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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

Health Technology Assessment Programme
National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton, Alpha House
Enterprise Road, Southampton, SO16 7NS

tel: +44(0)23 8059 5586

fax: +44(0)23 8059 5639

email: hta@hta.ac.uk

web: www.nets.nihr.ac.uk

The diagnostic accuracy of hearing tests and cost-effectiveness of school entry hearing screening programmes

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STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:
Contact name

University of Nottingham
Mr Paul Cartledge
Head of Research Grants and Contracts
Research and Graduate Services
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Chief investigator:

Dr Heather Fortnum
Associate Professor and Reader in Hearing Research
NHBRU
Ropewalk House
113 The Ropewalk
Nottingham
NG1 5DU
Phone: 0115 8223601
Fax: 0115 8223618
Email heather.fortnum@nottingham.ac.uk

Co-investigators:

Professor Rod Taylor
Professor in Health Services Research
Peninsula Medical School
Universities of Exeter and Plymouth
Veysey Building
Salmon Pool Lane
Exeter
EX2 4SG
rod.taylor@pms.ac.uk

Dr Obi Ukoumunne
Senior lecturer in medical statistics
PenCLAHRC
Veysey Building
Salmon Pool Lane
Exeter
EX2 4SG
obioha.ukoumunne@pcmd.ac.uk

Professor Chris Hyde
Prof of public health and clinical epidemiology
Peninsula College of Medicine and Dentistry
University of Exeter
Veysey Building
Salmon Pool Lane
Exeter
EX2 4SG
'c.j.hyde@exeter.ac.uk'

Claire Benton
Clinical Scientist (Audiology)
Nottingham Audiology Service
Ropewalk House
113 The Ropewalk
Nottingham
NG1 5DU
Claire.benton@nuh.nhs.uk

Joanne Moody
Audiological Scientist
Cambridge University Hospital Foundation Trust
Addenbrookes Hospital
Hills Road
Cambridge
CB2 0QQ
joanne.moody@addenbrookes.nhs.uk

Ann Allardice
Head of service - interim
Health Visiting and School Nursing
Nottingham East

Park House Health and Social Care Centre
61 Burton Road
Nottingham
NG4 3DQ
ann.allardice@nottshc-chp.nhs.uk

Parent representatives: Julian and Sarah Watson
julian@juleswatson.co.uk
Sarah.C.Watson@nottingham.ac.uk

Study Statistician: Dr Obi Ukoumunne
Senior lecturer in medical statistics
PenCLAHRC
Veysey Building
Salmon Pool Lane
Exeter
EX2 4SG
obioha.ukoumunne@pcmd.ac.uk
Tel: 01392 726070

Study Researchers: Ms Mara Ozolins, Research Fellow
Ms Sam Catterick, Research Associate
NHBRU
Ropewalk House
113 The Ropewalk
Nottingham
NG1 5DU
Phone: 0115 8232827 / 8232607
Fax: 0115 8232618
Email mara.ozolins@nottingham.ac.uk / samantha.catterick@nottingham.ac.uk

Study Coordinating Centre: NHBRU
Ropewalk House
113 The Ropewalk
Nottingham
NG1 5DU

SYNOPSIS

Title	The diagnostic accuracy of hearing tests and cost-effectiveness of school entry hearing screening programmes
Acronym	SES
Short title	School entry hearing screening programmes
Chief Investigator	Dr Heather Fortnum
Objectives	The overarching aims of this project (comprising 5 sub-studies S1-S5, also known as SES1-SES5) are evaluation of the diagnostic accuracy of hearing screening tests and the cost-effectiveness of screening for hearing impairment at school entry. The specific research objectives of this project are: • To determine and compare the diagnostic accuracy of two methods for screening for the identification of sensorineural or permanent conductive hearing impairment at or around school entry. • To develop an existing SES economic model and synthesise the findings of the research in order to provide robust estimates of key parameters in the economic model beyond accuracy. In particular the yield and nature of hearing loss detected in a system with no SES; the yield, impact and costs of screen positive individuals in an SES system; and the costs of setting up an SES system.
Study Configuration	Case control study; prospective and retrospective observational cohort studies, health economic analyses: S1: case control comparison of two screening methods. S2: retrospective and prospective observational cohort study (Cambridge; no school screening) S3: prospective observational cohort study (Nottingham; school screen); questionnaire on impact of screen S4: costs of a school screen S5: Health economic analysis and modelling
Setting	Secondary care, community, schools and research facility (NHBRU),
Sample size estimate	*(Applicable to study 1)* Eighty (80) case children will be selected from a range of centres in order to estimate the sensitivity of the screening tests. This sample is large enough to estimate a sensitivity of 75% with a margin of error of +/- 10% (based on a 95% confidence interval). One hundred and sixty (160) control children, recruited from schools, is a large enough sample to estimate a specificity of 90% with a margin of error of +/- 5% The margin of error for the estimated sensitivity and specificity will provide plausible ranges of values within which to test the stability of the results from the economic model (Study 5) to our assumptions about screening accuracy.
Number of participants	S1: 80 case children (aged 4-6 years) with a sensorineural or permanent conductive hearing loss either bilaterally (average of 20 to 60dBHL) or unilaterally (any level >=20dBHL) identified from collaborating audiology services, and 160 control children (aged 4-6 years) with no identified hearing loss recruited through Nottinghamshire schools S2: Data collection over a period of 7 years for 600-700 children referred per year to 2nd tier services for investigation of possible hearing loss and 20-30

	children per year referred from 2nd tier to 3rd tier audiology services in Cambridgeshire for further investigation of possible sensorineural hearing loss. Data appropriate to the analysis will be extracted. S3: Data collection of all referrals aged 3 to 6 years and 364 days to Nottingham audiology service for 24 months, plus 3 months for outstanding follow-up, Responders to a questionnaire from around 200 children and their families referred from the school entry hearing screening programme to Nottingham Audiology Services in a period of 24 months, once individual follow-up is complete. S4: At least 4 schools will be recruited to take part in the study. Each school will be visited on one or more days according to routine practice by one screener accompanied by a researcher. All children in the appropriate classes who have parental consent to take part will be screened using both technologies (N~180 children). S5: Health economic analysis and modelling with no study subjects involved.
Eligibility criteria	S1: Inclusion: Cases Children aged between 4 and 6 years, with a sensorineural or permanent conductive hearing loss either bilaterally (average of 20 to 60dBHL) or unilaterally (any level >=20dBHL) confirmed by gold standard pure tone audiometry under headphones in sound–proofed rooms, identified from the service records of collaborating paediatric audiology services. Inclusion: Controls Children aged between 4 and 6 years, with no known hearing loss, identified through local Nottinghamshire primary schools. S2: Data will be included if they relate to children referred to the Cambridge service between October 1st 2007 and August 31st 2014 (follow-ups to 30th November 2014), who were referred by any source other than the newborn hearing screen. Children for whom one or more data items are missing will not be excluded at the data collection stage, but such missing data will be accounted for in analyses. S3: Inclusion: All children aged 3 to 6 years and 364 days attending the paediatric audiology service in Nottingham, having been referred, from 1st September 2012 through to 31st August 2014 (follow-ups to 30th November 2014). Exclusion: Children already identified with a permanent loss or under active management with the audiology service and for whom records of audiological assessments exist. S4: Children will be included in the screening process following protocols and guidelines for parental consent normally administered by the service.
Description of interventions	S1 and S4: Hearing screening performed on one occasion using two methods. (i) currently standard pure-tone sweep screening under headphones, (ii) Siemens hand held ear level HearCheck hearing screening device. S1: Pure-tone audiometry under headphones to assess detailed hearing level on one occasion for controls, also cases who have not had one in last 12 months S3: self-completion questionnaire to parents
Duration of study	1st August 2012 for 30 months to 31st January 2015, participants involved on a single occasion
Randomisation and blinding	S1: Each child will undergo two screening tests and control children will also have a gold standard hearing assessment and we will aim, as far as possible within available resources, to blind those undertaking the assessments to the results of the other assessments. The order of the two screening assessments

