, will be obtained from routine sources (i.e. NHS Agenda for Pay, the Personal Social Services Resource Unit (PSSRU), NHS Reference costs) or will be collected from the trial directly where they are not available in routine sources.

Within trial analysis will be undertaken in STATA (StataCorp, TX, USA), adhering to good practice guidance (75, 76). Missing data will be explored by employing multiple imputation methods (77, 78). Unit cost data will be identified from several sources including 'Unit Costs of health and Social Care' (79) which contains costs for services for children and their families.

In addition to a typical health economic evaluation, this early years public health intervention requires an approach which pays particular attention to long term population health impacts on wider society (80, 81). Therefore, a population health economic model will be developed to model the long-term impacts on multiple sectors of investment in child health via the NIM intervention compared to CM. This multi-sector lifetime decision model will be based on the theory of 'Investing in Child Health' (82-84) and will be adapted to model the long term cost and outcomes from NIM and CM for key sectors in society, e.g. education system, child welfare system, criminal justice, NHS & social services. See Appendix Bwhich illustrates the economic logic model under development for this application. The model will use the trial outcome measures at 15 months and 2.5 year follow-up as predictors for parameter estimates in the lifetime model, and will be supported by evidence from a systematic literature review to inform the development of the model and inform key parameter inputs. The model will calculate key lifetime cost and sector specific outcomes for each of the 4 key sectors, for the NIM intervention in comparison to CM. Probabilistic sensitivity analysis will be undertaken to characterise uncertainty in the parameter estimates of the model, while structural uncertainty in the model will be addressed with scenario analyses.

10 TRIAL CLOSURE / DEFINITION OF END OF TRIAL

The trial will end when the SSC agrees that one or more of the following situations applies:

i. The planned sample size has been achieved, and follow-up is complete;
ii. The Independent Data Monitoring Committee (IDMC) has advised discontinuation, e.g. because of safety concerns about the trial, or a statistically significant difference in clinical outcomes is evident between the two treatments;
iii. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;
iv. New information makes it inappropriate to continue to randomise patients to one or other arm of the trial;
v. Recruitment is so poor that completion of the trial cannot reasonably be anticipated.

11 DATA HANDLING

Case Report Forms (CRFs) will be developed by the study Data Centre at the Robertson Centre for Biostatistics, University of Glasgow and will be supplied electronically by the BeST$^{?}$ Trial administrator. It is the investigator's responsibility to ensure completion and to review and approve data captured in the CRF.

Entries to the CRFs will be made in black ballpoint pen and must be legible. Any errors must be crossed out with a single stroke, the correction inserted and the change initialled and dated the appropriate site personnel with this delegated responsibility noted on the study delegation log. Correction fluid must not be used.

If a participant withdraws from the study at any time the reason must be noted and the database updated to ensure that no further contact is made.

