Clinical Investigation Plan

Trial Title:	Can the diagnostic accuracy of newborn eye screening for congenital cataract be improved with digital imaging? The Digital Imaging versus Ophthalmoscopy (DIvO) study.
Clinicaltrials.gov:	NCT05282147

Clinical Investigation Plan Version: 6.0

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1 Protocol Signatures:

I give my approval for the attached protocol entitled The Digital Imaging versus Ophthalmoscopy (DIvO) study version 6.0 dated 20 Feb 2025 .

Chief Investigator

Name: Dr Louise Allen

Signature:

Date:

Site Signatures

I have read the attached protocol entitled The Digital Imaging versus Ophthalmoscopy (DIvO) study version 6.0 dated 20 Feb 2025
2023 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC and any subsequent amendments of the clinical trial regulations, the Sponsor's 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

Principal Investigator

Name:

Signature: _____

Date: _____

2 Trial Management Group and Protocol Contributors

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3 Abbreviations

Term	Description
AE/AR	Adverse event/Adverse Reaction
ADE	Adverse Device Event
ANNB	Ante-natal and Newborn Screening Committee
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
IDMEC	Independent Data Monitoring Ethics Committee
DSUR	Development Safety Update Report
DTO	DIvO Trial Office
e-consent	Electronic consent
GCP	Good Clinical Practice
GDPR	General Data Protection regulation
GP	General Practitioner
HES	Hospital Episode Statistics
HIPAA	Health Insurance Portability and Accountability Act
HRA	Health Research Authority
ICD-10	International Classification of Diseases
ICF	Informed Consent Form
DI	Digital Imaging (intervention device)
IMP	Investigational Medicinal Product
IR	Infrared
LCD	Liquid Crystal Display
LED	Light Emitting Diode
LSHTM	London School of Hygiene and Tropical Medicine
MHRA	Medicines and Healthcare products Regulatory Agency
Neocam	Intervention imaging device
NHS	National Health Service
NIHR	National Institute for Health Research
NIPE	Newborn and Infant Physical Examination
NRES	National Research Ethics Service
O	Ophthalmoscopy (existing test)
OPCS	NHS Classification of Interventions and Procedures
PHE	Public Health England
PI	Principal Investigator
PIS	Participant Information Sheet
PIV	Participant Information video
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
REDPill	Research Electronic Data capture software
S4N	Smart4NIPE newborn examination database
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SADE	Serious Adverse Device Event
SIV	Site Initiation Visit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
Unexpected Related Event	An event which resulted from the administration of any of the research procedures.

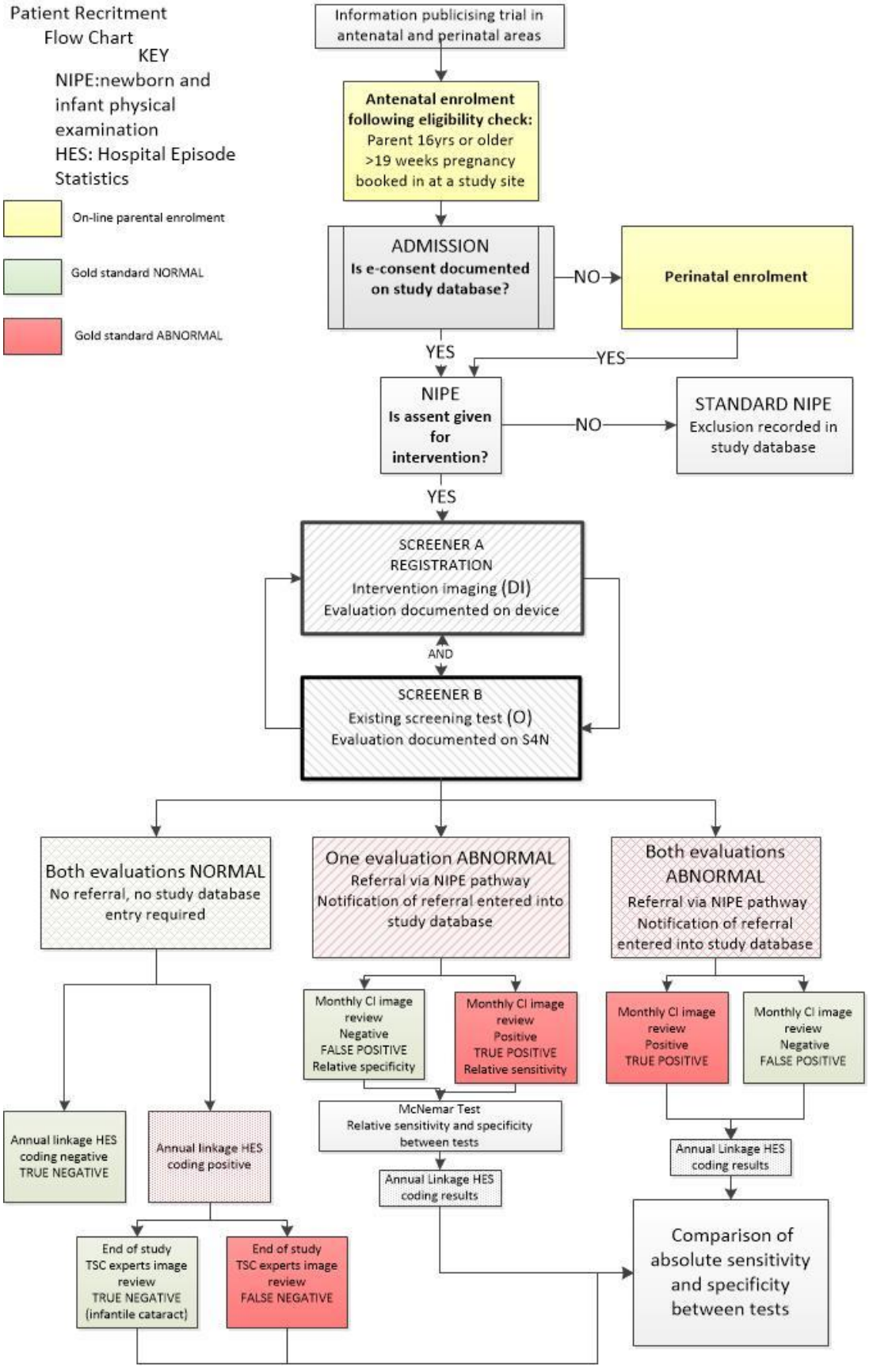
4 Trial Synopsis

Title of clinical trial	Can the diagnostic accuracy of newborn eye screening for congenital cataract be improved with digital imaging? The Digital Imaging versus Ophthalmoscopy (DIvO) study.
Sponsor name	Cambridge University Hospitals NHS Foundation Trust
ClinicalTrials.gov	NCT 05282147
Medical condition	Congenital cataract
Purpose of clinical trial	Confirm or refute the hypothesis that the sensitivity and specificity of screening with digital imaging (DI) using the Neocam device is superior to the standard ophthalmoscopic red-reflex (O) test.
Primary objective	Determination of relative and absolute sensitivity and specificity of the standard test and Neocam imaging: comparison of accuracy with each test overall
Secondary objectives	Determination of the effect of subject's ethnicity or screener experience on screening accuracy with each test. Assessment of usability and preference.
Active comparator products	Standard: Screener evaluation of the red-reflex using the standard ophthalmoscope used in the unit. Intervention: Screener evaluation of Neocam digital imaging.
Trial Design	Multi-centre, prospective population-based superiority trial
Trial Outcome Measures	Primary outcome measures: • Screener evaluation "normal" or "abnormality suspected" of each eye using the standard test (ophthalmoscopic red-reflex). • Screener's evaluation "normal" or "abnormality suspected" of each eye using the Neocam digital imaging test. • Cataract diagnosis gold standard: • The presence or absence of diagnostic ICD10 or procedure codes for cataract in HES records a minimum of one year after the screening test o For eyes with "normal" screener evaluations but subsequent HES data with coding for cataract, expert evaluation of the digital images by two members of the TSC will determine the presence of the cataract at the time of the screening test Secondary outcome measure: •Differential diagnosis gold standard: o The presence or absence of diagnostic ICD10 or procedure codes for eye disorder(s) which may cause an abnormal red / IR-reflex, which could be mistaken for cataract and require referral for diagnostic

