Centre for Trials Research
Canolfan Ymchwil Treialon

South East Wales Trials Unit
Uned Ymchwil De-ddwyrain Cymru

STATISTICAL AND HEALTH ECONOMICS ANALYSIS PLAN
FOR
BB: 2-6

Study title: Evaluating the long-term effectiveness, and the cost and consequences of the Family Nurse Partnership parenting support programme in reducing maltreatment in young children

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Chief Investigator:
Professor Mike Robling,
Director of Population Health Trials
South East Wales Trials Unit, Centre for Trials Research
College of Biomedical & Life Sciences,
Cardiff University
7th Floor, Neuadd Meirionnydd
Heath Park, Cardiff
CF14 4YS

Co-Investigators:

Professor Kerenza Hood
Professor Christopher Butler
Prof Alison Kemp
Professor Deb Fitzsimmons
Dr Sue Channon
Dr Tom Slater
Dr Kirsten McEwan
Dr Rebecca Cannings-John
Dr Eleri Owen-Jones
Dr Kerina Jones
Dr Thomas Winfield
Professor Joyce Kenkre
Dr Jeremy Segrott
Mr Gareth Watson

Study Manager: Dr Fiona Lugg-Widger
Data Manager: Dr Gwenllian Moody, Lianna Angel
Study Statistician: Dr Rebecca Cannings-John
Health Economist: Dr Thomas Winfield (until 01 November 2018)
Rhys Pockett (from 02 November 2018)

R. CANNINGS-JOHN — 01/05/2019

Author's Name — Date and Signature

Senior Statistical Advisor — 7/5/19

Date and Signature

Senior Health Economist — 01/05/2019

Date and Signature

Chief Investigator — 2.5.19

Date and Signature

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1. Purpose and scope of the plan

This document details the proposed presentation and analysis for the main paper(s) reporting results for the BB:2-6 study. The results reported in these papers should follow the strategy set out here. Subsequent analysis of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analyses (for e.g. to decide cut points for categorisation of continuous variables), nor to prohibit accepted practices (e.g. data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the study.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the study. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

2. Statistical analysis plan authorship

Dr Rebecca Cannings-John is the study statistician for BB:2-6 and the author of this SAP. All statistical analysees will be carried out by Dr Rebecca Cannings-John under the supervision of Professor Kerry Hood. This SAP will be finalised for presentation to the Study Management Group and will be agreed by them and signed off by the author, a senior statistician and the Chief Investigator. A copy will then be sent to the Study Steering Committee.

This statistical analysis plan has been developed in compliance with 'Statistical Principles for Clinical Trials' (ICH E9)[i], 'Guidance for Good Clinical Practice' (ICH E6)[ii], 'Structure and Contents for Clinical Study Reporting' (ICH E3)[iii], 'Standard Operating Procedure (SOP) for Statistical Analysis'[iv] and the Building Blocks trial protocol[v]. Any amendment to this plan after the commencement of the analysis should be documented in the log provided.

3. Study overview

A programme of home visiting by specially trained nurses called the Family Nurse Partnership (FNP) aims to support teenagers expecting their first child. The programme has been compared to usual health and social care in a study involving 18 English centres which followed mothers and their children until the child's second birthday[vi].

The current study will follow up the same women (a total of 1562) and their children for a further four years until their child is six years old. The FNP programme has been shown to reduce maltreatment of children in US studies. In this study we will measure whether the FNP programme reduces child maltreatment by accessing medical and education records of participating women and their children. The study will examine what aspect of programme delivery or of the participants themselves may affect outcomes. Approval will be sought to collect information from the health and educational records of former trial participants. These data will be linked to trial records using an established method (Secure Anonymised Information Linkage (SAIL)) so that the researchers cannot identify any individual in the resulting data set. The study team will use an established process for managing and linking data in an anonymised manner to satisfy the requirements of data providers for preservation

of confidentiality and anonymity. All information collected will be entered onto secured computer databases for analysis. The applicants include the team conducting the current effectiveness study of FNP in England which has successfully recruited the largest number of trial participants for this intervention to date in the world (n=1645). This study will determine programme effectiveness over the next developmental stage in an existing group of women and children, reducing the costs over a new trial of a similar intervention.

3.1 Study objectives

Primary objectives

To determine the effectiveness of the FNP programme in reducing objectively measured long-term maltreatment outcomes when compared to usually provided health and social care alone. Using a multi-method multisource approach to maltreatment research main outcomes will be:

- Child in need status, child protection registration, referral to social care (overall; child protection; Child in Need)

Secondary objectives

To determine the long-term effectiveness of the FNP programme in reducing maltreatment when assessed using associated measures of injuries and ingestions, and hospital DNA rates.

- To determine the long-term impact of the FNP programme upon intermediate programme outcomes, most notably subsequent pregnancies.
- To explore the impact of theoretical moderators of programme effect, including domestic abuse and baseline client characteristics
- To determine the costs and consequences of the FNP programme over the full period of available follow-up.

4. Study design

This is a data linkage study, which will generate a linked anonymised research database. Recruitment to original BB:0-2 study used individual randomisation and stratification by study site, gestation, and preferred language of data collection. Eligible participants will therefore be those women and children enrolled into the BB:0-2 study. The current study will conduct follow-up with mothers and children until that child is aged 6 years old. Half of the proposed study participants will have been offered FNP from time of antenatal booking until their child was aged 2, the other half will have continued to receive only usual health and social care services locally available. Follow-up will be by linked anonymous data abstraction from routine health and education records. Existing baseline and follow-up data from BB:0-2 will be incorporated in the proposed follow-up study analysis following a process of de-identification where necessary. No active trial intervention will be delivered. Women and their children will continue to be able to access existing locally available health and social care services. For FNP clients, care would have formally passed to the local health visiting service on the child's second birthday (FNP nurses fulfil the health visiting role until that point, other universal services are available to both study groups before and after the child's second birthday).

Access to personally identifiable medical records is supportable under arrangements managed by the Health Research Authority's Confidentiality Advisory Group (formerly via the former National Information Governance Board). The study team hold personally identifiable data with current ethical approval and legally obtained participant consent. The study will require identifiers to be passed to the Department of Health, the Health and Social Care Information Centre (HSCIC) and Department for Education to establish linkage with routine data sets. It is this initial data transfer that requires HRA

approval. With the establishment of rigorous data anonymised data linkage methods (Lyons et al 2009), any potential breach of patient confidentiality that may otherwise be entailed can be minimised through data safeguarding methods that can satisfactorily link, maintain and allow analysis of anonymous records (for example, through the use of trusted third party services and data safe havens). Therefore, we will seek governance approval (s251 approval, via CAG) and through required data providers (Department of Health, Department for Education) to link data to study data resulting in a linked anonymised data set. This will be maintained in a safe data haven (i.e. not by the research team in Cardiff University but at SAIL at Swansea University) within which all analyses will be undertaken. The research database will not be made available to other researchers (i.e. it will be a project specific resource) but also has the potential to accrue further datasets in the longer term (NB all such additional data acquisition would still be subject to governance and ethics approval). The linkage process and governance arrangements will use existing approved processes to ensure patient confidentiality and data security and integrity.