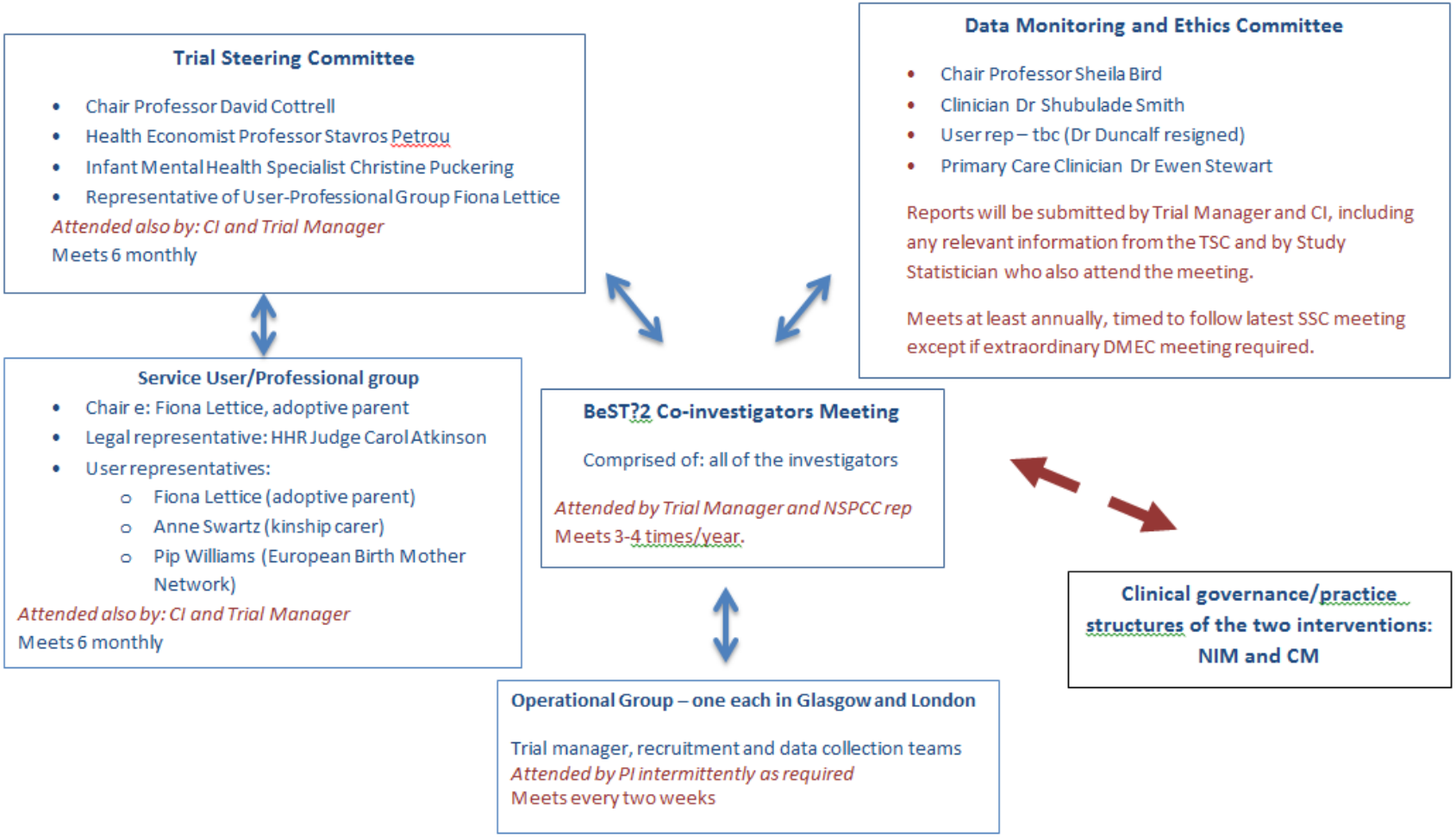
Completed CRF pages should be copied and sent on a monthly basis and returned to the BeST trial team:

All the CRFs must be returned for data entry and ultimately, statistical analysis.

CRFs from the study will be stored in line with current regulatory requirements. Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required. BeST? services trial has a large amount of data collected in many different formats. All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).All data should be returned to the BeST services team

12 TRIAL MANAGEMENT

Proposed Management Flowchart



12.1 ROUTINE MANAGEMENT OF TRIAL: TRIAL MANAGEMENT GROUP

The trial will be co-ordinated from Glasgow by the Research Management Group. This group normally includes those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, other co-investigators and the Trial Manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

12.2 STUDY STEERING COMMITTEE (SSC)

The role of the Study Steering Committee (SSC) is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The SSC should:

- Agree the trial protocol and any amendments
- Provide advice to the investigators on all aspects of the trial
- Have members who are independent of the investigators, in particular an independent chairperson

Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the SSC.

12.3 INDEPENDENT DATA MONITORING AND ETHICS COMMITTEE (IDMC)

The role of the IDMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The IDMC will be independent of both the investigators and the funder/sponsor and will be the only body that has access to unblinded data. It will make recommendations to the SSC.

13 STUDY AUDIT

This study will undergo study set-up visit and site files will be provided. Study may be selected randomly for a routine audit visit.

14 PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the sponsor.

The CI will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.

Before the amended protocol can be implemented, favourable opinion/approval must be sought from the original reviewing REC, and Research and Development (R&D) office(s).

15 ETHICAL CONSIDERATIONS

15.1 ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and all subsequent revisions..

Favourable ethical opinion will be sought from West of Scotland Research Ethics Committee before participants are entered into this clinical trial. Participants will only be allowed to continue in the study once they have provided written informed consent.

The CI will be responsible for updating the REC of any new information related to the study.

15.2 INFORMED CONSENT

Written informed consent will be obtained from the parent and/or foster carer of each trial participant.

The Recruitment Coordinator (a social worker) or research assistant will explain the exact nature of the study in writing, provision of patient information sheet, and verbally. This will include the risks of participating in this clinical trial. Participants will be informed that they are free to withdraw their consent from the study.

