FOLLOW-UP STUDY PROTOCOL

[Study logo]

Long Title: Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.

Short Title: Healthy Start, Happy Start: Long-term follow-up

Research Reference Numbers:

IRAS number: 310487

Sponsor's number: [tbc]

Funder's number: NIHR132896

Study registration: researchregistry7577

Protocol Number: **1.2**

Date: 19th April 2022

Sponsor: University of Cambridge

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Co-Chief Investigators agree to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date: ...../...../.....

Name (please print):

.....

Position:

.....

Co-Chief Investigator:

Signature: Date: ...../...../.....

Name: (please print):

PROFESSOR PAUL RAMCHANDANI

Co-Chief Investigator:

Signature: Date: ...../...../.....

Name: (please print):

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i. LIST OF ABBREVIATIONS

AE	Adverse Event
BPSES	Brief Parental Self Efficacy Scale
CACE	Complier Average Causal Effect
CA-SUS	Child and Adolescent Service Use Schedule
CBCL	Child Behaviour Checklist
CHU9D	Child Health Utility 9 Dimensions
CI	Chief Investigator
eCRF	Electronic Case Report Form
EF	Effect Size
GAD7	Generalised Anxiety Disorder-7
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HSHS	Healthy Start, Happy Start
ICF	Informed Consent Form
ICTU	Imperial Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute for Health Research Health Technology Assessment Programme
PACS	Parental Account of Children's Symptoms
PI	Principal Investigators
PIS	Participant Information Sheet
PHQ-9	Patient Health Questionnaire 9
PMG	Project Management Group
PPI	Patient and Public Involvement
PSSRU	Personal Social Services Research Unit
QA	Quality Assurance
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled Trial

RDAS	Revised Dyadic Adjustment Scale
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDQ	Strengths and Difficulties Questionnaire
SOP	Standard Operating Procedure
SSC	Study Steering Committee
VIPP-SD	Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline

ii. STUDY SUMMARY

TITLE	Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.
SHORT TITLE	Healthy Start, Happy Start: Long-term follow-up
DESIGN	This study builds on the success of a previous trial: Healthy Start, Happy Start (HSHS; Ref 13/04/33; 2014-2019); which used a two-arm, parallel group, assessor-blind, randomised controlled trial design to test the clinical and cost effectiveness of a video-feedback intervention (VIPP-SD) for parents of young children (12-36 months) at risk of behaviour problems. This follow-up study will assess the long-term clinical and cost-effectiveness of the intervention in a Bayesian analysis framework.
PARTICIPANTS	Participating families have already been recruited from NHS services across six NHS sites in the UK. Target population: Young children who were aged 12-36 months when recruited to the original HSHS RCT and who had high levels of behaviour problems (originally recruited on the basis of scoring in the top 20% of population norms for the Strengths and Difficulties Questionnaire externalising subscale) and their caregiver(s). Children's teachers will also be asked to complete a short questionnaire.
PLANNED SAMPLE SIZE	300 families
ELIGIBILITY CRITERIA	All participants in the original trial will be invited to participate in this follow-up study. Participants must meet the following eligibility criteria: **Inclusion criteria** 1. Family participated in the original Healthy Start, Happy Start trial 2. Written informed parental consent from participating caregivers **Exclusion criteria** 1. Child or parent has severe sensory impairment, learning disability, or language limitation that is sufficient to preclude participation in the study. We will be mindful of possible reasons that a family may not be able to participate in the follow-up study (i.e., become lost to follow-up) including the child being removed from the caregiver(s) care, parental incarceration, and/or parent/child death. We will be sensitive to possible changes in families' circumstances in all communications.
OBJECTIVES	**Primary objective:** To assess whether, compared to usual care in the NHS, a brief parenting intervention (VIPP-SD) leads to long-term lower levels of behaviour problems in young children who are at high risk of developing these problems (5 years post-randomisation – children aged 6-9 years old). **Key secondary objective:**

	To undertake an economic evaluation to assess the cost-effectiveness of VIPP-SD compared to usual care in the long-term (5-years post-randomisation).
PRIMARY ENDPOINT	• **Severity of behaviour problems** assessed using the Parental Account of Children's Symptoms (PACS) interview, completed with children's primary caregiver at 5-years post-randomisation.
SECONDARY ENDPOINTS	• **Child health-related quality of life** assessed using the Child Health Utility 9 Dimensions (CHU9D) questionnaire, completed by children, or proxy completed by caregivers if the child is under 7 years of age, at 5-years post-randomisation. • **Resource use** assessed using a modified version of the Child and Adolescent Service Use Schedule (CA-SUS) • **Child behaviour** assessed by the Child Behavior Checklist (CBCL) questionnaire • **Child behaviour** assessed by the Strengths and Difficulties Questionnaire (SDQ) • **Child behaviour** assessed by the Callous Unemotional traits scale (comprised of four SDQ and three APSD items) • **Parental sensitivity and discipline** assessed using standardised observation scales applied to play-based parent-child interactions • **Parental mood** assessed by the Parent Health Questionnaire-9 • **Parental anxiety** assessed by the Generalised Anxiety Disorder-7 • **Parental efficacy** assessed using the Brief Parental Self Efficacy Scale • **Couple functioning** assessed by the Revised Dyadic Adjustment Scale
EXPLORATORY ENDPOINTS	• **Child health and education outcomes** measured using routinely collected data from the Department for Education National Pupil Database and databases maintained by the National Health Service, including NHS Digital and other central UK NHS bodies • **Language development** assessed using a pictorial vocabulary assessment • **Executive function** assessed using computerised tasks of executive function-related skills • **Prosocial behaviour** assessed using a doll's play task • **School enjoyment** using a short questionnaire • **Parents long-term reflections on the intervention** using a brief questionnaire

iii. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
National Institute for Health Research Health Technology Assessment Programme (NIHR HTA) National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, University of Southampton Alpha House, Enterprise Road Southampton SO16 7NS	Research costs of £442,589.26, awarded through the NIHR HTA Programme (HTA Project: NIHR132896)

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iv. ROLE OF STUDY SPONSOR AND FUNDER

The study's sponsor is the University of Cambridge. The sponsor takes on overall responsibility for proportionate, effective arrangements being in place to set up, run, and report this research.

The funders of the study will have no role in the study design, conduct, data analysis and interpretation, manuscript writing, or the dissemination of results.

v. ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

1) Study Steering Committee (SSC)

A Study Steering Committee (SSC) will be established to oversee the conduct of the study. The SSC will have a majority independent representation and will be comprised of the lead investigators, an independent chair, and additional independent members and user representatives. The SSC will meet on a six-monthly basis. Minutes from each meeting will be submitted to the study funder.

2) Project Management Group (PMG)

The Project Management group will be responsible for overseeing the management of the study and operational issues. The PMG will meet every 3 months during the set-up and conduct of the study. Membership will include the Co-Chief Investigators, key investigators, and the Study Manager. Two investigators are Patient and Public Involvement representatives.

3) Patient and Public Involvement (PPI)

A Patient and Public Involvement group will be set up at the establishment of the study. Members (parents, caregivers, educators) will be recruited from health and community services across the original study sites. The group will help the study team to develop materials for communicating with participants and will review key participant materials, including the Participant Information Sheet. A panel of children (aged 6-9 years old) will also be convened to advise on all aspects of the study including participant materials and data collection procedures. The dissemination strategy for study findings will be devised in collaboration with the PPI groups. Support and advice for best practice in PPI will be sought from the Public Involvement Coordinator at ICTU and the PPI co-investigators.