4.1 Sample size justification

Primary outcome (Child in Need status at any point between birth and six years):

For Child in Need status, available UK data on rates are not specific to the age-range of interest, but the rate in the general population aged 5-9 years is 4.6% (average rate of study sites in BB:0-2). The rate of CIN status would be expected to be greater in the specific study sample, and therefore we have assumed a rate of 8%. We hypothesise that FNP would reduce the detection of CIN in the first six years and thus assumed a difference of 4% as being important. To detect a difference of 4% (4% vs 8%) would require 602 children in each arm (1204 in total) using 80% power and a two-sided 5% alpha level.

BB:0-2 recruited 1645 women, with 1562 available for follow-up (i.e. excluding those subject to a mandatory withdrawal). Follow up through medical records assuming 10% loss in tracking and linkage would result in 1405 participants, thus securing enough data to test the primary outcome.

A key secondary outcome is referral to Children's Social Care (CSC). Data from the FNP implementation evaluation (n=1177 women) shows an observed referral rate of children (in the period up to child's second birthday) of 8.2%. A sample of 1319 for analysis will provide 90% power at the two-sided 2.5% alpha level to detect a difference between the two groups of 6.3% (14.5% to 8.2%) in the proportion having a referral to CSC. This represents a conservative estimate as further referrals to CSC will be observed in the remaining four-year period.

4.2 Randomisation

Randomisation has already been conducted in the BB:0-2 trial. Recruitment to BB:0-2 used individual minimisation using gestation at recruitment and preferred language of data collection and stratification by study site. We acknowledge that there are possible threats to the balance of baseline characteristics and potential confounders by loss of participants through linkage to routine data in section 6.6.

5. Study outcomes

5.1 Datasets, linkage and handling

Data sources

Table 1 lists all the outcomes and data sources that will be utilised in the BB:2-6 study along with the hypothesised direction of the effect.

Table 1 Outcomes and the data sources used

Domains	Outcomes	HES	ONS	NPD	Hypothesised direction of effect
Primary:					
Child in Need status recorded at any time during the follow-up period.	• CIN status as of 31 March each year			✓	Reduction in children classified as in need by 6 years Shorter interval to referral Less CIN referrals
Secondary:					
(i) Objective measures of maltreatment	• Referral to Social Services			✓	Reduction in children referred to social services by 6 years
	• Child Protection registration (Child protection plan (CPP))			✓	Reduction in children with a CPP by 6 years
	• Details of a child protection plan (initial category of abuse/neglect/physical/ sexual/emotional/multiple)			✓	Descriptive
	• CIN categorisation of primary need (abuse or neglect/child or parent disability/family in acute stress or dysfunction etc.)			✓	Descriptive
	• CIN duration			✓	Reduction of time child classed as in need
	• Looked after status			✓	Reduction in children looked after by 6 years
	• Child looked after (CLA) period of care			✓	Reduction of time child classed as looked after
	• Legal status of CLA			✓	Descriptive
	• Cause of death		✓		Reduction in deaths
(ii) Associated measures of maltreatment	• DNA appointments	✓			Reduction in DNA outpatient appointments by 6 years
	• Injuries and ingestions	✓			Reduction in admissions with at least one injuries and ingestions by 6 years

Domains	Outcomes	HES	ONS	NPD	Hypothesised direction of effect
Primary:					
(iii) Intermediate FNP programme outcomes	• Subsequent pregnancies	✓			Reduction in proportion of and number of subsequent pregnancies Longer inter-birth interval
(iv) Costs	• Health and Social Care resource use	✓		✓	Less resource use
(v) Child health, developmental and educational outcomes	• Special Educational Needs			✓	Fewer children with SEN
	• Disability	✓		✓	Fewer children with a disability
	• Day care attendance			✓	Better day care attendance
	• Early Years assessment			✓	Improved scores
	• School attendance			✓	Improved school attendance
	• Key stage one attainment			✓	Improved scores

Data linkage

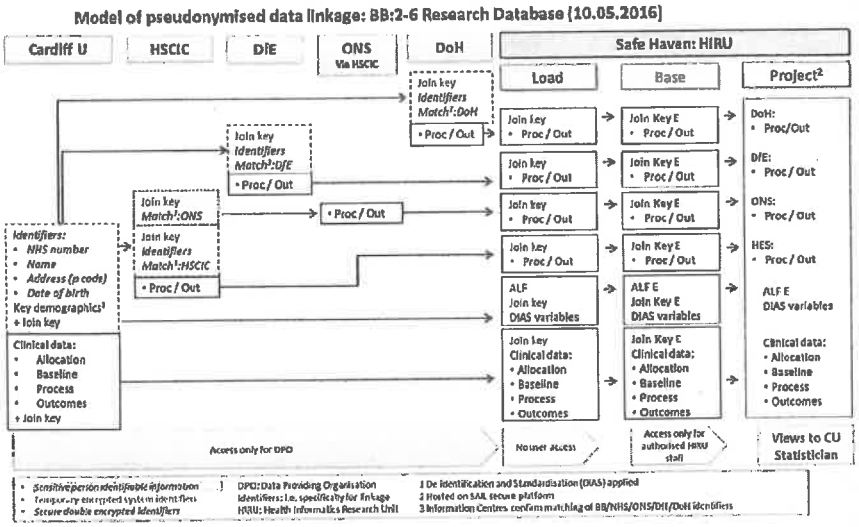
The process for linking clinical data held by Cardiff University on trial participants to health data (sourced via NHS digital) and deposited in a third party safe haven for storage and analysis in Swansea's Health Informatics Research Unit (HIRU) is illustrated in the flow chart schema below (Figure 1). This follows an established secure method for anonymised data linkage. Further detail is available in the BB2-6 protocol.

Data handling

The first wave of data collection from routine records will incorporate a formal pilot to develop and validate the process of data capture, to verify data linkage and to develop data management protocol and statistical scripts for the main analysis. This will be carried out alongside the data managers following a pre-specified data cleaning plan. With the piloting phase, we will also identify whether the data received is fit for purpose e.g. does the provided data enable us to answer our objectives. This will be assessed via examining match rates and the completeness of vital variables. This will enable us to examine the number of cases likely to be available for analysis, the overall proportion of CIN (primary outcome), feasibility of defining each secondary and exploratory outcomes, which data sources it arises from and any idenfitied problems. It also allows us time to develop syntax before the final analysis and identify whether any variables are to be derived by SAIL using sensitive information such as date of birth.

Small numbers will be handled according to SAIL rules where any cell counts under 5 will be reported as <5.

Figure 1.



5.2 Definitions/Calculations

Derived variables such as scales and deprivation scores have previously been defined in the BB SAP. Any derived variables that are derived from any of the NHS Digital datasets will be identified as such in the variable name: e.g. SubPreg_NHSD. Any variables that require being derived using sensitive information will be identified in the piloting phase and SAIL will be informed.