	will be randomised, with the gold standard last. S4: the order of the two screening tests will be randomised where possible, without preventing the standard PTS test from being carried out.
Outcome measures	**S1:** "pass" or "refer" for the screening tests as defined by the protocol compared with the result of the gold-standard PTA (normal or refer) **S2:** The primary outcomes are yield (the incidence of newly identified hearing loss in children) and age at referral. Secondary outcomes will be the referral source, pathway of care, number and types of assessments, interventions received, level of hearing loss, cause of hearing loss (when available). **S3:** The primary outcome measures will be the yield (from the school screen), age at referral, and the costs both to the service and the families of referral through to definitive identification of hearing loss or discharge from follow-up. Secondary outcomes will be the referral source, pathway of care, number and type of assessments, interventions received, level of hearing loss, cause of hearing loss (when available). **S4:** The primary outcome is the mean cost per child of implementing each of the two test technologies. Costs will include the staff type, grade and time taken in conducting the test plus the cost of the equipment. Outcome (pass/fail) will be recorded). Feedback from the school nurses on which screening method they prefer and why will also be sought. **S5:** Estimation of incremental cost per case detected, and cost to families of being referred.
Statistical methods	S1: Sensitivity will be estimated for each test as the proportion of the case children that test positive and specificity will be estimated as the proportion of the control children that test negative, precision quantified using 95% confidence intervals. McNemar's test will be used to compare each of sensitivity and specificity between the two tests, reporting p-values. S2: Quantitative characteristics summarised using means and standard deviations (or medians and inter-quartile ranges) and categorical characteristics summarised using percentages. Precision summarised using 95% confidence intervals. S3: Descriptive methods as per S2. Additionally, yield (proportion diagnosed) will be compared between a non-screened sample (S2) and a routinely screened sample (S3) with a test and confidence intervals. Referral ages will be compared between S2 and S3 using box and whisker plots and survival curves, adjusting where appropriate for sex and deprivation (postcode). In order to make inferences (from the questionnaire), costs will be summarised as means. Given the likely skewed nature of these outcomes, we will use the non-parametric bias corrected accelerated bootstrapping method (2000 replications) to validate the confidence intervals for the means. We will seek to estimate mean costs for referrals according to their outcome i.e. true positives, false positives and false negatives. S4: The mean cost of the two tests will be compared using the paired t-test. Again, the bootstrap method will be used to validate the confidence intervals for the mean difference. S5: Methods will include cost-effectiveness planes and curves.

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator overall
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
NDCS	National Children's Deaf Society
NHBRU	Nottingham Hearing Biomedical Research Unit
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
PIS	Participant Information Sheet
PSC	Project Steering Committee
PTA	Pure Tone Audiometry
REC	Research Ethics Committee
R&D	Research and Development department
SES	School Entry Hearing Screening
SNHL	Sensorineural Hearing Loss
UNHS	Universal Newborn Hearing Screening

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STUDY BACKGROUND INFORMATION AND RATIONALE

Identification of permanent hearing loss at the earliest possible age is crucial to maximise the development of speech and language and contribute to the best opportunities for educational achievement and quality of life [8]. The introduction of the highly sensitive and specific universal newborn hearing screening (UNHS) has led to the identification of the vast majority of children born with a hearing loss who undergo the screen [4,6]. However, not all children who will ultimately have a hearing loss are identifiable at birth. Data published in 2001 [3] reported an adjusted prevalence of hearing loss at age 3 of 1.07 per 1000 and a prevalence for children aged 9-15 of 2.05 per 1000. Thus, due to acquisition, progression or late-onset of the hearing loss and/or geographical movement of families, there remain a significant number of children with a hearing loss to be identified after the newborn period. The incidence of hearing loss in children after the neonatal period can occur at any time which means there is no optimum time for a further universal hearing screen. Following the introduction of UNHS, the universal distraction hearing test undertaken by health visitors at around 8 months of age was abandoned based on a lack of robust implementation and a low yield of cases [2,5]. The school entry screen (SES), however, remained in place in many parts of the UK and is considered as a "back-stop" screen to identify children as part of a "captive population at school entry. Identification of hearing impairment in children in the time between the newborn period and school entry is achieved through parental and professional awareness and a close follow-up of children who pass the neonatal screen but who are considered to be at risk [7]

In order to best provide a service for the identification of permanent childhood hearing loss whilst making best use of scarce NHS resources it is important to gather robust evidence to support particular cost-effective implementations of service delivery at times relevant to the aetiology of hearing loss and the child's development. There is no question that screening for hearing impairment at birth is efficient and cost-effective [4] but questions remain about the value of any further universal screen. A previous HTA-commissioned study to evaluate the SES undertaken by a number of the co-applicants of this project (HF, RT) [1] reported a survey of current practice, longitudinal data on yield, a systematic review of effectiveness and a model of cost-effectiveness. It concluded that there was insufficient, good quality data on which to base a decision about the value of the SES following the introduction of UNHS. The study did however report longitudinal data from a single district in London which indicated a small but significant number of children with a hearing impairment that was first identified via the SES in that particular population [7], and national survey data which reported examples of children not identified by other methods, for example, those who had moved into the country or who were highly mobile within it. One of the recommendations of the report was the need for comparative trials to compare the effectiveness and cost-effectiveness of alternative approaches to screening for identification of hearing impairment in the post-newborn period.