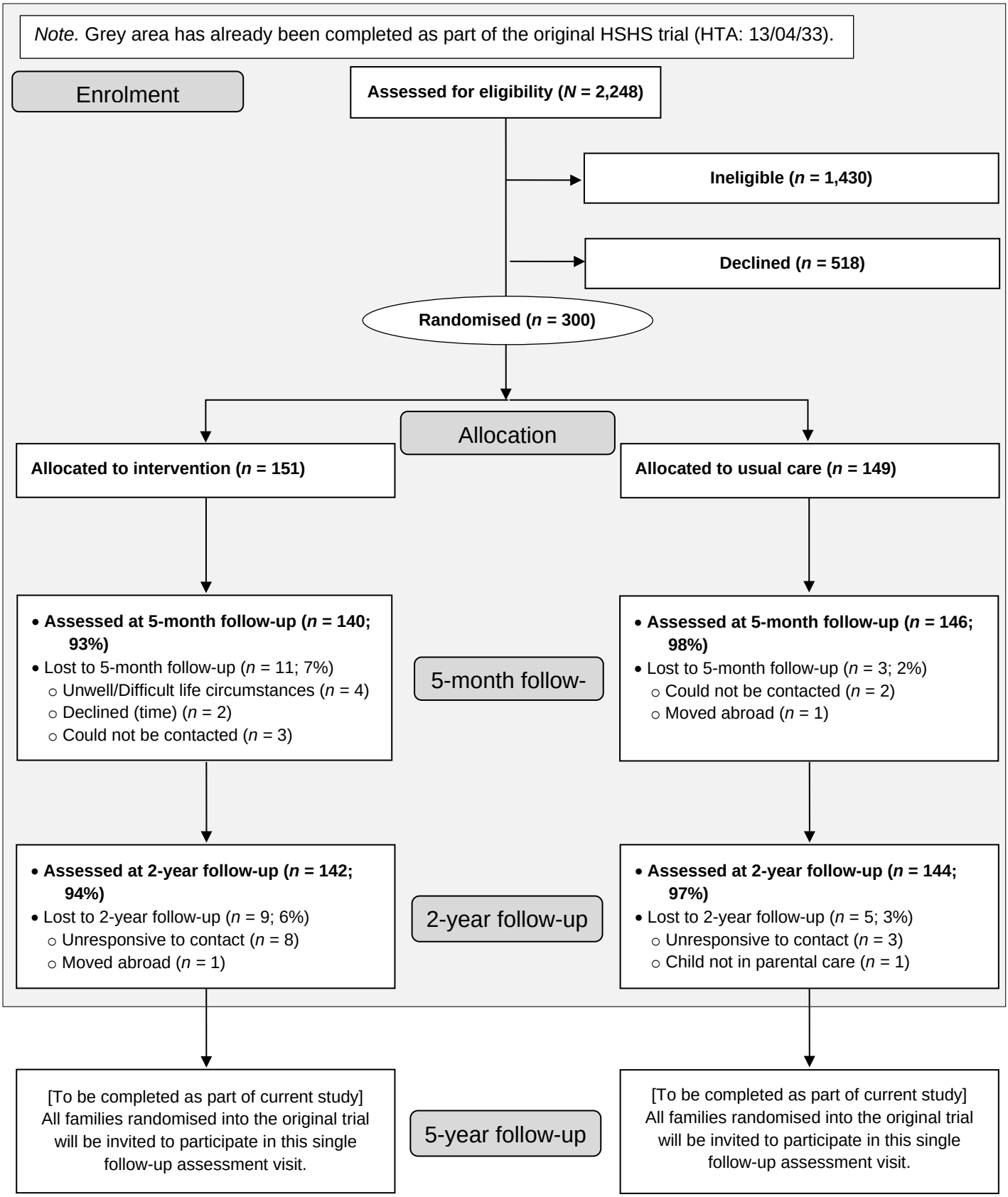
vi. PROTOCOL CONTRIBUTORS

This protocol has been written and/or reviewed by the Co-Chief Investigators and all study Investigators. Two study Investigators are members of the study's Patient and Public Involvement group. The data analysis plans to test the clinical effectiveness and cost effectiveness of the intervention were written by the study's lead Statistician and Health Economist respectively.

vii. KEY WORDS

early intervention, behaviour problems, parenting, child development, mental health

viii. STUDY CONSORT



1 BACKGROUND AND RATIONALE

The case for intervention for early onset behaviour problems

Behaviour problems form the bulk of the burden of psychiatric morbidity in early childhood (1). These disorders typically include attention deficit hyperactivity disorder (ADHD), conduct disorder, and oppositional defiant disorder (2). According to the National Institute for Health and Care Excellence (NICE), about 30% of a typical GP's child consultations are for behaviour problems and 45% of community child health referrals are for behaviour disturbances (3). Behaviour problems are also one of the most common reasons for children to be referred to mental health services (3, 4). These problems often start early in life and children with early onset problems tend to experience particularly poor long-term prognosis (5, 6). This includes an increased risk of psychiatric disorders, antisocial behaviour and criminality, drug and alcohol misuse, and physical ill health through into adult life (1, 4, 7, 8). As well as the distress caused to children and families, large costs are also incurred by society through the health, social care and criminal justice systems (9). Estimates show that the costs of support for children with conduct disorder are ten times higher than costs for peers with no problems (10).

Evidence suggests that interventions may be particularly effective when delivered early in life and early intervention has become a key research and policy priority (11-13). However, despite the promise of early intervention and the substantial referral burden and long-term costs associated with conduct problems, there is currently no standard NHS care pathway for early onset behaviour problems. This follow-up study will offer the evidence needed on a scalable intervention to inform decisions about this.

Need for long-term follow up of effective interventions

One key barrier to an NHS care pathway has been the lack of evidence-based effective early intervention programmes that can be delivered successfully through the NHS. This has been addressed by the NIHR HTA funded randomised controlled trial (RCT) Healthy Start, Happy Start (HSHS) which has shown that a brief intervention (VIPP-SD) is effective in reducing behaviour problems at their earliest onset in one and two-year-olds. A critical outstanding question is whether the VIPP-SD intervention can continue to demonstrate sustained benefits to children and families into middle childhood. Long-term follow up of early intervention programmes is essential to demonstrate the effects of early preventative intervention and to generate more concrete estimates of cost-effectiveness.

There is a limited evidence base regarding the long-term benefits of interventions that target behaviour problems in young children. A thorough search for systematic reviews and other relevant trials of interventions for behaviour problems was conducted using the Cochrane database, Medline, Embase and Psycinfo, other published systematic reviews, ongoing registered trials, and direct contact with experts in the field. Meta-analytic evidence demonstrates that parenting interventions are effective in reducing behaviour problems in children. Mingebach et al's (14) meta-analysis of meta-analyses (441 studies; children aged <13 years) and van Aar et al's (15) meta-analysis both demonstrated that treatment effects for children's behaviour are stable to follow up. But length of follow up was relatively short (length of follow-up 2.8-31.2 months (14)), very few studies targeted children under the age of three, and sample sizes in studies with younger children were small (only two studies included group sizes >100). The HSHS study builds on this

evidence in demonstrating a treatment effect in much younger children (aged 1-2 years) which is sustained at a two year follow up. It also has a larger sample size than most previous studies.

An effective early intervention: Evidence from the Healthy Start, Happy Start trial

The current study will determine the long-term impact of an effective early intervention. This will be enabled through a follow up of the HSHS trial (Grant: Ref 13/04/33; 2014-2019). The trial assessed the clinical- and cost-effectiveness of a brief (six-session) video-feedback intervention (VIPP-SD) for parents of young children (12-36 months) at increased risk of behavior problems. In a two-arm, parallel group, research-blind RCT, a total of 300 families were randomised to either the VIPP-SD intervention plus usual care (*n* = 151) or usual care only (*n* = 149). Retention was very high (94% of families completed the 24-month follow up). The clinical outcomes from this trial demonstrated an initial treatment effect on child behaviour (equivalent to a standardised effect size of 0.2) at 5-months post-randomisation. The findings of the trial demonstrate a clear benefit of the intervention which may be expected to make a real difference when rolled out across a large population (16, 17).