Table 2 Summary of data sources

BB: 0-2	BB: 2-6	Provided by	Dataset		Time period*	Eligibility / Coverage	Mother	Child	Indicative / key data items
✓		Trial participants maternal self-report	Baseline		2009-2013	Trial participants	Yes	No	Socioeconomic; Maternal health & well-being; Health behaviour; pregnancy complications, Neonatal outcomes; Feeding & development.
✓			Late Pregnancy					Yes	
✓			6 month	Post -birth					
✓			12 month						
✓			18 month						
✓			24 month						
✓			SAEs						Adverse events (GCP and BB)
✓			Withdrawals						Elective withdrawals
✓		Maternity records	Maternal outcomes		2009-2010	UK	Yes	Yes	Maternal health & well-being; Neonatal outcomes
✓		Smoking status adjusted for cotinine:	Baseline and late pregnancy		2009-2013	Trial participants	Yes	No	
✓		FNP	FNP dosage and fidelity data		2009-2013	Trial participants	Yes - receiving FNP only	No	
✓		Trial participants maternal self-report	Maternal sensitivity (video recordings)		2009-2013	Trial participants	Yes for a subgroup	No	
✓		GP records	GP consultations		2009-2013	UK	Yes	Yes	Immunisations; safeguarding
✓		PCTs	Immunisation		2009-2013	England	No	Yes	Immunisations
✓	✓	DoH	Abortions		2009-2013	England and Wales All abortions performed in the NHS or an approved independent sector	Yes	No	Abortions

BB: 0-2	BB: 2-6	Provided by	Dataset	Time period*	Eligibility / Coverage		Mother	Child	Indicative / key data items
✓	✓	ONS	Mortality	2009 - 2017	UK		Yes	Yes	Mortality data
✓	✓	NHS Digital / HES	Inpatient	2009 - 2017	Any NHS hospital in England		Yes	Yes	Injuries and ingestions; subsequent pregnancies;
✓	✓		Outpatient						
✓	✓		A&E						
	✓	Dept. for Education / NPD	CIN	2009 - 2017	< 18 years Registered with social services in England		Yes	Yes	Child in need status and child looked after status
	✓		CLA						
	✓		EYFSP	2013-2017	Public Schools in England	4 yrs	No	Yes	Indicators of maltreatment; educational development and attainment; eligible for free school meals;
	✓		Census			2-19 yrs			
	✓		Alt Provision			2-19 yrs			
	✓		PRU			2-19 yrs			
	✓		Key stage One	2016-2017		5-7 yrs	No	Yes	

5.3 Participant population

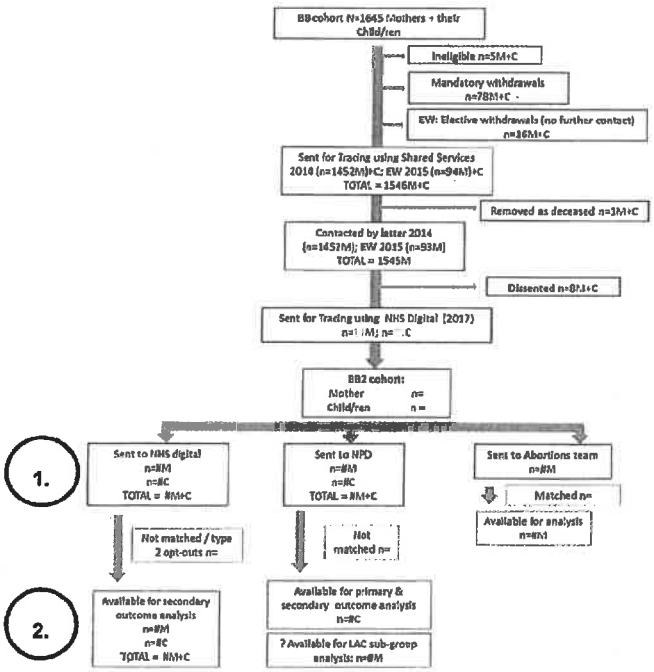
The eligible population will be all mothers and their first born (including twins) from the Building Blocks (BB) trial excluding those who:

- were ineligible or mandatory withdrew from the trial;
- electively withdrew (did not consent to their data to be used and no further contact made) from the trial;
- dissented from BB2-6;
- had deceased.

This is the population whose identifiers can be sent to the information centres, denoted as #1 in Figure 2. Participants in #2 (Figure 2) are those whose identifiers can be sent, linked and data released by the information centres. They will not include:

- participants whose individual data can be used but cannot be matched due to:
    - incorrect linking fields;
    - other exclusions from health or education: e.g. private or home schooling (would not appear in any NPD datasets).
- any Type 2 opt outs[1]. Patients within England are able to opt out of their personal confidential information being shared by NHS Digital for purposes other than their own direct care. Type 2 opt outs only apply to health data (NHS digital) and do not apply to that held by NPD.

Figure 2. Dummy consort flow chart for linkage process



[1] http://content.digital.nhs.uk/article/7092/Information-on-type-2-opt-outs

The study populations for analysis (mother and child) will depend on which information centre and outcome the data is coming from. For example, for the primary outcome of Child in Need, the denominator would be all children who were matched to and appears in ANY of the NPD datasets requested:

- Pupil Level Annual School Census (PLASC);
- Child in Need (CIN);
- Children looked after (CLA);
- Early years foundation stage profile (EYFSP);
- Early Years Census (EYC);
- Pupil referral unit (PRU) Census;
- Alternative Provision;
- Key Stage one (KS1) assessments.

We would expect that all children by the age of 6 would be registered with a primary school or alternative provision so would be linked to the PLASC and Alternative Provision datasets. If they are not in PLASC/Alt.Prov but appear in another dataset, for example CIN, then we would conclude that they are in the study population but for some reason are missing from the PLASC/ Alternative Provision dataset (e.g. Home or privately schooled). Similarly for NHS digital data, for any health data outcome the denominator would be all participants who have their identifiers matched to ANY of the HES datasets (Inpatients, outpatients/ A&E). We would expect each mother and child to have had at least one hospital admission event (birth of baby/being born respectively) and so each participant should appear in the inpatient data.

5.4 Missing data

Table 3 shows each outcome and how the denominators and numerators will be defined as well as missing data considerations. Children who are not included in any of the NPD datasets will be classed as missing and we will explore using multiple imputation on this population. If a participant from the study population did not appear in an outcome dataset (e.g. Children looked after or child in need dataset), then the assumption is that they did not have that event (instead of assuming that they were missing). If within an outcome, a variable/field is missing data then we will examine any proxy variables that could be used (for example, for CIN duration, if the end of the episode is missing then a proxy will be examined or the child will be excluded from analysis). Primary and secondary comparative analyses will be conducted on an intention-to-treat (ITT) basis with complete case population (those that have complete follow-up data). This modified ITT population uses all randomised participants in the groups they were randomised to in the BB trial regardless of the intervention they actually received.

Loss to follow up in this study is defined as a child death or an adoption, both of which we will be able to measure. With binary outcomes where a child has no event, and incomplete follow up, these will be excluded. With time to event analyses children will be censored at these events.

5.5 Pooling of investigational sites

In the original Building Blocks trial, randomisation was stratified by the 18 research sites and adjusted for in the analysis by including site as a random effect in all models.