	assessment by an ophthalmologist, in HES records a minimum of one year after the screening test ○ For eyes with "normal" screener evaluations but subsequent HES data with coding for eye disorder(s) which may cause an abnormal red / IR reflex, expert evaluation of the digital images by two members of the TSC will determine the presence of the abnormality at the time of the screening test • Usability feedback and test preference using screener questionnaire.
Sample Size	Approximately 140,000 newborn babies (number dependent on recruiting 67 babies with congenital cataract)
Summary of eligibility criteria	Eligibility criteria for maternal enrolment: • prospective mothers aged 16yrs or over • 19 weeks or more into a normal pregnancy or within 72 hours of eligibility for the newborn screening assessment (NIPE) • maternity care booked with a participating site Eligibility criteria for baby registration: All babies undergoing newborn NIPE screening Exclusion criteria for registration: • failure of previously consented parents to assent to the intervention at the time of screening • device unavailable at the time of screening • no assigned NHS number
Route of administration	Illumination of each eye from a distance of 30 cm using hand-held ophthalmoscope or Neocam device
Study duration	56 months
Maximum duration of treatment of a participant	Active phase (Intervention): Neocam imaging taking approximately 2 minutes in addition to and within 72 hours of the the standard red-reflex test. Passive phase: the interval between the intervention and data linkage, ranging between 12 and 36 months.
Study action: Approach	Clinical staff, leaflets & posters in antenatal clinics and wards will direct mothers to the public study website. Social media advertising campaigns.
Study Action: Informed consent	The informed e-consent process is undertaken on the research website.
Study action: Intervention	One encounter for Neocam digital imaging within 72 hours of eligibility for NIPE assessment.
Study action: Data linkage	Bespoke data linkage requests will be sent to NHSEI and NHS Digital to retrieve red-reflex evaluation data and HES outcome data on the registered babies following the intervention.
Study action: End of trial	Six months after the last data linkage capture.

Procedures for safety monitoring during trial	Any safety notifications will be reported within 24 hours to the CI and forwarded to the study Sponsor.
Criteria for withdrawal of participants after registration	• Device malfunction during imaging or loss of data from the Neocam device. • Parents withdraw consent after the intervention up to the time of data linkage.

5 Trial Flow Charts



6 Introduction

6.1 Background

Congenital cataract is the main treatable cause of global childhood blindness. 'Red-reflex' assessment with an ophthalmoscope during the UK Newborn and Infant Physical Examination (NIPE) screening programme enables early detection and timely surgery, preventing permanent visual impairment. Other eye disorders may also result in an abnormal red-reflex that, on screening, is not distinguishable from cataract and require diagnostic assessment by an ophthalmologist, but the NIPE eye assessment is designed primarily to detect congenital cataract to enable timely treatment.

Evidence for red-reflex screening accuracy is lacking but surveys suggest a high false negative and positive rate, particularly in minority ethnic babies. Recently, a digital imaging (DI) device, Neocam has been developed; this is a hand-held digital camera incorporating co-axial LED (Light Emitting Diode) illumination. Directed at the eye from arm's length, it images and records the infrared (IR) reflex. Superiority of IR imaging to ophthalmoscopic red-reflex assessment (O) has been demonstrated in cataract enriched childhood cohorts. (1, 2)

We aim to determine whether the sensitivity and specificity of newborn eye screening is better using assessment of the Neocam IR-reflex image than the existing assessment, potentially improving the accuracy of the UK NIPE screening programme.

6.2 Clinical Data

6.2.1 Congenital cataract and the current screening programme

Congenital cataract is the main treatable cause of childhood blindness worldwide. (3-5) Red-reflex screening is recommended by the National Screening Committee within 72 hours of birth and at 6-8 weeks as part of the NIPE undertaken in the c.730,000 UK babies born each year. Screening is primarily directed at early detection of congenital cataract which affects 1/3000 UK births and is bilateral in 60% of cases. The management of severe cataract is time critical, with surgery required within the first months of life to prevent permanent visual deprivation amblyopia. Newborn screening is undertaken by trained midwives and paediatricians using a direct ophthalmoscope. This examination has remained unchanged for 25 years, despite the routine broad application for digital imaging and documentation in Ophthalmology and an increasingly litigious society. The digital collection of NIPE outcome data, however, has become digitalised, with screeners now routinely uploading outcome data directly into an NHS database via the SMaRT4NIPE (S4N) webserver.

Red-reflex assessment by paediatric ophthalmologists has good sensitivity and specificity (99.6% and 95.1% respectively) in detecting anterior ocular pathology. (6) However non-specialist screeners find red-reflex assessment difficult because of their unfamiliarity both with rare eye conditions and the technique of ophthalmoscopy. Additionally, the baby's pupillary constriction, dark ocular pigmentation and aversion reflexes to bright light can limit the quality of the assessment. (7–10)

Sensitivity and specificity data for population screening by non-specialists using the red-reflex are unavailable (MEDLINE and EMBASE search 2020). A national surveillance study found that only half of all children newly diagnosed with congenital cataract in 1995 were detected purely through the NIPE screening programme. (11) Preventable, life-long visual impairment arising from late treatment has grave consequences for the

baby, the family and society especially due to the need for educational support and loss of potential income. Conversely, S4N audit data record 955 (0.2% of those screened) babies born in England urgently referred from newborn eye screening in 2018-19, but a recent unpublished survey of paediatric ophthalmologists indicates that more than 75% of this referral type are 'false positives' disproportionately affecting ethnic minority infants. As paediatric ophthalmology departments suffer increasing capacity pressures due to insufficient clinic space and staff recruitment, these unnecessary urgent referrals add an excessive burden in addition to creating unwarranted anxiety for families.

Although published screening accuracy data are limited, the surveys support the opinion that there are a high number of both late referrals and of false positives with the existing screening method, and suggest that a different approach, robust to screener skill and patient ethnicity, may be warranted. A more accurate screening test could minimise the number of false negatives (delayed detection of affected babies) causing preventable visual impairment as well the reducing the number of false positive (babies who fail the screening test but do not have cataract) referrals to specialist clinics. Additionally, photographic documentation of the examination may improve parental understanding, enable virtual specialist review and perhaps also reduce litigation. By accessing digital images taken at newborn screening, specialists could better balance the potential visual benefit against the risks of surgery in older infants and children presenting with cataract.