The trial results also demonstrate that the VIPP-SD treatment fits well within the Healthy Child Programme. It is scaleable, having been found to be feasible for health visitors to deliver, and acceptable to families as demonstrated by the high rate (80%) of uptake of all six programme visits. Thus, the findings of the HSHS trial suggest we have an early intervention that is effective in reducing behaviour problems in young children, is highly acceptable to parents, and can be successfully delivered in routine NHS practice. However, cost-effectiveness analyses were inconclusive, suggesting that VIPP-SD may be cost-effective, depending on the willingness to pay threshold adopted for improvements in the primary clinical outcome, a measure which is not associated with a clear decision threshold. The cost-effectiveness analysis was hampered by a lack of available tools to calculate quality adjusted life years (QALYs) in very young children. The collection of data in the current follow-up study will provide the evidence needed by NICE to determine whether the treatment should be recommended as part of routine care since measures capable of generating QALYs (which are associated with a decision threshold) are available for self-completion by children aged 7+ or proxy completion for younger children (aged 5-6). The challenge of estimating cost-effectiveness in the original trial is in keeping with other early preventative interventions, with later follow up recommended to better capture the full economic impact of early interventions (18).

Contribution of the HSHS follow up study to knowledge and NHS policy and practice

This follow-up study will provide key evidence regarding the potential impact of an early childhood intervention. Specifically, in whether the intervention prevents some of the well-established later risks associated with early onset behaviour problems which impact on children, families, health services and schools. Behaviour disorders are more marked at age 7 (19). Additionally, as children navigate the transition to school the associated psychosocial, behavioural, and cognitive challenges are expected to intensify existing behaviour problems and undermine children's academic competence (20).

Early intervention and prevention programmes targeting parenting behaviour have become a key focus of domestic policy. The NHS Five Year Forward View for Mental Health (21), the NHS Long-Term Plan (22), the Healthy Child Programme (23), the 2017 Green paper on children and young people's mental health (13), and the 2019 Green paper on advancing health through

prevention (24) all emphasise the need for timely provision of intervention to children and their families, and the economic benefits of very early intervention. NICE highlights the importance of selective prevention and early intervention for children at risk of early onset conduct disorders, but the evidence currently only supports this provision from three onwards. The current study will provide key evidence to address this important, and potentially costly, gap in knowledge (25).

2 OBJECTIVES AND OUTCOME MEASURES

2.1 Primary objectives

The aim of the research is to evaluate the long-term (5 years post-randomisation) effectiveness and cost-effectiveness of a brief early parenting intervention (Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline; VIPP-SD), designed to reduce behaviour problems, compared to usual care.

The primary objective is:

> To assess whether, compared to usual care in the NHS, a brief parenting intervention (VIPP-SD) leads to long-term lower levels of behaviour problems in young children who are at high risk of developing these problems (5 years post-randomisation – children aged 6-9 years old).

2.1.1 Primary hypothesis

Among children initially recruited at 12-36 months old with high levels of behaviour problems, adding a brief video-feedback parenting intervention (VIPP-SD) to usual care will reduce enduring behaviour problems measured at five years post-randomisation, using the Parental Account of Children's Symptoms (PACS) interview. The hypothesis will be examined in a Bayesian framework which will provide the probability for VIPP-SD being superior to usual care.

2.2 Secondary objectives

The secondary objectives are:

1. To undertake an economic evaluation to assess the cost-effectiveness of VIPP-SD compared to usual care in the long-term (5-years post-randomisation).
2. To assess whether, compared to usual care in the NHS, a brief parenting intervention (VIPP-SD) leads to changes in parenting and parental wellbeing.
3. To assess whether, compared to usual care in the NHS, a brief parenting intervention (VIPP-SD) leads to changes in children's cognitive, social, and biological functioning.
4. To obtain and utilise routinely collected healthcare and education data to supplement and further inform the effectiveness and cost-effectiveness objectives above.

2.2.1 Secondary hypotheses

i. Among children initially recruited at 12-36 months old with high levels of behaviour problems, adding a brief video-feedback parenting intervention (VIPP-SD) to usual care will provide a cost-effective use of resources compared to usual care, measured five years post-randomisation, using QALYs as the measure of effect.

ii. Among children initially recruited at 12-36 months old with high levels of behaviour problems, adding a brief video-feedback parenting intervention (VIPP-SD) to usual care will reduce

enduring behavioural problems measured at five years post-randomisation, using the Child Behaviour Checklist (CBCL), and Strengths and Difficulties Questionnaire (SDQ), completed by parents/carers, and the SDQ completed by a schoolteacher.

iii. Among children initially recruited at 12-36 months old with high levels of behaviour problems, adding a brief video-feedback parenting intervention (VIPP-SD) to usual care will result in higher levels of parental sensitivity during parent-child interactions, measured at five years post-randomisation.

2.3 Outcome measures/endpoints

2.3.1 Primary endpoint/outcome

Assessment of severity of behaviour problems at five-years post-randomisation (age 6 to 9 years) using a structured interview assessment (Parental Account of Children's Symptoms; PACS) completed with the child's primary caregiver

2.3.2 Secondary endpoints/outcomes

1. Health-related quality of life assessed by the Child Health Utility 9 Dimensions (CHU9D), capable of generating quality adjusted life years (QALYS)
2. Resource use assessed using a modified version of the Child and Adolescent Service Use Schedule (CA-SUS)
3. Child behaviour and mental health assessed by the Child Behavior Checklist (CBCL), Strengths and Difficulties Questionnaire (SDQ), and Callous Unemotional Traits subscale
4. Parental couple functioning assessed by the Revised Dyadic Adjustment Scale
5. Parental mood assessed by the Patient Health Questionnaire-9 (PHQ9)
6. Parental anxiety assessed by the Generalized Anxiety Disorder-7 (GAD7)
7. Parental sensitivity assessed using a standardised observation scale applied to parent-child play-based interactions
8. Parenting style assessed using the Brief Parental Self Efficacy Scale

2.3.3 Exploratory endpoints/outcomes

1. Executive function assessed using computerised computer tasks
2. Language development assessed using a pictorial measure of vocabulary
3. Prosocial behaviour assessed using a dolls play story stem battery
4. School enjoyment assessed using a short questionnaire
5. Parents long-term reflections on receipt of the intervention using a brief questionnaire
6. Child health and education outcomes measured using routinely collected data from the Department for Education National Pupil Database (Early Years Foundation Stage assessment; Children in need referrals; Special educational needs; Pupil absences and exclusions) and to databases maintained by the National Health Service, including NHS Digital

(Hospital Episode Statistics for attendance at accident and emergency and outpatient services as well as hospital admissions)

3 STUDY DESIGN

The study is a follow-up at 5 years post-randomisation of a two-arm (1:1), parallel group, multi-site, pragmatic randomised controlled trial with blinded outcome assessment comparing the use of VIPP-SD to usual care. Although the initial study results are known, new outcome assessors will be employed who will be kept blind to initial group allocation.

This study will use gold-standard interview and questionnaire measures to assess child outcomes five years post-randomisation, with a focus on child behaviour. Alongside this we will also use a mix of home assessment, questionnaire and routinely collected data (HES and other related health data and the National Pupil Database, where feasible and available within required timescales) to investigate treatment effects on child socio-emotional and educational outcomes. We will be following up with a well-engaged cohort (follow up rates of 94% and 95% at previous follow ups).

4 STUDY SETTING

The Sponsor of the follow-up study is the University of Cambridge. Recruitment for the 5-year post-randomisation assessment will be conducted by the research team based at the University of Cambridge. The follow-up study does not rely on the support of NHS sites.

The Sponsor of the original Healthy Start, Happy Start trial (HTA: 13/04/33) was Imperial College London. Families were recruited from NHS healthcare settings in London (Camden, Hillingdon, Islington, and Barking and Dagenham), Peterborough, Oxfordshire, and Hertfordshire between July 2015 and July 2017. Recruitment was primarily conducted through health visiting services.

5 PARTICIPANT ELIGIBILITY CRITERIA

As no participants withdrew consent from the original trial, all participants in the original study are potentially eligible participants in the proposed research. Participants will need to meet the following eligibility criteria.