Table 3 Study populations for each outcome

Outcomes	Population/ Denominator	Numerator source	Missing data
Primary:			
Child in Need status recorded at any time during the follow-up period.	All children linked with any NPD datasets	Child in Need: presence in/linked to CIN dataset excluding children with no further action reqd.	Absence of linkage to CIN indicates no CIN referral (not missing)
Secondary:			
Referral to Social Services	All children linked with any NPD datasets	Any child appearing in the Child in Need dataset	Absence of linkage to the CIN dataset indicates no CIN referral (not missing)
Child Protection registration (child protection plan)	All children linked with any NPD datasets	Child in Need: Child with a CP Plan flag	
Details of a child protection plan	All children linked with any NPD datasets	Child in Need: initial category of abuse	
CIN categorisation	All children linked with any NPD datasets	Child in Need: Reason for CIN status (primary need)	Absence of linkage to the CIN dataset indicates no CIN referral (not missing)
CIN duration	All children linked with any NPD datasets	Child in Need: CIN start and end date	
Looked after child status	All children linked with any NPD datasets	Child looked after: presence in /linked to CLA dataset	Absence of linkage to the CLA dataset indicates not looked after (not missing)
CLA period of care	All children linked with any NPD datasets	Child looked after: date episode starts and ends	
Legal status of CLA	All children linked with any NPD datasets	Child looked after: Categorisation of CLA	
DNA appointments	All mothers linked with any HES datasets	Outpatients: Flag for DNA	Absence of data indicates no OP appts but absence of a DNA code attached to an attendance will.
Injuries and ingestions	All children linked with any HES datasets	Flag for injuries /ingestions	Absence of an injury or an ingestion indicates no event (and not missing)

Outcomes	Population/ Denominator	Numerator source	Missing data
Subsequent pregnancies	All mothers linked with any HES datasets	IP/OP/A&E/Abortion: Flag of a subsequent pregnancy	Absence of a pregnancy indicates no pregnancy (not missing)
Special Educational Needs (SEN)	All children linked with any NPD datasets	PLASC/PRU/ Alt Provision: presence of flag under 'SENprovision '	Absence of data 'SENprovision' indicates no SEN
Disability	All children linked with any NPD and HES datasets	Flag for disability	Absence of flag will indicate no disability
Day care attendance (funded early education (Ofsted registered PVI provider)/pupils registered at school) (aged 2-4)	All children linked with any NPD datasets	EYC/PLASC: Presence in the EYC and/or PLASC	Absence in the EYC will indicate no daycare attendance
EYFS profile assessment (to be carried out in the final term of the year in which a child reaches age 5	All children linked with any NPD datasets	EYFSP: presence in the EY census with assessment scores	Absence of any assessment scores
School attendance	All children linked with any NPD datasets	PLASC/Alt.prov/PRU: Presence in any of these three datasets	Absence in any of these three datasets will indicate no schooling (unless home or private).
Key stage one attainment	All children linked with any NPD datasets	KS1 data	If the child is linked to PLASC but has not a KS1, then imputation will be explored

5.6 Withdrawals

In the case of individuals that had mandatory withdrawn their data from the study they will be excluded from all analyses. For elective withdrawals that can be approached (with no evidence that either mother or child are no longer alive – see page 29 Consent section in protocol), these will be included.

5.7 Outliers

Values identified as possible outliers will be cross-checked with other data sources/variables if possible. The influence of these outlier values on analyses will be checked. Any significant influence detected will be reported and discussed with the Study Steering Committee.

5.8 Analysis Time Frame

Piloting and refining of syntax analysis files will be carried out in 2017 and final analysis in late 2017/early 2018.

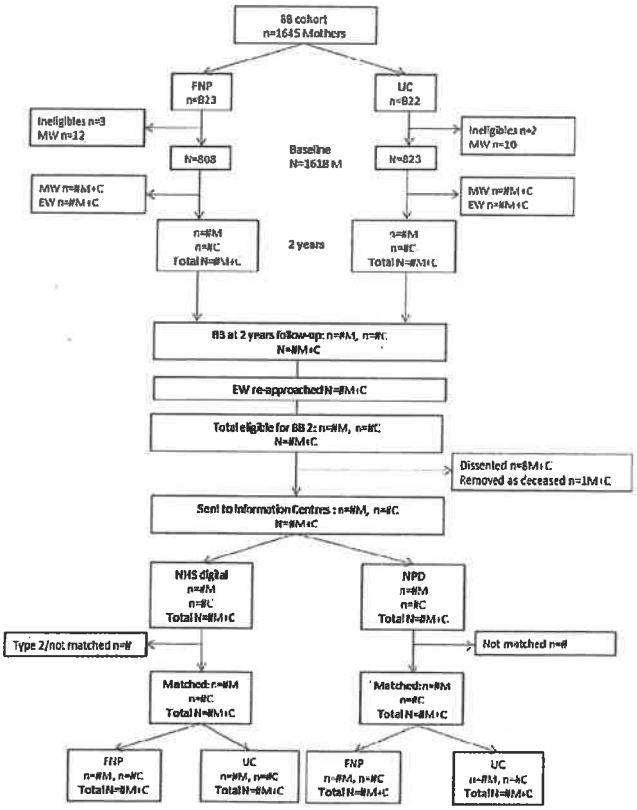
6. Statistical analyses

6.1 Descriptive analysis

Participant flow and recruitment

The starting point of the BB2 participants flow chart will summarise the participants (by mother and children separately and by trial arm), that are eligible for the follow-on study at the end of the BB trial. It will then summarise those whose details will not be sent to the information centres due to dissent or death. For NHS digital, the number who were not linked to any datasets (type 2 opt-outs/not matched) will be described and for NPD those not matched. For those matched, we will summarise the match rates for each information centre, detailing the denominators available. A draft cohort is in Figure 3. We will report our results in accordance with the RECORD[vii] statement to ensure the comprehensive reporting of our follow-on study using routinely collected data. There currently are no guidelines for long term follow-up from a trial; we will explore the best way to present this data.

Figure 3 Draft consort flow chart



NB: Final version will include ONS/Abortions data

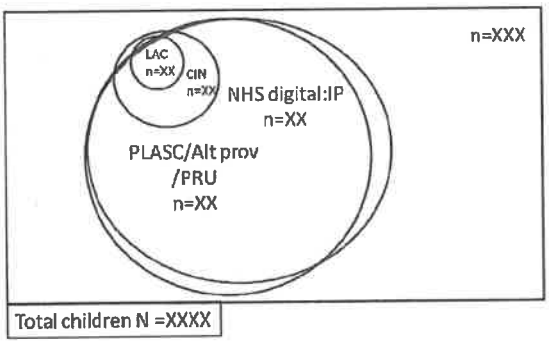
Baseline data

For all participants (mother and children) eligible and linked to IC data, appropriate descriptive summaries and graphical illustrations of baseline maternal, birth and baby demographics, clinical and questionnaire data will be presented by trial arm. Descriptive statistics (N (%), mean (SD), median (interquartile range)) will be used to summarise baseline variables and any marked imbalance between the study arms will be identified. There will be no formal testing of between-arm differences for any variables at baseline.