6.2.2 Digital Imaging tests

Newborn population eye screening using specialist wide-angle retinal digital camera has been studied. (6) Unsurprisingly, such specialist imaging detected a high prevalence (29%) of abnormalities not requiring intervention, such as birth-related retinal haemorrhages. This technique is not justified for population screening due to the resources required, invasiveness of the examination (pupil dilating drops are needed), medicalisation of common and self-limiting conditions, and resultant unnecessary parental anxiety and specialist follow up.

Digital IR imaging is an established non-contact technique, ubiquitous in ophthalmic diagnostic imaging and integral to commercially available childhood photoscreeners (used for assessing refractive error or strabismus in older children). The advantage of IR over white light is the lack of both an aversion response and pupil constriction. It is also optimally reflected from the fundus regardless of ethnic pigmentation. (12) However, all current commercial devices are primarily designed for assessing refractive error and require visual fixation from a distance of 1m, making them inappropriate for newborn eye screening.

Recently a modified smartphone (CatCam, Figure 1) was developed by the Lead Applicant. Its development was funded by Addenbrooke's Charitable Trust through public donation. Two pilot studies comparing CatCam IR-reflex imaging to red-reflex imaging have been undertaken in enriched clinic populations, both found a significant improvement in diagnostic accuracy using IR-reflex of CatCam compared to red-reflex assessment (Table 1). (1)

Figure 1: CatCam prototype,

Table 1a) Cambridge & b) Tanzanian CatCamresults

Device	Sensitivity %	Specificity%
IR-reflex	100	100
Red-reflex	71	63

Device	Sensitivity %	Specificity %
IR-reflex	97.6	100
Red-reflex	92.7	96.7

Outcome: IR-reflex superior to red-reflex $p<0.05$

6.2.3 Development of the study digital imaging (DI) device-Neocam

Following the Tanzanian pilot study led by the London School of Hygiene and Tropical Medicine (LSHTM) (Table 1b), an IR-imaging cohort was incorporated to be compared against a red-reflex screening in a large three African nation cluster study led by Mr Richard Bowman, Associate Professor for Public Health Ophthalmology at the LSHTM. Funding from a Seeing is Believing grant (International Agency for the Prevention of Blindness) included a contribution to support the development and purchase of 60 DI prototypes for the study, recently completed, comparing rural screening using red-reflex or DI. Although not yet published, the review of the 30,000 collected images has informed the modifications required in the prototype DI prior to its use in this study.

The Neocam prototypes to be used in this study (Figure 2 & 3) have now been used in over 50,000 children. Although the significance is unclear at present, interim results of the first 25,000 children recruited to the African study indicate twice the prevalence of detected cataract in the Neocam screened population compared to the red-reflex screening group. Usability feedback has been good and specialist review of 30,000 images has shown 98% of images to be interpretable. The device is robust and designed to be used in UK normal indoor ambient lighting conditions. The current prototype uses an IR and green LED. The monochrome images from IR and green light imaging enables the generation of a pseudo-colour image, giving a digital IR-reflex and red-reflex image to be evaluated by the screener.

Figure 2. Neocam: normal bright IR-reflexes

Figure 3. IR-reflex obscured by cataract, baby's left eye

The following modifications have been made to the current Neocam prototype to optimise performance for this study:

- Software modification to optimise Neocam illumination and reduce glare
- Improvements to camera sensitivity and exposure
- A virtual calliper guide to optimise the imaging distance
- Improved resolution
- Safety testing and technical documentation (verification and validation) for MHRA approval to use the device for clinical investigation

Following the study, a commercial device may be developed and registered as a Class IIa medical device to aid the international effort to reduce blindness from childhood cataract. The device may prove to be a cost-effective replacement for newborn red-reflex screening when balanced against the healthcare savings associated with improved screening sensitivity and specificity.

7 Rationale for Trial

The aim of this study is to determine whether the sensitivity and specificity of newborn eye screening is better using imaging of the IR reflex with Neocam (DI -the intervention) than with the existing standard assessment with an ophthalmoscope (O). Newborn eye screening using the device may prove to be a cost-effective replacement for newborn red-reflex screening when balanced against the healthcare savings associated with improved screening sensitivity and specificity.

8 Trial Design

8.1 Statement of Design

This is a multi-centre, prospective population-based superiority trial. All participants will have both the existing standard test (O) and the intervention test, Neocam digital imaging (DI).

8.2 Number of Centres

This trial will be conducted in at least 13 large maternity units across England. This number may be increased if necessary to recruit the required number of participants. All sites will have a minimum expected number of births of 5000 babies per year and a good track record of clinical research. Units in devolved countries are excluded due to the absence of SmART4NIPE (S4N) data.

8.3 Number of Participants

Recruitment will continue until 67 cases of congenital cataract have been identified, as determined by an abnormal evaluation on red-reflex or Neocam imaging, with the abnormality confirmed on specialist review of the Neocam images. The estimated number of participants required is approximately 140,000 babies with broad diverse ethnicity.

8.4 Participants Trial Duration

Within 72 hours of birth the usual standard of care eye test (O) and the intervention test, Neocam digital imaging (DI) will take place. This completes the active phase; no further visits or study examinations or interventions are required. The subsequent passive phase of the trial is a minimum of 12 months to a maximum of 36 months after the intervention when data linkage occurs.

8.5 Trial Objectives

8.5.1 Primary objective

To compare the sensitivity and specificity of screening evaluation with the existing test (O) to the intervention Neocam Digital Imaging (DI) test in newborn babies.

Population: infants having the Newborn (and Infant) Physical Examination NIPE
Intervention: evaluation of IR-imaging using the Neocam imaging device
Existing test: standard red-reflex screening test using an ophthalmoscope
Outcome: absolute accuracy of each test and comparison between them
Time: following completion of data linkage at least 12 months after the last recruitment

8.5.2 Secondary objectives

Comparison of accuracy between tests with respect to ethnicity, comparison of accuracy between tests with respect to screener experience and usability feedback and test preference.

8.6 Trial Outcome Measures

8.6.1 Primary outcome measure

The primary outcome measures are:

- Screener evaluation "normal" or "abnormality suspected" of each eye using the standard test (ophthalmoscopic red-reflex).

- Screener's evaluation "normal" or "abnormality suspected" of each eye using the Neocam digital imaging test.

- Cataract diagnosis gold standard:
    - The presence or absence of diagnostic ICD10 or procedure codes for cataract in HES records a minimum of one year after the screening test
    - For eyes with "normal" screener evaluations but subsequent HES data with coding for cataract, expert evaluation of the digital images by two members of the TSC will determine the presence of the cataract at the time of the screening test

8.6.2 Secondary outcome measure

The secondary outcome measures are:

- Differential diagnosis gold standard:
    - The presence or absence of diagnostic ICD10 or procedure codes for eye disorder(s) which may cause an abnormal red / IR-reflex, which could be mistaken for cataract and require referral for diagnostic assessment by an ophthalmologist, in HES records a minimum of one year after the screening test
    - For eyes with "normal" screener evaluations but subsequent HES data with coding for eye disorder(s) which may cause an abnormal red / IR reflex, expert evaluation of the digital images by two members of the TSC will determine the presence of the abnormality at the time of the screening test

    -

- Usability feedback and test preference using screener questionnaire.