5.1 Inclusion criteria

1. Family participated in the original Healthy Start, Happy Start trial
2. Written informed parental consent from participating caregivers

5.2 Exclusion criteria

1. Child or parent has severe sensory impairment, learning disability, or language limitation that is sufficient to preclude participation in the study.

We will be mindful of possible reasons that a family may not be able to participate in the follow-up study (i.e., become lost to follow-up) including the child being removed from the caregiver(s) care, parental incarceration, and/or parent/child death. We will be sensitive to possible changes in families' circumstances in all communications.

6 STUDY PROCEDURES

Assessment visits will be undertaken by research assistants who are blind to treatment allocation, at a time convenient for the family. At the commencement of this study, all participants of the original trial will be notified of the opportunity to participate in the 5-year follow-up assessment. Then, approximately two months prior to their planned follow-up time (5-years post-randomisation, ± 18 months), families will be emailed and posted an invitation flyer about the follow-up visit. The research team will then follow-up with families via telephone and email to discuss the visit and schedule in a time and date for the assessment if the family is willing to participate.

It is anticipated that data will be collected via home-based assessments. However, if COVID-19 restrictions or other logistical issues (e.g., family relocation) preclude direct participant contact, assessments will be conducted by the researcher remotely through online video call or telephone.

This follow-up visit will be approximately two-and-a-half hours in duration. Previous study visits of this population were of similar duration and proved to be feasible to deliver and acceptable to children, caregivers, and researchers. The follow-up visit will be split into two parts. The first part will be approximately one hour in duration and will involve a telephone call with the child's primary caregiver where they will be consented and asked to complete the study's primary outcome (PACS interview) with a researcher. The second part is a home-based visit that will be approximately 90 minutes in duration and will involve both the child and caregiver.

6.1 Recruitment and response monitoring

A total of 300 families (child aged 12-36 months, and one or two participating caregivers) were recruited into the Healthy Start, Happy Start trial between July 2015 and July 2017. Five and 24-month follow-up data were collected between December 2015 and July 2019, with outcome data collected at one or both post-intervention time points for 294/300 (98%) families. There was a very high retention rate at 24-month follow-up (*N* = 282; 94%) and it is anticipated that a minimum of 85% of the original sample (*N* = 256) will re-engage at the 5-year follow-up.

On the advice of the patient and public involvement group, all families who were randomised into the original trial will be notified of the opportunity to participate in the 5-year post-randomisation assessment using a multipronged approach. Families will first be informed of the assessment via email and post, and then contacted via telephone to discuss the visit. This comprehensive approach to participant reengagement may circumvent issues related to changes to participant contact details since the last study contact.

Even if the recruitment rate is lower than the estimate of 85%, previously collected data will be used to provide additional statistical power for analyses (previously collected data from at least two time points is available for over 95% of the sample). Due to the longitudinal analysis being used and previously high retention rate, with 200 participants (67%) simulations demonstrate that it will still be possible to obtain a high expected posterior probability of 90% or greater if the treatment effect is sustained. However, low retention would raise concern for the introduction of bias if unequal between arms and concerns for reducing the generalisability of the results. A lower bound of 70% recruitment rate will initially be set (families successfully contacted and scheduled for the assessment visit). These numbers will be monitored on a monthly basis and the SSC will be notified if recruitment is consistently below 70% for any period of the study. A stop-go decision will

be made after 6 months of recruitment, as follows:

- Minimum rate recruited (contacted and scheduled) at Month 10 of study (after 6 months of recruitment) = 70% of those approached
    - If ~<70% stop study
    - If ~≥70% but below 80% continue but monitor consent rate once a month via project management group
    - If >80% continue with no changes

6.1.1 Participant identification

Participants will be contacted by members of the research team to notify them of the 5-year follow-up assessment. All participants in the original trial consented for their data to be stored and used to contact them again for research related to the Healthy Start, Happy Start study. Participants will be contacted by post and email to notify them of the opportunity to participate in the 5-year follow-up. All participants will be assessed in a one-year period of data collection, when children will be 6-9 years old. Participants will be scheduled to be seen at 5-years post-randomisation (±18 months).

6.1.2 Payment

Research assessments will be carried out in the family home. In instances where this is not practically feasible or the participating family would prefer to complete the visit elsewhere, participants will be offered the opportunity to complete the assessment remotely (telephone or video call) or in a community venue (e.g., local children's centre). Where participants must travel, expenses will be reimbursed.

All participating families will be offered a nominal (£20) voucher to recompense their time. The amount offered is in keeping with the original trial and is chosen to ensure that it does not unduly influence participation so that consent is given freely. Participating children will be given small thank you tokens and a certificate of participation.

6.2 Consent

All adult research participants (participating caregiver(s); teachers) will sign and date an Informed Consent Form (ICF) before any study specific procedures are performed. Where research assessments are conducted in-person, participants will provide written consent. Where research assessments are conducted remotely, participants will provide electronic consent.

All caregivers will be sent an electronic/postal copy of the Participant Information Sheet (PIS) before their scheduled 5-year follow-up visit to ensure they have ample time to consider the information and discuss any questions they have. The PIS and ICF will inform participants of their right to refuse participation or withdraw at any time without giving reasons. Participants will be provided with the Co-Chief Investigators' contact details so that they can obtain further information about the study. Consent for study participation will be obtained at the beginning of the call with participating caregivers. A trained research assistant will take the participant through the Participant Information Sheet and the clauses on the ICF. Participants will be encouraged to spend as much time as they need asking questions about the study. Participants will then record their written consent. A copy of the PIS and ICF will be given to the parents/caregivers for their records

and a further copy stored in the participant file. If a participant withdraws from the study, data and samples collected up to the point of withdrawal will only be used after the withdrawal if the participant has consented to this.

While consent for children's participation will be provided by their caregiver(s), participating children will also undergo child assent procedures, to inform them of the study's aims and what their participation would involve. The Child Information Sheet will be presented in a format easily understood by young children (e.g., an illustrated leaflet, an animation). Participating children will be advised of their right to refuse participation or withdraw at any time without giving reasons. If a child does not assent to the completion of a measure, or they show signs of fatigue/disinterest, then the measure will not be completed.

All researchers leading the informed consent process with families will be authorised, trained, and competent to participate according to the ethically approved protocol, Research Ethics Committee guidance, the Declaration of Helsinki, and the principles of Good Clinical Practice.

As with the main trial, the study's PPI co-applicants and panels (adult and child PPI groups) will advise on participant materials to ensure consent procedures are accessible (e.g., adding study specific visuals and schematics to aid understanding).

6.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

Data and biological specimens for ancillary studies will be acquired, transferred, and stored during the study. Participants will be asked to provide consent for their data to be used for future unspecified research. Participants may opt out of taking part in ancillary research but still participate in the main study. No information derived from the biological samples will be provided to participants. The data and biological samples used in ancillary research will be pseudonymised and linked to a separate securely held identifiable list, meaning that withdrawal from the ancillary research will also remain possible. Participants will be asked to provide consent to be contacted by trial investigators for further informational and consent-related purposes.

6.3 Blinding

Participants (i.e., caregiver(s)) will have been informed of their randomised allocation at the beginning of the original HSHS trial. Researchers assessing study outcomes at the 5-year follow-up study will be blind to group allocation (VIPP-SD or usual care). To minimise the risk of bias, in instances where outcome assessors become unblinded (e.g., participants reveal their allocation during the assessment), audio recordings of the PACS (primary outcome) will be double scored by a second assessor who remains blind to allocation. Such instances are likely to be rare given the length of time since randomisation and the minimal levels of unblinding in the original trial (4% and 2% at previous follow-up visits).

6.4 Withdrawal of individual participants

Participants may withdraw from the study for the following reasons:

- At the request of the child's family

- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study

If a participant withdraws from the study, this will be documented in the participant records and electronic Case Report Form (eCRF) including the reason for withdrawal, whether study data collected up to that point can be used, and whether further follow-up can be conducted.