The practice population will vary depending on which information centre is examined (NHS digital/NPD) and so baseline data will be examined for each population/data source combination. To assess potential bias, we will describe those that were sent but not linked to NPD/NHS digital data and also compare to the original BB population.

Additionally we will assess the characteristics of children that are not in any school dataset but do appear in either health or Social care datasets to examine if they are different or at higher risk of adverse outcomes. A Venn diagram will be used to pictorially examine the overlapping datasets (Fig 4).

Figure 4 Venn diagram



6.2 Main analysis

All analyses will be conducted on a modified intention-to-treat basis and due emphasis placed on confidence intervals for the between-arm comparisons.

First of all we will examine binary outcomes in twins with an outcome to examine the correlation between them. If outcomes tend to always apply to both twins (for example in maltreatment data we would expect both children to be under child protection) then we will reduce the multilevel nature of the data (children within mother) to one child as opposed to adjust for twins.

Three level multilevel modelling will be used to allow for clustering of effect within a site and family nurse where both will be fitted as random effects. Where there is little impact of clustering at the family nurse level then the results from the two-level model (site, participant) will be presented. The Akaike information criterion (AIC) will be used to select the best fitting model. All parameter estimates will be reported alongside a 95% confidence interval and p-value. We will adjust for variables used in minimisations such as smoking status, gestational age and language.

6.2.1 Primary outcome

The primary comparative analysis will be to examine whether the firstborn (Building Blocks child) had ever been referred to social services and classed as a child in need at any point between birth and 6 years of age. There is no flag in the dataset to identify whether a Child is in need after they have been referred to social services. Children in need will be defined (as per department of education methodology[2]) as all children referred to social services, excluding cases where:

a) the referral is flagged as being a referral resulting in no further action;

or

b) the only activity recorded is an assessment and the reason for the closure of the case being that case was closed after assessment with no further action.

As the outcome is binary (CIN or not) then will use a logistic multilevel modelling to investigate differences in the proportion defined as in need between the trial arms (FNP compared to Usual care). The resulting estimate will be presented as an odds ratio.

6.2.2 Secondary analysis of primary outcome

- For children classed as in need, the duration between birth and the date (age) that the child was classed as in need for the first time (based on referral date) will be calculated and group differences examined using Cox multilevel regression analysis to calculate hazard ratios for referral, together with 95% confidence intervals. Those who are not ever classed in need will be censored at 6 years and those who die in this period will be censored at date of death.
- The number of Child in need referrals will be examined using multilevel Poisson regression modelling appropriate for count data. If the distribution of events displays signs of over dispersion (greater variance than might be expected in a Poisson distribution), then a Negative Binomial model (NBM) will be used (or a zero-inflated model if there are an excess of zero events). Results will be presented as the (adjusted) incidence rate ratio (IRR) in the FNP arm compared to the usual care arm.

6.2.3 Sensitivity analysis on primary outcome

The BB:0-2 sample is well characterised (in terms of demographic and clinical data recorded at baseline), and there are detailed records on programme fidelity. We will explore:

- Adjustment for any hypothesized confounders of outcomes at baseline.
- How such variation in adherence to programme fidelity (e.g. dosage) is associated with outcome variation. The efficacy of FNP visits on the primary outcome will be estimated in a way that preserves randomisation using complier averaged causal effects (CACE) modelling by fitting a structural mean model Adherence will be defined as in the original trial, as the total number of FNP visits that a woman received up until the child's second birthday (pregnancy, infancy and toddlerhood phase combined).
- The role of potential moderators and mediators of programme effect. These will be explored by extensions to the primary outcome model including predictive factors (main effects) and interaction terms. Sub-group analysis is an investigation of whether any between-arm effects differ according to characteristic measured at baseline. Variables prioritised as a priori sub-group analyses on the primary outcome will be:

2 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/469740/SFR41-2015_Methodology.pdf

- Maternal deprivation;
- Adaptive functioning;
- Not In Education, Employment, or Training (NEET) status (applicable only in women aged >16 at baseline);
- Maternal age at recruitment.

In addition, gender of child will be examined as a possible effect moderator of effect (NB: this is not specified in protocol paper). These pre-planned analyses will be conducted by the inclusion of appropriate interaction terms in the regression models. Results will be presented using interaction coefficients (trial arm *subgroup), 95% CI and p-value. The role of potential moderators of programme effect (e.g. domestic violence self-reported at 24 months) will also be explored.

- The role of the mothers care status (ever/never been placed in care) will be examined as a potential moderator of programme effect.
- The duration of the maternal care status will be examined as a possible mediator effect.
- Missing data will be explored in children not linked (and not appearing in any datasets) and multiple imputation carried out using the mi command in Stata.

6.3 Analysis of secondary outcomes

Although the study will be powered to examine a 4% difference in CIN status, secondary analyses (using logistic multilevel regression modelling) will assess group differences in referral rates to social services and maltreatment profile. Levels of concern will be examined by looking at extent of action taken (for example, category of abuse, subjected to a child protection conference and plan etc.).

6.3.1 Objective measures of maltreatment

- Referral to Social Services or not
- Subjected to Child Protection registration (Child protection plan - CPP)
- Child protection plan details -- initial categorisation of abuse (neglect, physical, emotion, sexual, multiple)
- CIN categorisation of primary need (neglect, abuse, family disability, family stress etc.)
- Duration of Child in need episodes (days from referral to CIN Closure date)
- Looked after status (looked after or not)
- Child looked after total period of care (date episode of care commenced to ceased)
- Legal status of Child looked after (interim, full, placement order, emergency care)
- Cause of death

For binary outcomes (referral to social services, CPP, looked after status) a logistic multilevel modelling to investigate differences in the proportion defined as in need between the trial arms (FNP compared to Usual care). Estimates will be presented as odds ratios (ORs).

For categorical variables (CIN categorisation, CPP categories, Legal status of child looked after) group differences will be examined by multinomial regression and results presented as ORs.

The total period of care (days) as a CIN or a CLA will be examined using Poisson multilevel regression modelling appropriate for count data. If the distribution of events displayed signs of over dispersion (greater variance than might be expected in a Poisson distribution), then a Negative Binomial model (NBM) will be used (or a zero-inflated model if there are an excess of zero events). Results will be presented as IRR in the FNP arm compared to the usual care arm.

Numbers and cause of death will be descriptive if numbers are not disclosive.

6.3.2 Associated measures of maltreatment

- Recorded injuries and ingestions in only A&E, only hospital admissions, either A&E and /or admissions using the coding list in Appendix I
- DNA rates for hospital appointments: outpatient appointments binary

A similar approach will be taken to the BB trial. Logistic multilevel modelling will be used to analyse the associated outcomes (e.g. proportion of children with at least one injury and ingestion over 6 years) and these events will be grouped and described. The number of admissions per child will be analysed using Poisson or if skewed alternatives such as Negative Binomial or a zero-inflated model. Results will be reported as IRRs.