9 Selection and withdrawal of participants

9.1 Inclusion Criteria for maternal enrolment

To be enrolled in the trial the mother must:

- be 16 years of age or older
- be 19 weeks or more into their pregnancy or up to 72 hours post-partum
- booked in for maternity care at a participating site

9.2 Infant Eligibility Criteria

All babies undergoing the newborn physical examination.

9.3 Treatment Assignment

All babies recruited to the study will undergo both the standard test and Neocam digital imaging. There is no randomisation of tests.

9.4 Masking and concealment

Each baby will have the standard and Neocam imaging screening tests but these must be undertaken by different members of trained healthcare staff (see 11.7.5). The standard screening test will be undertaken by the NIPE trained screener and entered on S4N, as is standard practice. The Neocam screener will not access these records and will enter their evaluation results directly into the Neocam device, for subsequent upload into the study database. The screeners must not discuss results with each other or the parent until their evaluations have been completed and inputted into the relevant database. Only once this has occurred will the NIPE screener determine if any of the babies require specialist referral through the NIPE referral pathway due to abnormal evaluation on either test. The NIPE screener will ensure that the requirement for referral is documented in the study database under the maternal record. The parents of all babies will then be notified of the result and if specialist referral is necessary.

Any inadvertent discussion of screening results prior to the recording of the screening evaluation for both techniques will be recorded in the site file as non-compliance and reported to the Sponsor. Staff will be made aware that they will not be personally identified by the assessments they make, but that their role and level of experience will be recorded on both the Neocam evaluation record and the S4N database (standard practice).

9.5 Participant Withdrawal Criteria

9.5.1 Withdrawal from the study prior to registration

- Parents who have previously enrolled and consented for their child to participate may decide to withdraw their baby from the study in the antenatal or perinatal period. Their baby will not undergo the intervention or be registered as a participant.
- Device malfunction or unavailability.
- No NHS Number is assignable to the baby
- Staff unavailability

Withdrawal following parent enrolment should be entered in the study database, giving the reason for non-registration of the baby. Site recruitment success will be calculated by the number of infants enrolled compared to the number of births at the site.

9.5.2 Withdrawal from the study after registration

Parents of registered babies may withdraw their consent for future data linkage to HES or S4N records or the use of the images in future development work by contacting the DIvO Trial Team (details on the e-Patient Information Sheet, the public website. The website address is available on all the study documentation and emails). The withdrawal reason will be documented on the CRF in the trial database.
The data and images for registered babies in whom consent has been withdrawn will be retained in the study database and only event data up to the withdrawal date will be collected via data linkage. Given the absence of risk and the single use of the intervention, these numbers are not predicted to be high but further recruitment would be required to replace their loss.

10 Trial Device

Device training will take place in all sites and repeated either with face-to-face or virtual training updates throughout the trial, to coincide with staff rotations. A Device Manual will be available in the site file.

10.1 Device Summary

Neocam is a prototype digital imaging device which displays and stores images of the eye when illuminated with co-axial IR light. This is a hand-held, non-contact camera which is similar in appearance to a barcode scanner. The device is checked out in the study database with the operator giving their logon code.

Figure 4. Starting the Neocam Device

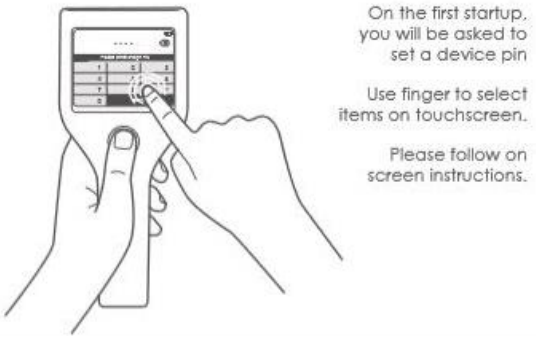
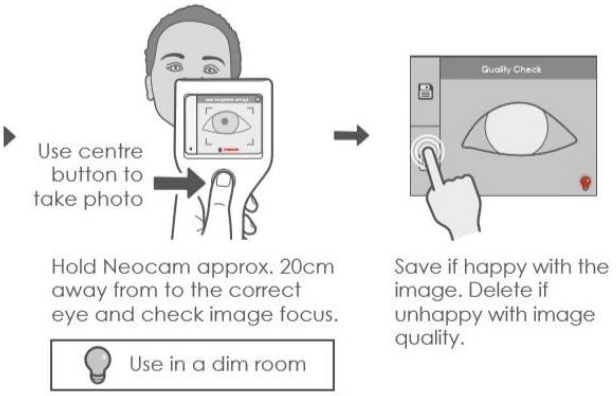


Figure 5: Viewfinding and imaging



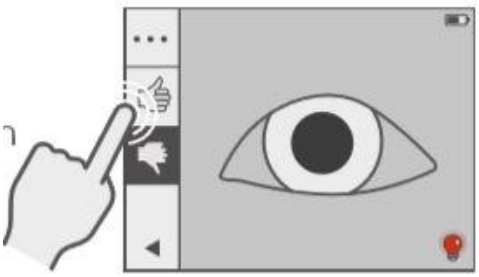
The device is switched on using the single button below the LCD screen and the user is prompted for the device access code (Figure 4). Once correctly entered, the intervention screener inputs their screener code and enters the mother and baby's NHS number and the baby's date of birth using the keypad. The NHS numbers and DoB are stored as labels within the subsequent image files.

The button is depressed again to trigger the IR illumination. The device has a virtual calliper visible in the display which, when aligned with the infant's corneal limbus, ensures the correct distance of operation from the eye (approximately 30cm). When the operator is satisfied with the image in the display, they press the button to record the image. (Figure 5).

The quality of the IR image is assessed and the photo retaken if necessary (e.g. because of a blink or eye movement). The image is then graded as normal or abnormal by the operator. The following evaluation codes are used:

Figure 6: evaluation screen

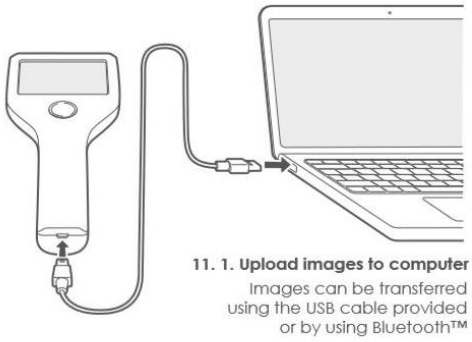
OD / OS= right / left eye
IR=infrared image
A/N= abnormal/normal



The files containing the images of each eye under both illumination conditions is labelled with the filename sequence, for example: [screener code]_[maternal NHS #]_[infant NHS #]_[DOB ddmmyy]_[date ddmmyyyy]_[ODIRN].png.

Everyday the images are uploaded via USB port into the study database. After checking that the images have been uploaded, the images on the device are deleted by the screener. A coding script within the database will transfer the image file into the maternal CRF by linkage to the maternal NHS number. An infant CRF will be created using the infant NHS number and DOB on the filename and the evaluations. (Figure 7).

Figure 7: Uploading the images



10.1.1 Version of the Device

Neocam digital imaging camera prototype version 2.0.