6.5 Contact with General Practitioner

It is the investigator's responsibility to inform the child's General Practitioner by letter that the child is taking part in the study provided the child's primary caregiver agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent Form. Copies of the letters will be stored at the Sponsor site, using secure data storage systems or secure filing if stored through paper records.

6.6 End of study

The end of the study will be defined as the last data capture for the last participant visited. A notification of the end of the trial will be submitted to the REC within 90 days of the final data capture taking place.

7 STUDY MEASURES

7.1 MEASURES OF CHILD BEHAVIOUR

7.1.1 Parental Account of Children's Symptoms

The Parental Account of Children's Symptoms (PACS) interview (26) is an age-appropriate version of the PPACS (the primary outcome in the original HSHS trial) for assessment of children aged over five years. This is a standardised, investigator-based interview. The PACS, and its age-modified version, have been utilised in a number of epidemiological and intervention studies (27). It is administered by a trained interviewer who scores a series of behaviours on a 4-point rating scale (0-3) against pre-specified criteria for severity and frequency. The PACS has been found to have good psychometric properties demonstrating a two-factor structure and discrimination between hyperactivity and conduct disorder, and good inter-rater reliability (correlations 0.89-0.95) and internal consistency (hyperactivity $\alpha = 0.89$; conduct $\alpha = 0.87$) (27). The PACS has also been found to correlate with clinician observed behaviour and caregiver reported measures and has strong predictive validity for disruptive behaviour 10 years later (27). Such interview measures are the gold standard assessment for psychopathology. They are more objective as they use investigator-based criteria for scoring symptoms and are thus less prone to the parental biases (e.g., knowledge and expectations of child behaviour) seen when using parent-reported questionnaires. Where two parents/caregivers are participating in the trial the PACS will be completed by the parent who identifies as being the primary caregiver.

7.1.2 Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ; (28)) is a robust and reliable measure of child behaviour. The questionnaire is made up of 25 items that make up five subscales (5 items per subscale). The subscales include conduct problems, hyperactivity-inattention, emotional symptoms, peer problems and pro-social behaviour. Each question asks about a specific behaviour and is rated as 0 = Not True,1 = Somewhat True or 2 = Certainly True. The subscale scores (not including the prosocial behaviour subscale) can be combined to generate an overall difficulties score (range 0-40). Higher scores in the overall difficulties scale indicate increased difficulties. The scoring for the prosocial behaviour items is reversed, and scores range between 0-10. The lower scores on this subscale indicate increased difficulties. The SDQ will be completed by one or two caregivers depending on their participation in the trial, in addition to a schoolteacher who knows the child well, where parental consent for contact is given. Teacher-reported data will provide an independent report of the child's behaviour.

7.1.3 Child Behavior Checklist

Child behaviour will also be measured using the Child Behaviour Checklist (CBCL/6-18; (29, 30). The CBCL is a well-validated and widely used 113-item questionnaire. Each question asks about a specific behaviour and respondents are asked to rate how true the behaviour is of their child over the last six months on a three-point scale (0 = not true, 1 = somewhat true, or 2 = very true or often true). For behavioural problems (externalising problems) it yields an overall score, as well as specific subscales for attention problems and aggressive behaviours. The CBCL will be completed by one or two parents/caregivers depending on their participation in the study.

7.1.4 Callous Unemotional Traits

Children's callous unemotional traits (CU traits) will be assessed using a seven-item scale. This questionnaire will be composed of four Strengths and Difficulties Questionnaire (described in section 7.1.2) items and three Inventory of Callous-Unemotional Traits (ICU; (31)) subscale items. The CU traits measure will be completed by one or two parents/caregivers depending on their participation in the study.

7.2 MEASURES OF COST-EFFECTIVENESS

7.2.1 Child health-related quality of life

Effectiveness for the economic evaluation will be measured using the Child Health Utility 9 Dimensions (CHU9D; (32)), a preference-based, generic measure of health-related quality of life capable of generating QALYs. In line with guidance provided by the developers, children aged 7 years and older will self-complete the CHU9D whilst parents/caregivers will proxy-complete the measure for children under 7. Baseline values, which are necessary to estimate QALYs (an area under the curve measure) will not be available as the CHU9D could not be used in the original HSHS trial given the very young age of the children. Instead, baseline values will be estimated using the SDQ mapping function (33) and explored in sensitivity analysis, potentially using values from the literature from similar populations, if available.

7.2.2 Child and Adolescent Service Use Schedule

Resource use will be recorded using a modified version of the Child and Adolescent Service Use Schedule (CA-SUS), developed, tested and successfully employed in the original HSHS RCT (16). Given the length of the follow-up period and issues with recall, we will use a two-stage process involving the application of the full HSHS CA-SUS covering the 3-month period prior to the 5-year follow-up interview and a briefer version focused on key and more easily recalled resources (high cost and/or high use) covering the full period from the 24-month final follow-up in the original trial to the date of interview at the 5-year follow-up. Both versions of the CA-SUS will be completed in interview with parents.

7.3 ROUTINELY COLLECTED MEASURES OF HEALTH AND EDUCATION DATA

7.3.1 Linkage to education records via the National Pupil Database

Participants will be asked to consent to access to routinely collected data via the National Pupil Database, which is maintained by The Department for Education. This database holds information about children's educational attainment, attendance, and referrals to alternative provision. For the current study, this database will primarily be used to collect information on the Early Years Foundation Stage Profile, an assessment conducted at the end of children's first year of schooling. Data from this assessment measures children's personal, social, emotional, creative, and physical development, and their communication, language, literacy, problem solving, reasoning, and numeracy skills. Data on children's special education needs, referrals to social care services, attendance, and school exclusions will also be requested. Data will be analysed in accordance with the privacy preserving models and confidentiality standards set out by the Office for National Statistics.

7.3.2 Linkage to health records via the National Health Service databases

Participants will be asked to consent to access to routinely collected data stored in databases maintained by the National Health Service, including NHS Digital. This database holds information about a child's health status and service use. For the current study, Hospital Episode Statistics will be requested for attendance at accident and emergency units, hospital admissions, and attendance at outpatient clinics. Approval for the data request will be sought from the Independent Group Advising on the Release of Data panel and the Health Research Authority. Data will be analysed in accordance with the privacy preserving models and confidentiality standards set out by the Office for National Statistics.

7.4 MEASURES OF PARENTING AND PARENTAL WELLBEING

7.4.1 Patient Health Questionnaire 9

The Patient Health Questionnaire-9 (PHQ-9; (34)) is a widely used and reliable measure of depression severity. The measure is made up of nine statements, each corresponding to one of the 9 DSM-IV criteria for depression. Each statement is scored on the frequency the responder has experienced each problem over the past two weeks. Scores range from Not at all = 0, Several days = 1, More than half the days = 2 or Nearly every day = 3, and a total score is obtained by summing all items of the questionnaire. Scores range from 0-27, with higher scores indicating more

severe depression. The PHQ-9 will be completed by one or two parents/caregivers depending on their participation in the study.

7.4.2 Generalized Anxiety Disorder-7

The Generalized Anxiety Disorder-7 (GAD-7; (35)) is a seven-item questionnaire that has been extensively used in research as a general measure of anxiety in adults. Each statement is scored on the frequency the responder has experienced each problem over the past two weeks. Scores range from Not at all = 0, Several days = 1, More than half the days = 2 or Nearly every day = 3, and a total score is obtained by summing all items of the questionnaire. The GAD-7 will be completed by one or two parents/caregivers depending on their participation in the study.

7.4.3 Revised Dyadic Adjustment Scale

The Revised Dyadic Adjustment Scale (RDAS; (36)) is a reliable and valid measure of relationship adjustment. This 14-item scale consists of three subscales: dyadic consensus, dyadic satisfaction and dyadic cohesion. A total RDAS score is obtained by summing all items of the questionnaire. Scores range from 0 to 69, where higher scores indicate greater relationship satisfaction, and lower scores greater relationship distress. The RDAS will be completed by one or two parents/caregivers depending on their participation in the study and relationship status.