This proposal develops the findings of the previous HTA report [1] by gathering empirical data to address the questions posed by the funding call and to contribute to policy decisions on the future of the School entry hearing screen. The research question asks whether there should be a screening programme to identify permanent hearing loss in children when they start primary school. It asks if the cost of such a screen is appropriate for the outcomes achieved i.e. the number of children identified by this method compared with a system with no screen which is responsive to parental or professional concern. In addition it asks for a comparison of 2 different ways of doing the screen. One is the standard pure-tone sweep test whereby children listen to tones at frequencies between 500 and 4,000 Hz at specific levels usually 20-35 dBHL. The second screen uses a hand-held instrument, held at the child's ear that emits tones at 1,000 and 3,000 Hz at 20-75dBHL. In both situations the child indicates when they have heard the tones, by raising a hand, pressing a response button or other activity.

The questions are very relevant as previous research has shown that the number of children identified by this screen around age 5 (the yield) is low following the introduction of hearing screening at birth for all babies, and the subsequent widespread further development of a system that is responsive to professional and parental concerns at any age [1, 7]. We will address these questions with a series of 4 empirical studies which will feed into and inform an economic model of cost-effectiveness.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The overarching aims of this project are evaluation of the diagnostic accuracy of hearing screening tests and the cost-effectiveness of screening for hearing impairment at school entry.

PRIMARY OBJECTIVE

To determine and compare the diagnostic accuracy of two methods for screening for the identification of sensorineural and permanent conductive hearing impairment at or around school entry i.e. pure tone sweep audiometry across 4 frequencies and 1 level, and the HearCheck pure tone screen with 2 fixed frequencies and 3 levels (S1)

SECONDARY OBJECTIVES

For a service with a routinely applied school entry hearing screen and a service with no SES, to compare the yield, referral age and source through assessment to intervention for permanent childhood hearing impairment and to measure the costs of referrals.

- To evaluate the effectiveness and cost effectiveness of screening for hearing impairment relative to no implementation of a universal screen at school entry through an economic model
- To explore the impact for the child and the family of a positive result from a screen (both true and false positives) resulting in referral for further assessment.
- To determine the resource costs in implementing the two alternative screening methods in primary schools
- To develop an existing SES economic model and synthesise the findings of studies 1-4 in order to provide robust estimates of key parameters in the economic model beyond accuracy, and to determine the cost-effectiveness of SES. In particular the yield and nature of hearing loss detected in a system with no SES; the yield, impact and costs of screen positive individuals in an SES system; and the costs of setting up an SES system

STUDY DESIGN

STUDY CONFIGURATION

The project involves data collection from the audiology services in Cambridge and Nottingham and from children invited by collaborating audiology departments in England. It comprises 5 studies (S1-S5)
S1 – Case-control study of diagnostic accuracy
S2, S3 and S4 – Cohort studies including both retrospective (S2) and prospective (S2, S3, S4) data collection
S5 – Health economic analyses and modelling

Primary endpoint for project

Pass or fail of the hearing screen and confirmation of any hearing loss present. (Accuracy of the screening tests) (S1)

Secondary endpoints for project

Yield, age at referral (these are primary outcomes for S2 and S3), referral source, number and type of assessments, interventions received, level and cause of hearing loss (S2, S3).
Impact on family (S3)
Cost effectiveness, pass or fail of tests & user preference (S4, S5)

Safety endpoints

There are no risks to the participants in this project and adverse events are unlikely. None of the sound levels to be used are of a damaging level.

Stopping rules and discontinuation

Participants are free to withdraw from the study at any time without giving a reason.

RANDOMISATION AND BLINDING

S1 - Each child will undergo two screening tests and a gold standard hearing assessment (PTA) and we will aim, as far as possible within available resources, to blind those undertaking the assessments to the results of the other assessments. The staff based in the CTU in Plymouth will produce a randomisation list on paper which the researchers will use to determine for each participant the order of the tests, which ear is first for each test, and which researcher does which test. For the cases researchers will do one test each according to the list. For the controls one researcher will do both screening tests and the other will do the PTA. The PTA will always be done last so as not to influence the screening tests. Both researchers based in Nottingham will see the child at home or at the research facility in Nottingham. The screening assessments are automated and hence the influence of the person undertaking the screen is minimal and we feel will not lead to major or systematic bias. The researchers will be trained in implementing the tests.

It is not possible to blind the researchers to the knowledge of whether or not a child in Study 1 has a hearing impairment. Any child living out of Nottingham or wearing a hearing aid or exhibiting any hearing difficulty will be likely to be a 'case'. Indeed, to ensure the screening tests are assessed appropriately it is important to be aware that the child has hearing difficulties so that the researchers can be sure all instructions concerning the test are heard and understood.

S4 – the order of the two hearing screening tests will be randomised. The nurse may override this if they think that the child is unlikely to complete both tests, in which case the standard test (PTS) will be performed first to enable the school health check to be completed.

S2, S3, and S5 – randomisation is not appropriate for the data collection methodologies.

Maintenance of randomisation codes and procedures for breaking code

Randomisation relates only to the order in which the tests are completed.

STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management from her base in Nottingham (NIHR Nottingham Hearing Biomedical Research Unit). She will be responsible for day to day management of the project working with the two researchers appointed.

The project steering committee (PSC) will:

- provide overall supervision for the project on behalf of the Sponsor and Funder and to ensure that the project is conducted to the rigorous standards set out in the Medical Research Council's (MRC) Guidelines for Good Clinical Practice;
- provide advice, through its chair, to the Chief Investigator(s), the Sponsor, the Funder, the Host Institution and the Contractor on all appropriate aspects of the trial;
- concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question;
- ensure appropriate ethics and other approvals are obtained in line with the project plan;
- agree substantial protocol amendments and provide advice to the investigators on all aspects of the trial.

Membership of the committee will comprise:

- an independent Chair from a different institution to members of the research team.
- two independent audiologists with relevant expertise
- two individuals to independently represent expertise in statistics, epidemiology and diagnostics.
- the Chief Investigator (HF) and the study statistician (RT or OU) (neither will have voting rights, and they will be excluded from closed sessions of the PSC where data are discussed).
- at least one individual who is able to contribute a patient and/or wider public perspective.
- a representative of the sponsor and a representative from the research network as observers.

The committee will meet twice a year for the duration of the project

For this particular project the role of a separate data monitoring committee is not straightforward. The project comprises a series of observational studies. It is unlikely with only 80 cases that any interim analyses would be appropriate and it is unlikely that any adverse events will occur. We propose that the PSC described above would monitor data quality and adverse events. Given the nature of research questions being addressed in this programme of work, interim data analyses are not required for safety or efficacy.

The data custodian will be the Chief Investigator.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

The project started on 1st August 2012 and is due to complete on 31st January 2015 (30 months).

S1: each child will be involved on one occasion for screening tests and pure-tone audiometry (if appropriate). There will be no follow-up visits. Recruitment will begin in October 2012, or as soon as possible after then, and assessment will be complete by 31st August 2014. Non responses will be followed up by one reminder letter.

S2, S3: data collected from records by the audiologist. If the audiologists are short of time, the researchers may help with this which would mean they see the patient files in Cambridge/Nottingham or would need access to the hospital system.