10.1.2 Legal status

Neocam is the equivalent of a Class IIa medical device. It will have been certified safe for investigational use by the MHRA prior to the start of patient registration.

10.1.3 Supply

The Neocam device is supplied by the Sponsor.

10.1.4 Packing and Labelling

Neocam is packed in a padded box and requires charging via a USB connection prior to use. It is recommended that the Neocam device it is left charging overnight. Each Neocam device is labelled with an identifying number.

10.1.5 Storage conditions

The Neocam device should be stored at room temperature.

10.1.6 Maximum duration of treatment of a participant

Maximum duration of imaging of a participant is 2-5 minutes.

10.1.7 Administration

Neocam is a hand-held non-contact camera, held approximately 30cm away from the eye.

10.1.8 Procedures for monitoring device compliance

Training in the use of Neocam will be given prior to study recruitment and throughout the recruitment period through face-to-face and virtual sessions. Ongoing image evaluation by an assigned paediatric ophthalmologist will take place and quality assessments will be communicated with the site PI.

10.1.9 Comparator Device

Any model and brand of direct ophthalmoscope currently used in the maternity unit of the site for the purpose of newborn red-reflex screening.

10.2 Ongoing Image Evaluation and quality control by the CI

Every month, a database report will be generated for image evaluation and quality control for the expert reviewer. This report will include:

- a random selection of 10% of subject images from the database from each maternity site
- any images that have been reported as positive from Neocam screening
- images from any babies that have been referred for specialist examination via the NIPE pathway

The CI will review these images and will document in the study database:

- if quality precludes evaluation= VOID (U)
- image evaluation in terms of ODIRN etc.

Additionally, a monthly database report will identify cases where there is a mismatch in the Neocam screener's evaluations, the referral status of the infant (referral will have been made for abnormality either in the Neocam or standard screening examination) and the CI's image evaluation. Where the CI has evaluated the images as abnormal but the infant has not been recorded as being referred, the PI at the site will be informed within 48 hours. The site PI will communicate the finding to the parents and a specialist ophthalmic examination will be organised within 2 weeks. Study sites will receive feedback on image quality and have retraining if considered necessary by the assessor. Where an image has an expert evaluation of VOID, the gold standard will be determined by absence or presence of HES data indicating a cataract (primary outcome measure) or other eye disorder which may cause an abnormality of the red / IR reflex diagnosis (secondary outcome measure).

Reports will be generated for each TSC meeting detailing:

- The number of participants registered at each side
- The number of screening double positives which have been confirmed or refuted by image review
- The number of discordant positives which have been confirmed or refuted by image review
- The number of screening double negatives in the randomised image selection which have mismatched evaluations after image review

- The proportion of VOID images from each recruitment site

11 Procedures and assessments

11.1 Parent Approach

11.1.1 Antenatal approach

DIvO study posters and leaflets will be displayed in the antenatal clinic areas where they are likely to be seen by parents attending their 20 week ultrasound scan. The trial will also be publicised using the National Childbirth Trust and social media advertising (instagram, facebook and twitter). The leaflets and posters will have QR codes which will link the user to the public facing DIvO website. Parents who have not already heard about the study by the time of admission for their delivery can be approached to consider participation by site healthcare staff and posters will be displayed in the delivery wards.

11.1.2 Post-natal approach

Site screening staff will also approach post-partum mothers who have not already enrolled, to introduce the study. Parents can access the public website on their own digital devices in the same way as pre-natal mothers or on hospital devices if necessary.

11.2 Parent Enrolment

The public facing DIvO Study website (www.divostudy.org) will give general information about the study and the participating sites, include an introductory video for parents and a summary of the PIS. The DIvO study website allows mothers to check their eligibility which, if met, will result in transfer to the secure research website (hosted by Sealed Envelope) where mother enrolment takes place. Enrolment consists of completing the following fields and confirming GDPR permission for these fields to be collected and stored securely in the research website.

- Name
- Maternal NHS number
- Email address
- Postcode
- Maternity Unit (drop down menu)
- Preferred language (drop down menu of up to 15 available)

Maternal NHS number is collected at enrolment and encrypted to provide a searchable identifier for authorised site investigators to determine the consent status of mothers admitted to the maternity unit. Its use reduces the risk of incorrect identification of consented mothers through name alone and eliminates the need for mothers to remember their Study ID. The parent's name provides a check that the staff have identified the correct enrolment and consent form. The postcode will be used as additional identifiers for future data-linkage to the baby's NHS Digital HES records. An allocated Study ID will be used for other study steps and through the lifetime of the trial.

If an email address is not available during antenatal enrolment, a pop-up message will inform the parents that the clinical team will be able to help them to enrol them at the maternity unit using a site study email address.

11.3 Consent process

Once enrolled, an automated validation email will welcome parents to the study. A link will give access to the localised PIS in their chosen language on the DIvO website. An option to download the PIS as a PDF is provided. A unique link on the email will transfer them to the e-Informed Consent Form (e-ICF) in their chosen language on the Sealed Envelope research website. The links will remain active for 30 days, with a reminder email sent after 21 days. All consent statements must be ticked for the e-ICF to be submitted.

Given the large numbers of participants and absence of risk associated with the intervention, e-consent will use a typewritten signature without co-signing by the site study team. The completed e-ICF will be time stamped and converted to PDF. A copy will be attached to the e-CRF and another attached to an email to the parent.

Parents without an email address will be able to enrol and e-consent on a hospital digital device, their identity will be validated by a member if the site staff. A PDF of the completed e-ICF will be sent to an allocated site NHS email address and printed for the parent.

The PIS and e-ICF will be approved by the REC and comply with GCP, local regulatory requirements, GDPR and legal requirements. To ensure equal opportunity for recruitment, participant information will be available in up to 15 of the most frequently spoken languages in the UK. The translated documents will mirror the English language material and will have been approved by the study Sponsor and version controlled. Any future changes to either form will be prospectively approved by the REC.

11.4 Co-enrolment in other studies

Although unlikely, parents may be approached for their baby to participate in other trials. All participating study sites will be experienced in recruiting infants to multiple trials and our experience (and that reported in the literature) is that this can be conducted appropriately and sensitively, and that mothers in this situation are capable of making an informed decision about whether they wish to participate. Where necessary, the CI will discuss other Studies with the Trial Steering Committee and agree whether co-enrolment is acceptable with the other study Investigators.

11.5 Actions on admission

On admission to the maternity unit, an authorised site investigator will search the study database record by maternal NHS number to determine if the mother has consented to study participation. If the parent has not already consented, they will be invited and supported to do so.

11.6 Participant (infant) registration

All babies undergoing NIPE checks are eligible for participation in the study. The following issues may prevent registration:

- the parent does not assent to the intervention
- the device is unavailable or not working
- the baby is not eligible for NHS number allocation
- there is unexpected staff unavailability

Where the parent has given consent but Neocam screening is not undertaken for one of the reasons stated above, the NIPE screener, or allocated site investigator, will document this in the e-CRF together with the reason.
Registration of the baby occurs at the time of the intervention test when the maternal and baby NHS number and baby date of birth are entered onto the device. The maternal and baby's NHS numbers and baby's date of birth are digitally combined to label the Neocam images and this is uploaded to the study database to automatically create the baby's e-CRF.