7.4.4 Brief Parental Self Efficacy Scale

The Brief Parental Self Efficacy Scale (BPSES; (37)) is a short, 5-item measure of parental self-efficacy. Items are scored on a five-point Likert scale (1 = Strongly disagree; 3 = Neutral; 5 = Strongly agree), with scores ranging from 5 to 25 with higher scores indicating higher levels of parental self-efficacy. The BPSES will be completed by one or two parents/caregivers depending on their participation in the study.

7.4.5 Parental sensitivity and parental discipline

Parental sensitivity and parental discipline will be rated based on video-recorded, play-based parent-child interactions, using a standardised rating scale, by raters blinded to group allocation.

7.4.6 Parental reflections on receipt of the intervention

The ongoing utility of the VIPP-SD intervention will be measured through parents' own perspectives (e.g., whether families have used what they learnt consistently, on specific occasions, with siblings, or not at all; and whether families would have liked to have booster sessions following the original intervention). This data will be collected from parents who were originally randomised to receive VIPP-SD via online survey after the completion of their follow-up assessment to maintain blinding of research assistants.

7.5 MEASURES OF CHILD DEVELOPMENT

7.5.1 Language development

A brief pictorial measure of children's language will be used to assess children's vocabulary. The assessment involves the researcher saying a word (e.g., animals, toys, emotions) and the child being asked to select a picture that best illustrate the word's meaning. The assessment takes 10-15 minutes to administer.

7.5.2 Executive functions

Children's executive functions will be assessed using a set of brief and engaging computerised tasks. These game-like assessments will measure children's capacity for skills such as inhibition and attention shifting.

7.5.3 Prosocial behaviour

Children's prosocial behaviour will be assessed using a dolls play activity. The child will be asked by the researcher to tell some stories using dolls and props. This task is designed to provide an index of the child's prosocial behaviours and their representations of their behaviour. Recordings will be coded using a standardised rating scale by raters blind to group allocation.

7.5.4 School enjoyment

The extent to which children enjoy school will be assessed using a small number of questions related to school enjoyment (e.g., How much do you like going to school? *I like it a lot, I like it a bit* and *I don't like it*).

8 SAFETY REPORTING

In this study, we will adopt a risk proportionate approach to safety monitoring, to ensure reporting is appropriate and useful for the research and participants. Participating families will not receive any intervention as part of their participation in this follow-up research assessment. The intervention tested in the original HSHS intervention (delivered to half of participating caregivers between 2015-2017) was supportive in nature, brief (6 home-based sessions), and delivered at least five years before the families will be followed up in the current study. It is highly unlikely that any serious adverse events seen in the current study would be related to the intervention delivered as part of the original HSHS trial. Because of this, only AEs and SAEs related to study procedures undertaken as part of the follow-up assessment will be monitored and collected.

All members of the research team with direct contact with participants will be trained in procedures and standards for safety reporting. Judgements around the categorisation and seriousness of these events will be discussed with the Study Manager and/or the co-Chief Investigators.

8.1 Definitions

Term	Definition
Adverse Event (AE)	An AE is any untoward medical occurrence which does not necessarily have a causal relationship with the study's procedures. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the research assessment, whether or not considered related to the study's procedures.
Serious Adverse Event (SAE)	An SAE is defined as any adverse event that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing inpatient's hospitalisation**

	• Results in persistent or significant disability or incapacity • Is a congenital abnormality or birth defect*** * “Life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** “Hospitalisation” means any unexpected admission to a hospital department. It does not apply to scheduled admissions that were planned before study inclusion or visits to an accident and emergency department (without admission). *** “Congenital abnormality or birth defect” will not be applicable for this study as all participants will be children aged 6-9 years old and their parents/caregivers. Medical judgement should be exercised in deciding whether an adverse event is serious in other situations. Important adverse events that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
Related and Unexpected Serious Adverse Event	A Related and Unexpected Serious Adverse Event is an Adverse Event that is classed as serious, believed with reasonable probability to be due to the study assessment, based on the information provided, and is unexpected.

8.2 Severity of Adverse Events

Severity of AEs will be assessed according to the following definitions:

Category	Definition
Mild	Awareness of event but easily tolerated
Moderate	Discomfort enough to cause some interference with usual activity
Severe	Inability to carry out usual activity, including play for infants and children

8.3 Causality of Adverse Events

Causality of AEs, i.e., relationship to the study procedures, will be assessed according to the following definitions:

Category	Definition
Unrelated	No evidence of any causal relationship
Related	There is evidence to suggest a causal relationship between study procedures and the event. The influence of other contributing factors is unlikely or can be ruled out.

8.3.1 Recording and reporting of SAEs

The safety reporting period for this study is defined as beginning at the start of the study visit and ending at the completion of research activities. If a participant spontaneously reports relevant safety information following the completion of research activities, that appears to be related to study procedures, this will also be reviewed and recorded where necessary.

All SAEs will be recorded on the Serious Adverse Event Form via the eCRF and emailed to the Sponsor within 24 hours of the research staff becoming aware of the event.

For each SAE the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to study procedures), in the opinion of the investigator
- whether the event would be considered anticipated. Note, in this study, there are no 'anticipated SAEs' so all occurrence of SAEs would be considered unexpected.

All reported SAEs will be reviewed by the co-Chief Investigator(s) (or designee) within two working days of receiving notification of the SAE report. The SAE review will be recorded on the eCRF. Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All Related and Unexpected Serious Adverse Events will be notified to the Research Ethics Committee (REC) and the Sponsor within 15 days of becoming aware of the event. Follow up of participants who have experienced a Related and Unexpected Serious Adverse Event should continue until recovery is complete or the condition has stabilised. Safety reporting will be included in the progress report sent to the REC, on the anniversary of ethics approval.

9 STATISTICS AND DATA ANALYSIS

A detailed statistical analysis plan will be prepared and signed off by the Chief Investigators and study statisticians prior to any analyses being conducted.

9.1 Sample size and power considerations

The original HSHS trial randomised 300 children; 294 (98%) had at least one post-baseline measurement and will be included in the follow-up analysis. With 294 children and assuming 85% (*n* = 256) retention at 5-year follow-up, we expect to obtain a posterior probability for superiority of VIPP compared to usual care in the region of 93% if the intervention effect observed at 2 years is sustained at 5 years (ES = 0.22). If the intervention effect is diminished by 50% (ES = 0.11) or completely diminished (ES = 0.0), the probability for superiority of VIPP will be in the region of 78% and 48% respectively. These probabilities will provide valuable evidence to make judgments on the impact of early intervention and whether it is sustained long-term.

9.2 Data analysis

The primary estimand will be the treatment policy estimand. The primary analysis will follow an intention-to-treat principle and will include all participants randomised with at least one post baseline measurement (98%, *n* = 294) in the longitudinal model. The number and proportion lost to 5-year follow-up will be reported with reason where known. All missing outcome data will be summarised by group and time point. Baseline data and outcome data will also be summarised by group and time point. Suitable descriptive statistics will be calculated for continuous variables (means and standard deviations, or medians and inter-quartile ranges) and frequencies and proportions for categorical variables. No between group testing will be performed on variables at baseline as any imbalance will be due to chance and will not invalidate the inference from the trial (38, 39).

The primary aim is to estimate the probability that VIPP-SD is superior to usual care at 5 years post randomisation. A Bayesian mixed effects linear regression model will be used to calculate the probability that the PACS primary outcome score in the VIPP-SD group is greater than in the usual care group. The primary outcome at 5M, 24M and 5 years will be standardised in order to make Pre-PACS and PACs comparable in the model. The model will include treatment group, time, group by time interaction, baseline Pre-PACs score, the randomisation stratification variable center, and subject random effect (intercept and slope). Alongside the probability of superiority for VIPP, we will report the standardised between-arm mean difference with 95% credible interval. No multiple imputation will be used as 98% of the randomised sample will be included in the analysis model and the analysis is valid under a missing at random (MAR) assumption. This assumes the probability of missing data occurring is not dependent on the values of unobserved data, instead it is conditional on the observed variables included in the analysis models. We will perform a sensitivity analysis to the primary analysis to examine the MAR assumption using controlled multiple imputation. With controlled imputation we can induce missing not at random (MNAR) using a δ approach (40). The parameter levels used for δ will be pre-specified in the statistical analysis plan after discussion with the clinical team, likely values examined will correspond to +/- 25% and 50% of the treatment effect applied to those missing in both arms then each arm in turn to examine the possibility of the missing being informative in one arm only.