16 INSURANCE AND INDEMNITY

The BeST$^{?}$ study is sponsored by NHS Greater Glasgow and Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

17 FUNDING

Funder Grant Reference: **PHR Project: 12/211/54, total research funding £3,437,345.80**

The NIHR PHR funding will begin on 1st September 2015.

18 ANNUAL REPORTS

Annual reports will be submitted to the REC, regulatory authority and Sponsor with the first submitted one year after the date that all trial related approvals are in place.

19 DISSEMINATION OF FINDINGS

Our strategy for dissemination will include feedback to participants, the public and communication within scientific and policy communities.

• Participants: Some of our participating families have literacy problems and we have given much thought to the way we communicate study information to them. We have a lay-friendly study website (http://www.bestservicestrial.org.uk/best_services_trial/home.html) that includes a short information film about the study and Frequently Asked Questions (FAQs) sections for foster carers and social workers (FAQs for birth parents are under development). When the study is complete, we plan to develop another short film and will update our FAQs to reflect the key study findings. We will take the advice of our Advisory Group as to which will be the most efficient fora for communication of findings, including conferences for practitioners and service users. We will also write "user friendly" articles, possibly co-authored with members of our Advisory Group, in practitioner and parent journals.

• Public: In addition to the dissemination strategies above, we will have the help of both the National Society for the Prevention of Cruelty to Children (NSPCC www.nspcc.org.uk) and WAVE Trust (http://www.wavetrust.org/) in disseminating our findings to the public. Both of these organisations put considerable funding and energy into ensuring that the public are aware of key recent research findings regarding improving the lives of maltreated children.

• Scientific community: We will publish our findings in high impact peer reviewed journals including open access journals and the HTA journal series. We will also present at relevant high profile international scientific conferences.

• Policy-makers: our dissemination partners, the NSPCC and WAVE Trust, have excellent links with policy-makers and will ensure that the results of the trial are highlighted to the right individuals and public bodies in order to ensure that findings are translated into practice as soon as possible. WAVE Trust will prepare policy briefings; disseminate these across its own networks (including in law enforcement, health and other relevant forums); write popular articles and opinion pieces that connect the results to the wider policy context and tailor the output to a variety of audiences. This will complement and extend the NSPCC dissemination strategy and will be independent of the interventions tested in the trial. We have costed for production of accessible research briefings for non-academic audiences including care service commissioners in local authorities and the NHS, and user-led voluntary organisations working to support the development and delivery of services. It is envisaged that this will have a long-term effect on service development for these children and their families in the UK.

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Appendix A – Outcome Measures