S3: parents of children who fail a routine screening test (performed outside of the study) and who are referred to the audiology service will be sent a questionnaire for self-completion. Non-response will be followed up with one reminder. Questionnaires will be sent for all children referred to the service between November 2012 and September 2014, once their final outcome is known. If recipients of the questionnaire agree, their answers may be followed up by a telephone interview.

S4: children will be screened in their usual school using two methods. If the result of the standard screen is negative (fail) or unclear, the child will be re-screened and referred onward as appropriate according to usual practice. If a child does not pass the new Hearcheck method, the researchers will make a note of it as evaluation of the equipment and children will not be retested. The nurses will not record this information as the screen is not currently a validated method to test children's hearing. For this parental notification will not be necessary. Testing will take place in schools between September 2013 and July 2014 inclusive.

S5: no patient involvement

End of the Study

The end of the project will be when the last of the data has been entered into the model.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Data will be gathered in the community (family homes), in secondary care (NHS audiology services), the research facility (NHBRU) and in primary schools.

The project concerns the identification of hearing loss in children between the ages of 4 and 6 years. Participants therefore are required to be such children.
S1: "Case" children as those aged 4-6 years at time of screening identified from collaborating audiology services in England as having a sensorineural or permanent conductive hearing loss. They will be identified by local services and we will ask a senior paediatric audiologist to contact families on behalf of the research team and to send them an invitation to take part in the study with a summary information sheet plus a separate pictorial information sheet for children. Once a parent has expressed interest in thier child taking part by returning a reply slip to the researchers, we will send them a full detailed information sheet containing all aspects pertaining to the study. This will enable parents to have another chance to consider taking part, before they come to an appointment. We have agreed commitment from the services in Nottingham, Sheffield, Leicester, Chesterfield, Derby, Mansfield and Lincoln. We will also approach audiology services in other areas as needed to reach recruitment targets.Some audiologists may choose to create a list once only, including some younger

children (from age 2) who will reach the required age range within the time period of the study. Those wishing to take part, but who are too young at the time of invitation will be sent a holding letter. If the response rate to our invitation letters is low, we will post a reminder on websites of regional branches of the National Deaf Children's Society (NDCS). This may give some parents a second opportunity to consent to their children participating. In addition we will ask audiologists from the collaborating centres to send out reminder letters to parents who have not responded to the initial invitation letters, which will give them a second opportunity to take part.

The children in the control group will be recruited from the reception and year 1 population of schools in Nottinghamshire by a letter of invitation either sent to parents at the time of routine school screening, or to all parents of a class of children at another time to be agreed with the school. Letters will be sent by the school.

S2 and S3: Data will be accessed by the member of the research team with clinical responsibility for the audiology service in Cambridge (JM) and Nottingham (CB). Data will be transferred to other members of the research team for analyses, identified by a study number, with hospital number removed. The researchers (conducting, but not analysing the study) may need to see the patient files in Cambridge/Nottingham, or PAS in order to help the audiologists with the data collection,
S3: the parents of children who have been referred following a failed school screening test will be sent questionnaires by the local paediatric audiology service on behalf of the research team. If they wish to complete the questionnaire they will be asked to return it directly to the research team. The questionnaire will give parents the option to take part in a follow-up telephone interview. Contact details will be provided voluntarily on a separate sheet to the main questionnaire so they can be destroyed later.

The letter of invitation for S1 and S3 will include a statement in locally common languages offering to translate the participant information sheets, and consent forms into these languages.

S4: It is routine practice for children to have their hearing checked at school in the term in which they become 5years old. Some will be tested in reception year and some in year 1. We will follow the routine practice of each participating school in notifying parents that this will be happening. Parents will be sent a letter from the research team. They can opt out of the research by returning the reply slip on our invitation letter to the school nurses (in an envelope provided).

For all studies it will be explained to the potential participant that entry into the project is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will use the data in the final analyses where appropriate.

Eligibility criteria

Consent from parents will be sought for the children involved in study 1 and the opportunity to opt-out will be given for study 4. Any of the control children in study 1 and any of the children in study 4 could potentially have a hearing loss to be identified. The case children in study 1 will be known to have a hearing loss and their involvement in the study will provide no further information to contribute to their individual clinical management. The tests are easy to perform and relatively quick and will result in no side effects.

Inclusion criteria
S1: "Case" children as those aged 4-6 years at time of testing, identified from collaborating audiology services in England as having a sensorineural or permanent conductive hearing loss, averaged across 0.5, 1, 2, and 4kHz, either bilaterally (average of 20 - 60dBHL) or unilaterally (any level ≥20 dBHL).
"Control" children will be aged between 4 and 6 years, with no known hearing loss, identified through local Nottinghamshire primary schools.

S2: Data will be included if they relate to children (between the ages of 3 years and 6 years 364 days, though data on all ages are collected by the service) referred to the Cambridge service between October 1st 2007 and 31st August 2014, who were referred by any source other than the newborn hearing screen. Children for whom one or more data items are missing will not be excluded at the data collection stage, but such missing data will be accounted for in analyses.

S3: Data related to all children aged 3 to 6 years and 364 days attending the paediatric audiology service in Nottingham, having been referred from 1st September 2012 through to 31st August 2014.

S4: Children will be included in the screening process in the term in which they reach the age of 5 years following protocols and guidelines for parental consent normally administered by the service.

Exclusion criteria

S1:

- Families identified by the audiology services will not be invited to take part if the responsible audiologist feels it would be inappropriate or cause added unnecessary burden e.g. seriously or terminally ill family member.
- Children of families who do not agree to take part.
- Case children who have no record of a PTA in the last 12 months and who are unwilling to travel to their local service or to Nottingham.
- Children who are unwell such that their illness would affect the results of the tests (unable to carry out the test)

S2: Children referred as a result of the newborn hearing screen

S3: Children already identified with a permanent loss or under active management with the audiology service and for whom records of audiological assessments exist.

S4: children for whom we receive an opt out reply slip.

Expected duration of participant participation

Study participants will be participating in the study for a single occasion of assessment.

Removal of participants from therapy or assessments

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

S1: Consent from the parent or legal guardian will be sought for all participants. The Informed Consent Form will be signed and dated by the parent or legal guardian before the child enters the study. For case children, the local audiologist will post a summary information sheet to the parent or legal guardian, ensuring that the parent or legal guardian has sufficient time to consider whether the child should participate or not. For control children, the summary information sheet will be posted home from school with the invitation letters. The researchers will answer any questions that the parent or legal guardian has concerning study participation. Once a parent returns the reply slip expressing interest in their child taking part, we will send a full detailed information sheet for them to have another opportunity to decide whether to take part.