A supplementary analysis to the primary analysis will be performed in order to estimate the intervention effect in those that ‘complied’ (received four or more sessions of VIPP-SD) using a complier average causal effect (CACE) analysis. We will use either the calculation in a Bayesian framework guided by Imbens & Rubin (41) or the use of a two-stage least squares instrumental variable regression approach (42).

A second analysis on the primary endpoint of this follow-up study (PACS at 5 years) using a Bayesian linear regression model with an informative prior distribution on the treatment effect model parameter will also be conducted. The informative prior distribution will be constructed based on the Pre-PACs results in the original trial using data and clinical judgment to translate to an approximate PACs distribution. Missing data will be imputed to allow all original participants to be included in the model. The results from this model will provide information of the difference between arms on the original PACs scale.

Analysis of continuous secondary outcomes will follow the principle of the primary analysis and use a Bayesian analysis with uninformative prior on the treatment effect. Where secondary outcomes are only collected at one time point (5-year follow up) multiple imputation will be used to include all randomised participants. The multiple imputation model will include the variables in the primary model and outcome and other variables as advised by the clinical study team. Where outcomes are repeatedly collected and the same we will use a Bayesian mixed effects longitudinal model. Probabilities for superiority of ViPP as well as treatment effect estimates and 95% credible intervals will be reported for all timepoints (5M, 12M and 5yrs). The results will be displayed visually to display the intervention effect and uncertainty around that estimate over time.

Binary and count outcomes will follow a similar principle for model covariate adjustment and imputation and with use of logistic and negative binomial regression models. CACE analysis will also be repeated for all secondary outcomes to obtain an estimate of the intervention effect in those that received it.

Issues with the availability and completeness of data obtained through data linkage are anticipated. Impacts of the COVID-19 pandemic mean that delays in accessing this data and a greater degree of missing data are likely. With these issues in mind, the main analysis of data will focus on data collected directly from participants. Secondary data analysis will be conducted on the routinely collected data accessed through the National Pupil Database and NHS Digital as an exploratory outcome if and when it becomes available. The exploratory analysis will follow the same principle of the secondary outcomes to compare between arm differences using adjusted regression modelling.

If acquired within the timeframe of the study, the availability of routinely collected data will allow us to examine additional health and education outcomes. Those for educational attainment will be examined in a longitudinal model for the years available and the analysis will be undertaken using a proportional odds model. School absences will be treated as a continuous variable taking account of the observation period for each child. The number of children with school exclusions and categories of special education needs will be tabulated by arm with no formal between arm comparison. We will also compare how both the usual care and intervention arm compare to their peers on the educational data collected. Similar analyses will be undertaken for routine health data if it becomes available within the required timeframe. Specifically, between arm comparisons will be made for children's hospital admissions and attendance at accident and emergency and outpatient appointments.

All descriptive analysis, statistical models, multiple imputation models, and δ's for controlled multiple imputation will be contained in a detailed statistical analysis plan (SAP) that will be written and signed off prior to first data extraction.

9.3 Economic analysis

The long-term economic analysis will be a cost-utility analysis comparing VIPP-SD to usual care at 5-year follow-up with effects measured in terms of QALYs calculated from the CHU9D. The economic perspective will be the NHS/personal social services perspective, including those health and social care services provided within education settings. A secondary analysis will additionally include the cost of education facilities attended, given the age of the population.

Resource use, collected using the two versions of the CA-SUS, described above, will be costed using nationally applicable unit costs (e.g., NHS Reference Costs for hospital contacts, PSSRU Unit Costs of Health and Social Care for community health and social services, British National Formulary for medications). The intervention cost has already been calculated in the original trial and thus will not need costing. Discounting will be applied to both costs and outcomes, following the approach and the discount rate preferred by NICE at the time of the analysis (Note: NICE are currently reviewing the discount rate alongside other methods of economic evaluation and thus analyses will be finalised once this review is complete). The primary analysis will use costs generated from the detailed version of the CA-SUS focusing on all health and social care service use over a 3-month recall period. A sensitivity analysis will use costs generated from the shorter version of the CA-SUS focused on key services (high cost/high usage) over the full follow-up period from final 24-month follow-up to 5-year follow-up. Both analyses will include the costs of service use between baseline and 24-month follow-up estimated in the original trial.

Costs and outcomes will be compared in terms of mean differences and 95% confidence intervals from non-parametric bootstrap regressions (1,000 replications) to account for the non-normal distribution common to economic data. Cost-effectiveness will be assessed using the net benefit approach following standard approaches (43). A joint distribution of incremental mean costs and effects for the two groups will be generated using non-parametric bootstrapping to explore the probability that each of the treatments is the optimal choice, subject to a range of possible maximum values (ceiling ratio) that a decision-maker might be willing to pay for improvements in outcome (QALYs). Cost-effectiveness will be explored using incremental cost effectiveness ratios (44), with uncertainty represented by cost-effectiveness planes and cost-effectiveness acceptability curves (45). The approach to missing data and adjustment for baseline covariates will be in line with the clinical analyses described above.

Sensitivity analyses will test the sensitivity of the results to: a) the two approaches to parental-report resource use data collection using the CA-SUS (base case analysis: detailed over 3 months; sensitivity analysis: key service use over full follow-up period); b) the source of data on hospital contacts (base case analysis: CA-SUS; sensitivity analysis: HES data from NHS Digital, if available); c) the measure of effect (base case analysis: CHU9D; sensitivity analysis: primary clinical outcome measure); and d) the baseline utility values (base case analysis: SDQ mapping function; sensitivity analysis: values from the literature, if available).

10 DATA MANAGEMENT

10.1 Data collection tools

10.1.1 Source data

Paper records and secure electronic records of participant contact details will be kept. Pseudonymised data (linked by unique study code/identifier) will be entered directly onto the eCRF report form, either by the researcher conducting the assessment or the participating caregiver under the supervision of the researcher (dependent on which data/outcome measure is being collected as some of the proposed measures are researcher-led while others are participant self-report). For the majority of participants, the eCRF will be considered the source data as data will be entered directly onto the electronic database. Paper data collection will be offered as an alternative if requested. In these cases, the paper records will be considered the source data and will be transcribed onto the eCRF by the research assistants.

Multiple methods will be used to maximise the completeness of data (e.g., following up with teachers who have not returned their questionnaire via email).

10.1.2 Case report forms

Data will be entered onto an electronic Case Report Form (eCRF) developed in REDCap. Its use will be GDPR and GCP compliant. The eCRF will allow for audit trails to be kept to demonstrate the validity of the study (both during and after the study). Access will be restricted to trained staff with unique password-protected accounts. Forms completed directly by participants will be via a secure participant-specific link provided by email. The eCRF will only collect information directly relevant to the objectives and outcome measures detailed in the protocol. Identifiable data will not be recorded in the eCRF and participants will be identified by a unique trial ID only. Instructions for completion of the eCRF by researchers will be provided in a separate eCRF manual.

10.2 Data handling and record keeping

In line with GCP guidance, the Sponsor operating the eCRF will test the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorised access, maintain a list of the individuals authorised to make data changes, maintain adequate backup of the data, safeguard the blinding of the trial and archiving of any source data (i.e., hard copy and electronic). If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The Sponsor will use an unambiguous participant identification code that allows identification of all the data reported for each participant. The Sponsor will be responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted.