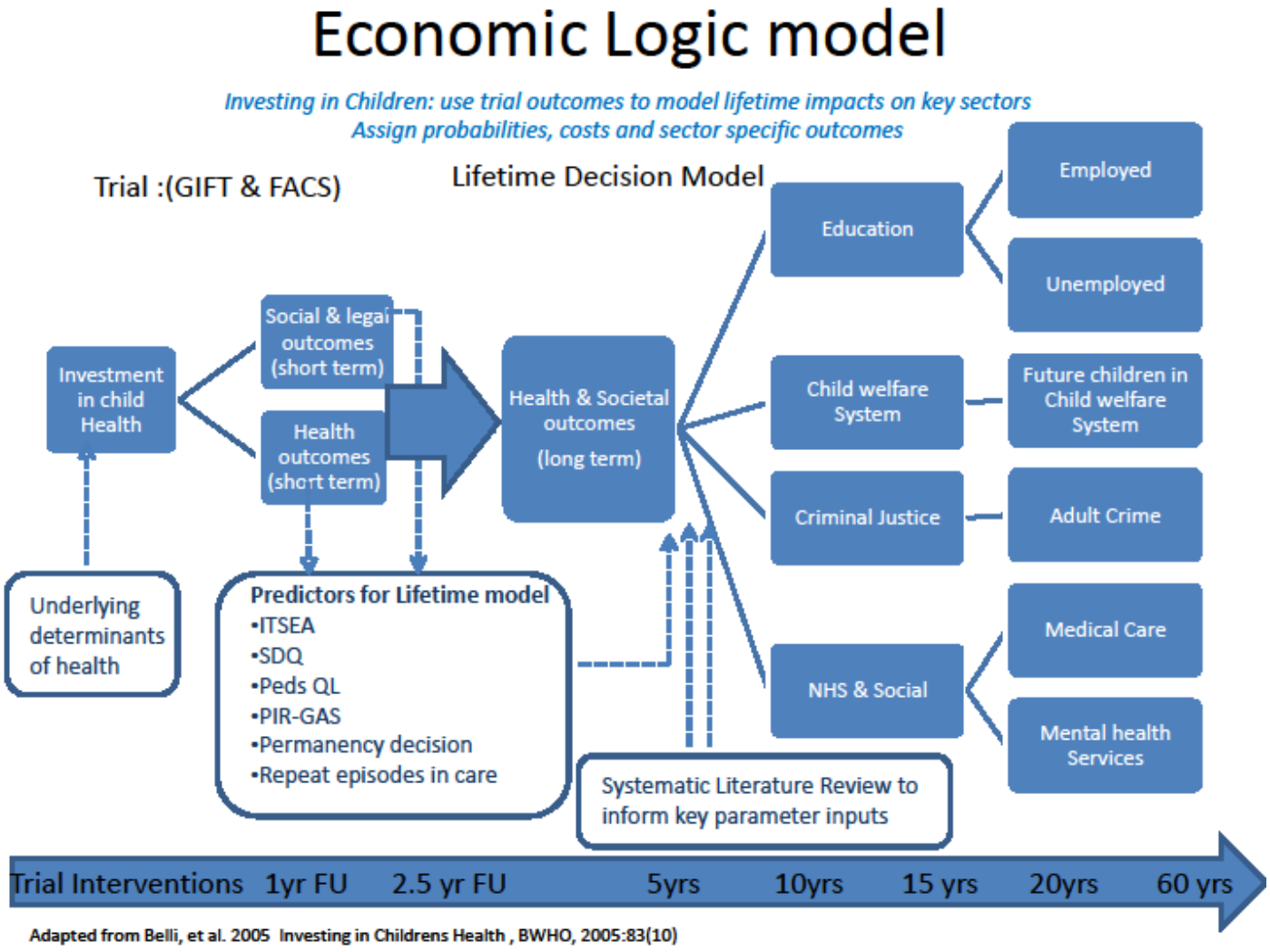
Measure	Baseline	15 mnths	2.5yrs	Respondent	What measuring/type of measure
Primary Outcome Measure					
• **SDQ**	x	x	x	Parent/carer Teacher (if child in pre-school)	Mental health - **Outcome**
Secondary Outcome Measures					
• PIR-GAS	x	x	x	Direct observation	Relationship functioning -**Outcome**
• PEDS-QL – depending on validity data	x	x	x	Parent/carer	Quality of life - **Outcome**
Other measures					
• Time to permanent placement			x	Routine data	Time between first care episode and placement in permanent family (adoption, permanent foster care or rehabilitation) **Outcome**
• Emotional Signalling Scale	x	x	x	Direct Observation	Degree to which the child signals emotions to caregiver - **Outcome**
• ITSEA	x	x		Parent/carer	Infant functioning - **Mediator**
• WPPSI			x	Direct Observation	Cognition – **Moderator**#
• DAI/RPQ	x	x	x	Parent/carer	Reactive Attachment Disorder/Disinhibited Social Engagement Disorder –**Moderator$**
• DAWBA (developmental section-birth parent)	x		x	Parent/carer	Psychiatric Diagnosis - **Outcome**
• Service use questionnaire		x	x	Parent/carer	Feature of the interventions
• TIMB	x	x	x	Parent/carer	Carer commitment - **Mediator**
• Observational checklist for RAD	x			Direct Observation	Contributes to RAD/DSED diagnosis
• Data on mental and physical diagnoses and treatment and child's care journey			x	Routine data	e.g. degree of contact with birth parents; number of children's hearings/court appearances; delay between recommendation from NIM or CM and implementation of recommendation - **influencers**

*we are defining an "influencer" as something that could be a moderator, mediator but where status is not yet clear.

#although cognition in other studies (e.g. Bucharest early intervention study) could be considered an outcome, in the feasilibity study we did not see major changes between baseline and 1 year follow up so suspect it is better considered a moderator. This could be revised once we see the full study and both follow-up periods.

$RAD and DSED symptoms, in a preliminary analysis of the feasibility data, seem to be associated with birth and pre-care factors (where more traditional mental health problems are not) and might pre-date mental health problems as measured by SDQ.

Appendix B Health Economics Logic Model



Adapted from Belli, et al. 2005 Investing in Childrens Health , BWHO, 2005:83(10)