We shall also provide an age appropriate Participant Information Sheet for each child. This will take the form of a pictorial description of what will happen in the study that can be shared with the child and explained by the parent or legal guardian

Informed consent will be collected by the researcher from the parent or legal guardian of each child before they undergo any interventions related to the study. One copy of this will be kept by the parent or legal guardian, one will be kept by the researcher, and, for case children, a third will be retained in the child's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

S3: consent to participate in the study will be implied by return of a completed questionnaire. For those returning the questionnaire, consent will also be sought to explore responses by telephone interview.

S4: Consent will not be sought from the parent of legal guardian for all children undergoing screening for hearing loss at school as we shall follow the routine practice of the school nurse teams which involves giving parents a chance to opt out of screening instead. We are not collecting identifiable information on the participants during this study.

STUDY TREATMENT AND REGIMEN

Participants will not receive any treatment. The intervention being assessed is the methodology to screen for hearing loss in children at the age at which they start school. As such there is no schedule of treatments

Each child who participates in studies 1 or 4 will be seen on one occasion with no individual, personal follow up. As such it is not appropriate to include a schematic diagram of trial design, procedures and stages, specifying the points of randomisation, baseline & intermediate visits, interim analyses, final visit + any follow-up contact/monitoring.

Issues of concomitant treatments are not applicable to this project.

To address the objectives this project consists of five studies, S1 to S5.

S1: A case-control study to look at which of 2 different implementations of the screen is more accurate in correctly identifying children with and without a hearing loss i.e. to assess the diagnostic accuracy. Both alternatives are implementations of using a pure tone listening task to screen for permanent childhood hearing loss. We will compare a traditional pure tone sweep across 4 frequencies (.5, 1, 2 and 4 kHz) at a level of 20 dBHL, with the HearCheck (Siemens) pure tone screener at 2 fixed frequencies: 1 kHz, with levels 55, 35 and 20 dBHL, & 3 kHz with levels 75, 55 and 35 dBHL).

80 case children (4-6 years) with a sensorineural or permanent conductive hearing loss either bilaterally (average 20 to 60dBHL) or unilaterally (any level >=20dBHL) identified from collaborating audiology services, and 160 control children with no identified hearing loss recruited through Nottinghamshire schools will undergo hearing screens with both implementations and the results compared with gold-standard pure-tone audiometry.

The “case” children will be identified by local services and we will ask a senior paediatric audiologist to contact families on behalf of the research team and to send them an invitation to take part in the study. Families who agree to take part will be invited to undergo the two screening tests either in their own homes or in the research facilities at NHBRU in Nottingham City Centre depending on their preference. In either location the screening tests will be performed to an identical protocol, by researchers trained in the procedures, in rooms that are quiet but not soundproofed. A reminder letter may be sent to some of the families who have not responded.

The children in the control group will be recruited from the reception and year 1 children (aged 4-6) through schools in Nottinghamshire by a letter of invitation either sent to parents at the time of routine school screening, or to all parents of a class of children at another time to be agreed with the school. Families who agree to take part will be invited to undergo the two screening tests in the research facilities at NHBRU in Nottingham City. The screening tests will be performed by researchers in the research team in rooms that are quiet but not sound-proofed. The children in the control group will need to attend a facility where PTA can be measured and hence the option to have the screening test at home is not possible. Thus, all control children will undergo full pure tone audiometry under headphones in sound proofed booths either in the Nottingham audiology service or in NHBRU. As for cases, the representativeness of the control group is important to obtaining as unbiased assessment of specificity as possible. The results obtained by testing the children stated will be generalisable to the population of children with “normal" hearing defined at an average of ≤20 dBHL and the group will contain a typical spectrum of educational levels and socio-economic deprivation in order to ensure that controls are not limited to children in whom the tests are likely to be easiest to conduct

Based on diagnostic accuracy data from a previous UK study of SES, this sample size is large enough to estimate a sensitivity of 75% with a margin of error of +/- 10%, and a specificity of 90% with precision of 5%.

What will happen for case children?
Case children will be tested on one occasion with the two versions of the screening test. The order of the tests will be randomised between children and each test will be undertaken by one of two researchers working together. These tests will be carried out in the child’s home, or the research facility on Nottingham (NHBRU) subject to parent preference. If the child has not had a pure tone

audiogram recorded in the past 12 months or scheduled in the following three months we will ask the parent and child to attend the research facility to record this gold-standard measure against which we will assess the two screening tests. If an audiogram has been recorded in the past 12 months or is scheduled in the following three months we will ask the local audiologist to provide those data to us, via a secure route.

What will happen for control children?
Control children will receive the same two screening tests but will require a recording of a pure tone audiogram (done after the screening tests). All tests for control children will be undertaken at the research facility in Nottingham (NHBRU). If the child does not pass the PTA (on one occasion) they will be referred to the audiology service: failure means a threshold of 30 dBHL in either ear (air conduction) at any frequency. Failure of the screening tests alone will not result in referral. The CRF contains a referral form.

The pure-tone sweep screening method.
The pure tone sweep methodology for screening is implemented in many different configurations throughout the country. The most commonly used frequencies are the four we will use (1, 2, 4 and 0.5 kHz) which assess hearing at speech frequencies and include 4 kHz as an assessment of high frequency hearing. Each child listens to tones through headphones and indicates (e.g. by pressing a response button) when they hear a tone. The tones are altered in frequency and delivered at specific levels to determine the lowest level at which the child can hear. Each ear is tested separately. We will use a “pass” level of 20 dBHL to enable direct comparison with the HearCheck screen for each child, but a 30 dBHL level for referral. For each frequency and each ear a pass will be hearing at least 2 out of 3 of the repeated tones (no need to present a third time if the tone is heard twice).
The HearCheck screening method
For the HearCheck the child is presented with 6 tones in total; 3 at 1 kHz at 55, 35 and 20 dBHL and 3 at 3 kHz at 75, 55 and 35 dBHL. Tones are delivered via a hand held machine held next to the child’s ear using a disposable cardboard ear cover. The machine automatically generates tones at 2 frequencies and 3 levels. The child indicates when they have heard the tone. Each ear is tested separately. We are aiming to identify hearing loss of greater than 20dBHL, either bilaterally or unilaterally and hence a “fail” criteria for the HearCheck will be anything less than 6 tones heard for each ear.

Detailed procedures for each of the screening tests will be contained in working documents. This will improve standardisation and off-set to some extent the possibility of bias arising from not being able to blind the clinical staff administering the tests from whether the child has hearing loss or not.