As an added exploratory analysis we will describe the length of inpatient stay subsequent to a recorded injury. For children with more than one injury, we will examine the distribution of the length of stay, and take the most appropriate measure of central.

6.3.3 Intermediate FNP programme outcomes

- Subsequent pregnancies (sourced from HES and abortions data)

A similar approach will be taken to the BB trial with a combination of the following data sources:

  - self-report and GP (0-2 years post BB baby) ;
  - inpatient/outpatient/A&E/abortions (0-6 years post BB baby).

Any non-BB related pregnancy related attendances /admissions will be flagged using the code list in Appendix II. Two time periods will be examined (a) from birth of BB baby to 2 years post pregnancy (to replicate the results from BB using updated data) and (b) from birth to six years post pregnancy just using the HES and abortions data.

The proportion of women with at least one subsequent pregnancy recorded in either inpatient/ outpatients/abortions data and logistic regression model will assess group differences. Results will be reported as adjusted odds ratios alongside 95% CIs. Number of pregnancies will also be described as before using a Poisson model if suitable. If data is sparse then a multinomial regression model will be used and categories such as none, 1, 2, 3 plus subsequent pregnancy used.The time to the first subsequent registered birth (inter-pregnancy interval) will also be examined and analysed using a Cox regression model with hazard ratios alongside 95% CIs.

6.3.4 Child health, developmental and educational outcomes

- Reported disability (binary) – flags using HES and NPD data
- Special educational needs (binary)
- Early educational attendance (binary) and type of daycare (Ofsted registered PVI provider /pupils registered at school);
- School attendance as defined by Overall absence rate (overall absence sessions/total number of sessions). If data allows we will break these into unauthorised[3] and authorised sessions[4].

3 If the school is not satisfied with the reason given for absence they should record it as unauthorised. The unauthorised reasons schools can use to record absences via the school census are as follows:

- Holiday not authorised by the school or in excess of the period determined by the head teacher
- Arrived in school after registration closed
- Reason for absence not yet provided
- Other unauthorised absences
- Any unauthorised absences not covered by the groups above

4 Authorised absence reasons:

- Illness (NOT medical or dental appointments)
- Medical/dental appointments
- Religious observance

- Early years assessment (at 5 years):
  - % of children achieving a good level of development. Good level of development is defined as children achieving at least the expected level (2+) within the following areas of learning:
    - Communication and language;
    - Physical development;
    - Personal, social and emotional development;
    - Literacy;
    - Mathematics.
  - % of children achieving at least the expected level in ALL 17 early learning goals (score of 2+).
  - Average total point score (over all 17 early learning goals) (Score can range from 17 to 51).[5]

The EYFS framework contains 17 early learning goals in seven areas of learning covering children's physical, intellectual, emotional and social development;

Area of learning		Early learning goal	Part of the good level of development measure
Prime areas of learning	Communication and language	1: Listening and attention	Yes
		2: Understanding	Yes
		3: Speaking	Yes
	Physical development	4: Moving and handling	Yes
		5: Health and self-care	Yes
	Personal, social and emotional development	6: Self-confidence and self-awareness	Yes
		7: Managing feelings and behaviour	Yes
		8: Making relationships	Yes
Specific areas of learning	Literacy	9: Reading	Yes
		10: Writing	Yes
	Mathematics	11: Numbers	Yes
		12: Shape, space and measures	Yes
	Understanding the world	13: People and communities	No
		14: The World	No
		15: Technology	No
	Expressive arts, designing and making	16: Exploring and using media and materials	No
		17: Being imaginative	No

- Key stage one (KS1) attainment

Commented [RC1]: May change subject to Mike input

  - Proportion of children achieving at least the expected level (2+) in Speaking and listening, Reading Writing, Maths, overall science

- Study leave
- Traveller absence
- Agreed family holiday
- Excluded, no alternative provision
- Other authorised circumstances

[5] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/652802/SFR60_2017_Text.pdf

- Proportion of children achieving lower than expected (Level 1), the expected level (level 2), a greater depth of knowledge (level 3) in Speaking and listening, Reading Writing, Maths, overall science

For binary and ordinal outcomes (disability status, SEN, early education attendance, school attendance, KS1 attainments) will use a logistic multilevel modelling to investigate differences in the proportion defined as in need between the trial arms (FNP compared to Usual care). Estimates will be presented as adjusted odds ratio, alongside a 95% confidence interval and p-values. Type of daycare per child will be described by type although children may appear in more than one):

- School (recorded in PLASC)
- Ofsted registered PVI provider (EYC) - Category of early years provider
  - Private, Voluntary, Registered Independent School, Local Authority Day Nursery, Childminding Network, Other, Childminder.

Early Years assessment scores: Linear multilevel regression models will be run and residuals of the fitted model examined (kernel density, histograms, qnorm, pnorm) to assess linearity. If not appropriate, we will explore transforming the data using LN, squared or cubed scores. Differences in scores between trial arms will be examined and estimates presented using adjusted mean differences plus 95% CI. If transformed data is used then each score will be presented as standardised mean differences (effect sizes = difference between groups divided by standard deviation) for ease of interpretation.

6.3.1 Sensitivity analyses of secondary outcomes

Sensitivity analyses (CACE, imputation for missing, subgroups) will be carried out on the following secondary outcomes:

- Early Years assessment (Foundation Stage Profile total score) ;
- Key stage one assessment (achieving at least the expected level);
- Referral to social services.

6.3.2 Exploratory analysis

a) Other variables included for subgroup examination as exploratory analyses will be self-efficacy, subjective social status, social support (i.e. MOS measure). These data will be sourced from the original trial dataset. A composite index of risk (based on these and other variables in the dataset) which predicts sub-groups which may particularly benefit from FNP will also be constructed. This could be clinically useful if trying to efficiently offer FNP in the context of financial restriction.

b) State transition model using Markov chains will be used to assess the probabilities of moving from one stage marker (states) to another. A Markov chain is an iterative process where subjects are assumed to stay in one cycle for a certain time and then make a transition to another cycle. The Markov chain will contain the following states:
   a. Referred to Social Services;
   b. Child identified as in need;
   c. Child protection plan;
   d. Child in need;
   e. Placement.

The transition probabilities (the probability of the various state-changes) in our model will be derived from our data and compared between groups if numbers allow. It will also include children that leave and then re-enter the system if numbers allow.

c) Since a more robust measurement of mothers experience in care will be determined using NPD data, this subgroup will also be examined for the BB0-2 outcomes (smoking in pregnancy and birthweight). We will also explore the BB baseline characteristics to see which are associated with ever being in care.
d) Restrict to those with a good match rate/probabilistic match
e) Possible variability of category of abuse by Local Authorities. Examine the patterning of codes by time and by site.

We are committed to deliver analyses a to c to the funders; d and e are exploratory and outside if the deliverable report.