11.7 Trial assessments

All registered babies will have both the standard (O) red-reflex screening test using the ophthalmoscope and the intervention, Neocam digital imaging (DI) once in each eye. All images captured by the Neocam device will be uploaded to the research website at the end of that day. Upon confirmation of successful upload, the images will be deleted from the Neocam device.

11.7.1 Screening personnel

The healthcare role of the NIPE screener varies between units, usually being a NIPE qualified midwife or a trainee / staff paediatrician. Midwives will have undergone formal training in red-reflex assessment, but other staff may have only had informal training. The standard and intervention screening test will be undertaken by different screeners who **must not** communicate before both tests are completed to prevent result contamination. Where there is insufficient staffing capacity to enable a second NIPE qualified screener to undertake the Neocam screening test, collaboration with alternative healthcare staff groups, for example audiometry technicians or photographers may be considered by the site Principal Investigator (PI). All study screeners will have standardised pre-study site training in both the standard and intervention test. All new medical staff will have training provided and can request additional refreshers throughout the duration of the study. The PI will communicate with the CI to coordinate online training courses for the incoming screeners. A screener code corresponding to job role will be inputted into the Neocam device and this information will be stored with the filename data (10.1). The NIPE screeners on the maternity ward, who will be authorised to access the study database, will be expected to have GCP certification.

At the end of each screener's rotation or at the end of the study, a feedback questionnaire will ascertain which technique he / she preferred and why (Appendix 24.2).

11.7.2 Timing of the intervention

The intervention will be undertaken once only, within 72 hours of the baby's eligibility for the NIPE either before discharge home or if the baby returns during this time period.

11.7.3 Existing test (red-reflex using ophthalmoscopy, O):

This test will be undertaken by the usual healthcare professionals undertaking NIPE screening in the participating maternity unit. Red-reflex screening will be undertaken in each eye using a direct ophthalmoscope set on "0" at a distance of approximately 0.3m, the standard (O) NIPE technique (Figure 8). The test takes around 2 minutes to perform. The standard (O) entry into the NHS EI S4N database will be made by the screener on the same day as the screening test is undertaken.

This information includes:

- Evaluation of each eye normal / abnormal
- screener's job code (midwife, consultant, paediatric training year, other)
- baby's ethnicity
- baby's sex

This information will be retrieved by data linkage to the S4N database at the end of the study.

Figure 8: Examination of the red-reflex with an ophthalmoscope.

Figure 9: Imaging the eye with the Neocam device

11.7.4 Intervention test, Neocam digital imaging (DI, see 10.1)

A site specific passcode will be used by the Neocam screener to access the camera and the stored image files. Imaging does not require pharmacological pupil dilatation, is non-contact, painless and takes approximately 2 minutes to complete at the cot-side. After explaining the procedure to the mothers, the screener enters the mother and baby NHS number and baby date of birth into the device using the keypad. The screener deletes and retakes the images as required to achieve documentation of good quality images. The screener then enters the screening evaluation which is digitally recorded within the image file name.
The images should be uploaded to the research database on the same day, or within 24 hours by intervention screener or the site team. Images will be deleted from the device only after checking the upload has been successful.

11.7.5 Test Outcome Notification

The standard screening test will be undertaken by the NIPE trained screener and entered on S4N, as is standard practice. The Neocam screener will not access these records and will enter their evaluation results directly into the Neocam device, for subsequent upload into the study database. The screeners will not discuss results with each other or the parent until their evaluations have been completed and inputted into the relevant database. Only once this has occurred will the NIPE screener determine if any of the babies require specialist referral through the NIPE referral pathway due to

abnormal evaluation on either test. The NIPE screener will ensure that the requirement for referral is documented in the study database under the maternal record. The parents of all babies will then be notified of the result and whether specialist referral is necessary.

Any inadvertent discussion of screening results prior to the recording of the screening evaluation for both techniques will be recorded in the site file as non-compliance and reported to the Sponsor and be kept with the site documents. Staff will be made aware that they will not be personally identified by the assessments they make, but that their role and level of experience will be recorded on both the Neocam evaluation record and the S4N database (standard practice).

Babies with abnormal light reflex assessment in either or both screening tests will be referred for ophthalmic examination via the standard 2 week urgent referral NIPE pathway. Babies identified with eye abnormalities other than abnormal light reflexes will be referred for specialist advice following local protocols.

11.8 Schedule of Assessments

Assessment	Approach	Enrolment	Informed e-Consent	e-Registration	Red-reflex test	Digital Imaging (DI)	Test Outcome Notification	Data Linkage
From 20th week gestation to within 72 hours of NIPE	X	X	X					
Within 72 hours of NIPE	X	X	X	X	X	X	X	
End of trial								X

11.9 Long-Term Follow-up Assessments

There are no follow up assessments required as part of the study.

11.10 End of Trial Participation

The active phase of trial participation is complete after discharge from hospital.
The passive phase of trial participation is complete following NHS Digital and NHSEI database record linkage.

11.11 Trial restrictions

There are no restrictions to the prospective mother or participant during the course of the study.

12 Assessment of Safety

12.1 Definitions

12.1.1 Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject who has received an investigational device, whether or not related to the investigational medical device. For this study, this will include adverse events occurring in the active phase of participation This definition includes events related to the device under investigation or the comparator or to the study procedures. For users or other persons, this definition is restricted to events related to the investigational device.

The following anticipated adverse events will not be recorded:

- Pre-existing medical conditions
- New illnesses or conditions not requiring concomitant medication or medical intervention/procedures
- Surgery or treatment for congenital abnormalities
- Jaundice
- Skin conditions / rashes
- Respiratory difficulties, respiratory and ENT infections
- Feeding, hernias and digestive tract issues
- Urinary tract infections
- Meningitis infection

12.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Accidental data loss through intentional misuse, user error, damage or malfunction.

12.1.3 Serious adverse event (SAE)

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect.
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'

Life-threatening in the definition of a serious adverse event refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe. Death of the participating infant during the study period will be identified by absence of HES data at the time of data linkage.

12.1.4 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

12.1.5 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the protocol.

An Anticipated Serious Adverse Device Effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the protocol.

12.1.6 Device Deficiencies

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. A device deficiency may lead to an Adverse Device Effect or Serious Adverse Device Effect. The following anticipated device deficiencies and device-related issues will not be recorded:

- Failure to charge
- Breakage or malfunction

12.2 Expected Adverse Events/Serious Adverse Events (AE/SAE)

The following anticipated adverse events will not be recorded:

- Pre-existing medical conditions
- New illnesses or conditions not requiring concomitant medication or medical intervention/procedures
- Surgery or treatment for congenital abnormalities
- Jaundice
- Skin conditions / rashes
- Respiratory difficulties, respiratory and ENT infections
- Feeding, hernias and digestive tract issues
- Urinary tract infections
- Meningitis infection

12.3 Evaluation of adverse events

The Sponsor expects that serious adverse events are recorded during the active phase of participation. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between digital imaging and/or concomitant therapy and the adverse event (causality).