Gold standard pure tone audiometry
We will assess the diagnostic accuracy of the two methods of screening assessed against the gold standard of pure-tone audiometry (PTA) under headphones in a sound proofed or sound attenuated room, without hearing aids for hearing impaired children. Tones are presented to the child at discrete frequencies (250 Hz, 500Hz, 1 kHz, 2 kHz, 4 kHz, 8 kHz) and levels variable by 5dBHL. The child indicates when they have heard the sound (e.g. by moving a coloured ball onto the stand). . This method will be carried out according to the BSA recommended procedures (see http://www.thebsa.org.uk/docs/Guidelines/BSA_RP_PTA_FINAL_24Sept11.pdf), without otoscopic exam or masking, air conduction only.
It will not be possible in all cases for the researchers assessing the children with the screening tests to be blind to the child’s hearing status. Any child living out of Nottingham or wearing a hearing aid or exhibiting any hearing difficulty will likely be in the case group. In fact, to ensure the screening tests are assessed appropriately it is important to be aware that the child has hearing difficulties so that the researchers can be sure all instructions concerning the test are heard and understood. The results of the tests will be recorded anonymously and entered into analytical software with no indication of the child’s hearing status or location and hence an element of blinding will be associated with the analyses.

Not all invited families will agree to participate. For the control children this is unlikely to be a problem and we will be able to continue to invite families from local schools until the required number have been tested. For the cases we anticipate that approximately 120 children will meet the criteria in the services who have agreed to collaborate (Nottingham, Mansfield, Chesterfield, Sheffield, Leicester, Derby and Lincoln). We shall require 70% of them to agree to take part to achieve a recruitment of 80 children. If this is not achieved we shall post a reminder on the NDCS

websites, and also ask the audiologists to send one reminder letter to the parents. Then we will extend the invitation to collaborating centres outside the East Midlands.,. Children will only need to attend on one occasion so there should be no loss to follow-up.

S2: Retrospective and prospective cohort study of children referred, from Oct 2007, for hearing assessment to the 2nd and 3rd tier audiology service in Cambridgeshire which has had no formal hearing screen at school entry since 1997. We will measure the number of children referred, their age, referral source, type and level of loss and resource use.

We will assess the service for the area of Cambridge City, and South and East Cambridgeshire which has offered no formal hearing screen at school entry since 1997. In collaboration with the 2nd and 3rd tier audiology service we will analyse retrospective data for children referred to the service from whatever source excluding newborn hearing screening, providing they are geographically within the target areas for the period from 1st October 2007 (when records are available) to 31st August 2012 and prospective data for children referred, from 1st September 2012 to 31st August 2014. The data to be collected will include the child's date of birth, date of referral, the source of the referral, the number and type of assessments and interventions, and the level and probable cause of any hearing loss, postcode, staff grade and time and equipment and interventions associated with the subsequent management and service delivery to children correctly identified as having a hearing loss (true positives) and those incorrectly identified as having a hearing loss (false positives). This healthcare utilisation will be collected on all referrals. Data on children aged 3 to 6 years and 364 days will be included in the analysis. Rates will be calculated from routine data for the population and ages at risk. Data will be collected in Cambridge by Miss Moody, a member of the research team with clinical responsibility for this population of children.

We will compare these data with the Nottingham and Nottinghamshire area which has an existing SES service (see Study 3 for details)

There are no planned interventions in this study; it is an analysis of cohort data.

S3: Prospective analysis of the costs of management, including impact on families, following referral from the screen for children referred to Nottingham Audiology Service from the SES for two years (N ~200). Measures of the resource costs of referral through to definitive identification of hearing loss or discharge, including questionnaire measures of impact for families of true and false positive cases will contribute to the economic modelling. All children will have either been definitively identified as having a hearing loss or will have been discharged with no follow-up by 30th November 2014. We will address the issue of false negatives through a review of the literature on the impact of delayed identification.

Data collection:
To assess the resource implications for the tertiary audiology service of referrals from the School Entry Hearing Screen we shall collect data prospectively for 24 months of referrals aged 3 to 6 years 364 days for the paediatric audiology service based in Nottingham. This service provides for children referred from schools in Nottingham and Nottinghamshire and has a total caseload of approximately 100 referrals from the SES annually. We will collect staff grade and time and equipment and interventions associated with the subsequent management and service delivery to children correctly identified as having a hearing loss (true positives) and those incorrectly identified as having a hearing loss (false positives). This healthcare utilisation will be collected on all referrals. In order to translate resource use into monetary values, unit costs will be applied according to staff type and grade based on local or national costs and prices. These staff costs include indirect overheads (the costs of support services such as human resources, finance, and estates needed to carry out the service's main functions). Equipment and consumables will be costed using manufacturers" list prices and amortised over a 5-year lifetime. This element of the project is service evaluation and as such does not require REC approval and we will not be producing participant information sheets for approval by REC.

The data collected will also include the child's date of birth, date of referral, the source of the referral, the number and type of assessments and interventions, and the level and probable cause of their hearing loss, plus postcode; the same data will be collected as in Cambridge (S2) plus the date of the school screen.

Questionnaire:
To explore the resource implications and impact on families of referral from the School Entry Hearing Screen we shall undertake a questionnaire study of all families of children who are referred for further assessment following the SES. Some of these children will be true positives, i.e. they will have a confirmed permanent hearing loss, and many more will be false positive, i.e. identified by the screen but found to have no permanent hearing loss. The questionnaire will be distributed to relevant families by Ms Benton, a member of the research team with clinical responsibility for this population of children. It will seek details on the amount of time, travel, cost, inconvenience, and anxiety experienced by families in undergoing the screen follow up process. Families will be sent the questionnaire by post by the audiology service. Questionnaires will be coded and the codes related to personal details held only by the responsible clinician. This will ensure only those not responding are sent reminders. Non-responders will be sent one reminder. As part of the questionnaire, parents can consent to further questions about the referral process in a telephone interview; they will need to provide contact details to the researchers for this (on a separate sheet).

Delayed identification in children who pass the screen but who do have a hearing loss (false negatives) is a further consequence of concern, but is not one we believe can be dealt with as part of the data we propose to collect. We will address this via a review of the literature, looking specifically for robust reports of data exploring the impact on the family and on the child's development and education, of an unidentified or late identified hearing loss.

Interventions for the children referred from the SES will be the routine clinical interventions applied to investigate the child's possible hearing loss, including audiometry, tympanometry etc. as appropriate and decided by the audiologist concerned with the child's care. There will be no contact with the research team. Families recruited to take part in the questionnaire part of the study will be asked to complete paper questionnaires.

S4: Determination of resource use in proposed physical setting, and practicalities of implementation, of two forms of screening test in schools within Nottinghamshire.

Study 4 will allow us to collect data on the practical application of the two screening methods. In collaboration with the Health Visiting and School service for NHS-County Health Partnership we propose to implement both screens in a number of schools throughout the county representing a range of catchment populations. We shall involve a number of personnel over all three terms of the school year (September 2013 to July 2014) to ensure a range of measurements consistent with differing staff methods of implementation, differing child characteristics at different times (maturity and seasonal infections i.e. colds) and different screening conditions in schools. We shall measure the time taken to implement the screens in school situations following current guidelines, the pass/fail results of the tests and gather opinions on use of the tests from the school nurses. We shall collect routinely available data on the costs for the service as a whole, including staff, buildings, equipment, administration and travel. These costs should not vary with the screen being implemented in the schools.