6.3.3 Bias

Possible bias in the followed-up BB:0-2 sample will be quantified by examining group differences (participants and non-participants) in baseline variables as already described in 6.1. Surveillance bias in detection of maltreatment during the child's infancy and toddlerhood can be assessed by examining subsequent reporting. The duration between birth and the date of first referral to social services will be calculated and group differences examined using Cox regression analysis to calculate hazard ratios for referral, together with 95% confidence intervals. Surveillance bias is most likely to occur during the intervention phase, although improved handover to other services at 2 years may lead to higher identification in the following year. Severity of the referral will also be compared between the two groups (an approach used in US trials of NFP to explore surveillance bias).

6.4 Safety analysis

Not applicable safety analysis will be carried out.

6.5 Interim analysis

No interim analyses are planned.

6.6 Software

SPSS version 20[viii] and Stata version 13 [ix] will be used for all statistical analyses.

7 Health Economic Analysis Plan (HEAP)

7.1 Purpose of the Health Economic analysis plan

This section presents the proposed structure for the health economic analysis. The approach in this HEAP intends to establish the analysis process and should be followed when undertaking the investigation and presenting the report. Any deviation from this HEAP will be explained and justified in the final report (e.g. due to data limitations).

7.2 HEAP authorship

This health economic analysis plan (HEAP) was written by Dr Thomas Winfield under the guidance of Professor Deborah Fitzsimmons. The plan will be finalised prior to data analysis after discussion with the Chief Investigator(s) and statistician, and circulation to the TMG. The final version will be signed off by the lead author, health economics lead, statistician, and chief investigator(s). The analysis will be conducted by the study health economist from Swansea Centre for Health Economics (SCHE) with support from Professor Deborah Fitzsimmons with final internal QA undertaken by a senior health economist from SCHE.

7.3 Objectives

The objectives of the health economic analysis are:

Primary objective

To determine the cost-consequences of the FNP programme in reducing objectively measured long-term maltreatment outcomes when compared to usually provided health and social care alone. Using a multi-method multisource approach to maltreatment research main outcomes will be:

- Child in need status, child protection registration, referral to social care (overall; child protection; Child in Need) and health and Social care costs.

The health economic analysis framework will consist of:

a. A descriptive summary of resource use, cost tables and a between group overview of incurred costs.
b. A cost-consequence analysis (CCA) of the intervention

NB-Additional work may consider the relationship between cost and child maltreatment outcomes but this does not form part of the original NIHR protocol and will be considered post-submission of the main report .

7.4 Description of a Cost Consequence Analysis.

The CCA is a form of economic evaluation where the range of disaggregated costs and outcomes are reported which allows the reader to form their own opinion as to the preference and respective importance to their own decision making process. The analysis follows a descriptive approach which presents effectiveness results (primary and secondary outcomes) separately to that of the costs. The CCA approach is recommended for complex interventions which look to observe a broad range of effects which are difficult to measure in a single common unit.* It enables capture of equity considerations as well as intersectoral costs and consequences.

Costs will be summarised against the range of outcomes collected within BB:2-6 without aggregation to allow weighing up changes in the various outcomes reported in BB:2-6 against the changes in costs in a consistent and transparent manner. This will contribute to providing more robust and valid medium-term estimates within the extended period.

7.5 Perspective of the health economic analysis.

A mixed public sector perspective will be taken in the analysis. The mixed public sector authority approach consists of three main costing groups: the NHS, the Department for Education and social care

costs. The routine data used in the BB2:6 study doesn't include certain cost groups (such as primary care) aged 2-6 years; we will therefore consider whether this cost group can be reasonably extrapolated from the BB:0-2 trial and/or published literature to the 6 years duration. This extrapolation approach will be dependent upon the consistency of costs over the 6 year period. Where recorded costs remain constant between the 0-2 and 2-6 periods an unweighted linear extrapolation approach will be used. If the costs reported from the 2-6 years period are inconsistent with those from 0-2 a consistent ratio approach between recorded and unrecorded costs will be employed. The feasibility of this approach will be reported to the SMG and TSC, on examination of the datasets.

7.6 Data collection to inform the health economic analysis

The health economic analysis will use the routine HES and, if feasible data avaliable from, Department for Education / NPD data to evaluate resource usage. Summative findings from the BB:0-2 analysis will be used in addition to the HES and NPD data to describe the costs for the follow-up period, as a whole. Individual level (Mother and child separately) resource use frequencies in BB2-6 will be calculated on an annual basis. If feasible and data allows, the resource use cateegories will be combined with their respective service costs to offer final resource group costs and an overall cost at the individual level.

The BB:0-2 costs will be presented alongside the BB:2-6 costs to give an overview of the cumulative trials duration (6 years). The isolated and summative approaches will use the appropriate cost year for BB:2-6.. Where 2017 prices are unavailable a CPI inflation rate will be applied according to the cost year that is available. Cost and consequences will be discounted back to the initial intervention date (3.5%).

Individual level costs which are identified as possible outliers, such a very high resource usage, will be highlighted in the results. The influence of these outliers will be assessed, and any individual cases that offer a significant impact will be removed in the outlier specific sensitivity analysis. These outliers will be maintained within the analysis and their impact upon the analysis noted in the final report.

7.7 Collection of resource use and costs

The intervention costs are already included within the BB:0-2 analysis, these will be used in conjunction with those reported in the BB:2-6 study. Unit costs will be sourced from published sources including the Personal Social Services Research Unit (PSSRU), British National Formulary (BNF) and NHS reference costs. Sources which are not included in the aforementioned publications will be sourced from other literature. The costs associated with resource utilisation for both groups (consultations, medications, operations, equipment, etc.) will be assessed on both, an annual approach and an overall total format. Costs will be valued in £ sterling using relevant prices. Any costs included that are reported in an alternative currency, for example, those costs which were sourced from the literature will be converted to 2017 GBP at the prevailing exchange rates, the rate and date of conversion will be reported.

Due to inconsistency surrounding the definition of the 'additional educational support' variable (which indicates the presence or absence of the support for an individual within a year) and a lack of contact frequency detail offered. , the costs associated with this variable will be sourced from the literature.

7.8 Outcomes for the health economic analysis

The CCA approach separates costs and consequences and reports them in a disconnected method. The primary and secondary outcomes described in the statistical analysis plan (section 6.2) are used in the CCA. Outcomes for BB:2-6 will be reported as a total of costs and consequences for the intervention as well as a disaggregation between mother and child. Sub-group analysis will be undertaken where appropriate and only where a significant statistical effect is identified.

7.9 Missing data

The missing data approach will follow the statistical analysis plan where appropriate. Participants' inclusion within analysis will be determined by the criteria described in section 5.5. Individuals will not be excluded from analysis subsequent to the statistical analysis. Where an individual has the absence of data in a resource variable it will be assumed that there was no usage. Missing components of data (where an event is identified but details are not recorded) will follow a three step process. Firstly, the identification of a precise replacement for the missing variable will be checked. Whilst the main variable of interest may have missing event components it is plausible that the health economic impact can be calculated from supporting information. An example of this is where duration of stay information is missing but an event date attached to the stay is able to establish the cost band to be used. Secondly, an appropriate proxy will be identified and used, the proxy assumptions will be noted in the report. If no suitable proxy is available, an analysis of the volume and pattern of missing data will inform the appropriate data imputation techniques.