12.3.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.3. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

12.3.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a

plausible time sequence between onset of the AE and the digital imaging . **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and the digital imaging . **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable, and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded, and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial intervention related
Definitely, Probable and Possible causalities are considered to be trial intervention related

12.3.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

12.3.4 Recording of adverse events

Adverse events and adverse reactions occurring during the active phase, See section 10.2. should be recorded in the medical notes. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 12.4.

12.4 Reporting serious adverse events

Each Principal Investigator needs to record all adverse events in participant medical records and report serious adverse events occurring in the active phase see section 10.2 to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event. The absence of HES records for a participant will indicate that the baby has died in the interval and will be reported by the Chief Investigator.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the Sponsor and the HRA/REC via an Annual Progress Report (APR). The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC

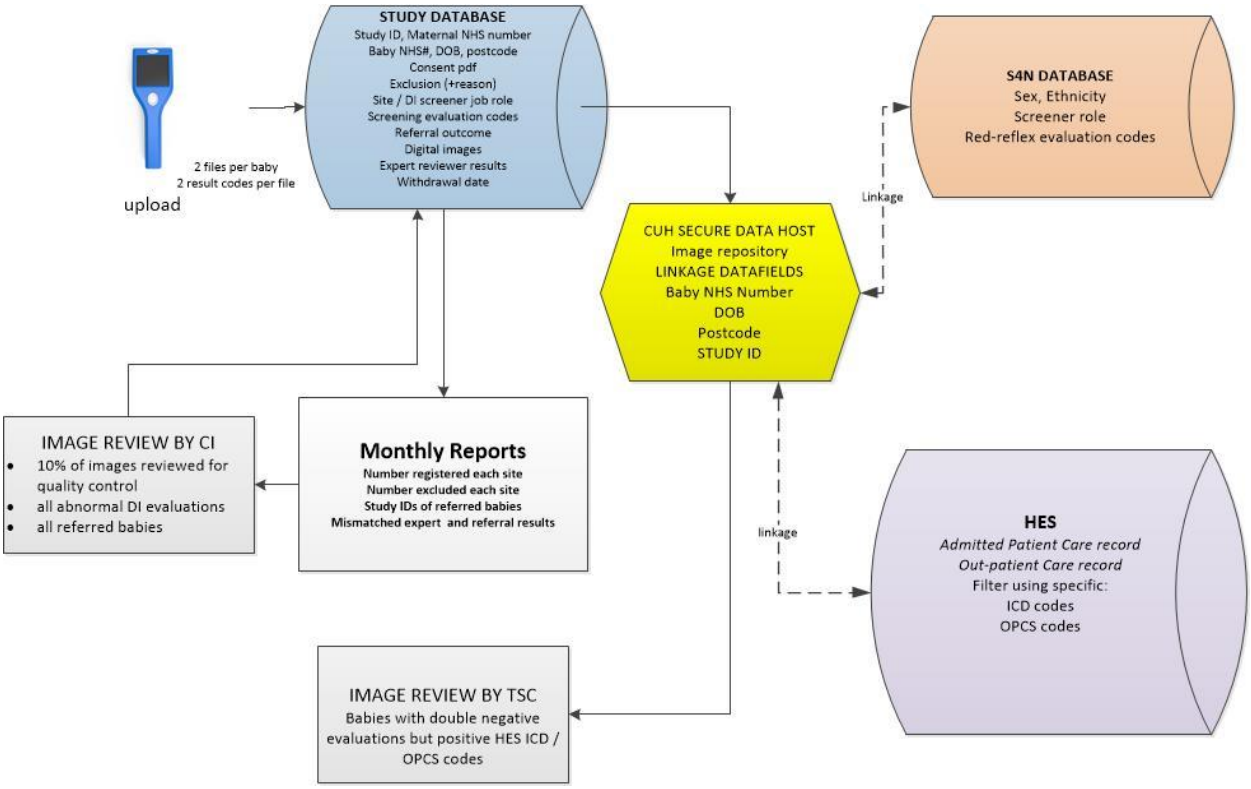
The completed SAE form can be emailed. Details of where to report the SAE's can be found on the DIvO SAE form and the front cover of the protocol.

12.4.1 Recording and reporting of device deficiencies

All device deficiencies will be documented throughout the study. The investigator at each site will be responsible for managing all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect. Breakage or malfunction of the device must be reported by email to the CI the next working day.
All device deficiencies that might have led to a serious adverse device effect(s) if: suitable action had not been taken; intervention had not been made, or if circumstances had been less fortunate, must be reported to the Sponsor as for SAEs/SADEs. These will also be reported to the MHRA via the sponsor.

13 Follow-up Data Linkage

Data Linkage Flowchart



13.1.1 NHS Digital

At the end of the study, a minimum of one year following screening was undertaken, data will be pulled from both the admitted care and out-patient care HES databases via the baby's NHS number, DOB and postcode for records with the following entries:

HES Digital data will be filtered for the presence of OPCS codes: beginning C71 to C79, admission date and /or ICD10 codes starting Q12-15, H17, H18, H21, H25-27, H33-35,

H43 and C69 . Data relating to ethnicity, Socio-economic factors, sex and current postcode will be requested.

13.1.2 NHSEI

At the end of the study the following data will be pulled from the S4N database using linkage to the baby's NHS number and DOB:

- screener's job title (midwife, consultant, paediatric training year)
- Each eye: No Abnormality Suspected / Abnormality Suspected.
- Ethnicity, sex

13.1.3 Neocam

During the study the following information will be loaded into the research database with the image files:

- site and screener job title code
- maternal NHS number
- baby's NHS number
- baby's date of birth
- date of the intervention
- Codes for each eye and illumination type and evaluation: normal / abnormal (10.1)

At monthly intervals during the study, abnormal screening evaluations as indicated by the Neocam evaluation on the baby's e-CRF or documented specialist referral on the maternal e-CRF, will be reviewed by an assigned paediatric ophthalmologist. This will provide a review examination for all babies who have had an abnormal screening evaluation from either device. Enabling assessment of true and false positive screening tests.

This will identify screener error and identify pathology other than cataract which might have resulted in an abnormal evaluation. For those cases where the screening evaluations were both negative but the HES records an ophthalmic clinic encounter with ICD-10 or OPCS codes relating to cataract specifically and, additionally, other eye disorders which may cause an abnormal red / IR reflex , two expert paediatric ophthalmologists (drawn from the Trial Steering Committee) will be asked to review the images to determine evidence of the cataract or other disorder was present at the time of the screening test, i.e. was a false negative assessment.

Image review by expert will be the gold standard examination. Only babies who have double negative evaluations on screening and no ophthalmic records on HES will not have routine image review.

Statistical analysis to calculate sensitivity and specificity can only be undertaken following data linkage at the end of the study.

14 Storage of Images

Neocam images will be stored in the device until a member of the site investigation team upload the images onto the research database. This should occur within 24 hours of the intervention. Once the images are uploaded the images on the Neocam devices are deleted. All study images will be pseudonymised and kept in secure storage for 5 years. Images may be used for future research - if mothers have agreed to this during informed consent.

15 Statistics

15.1 Statistical methods

Approximately 40% of children with congenital cataracts will have unilateral disease. Given the rarity of cataract, and in order to maximise the data from eyes with cataract captured in the study, the abnormal eye will be selected as the index eye for data analysis where there is a unilateral abnormal screening result. Where the screening test is abnormal bilaterally, the right eye will be selected as the index eye.