Routinely, children are identified by schools as eligible to undergo the hearing screen. Their parents are informed of this routine service and notified by letter, with the right to opt out. We propose to send an additional letter at the same time informing parents of the research study, again providing them with a chance to return an opt out reply, for their child to undergo a second screen with the HearCheck device at the same time as the routine screen. Those children for whom their parent has consented will undergo both tests. The order of the tests will be randomised where the school nurse feels it will be appropriate to do so. The school nurses will perform the tests and the researchers will be present as observers to collect data on the time taken to carry out the hearing screens, pass/fail results of the two tests and any feedback provided by the school nurses.

S5: Cost data will be collected for resource use in screening and follow-up assessment, or assessment following referral, including staff time, travel, equipment and facilities for all studies. These data will contribute to the development of a model of cost-effectiveness together with data derived from the literature and existing NHS data sources. All data will be collated, checked, cleaned and analysed by Peninsula Clinical Trials Unit.

Details of procedures for all the studies are contained in working documents for each study.

Compliance

No long-term follow-up. Compliance applies to one visit only

Criteria for terminating trial

As a diagnostic accuracy study through which all participant children will undergo hearing screening with both methods and a pure-tone audiogram, there should be no reason for stopping the trial as a whole.

If during an assessment session a particular child becomes upset or uncomfortable he/she will be withdrawn from the study and arrangements made, if necessary, to formally test his or her hearing at a later date.

STATISTICS

Methods

Statistical analyses of projects S1-S4 and the decision analytic modelling in project S5 will be led by a team of three methodologists experienced in quantitative analysis and decision analytic modelling (RT, OU and CH) based at the Peninsula Medical School at the University of Exeter. A variety of software packages appropriate to the data being analysed will be used including Stata. Analytic methods and sample size rationale for each study is detailed below, and further details will be given in separate analysis plans for each of these studies.

Given the nature of research questions being addressed in this programme of work, interim data analyses are not required for safety or efficacy.

S1: Sensitivity will be estimated for each test as the proportion of the case children that test positive and specificity will be estimated as the proportion of the control children that test negative. The precision of these estimates will be quantified using 95% confidence intervals. Because this is a "paired design" in which two diagnostic tests are evaluated on the same sample, McNemar's test will be used to compare each of sensitivity and specificity between the two tests, reporting p-values. Confidence intervals for the difference in sensitivity/specificity (percentages) between the tests will be constructed.

S2: Quantitative characteristics of the Cambridge cohort will be summarised using means and standard deviations (or medians and inter-quartile ranges) and categorical characteristics will be summarised using percentages. The precision of the estimated mean yield and referral age will be summarised using 95% confidence intervals.

S3: The yield (number of referrals with a hearing loss divided by number of children) and mean referral age in the non-screened sample (S2) will be compared to the yield and mean referral age from populations that routinely screen at school entry (4-5 years) (S3) using box and whisker plots and survival curves, quantifying the extent to which yield may differ and diagnosis of hearing loss may occur sooner or later in non-screened populations. Analyses may be adjusted for potential differences in population characteristics of the two cohorts including sex, and deprivation (based on postcode).
In order to make inferences from the questionnaire, costs and impact outcomes will be summarised as means. Given the likely skewed nature of these outcomes, we will use the non-parametric bias corrected accelerated bootstrapping method (2000 replications) to validate the confidence intervals for the means. We will seek to estimate mean costs for referrals according to their outcome i.e., true positives, false positives and false negatives.

The main outcomes are the yield, the age of referral and referral source. The study will provide key data to estimate important parameters for the economic modelling in Study 5 (by describing the cost experience for true positives and false positives).

S4: The mean costs of the two tests will be compared using the paired t-test. Again, the bootstrap method will be used to validate the confidence interval of the mean difference.

S5: Results from the modelling of cost-effectiveness will be presented in a disaggregated format (outcomes, resource use, costs), and also in the form of a cost-effectiveness ratio. Results will include estimation of incremental cost per case detected, Where appropriate, results will include presentation of cost-effectiveness consistent with the reference case used by NICE. Where probabilistic modelling is undertaken, probabilistic sensitivity analysis will be presented. Results will include presentation of cost-effectiveness planes, and cost-effectiveness acceptability curves. Univariate and probabilistic multivariate sensitivity analyses will be conducted, to explore structural and parameter estimates of greatest concern, such as test accuracy. This will include consideration of bias associated with use of a case-control methodology in study 1. This would use estimates of relative diagnostic odds ratio obtained from empirical investigations of the effects of study design features on test accuracy to deflate the observed accuracy to that which might have been expected if a less biased estimate from a traditional test accuracy study was available.

Sample size and justification

S1: Eighty (80) case children will be selected from collaborating centres in order to estimate the sensitivity of the screening tests. This sample is large enough to estimate a sensitivity of 75% with a margin of error of +/- 10% (based on a 95% confidence interval) and 160 controls is a large enough sample to estimate a specificity of 90% with a margin of error of +/- 5% The margin of error for the estimated sensitivity and specificity will provide plausible ranges of values within which to test the sensitivity of the results from the economic model (Study 5) to our assumptions about screening accuracy.

S2: Data collection over a period of 7 years for 600-700 (ie 4200-4900 in total) children referred per year to 2nd tier services for investigation of possible hearing loss and 20-30 children per year (140-210) referred from 2nd tier to 3rd tier audiology services in Cambridgeshire for further investigation of possible sensorineural or permanent conductive hearing loss. Of those 20-30, 5-10 may be confirmed to have a SNHL.

Assuming the standard deviation of the age of referral is approximately 0.5 years (6 months), the 40 subjects we might recruit is a large enough number to estimate the mean age of referral with a margin of error of +/- 0.16 years (1.9 months) based on 95% confidence intervals.

S3: We expect 200 children to be referred from the SES to Nottingham Audiology Services in a period of 24 months. For the questionnaire survey we will look to invite all referred families to complete a questionnaire to provide a spread of experience and opinion. This study has not been formally powered on statistical inference. We are confident, however, that a sufficient number of those referred will answer the questionnaire to allow us to address the S3 research questions.

S4: We intend to recruit at least 4 schools to take part in the study through contact with the Head teacher through the Health Visiting and School Nursing Service of NHS-County Health Partnership. Each school will be visited on one or more days, according to routine practice by one screener and the researcher. All children in the appropriate classes who have parental consent to take part will be screened using both technologies. We anticipate this will provide a convenience sample of about 180 children. This study has not been formally powered on statistical inference. We are confident, however, that N=180 will allow us to address S4 research questions.

Assessment of efficacy
Not applicable.

Assessment of safety
Not applicable

Procedures for missing, unused and spurious data
Rigorous data collection and checking procedures will be put in place to minimise the amount of missing data and to minimise the collection and processing of erroneous data. For each project, the amount of missing data will be assessed and appropriate imputation methods, where appropriate, will be employed.