The missing data situation will be initially observed using the 'misstab' command in Stata. The observed patterns will help to inform the type of missing data approaches that are appropriate. In the event that the data is shown to be missing completely at random then no additional data treatments will be undertaken for the HE component and analysis will follow the statistical analysis plan approach. Where the missing data pattern is missing at random then a multiple imputation approach will be implemented using appropriate predictive coefficients consistent with the statistical analysis. The MI command in Stata will be used with the predictive mean matching approach implemented for missing cost data. Missing data identified as missing not at random, the missing value is a predictor of the value being missing, will be described and reported to the Study Steering Committee. Where a logical and empirically supported interaction between the missing variable and the value of the variable can be ascertained then the assumption will be included as a scenario within the sensitivity analysis.

7.10 Calculation of Quality Adjusted Life years (QALYs)

The BB:2-6 study wasn't designed to collect quality of life measures which could be used to calculate QALYs. The initial BBO-2 study results will be reported alongside the overall study costs but no additional QALY calculations will be undertaken.

7.11 Discounting

The discounting rate to be used is 3.5%. The four study years will be discounted, both costs and effects, back to the original intervention date to offer the most appropriate representation for replication. Discounting will be undertaken on an annual basis upon both costs and consequences. Discounting represents the preference for current value when compared to future value. Discounting shows the societal preference for receiving benefits now as opposed to in the future and to defer costs into the future rather than pay them now.[xi] Higher (lower) discount rates represent greater (lesser) time preferences.

7.12 Descriptive statistics

The descriptive statistics approach will report mean values with standard deviation and mean differences in resource use, costs and outcomes all with 95% confidence interval values. The outcome statistics will repeat the figures reported in the statistical analysis

7.13 Sensitivity analyses

Sensitivity analysis will be undertaken by varying key assumptions made in the evaluation and reporting the subsequent impact to the findings. This approach helps to characterise the uncertainty inherent in the analysis. Whilst all efforts will be undertaken to report an accurate representation of costs there is an underlying uncertainty with generalised cost data. A range of one way and two way sensitivity analyses will be undertaken, appropriate variables and assumptions will be adjusted according to their confidence intervals and/or by 30%.

7.14 Costs associated with child maltreatment outcomes

If feasible, an additional analysis (outside of the main health economic analysis) of the relationship between total cost and child maltreatment outcomes will be estimated across the entire cohort. This pooled analysis will take the form of a generalised linear model (GLM) with total cost as the dependent variable. A binary identification of intervention arm and a range of individual level covariates will be included. The influence of the child maltreatment outcome variable will signal the change in resource costs associated with that event. The identification of the economic impact associated with each of the child maltreatment outcomes can offer an important context for individuals valuing the CCA.

7.15 Software

A combination of IBM SPSS version 22, STATA version 13, and Microsoft Excel 2010 will be used for all analyses.

7.16 Analysis time frame

The health economic analysis will be conducted in late 2017/ early 2018.

7.17 Identification of further research

Whilst not included within this analysis, when evaluating a varied set of effects within a CCA framework the question often arises regarding weighting of effects and preference valuations. The resulting consequences of the FNP intervention could be included in a discrete choice experiment in order to ascertain the relative importance of each effect. The resulting preference weightings would offer important transparency to the overall findings.

8 Log of changes to SHEAP

Version	Reason for amendment	Change made by	Date amendment made:
1.1	Clarification around the categories of primary need and the initial category of abuse.	RCJ	05/06/2018
1.2	Section5.1 added information on small numbers	RCJ	20/09/2018

	Section 6.3.4 Change to the EYFSP outcomes since data on stated outcomes finished collecting		
1.3	Section 6.3.2 additional exploratory descriptive analysis added looking at length of IP stay in injuries	RCJ	24/04/2019
1.3.	Inclusion of Rhys Pockett as main study health economist. Editorial revision of HEAP to reflect the final analysis agreed with the SMG/TSC following first examination of the data.	DF	24/04/2019

Appendix I - Diagnoses codes

The following codes were used to select events from HSCIC data sources for certain outcomes.

Table a) A&E attendances for injuries and ingestions in children

Table b) Hospital admissions for injuries and ingestions in children

a) Injuries and ingestion codes in A&E data

A&E Code	Description
01	Laceration
021	Contusion
022	Abrasion
03	Soft tissue inflammation
041	Concussion
042	Other head injury
051	Dislocation
052	Open fracture
053	Closed fracture
054	Joint injury
055	Amputation
06	Sprain/ligament injury
07	Muscle/tendon injury
08	Nerve injury
09	Vascular injury
101	Burns and scalds - electric
102	Burns and scalds - thermal
103	Burns and scalds - chemical
104	Burns and scalds - radiation
11	Electric shock
12	Foreign body
13	Bites/stings
141	Poisoning (inc overdose) - prescriptive drugs
142	Poisoning (inc overdose) - proprietary drugs
143	Poisoning (inc overdose) - controlled drugs
144	Poisoning (inc overdose) - other, inc alcohol
15	Near drowning
16	Visceral injury

b) Injuries and ingestions codes in inpatients data (hospital admissions)

ICD10 code	Description
S00-S09	Injuries to the head (includes open wounds, fractures, crushing and dislocation)
S10-S19	Injuries to the neck
S20-S29	Injuries to the thorax
S30-S39	Injuries to the abdomen, lower back, lumbar spine and pelvis
S40-S49	Injuries to the shoulder and upper arm
S50-S59	Injuries to the elbow and forearm
S60-S69	Injuries to the wrist and hand
S70-S79	Injuries to the hip and thigh
S80-S89	Injuries to the knee and lower leg
S90-S99	Injuries to the ankle and foot
T00-T07	Injuries involving multiple body regions
T08-T14	Injuries to unspecified part of trunk, limb or body region
T15-T19	Effects of foreign body entering through natural orifice
T20-T32	Burns and corrosions
T33-T35	Frostbite
T36-T50	Poisoning by drugs, medicaments and biological substances
T51-T65	Toxic effects of substances chiefly nonmedicinal as to source (sting, alcohol, solvents etc).
T66-T78	Other and unspecified effects of external causes (effects of radiation, heat and light, hypothermia, electric shock, asphyxiation, food deprivation)
X40-X49	Accidental poisoning by and exposure to noxious substances

Appendix II Pregnancy related episodes in inpatients data (hospital admissions)

ICD10 code	Description
O00-O08	Pregnancy with abortive outcome
O10-O16	Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
O20-O29	Other maternal disorders predominantly related to pregnancy
O30-O48	Maternal care related to the fetus and amniotic cavity and possible delivery problems
O60-O75	Complications of labour and delivery
O80-O84	Delivery
O85-O92	Complications predominantly related to the puerperium
O94-O99	Other obstetric conditions, not elsewhere classified
Z321	Pregnancy confirmed
Z33	Pregnant state, incidental
Z34	Supervision of normal pregnancy
Z35	Supervision of high-risk pregnancy
Z36	Antenatal screening
Z37	Outcome of delivery
Z38	Liveborn infants according to place of birth
Z39	Postpartum care and examination

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