10.2.1 Study documentation and data storage

The investigator will retain essential documents until notified by the Sponsor, and at least for ten years after study completion, in accordance with Sponsor requirements. Participant files and other source data (including copies of protocols, questionnaires, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) will be kept for the maximum period of time permitted by the institution. Documents will

be stored in such a way that they can be accessed/data retrieved at a later date. Consideration will be given to security and environmental risks.

Hard copies of data sheets linking the participant identification number to the person's contact details will be kept securely in the Investigator Site File, in a locked filing cabinet in a locked office, accessible only to key members of the research team. No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement will be obtained from the Sponsor.

All audiovisual recordings made by the research team will be immediately uploaded after each session via a secure digital platform that will be supported by the Sponsor, University of Cambridge. These audiovisual recordings will be backed up on secure servers and accessible only to specific members of the research team. The audiovisual recordings will be stored pseudonymously according to each family's study ID. All temporary video stored on video cameras will be deleted and permanently removed immediately after the video has been uploaded to the secure digital platform.

10.2.2 Access to Data

Direct access to data will be granted to authorised representatives from the Sponsor and the regulatory authorities to permit study-related monitoring, audits, and inspections in line with participant consent.

11 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with the Declaration of Helsinki, the General Data Protection Regulation (GDPR) Data Protection Act (DPA) and the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

11.1 Research Ethics Committee (REC) review and reports

Before the start of the study, approval will be sought from a REC for the study protocol, parent and child information sheets, informed consent forms, and other relevant documents. Substantial amendments that require review by the REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the Trial Master File.

A progress report will be submitted to the REC by the Co-CIs on an annual basis, within 30 days of the anniversary date on which the favourable opinion was given. The progress report will also include details of safety information. A notification of the end of the study will be submitted by the Chief Investigators to the REC within 90 days of the final data capture taking place. Within one year after the end of the study, the Chief Investigators will submit a final report with the results, including any publications/abstracts, to the REC.

11.2 Public and Patient Involvement

Parents of young children have been and will continue to be actively involved in the research process. The follow-up project's design was developed in consultation with the original PPI group of the Healthy Start, Happy Start study. At a dedicated meeting to discuss future research plans, the group strongly recommended that a long-term follow-up was important to understand how children are developing as they grow older and to provide more robust evidence about effectiveness and cost-effectiveness. PPI is also embedded within the study team, as two PPI representatives are Co-Investigators in the study. Both members have had the opportunity to review the protocol and have offered feedback on the design and content of participant materials. These two PPI representatives will continue to be active members of the Project Management Group to ensure positive study management and oversight. They will join meetings of external oversight groups, policy events, and assist with the coordination of the PPI panels. We will convene a parent PPI panel as well as a panel of 6–9-year-olds who will advise on all aspects of the study including participant materials, data collection, and the interpretation of the findings. A dissemination strategy of study findings will be devised in consultation with the PPI groups.

11.3 Protocol compliance

Prospective, planned deviations or waivers to the protocol will not be used. Accidental protocol deviations will be adequately documented on the relevant forms on the eCRF and reported to the Chief Investigators. Protocol violations will be reported to the Chief Investigators and Sponsor immediately. Deviations from the protocol that are found to frequently recur will not be acceptable, will require immediate action, and could potentially be classified as a serious breach.

11.4 Monitoring

The study will be monitored periodically by the Study Manager to assess the progress of the study, verify adherence to the protocol, Sponsor and ICTU SOPs, ICH GCP E6 guidelines and to review the completeness, accuracy and consistency of the data. Monitoring procedures and requirements will be documented in a Monitoring Plan.

11.5 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The study sponsor will notify the licencing authority in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with that study; or

(b) the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach

11.6 Data protection and participant confidentiality

All investigators and research team members will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

On the eCRF or other documents submitted to the Sponsors, participants will be identified by a study ID number only. Information linking study participants to their study ID will be stored in a separate location using an encrypted digital file within password protected folders and storage media. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) will be kept in a strictly confidential file by the investigator. Access to data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis. Data transmission between co-investigators will be undertaken using encrypted digital systems.

All audiovisual recordings made by the research team will be immediately uploaded after each session via a secure digital platform that will be supported by the Sponsor, University of Cambridge. These audiovisual recordings will be backed up to secure back-up servers and accessible only to specific members of the research team. The audiovisual recordings will be stored pseudonymously according to each family's study ID. All temporary video stored on video cameras will be deleted and permanently removed immediately after each session once the video has been uploaded to the secure digital platform. The Chief Co-Investigators will act as data custodians.

The investigator shall permit direct access to participants' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and the REC.

11.7 Quality Control and Quality Assurance

Quality Control and Quality Assurance will be performed according to the Sponsor's procedures. The Research Office's QA Manager will conduct a risk assessment prior to the start of the study to assign a risk category to the study. The monitoring plan will be developed in accordance with the outcome of the Risk Assessment. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

Quality Assurance for aspects relating to Statistics will also be carried out by the QA Manager at ICTU since ICTU is responsible for Statistics.

11.8 Financial and other competing interests for the chief investigator, PIs at each site, and committee members for the overall study management

The investigators and committee members declare no competing interests that might influence study design, conduct, or reporting.

11.9 Indemnity

Adequate provision is made for insurance or indemnity to cover liabilities which may arise in relation to the design, management and conduct of the research project by the Research Sponsor (University of Cambridge).

11.10 Amendments

Amendments to the protocol and information provided to participants will be submitted to the Sponsor and the REC for approval prior to implementation. The Project Management Group will be responsible for the decision to amend the protocol. The Co-Chief Investigators and Sponsor will be responsible for deciding whether an amendment is substantial or non-substantial prior to submitting the amendment for review. Substantial amendments may only be implemented after written REC approval has been obtained whereas non-substantial amendments can be implemented without written approval from the REC. The amendment history will be tracked using a protocol amendment summary of changes document, which will be stored in the TMF to identify the most recent protocol version.

11.11 Addition onto trial register

The study protocol will be registered with Research Registry in accordance with the International Committee of Medical Journal editors (ICMJE) requirements. Any protocol amendments will also be registered there.

11.12 Access to the final study dataset

The Co-Chief Investigators and Study Investigators will have access to the full dataset at the end of the study. No interim analysis is planned during data collection and there will be no restrictions in access for study investigators.

12 DISSEMINATION POLICY

12.1 Dissemination policy

The results from the study will be submitted for publication in a peer-reviewed journal irrespective of the outcome. The Study Steering Committee will be responsible for approval of the main manuscript prior to submission for publication. The study funders will be acknowledged in publications. The funders will not have review and publication rights of the data from the study.

Key study findings will be shared with all participating caregivers and children in the form of an animation and study newsletter. These outputs will be developed in collaboration with the parent PPI and children's PPI groups. At the end of the study, children's caregivers will be able to request a copy of the results of the study from the Co-Chief Investigators.

The trial protocol, deidentified participant data, and data dictionary will be made available through data sharing. Deidentified data will be available 12 months after publication and for 5 years after the date of publication. Data will be made available to researchers who provide a methodologically sound and hypothesis-driven proposal, and who have the required institutional approvals in place to achieve the aims in the approved proposal. To gain access to the data, proposals should be directed to the Co-Chief Investigators for approval by the investigator group. Requestors will be asked to sign a data access agreement.

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14 Signatures

SIGNATURE PAGE 1 (Co-Chief Investigator 1)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.

Protocol Number:

Signed: _____

Professor Paul Ramchandani

Date: _____

SIGNATURE PAGE 2 (Co-Chief Investigator 2)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.

Protocol Number:

Signed: _____

Dr Christine O'Farrelly

Date: _____

SIGNATURE PAGE 3 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.

Protocol Number:

Signed: _____

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

SIGNATURE PAGE 4 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.

Protocol Number:

Signed: _____

Name of Statistician
Title
Organisation/Company

Date: _____

SIGNATURE PAGE 5 (INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Long term effectiveness and cost-effectiveness of early mental health intervention: Follow up to the Healthy Start, Happy Start study.

Protocol Number:

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____