Definition of populations analysed
Various populations involved in this project are defined above.

ADVERSE EVENTS

The intervention to be assessed as part of the project protocol is a hand held device which emits tones to a maximum of 75 dBHL. All other assessments are part of routine service and will not be adapted in any way. None of the assessments will increase the hearing loss in any child who is hearing impaired nor will they trigger a hearing loss in a hearing child, when carried out according to protocol. Equipment will be checked each day before use. We do not foresee any adverse events, as defined, occurring in this project. If any serious or related adverse events do occur we will follow the University of Nottingham Standard Operating Procedures on reporting of adverse events; serious events will be reported to the Chief Investigator within 24 hours and, if related to the procedure, to the ethics committee, steering committee and sponsor within 7 days.

ETHICAL AND REGULATORY ASPECTS

When testing children in their own homes in study 1 the University of Nottingham Lone working policy will be adhered to. Two researchers will be involved in all visits.

ETHICS COMMITTEE AND REGULATORY APPROVALS

The project will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The project will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

S1: The process for obtaining participant informed assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the parent or legal guardian of the participant shall both sign and date the Informed Consent Form before the person can participate in the study – this is usually at the study visit, having previously received full information about the study.

The parent or legal guardian of the participant will receive a copy of the signed and dated forms and the original will be retained in the Project Master File. A second copy will be filed in the participant's audiological notes and a signed and dated note made in the notes that informed consent was obtained for the project (case children only).

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding the child's participation in the project may be withdrawn at any time without penalty or affecting the quality or quantity of the child's future medical care, or loss of benefits to which the child and his/her family is otherwise entitled. No project-specific interventions will be done before informed consent has been obtained.

The investigator will inform the parent or legal guardian of the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

S4: Parents will be provided with the opportunity to opt out of the research screen, which follows current practice for school hearing tests in the schools we shall be observing.

RECORDS

Case Report Forms

A case report form (CRF) will be generated for each child participating in the project or for whom data are collected from records. CRFs will be developed by the project researchers in liaison with the staff of PenCTU collaborating on the project.

Each form will be completed by the researchers involved in the study or by members of the research team. Each participant will be assigned a project identity code number for use on CRFs, other project documents and the electronic database. The documents and the database will also contain the date of birth (dd/mm/yyyy) and postcode.

For study 1, generated data from the results of the screening tests and pure-tone audiometry will be collected by the researchers and entered onto CRFs using the identity codes described above. A separate password protected electronic database will be used to maintain links between personal information and these codes for the resolution of queries.

For studies 2 and 3, data will be collected from audiology records in Cambridge and Nottingham by members of the research team with clinical responsibility for the participants (JM and CB). Identity codes will be used as described above. Personal data linked to these codes will be held by the responsible clinician in a password protected database for the purposes of query resolution. Data will be anonymised before transfer for analyses to other members of the research team. If clinician time is short, the Nottingham-based researchers may help the clinicians to collect data which will mean the data are not anonymous at the point of collection. Data will also be collected using questionnaires; these data will be anonymous, except where parents opt for further questions by telephone, in which case they will be asked to provide contact details on a separate sheet.

For study 4, the data to be collected are practical or nurse opinion, i.e. times, costs and preferences, and will not identify individual participants.

Paper copies of CRFs will be stored in locked filing cabinets in offices that are locked when unoccupied in the NIHR Nottingham Hearing Biomedical Research Unit. All electronic databases will be password protected, accessible only by members of the research team. Data transferred to collaborators in Plymouth and Exeter will identify participants only by study number and will be encrypted before transfer.

CRFs will be treated as confidential documents and held securely in accordance with regulations. Members of the research team with clinical responsibility and the investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Project identity code number (the Project Recruitment Log), to permit identification of all participants enrolled in the project, in accordance with regulatory requirements and for follow-up as required.
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Project Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned an identity code number for use on the consent forms and other study documents and the electronic database. The documents and database will also use date of birth (dd/mm/yyyy) and postcode.

Source documents

Consent forms, data extracted from current medical records, screening and hearing results and completed questionnaires are considered as source documents and shall be filed at the investigator's site. Each CRF will also completely serve as its own source data. Only project staff as listed on the

Delegation Log shall have access to project documentation other than the regulatory requirements listed below.

Direct access to source data / documents
The CRF and all source documents, including progress notes and copies of medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All project staff and investigators will endeavour to protect the rights of the project's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the project. CRFs will be held securely, in a locked room, and in a locked cupboard or cabinet. Access to the information will be limited to the project staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the project in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for project participants and project staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

PROJECT CONDUCT

Project conduct will be subject to systems audit of the Project Master File for inclusion of essential documents; permissions to conduct the project; Project Delegation Log; CVs of project staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Project Coordinator, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Project Steering Committee.

PROJECT DATA

Monitoring of project data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Project Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of project data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In

addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Project data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

See separate documents SES Monitoring and Audit Summary, and Summary and Procedures documents for each study.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Project Master File and project documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all project databases and associated meta-data encryption codes.

DISCONTINUATION OF THE PROJECT BY THE SPONSOR

The Sponsor reserves the right to discontinue this project at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Project Steering Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this project will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The findings of the project will be disseminated via a report to the funder expected to be published as an HTA monograph in 2015-6. Additional publications will be submitted to peer reviewed journals during 2014-15. Oral and poster presentations will be submitted from 2013 through 2015 to national and international conferences with audiences of audiologists, paediatricians, otorhinolaryngologists, speech and language therapists and teachers. Participants will not be identified in any publications. Parents of children involved in Study 1 will be offered the opportunity to receive a short summary of the findings at the end of the study.

USER AND PUBLIC INVOLVEMENT

We have parents of a hearing impaired child in Nottingham as part of the research team (funded). The individuals will be fully involved, attending all research team meetings and will make specific contributions to the design of approaches and literature to families, design and content of questionnaires, and to contribute the patient perspective to all dissemination. We have a project steering group comprising external experts to advise on and oversee the programme of research. This group includes further lay representation in the form of representation from the National Deaf Children's Society.

STUDY FINANCES

Funding source
This study is funded by the National Institute of Health Research Health Technology Assessment programme (NIHR HTA) reference 10/63/03.

Participant stipends and payments
Schools who agree to participate in study 1 will be entered into a prize draw to win £100. Participants in study 1 will be offered payment for their travel expenses to the research, as per standard NHBRU rates and procedures. In addition the funder has agreed to fund an allowance of £10* each for the 240 children taking part in Study 1 as compensation for their time and inconvenience. We propose to pay this in the form of a book token. *As of 1st Oct 2013 in line with a protocol amendment, the book token amount for the remaining children will be increased to £20.
Parents who complete and return a questionnaire to us for study 3 will be entered into a prize draw to win a £50 voucher of their choice.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)__Heather Fortnum__

Signature:____ 

Date: 21 Dec 2012_

Co- investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)

Signature:_____

Date: _____

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