The cataract diagnosis gold standard against which the accuracy of each screening test will be compared is the presence of an ICD-10 or OPCS code indicating the presence of cataract on Hospital Episode Statistics (HES) records.
A subsidiary analysis will be undertaken to include coding for additional eye disorders which may be expected to cause an abnormal red / IR reflex which could be mistaken for cataract and require referral for diagnostic assessment by an ophthalmologist . The gold standards will therefore only be established once HES data linkage is undertaken a minimum of one year from the date of each participant's screening test.

As an interim assessment of relative accuracy, and to estimate the number of babies with cataract recruited, the CI will review the digital images of babies with a positive, or abnormal, screening test, from either standard (O) or neocam (DI) test.

Babies with double negative (normal screening tests) but subsequent HES evidence of coding indicating a diagnosis of cataract will have their digital screening images reviewed by two independent expert ophthalmologists drawn from the Trial Steering Committee. This will determine if there was evidence of cataract orlens opacity at birth which was not detected by either screening evaluation. A similar review of images will occur for those babies with coding for other eye disorders which may have been expected to cause an abnormal red / IR reflex at screening.
A comparison of the relative sensitivity and specificity of the two tests will be possible using the counts of discordant pairs of screening tests, where one, and only one, of the Neocam and standard test results within a baby are positive. Thus this relative comparison will be estimable in a short space of time for the recruited population (see flowchart 2). Hence much of the statistics inference can be performed before the long term follow-up of the babies with both tests as negative.

For both the groups with and without congenital cataract (as determined by the gold standard) the sensitivity and specificity, respectively, will9 xdew be compared. McNemar's test will provide a p-value, and a 2-sided 2.5% significance level used to account for the two contrasts. The absolute difference and odds ratios will also be estimated and provide with 95% confidence intervals. A subsidiary analysis of those

babies with any coding relating to other eye disorder which might be expected to cause an abnormal red / IR reflex will be undertaken,

An estimate of the absolute values of, rather than differences between, sensitivity and specificity will be made following expert review of the newborn imaging for babies with double negative screening tests with a subsequent diagnosis specifically of cataract and secondarily for those with an eye disorder which might be expected to cause an abnormal red/IR reflex (since these disorders may develop after birth). A detailed statistical analysis plan will be produced before the final data base lock or before any interim analysis is performed.

Equivalent comparisons of sensitivity and specificity for each screening test will be made within ethnic groups and screener experience levels.

Quantitative comparison of the ease of O to DI evaluation will be analysed by screener questionnaire at the end of that staff member's rotation on the maternity ward or at the end of the study recruitment period, whichever is sooner. Summary statistics reporting on the numerical or categorical questions will be provided.

15.2 Number of Participants to be enrolled

From the Cambridge proof-of-concept pilot study using non-specialist screeners, the sensitivity is assumed to be 70% and 95% for red-reflex and digital imaging screening by non-specialist staff respectively. Hence the treatment effect is assumed to be a 25% difference. Power calculations need further assumptions regarding the joint distribution of the test within individual babies; we assume the maximum rate, 35%, of discordant tests consistent with these margins. A 2-sided hypothesis test (McNemar's) at the 2.5% significance level will have 90% power if 67 babies are recruited with cataracts, necessitating recruitment of an estimated 140,000 newborns for screening.

15.3 Criteria for the premature termination of the trial

Poor image quality on reviewed images which is due to technical device issues rather than user error may result in a temporary suspension of the trial in one or all sites to modify the device.

15.4 Procedure to account for missing or spurious data

Participants in whom the S4N or the Neocam dataset are missing will be excluded from statistical analysis.
Where the quality of scans is insufficient when reviewed by the assigned paediatric ophthalmologist evaluator, the site will receive additional training.

15.5 Definition of the end of the trial

The end of trial will be 6 months after the last data capture via data linkage.
CCTU will notify the REC the trial has ended, and a summary of the clinical trial report will be provided within 12 months of the end of trial. A plain English summary of the study results will be available on the study website alongside their publication in a

scientific journal. Results will be shared with sites at a results meeting once analyses are completed.

16 Data handling and record keeping

Site files will contain printed Informed Consent Forms which will be stored securely. Database entry onto the eCRF within the study database will be undertaken by the site research or clinical staff.

Maternal NHS number, postcode, consent, the baby's NHS number, DoB and evaluation of the Neocam images will be captured within the eCRF which will be hosted on the research database. All trial data in the eCRF will be consistent with the relevant source documents. The eCRFs are completed on the day of registration when the Neocam images are uploaded. It is the responsibility of the investigator for the timing, completeness and accuracy of the eCRF pages, the S4N database record and the Neocam data upload. The eCRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Data will not be editable in the eCRF once the record is saved. Please refer to the DIvO Trial Manual for further details on completion and retention of the eCRFs.

16.1 Source Data

To enable peer review, monitoring, audit and/or inspection, all eCRF data on the research database which will include eCRF, image files and linked data, and completed electronic informed consent forms will be kept securely.

Source data may include but is not limited to:

- Electronic Informed Consent Form
- Relevant sections of the Case Report Form (electronic), as defined by the TPM
- Medical Records (written or electronic)
- Hospital event data received via data linkage eg. HES data
- Test result data received via data linkage eg. S4N data

16.2 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 1998 and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

Trial participants will provide explicit consent to the use of patient identifiable data for the purposes of the conduct of the trial. The DTO will hold patient identifiable data on all trial participants including NHS number, DoB, postcode and email. Patient identifiable data will be stored and encrypted on a secure NHS server and in compliance with the Data Protection act. Patient identifiable data will be accessible to the DTO within the Cambridge Clinical Trials Unit, clinical trial monitors, auditors and inspectors as required. It is necessary to perform linkage to routinely collected datasets (NHS Digital, S4N Database) and is therefore imperative to the conduct of the trial.

16.2.1 NHS Digital & NHSEI

Applications will be made to the relevant bodies to access outcome data routinely collected by them. This will include Hospital Episode Statistics. The applications and resulting data will be managed by the DTO, Coordinating Centre at the Cambridge Clinical Trials Unit.

16.2.2 Identifiable Data Transfer from Local Site to DTO and Coordinating Centre

All identifiable data will be securely sent to the DTO and/or the Coordinating Centre by secure file transfer in compliance with the Data Protection act. Database access will be restricted to the delegated trial staff. Consent will be sought for the transfer of identifiable information.

17 Data Monitoring Committee/Trial Steering Committee

To eliminate any potential conflict of interest, the CI role will transfer to Prof Rahi on completion of the recruitment period. Given the lack of intervention risk and the absence of data analysis during the recruitment period, the NIHR has permitted a subset of independent members on the TSC to additionally fulfil the role of the IDMEC. The TSC comprises experts from the fields of paediatric ophthalmology, neonatology, statistics and midwifery in addition to a PPI representative and the CIs.

The Trial Steering Committee (TSC) is responsible for the review of the trial and related activities at regular intervals. The TSC also provides overall supervision for the trial, to ensure that it is conducted in accordance with the protocol and GCP and to provide advice through its independent chairman. The committee will aim to convene at regular intervals to review the Study. The details of the TSC are set out in the DIvO Trial Steering Committee Charter.
At the end of the study, once data linkage results are collected, two ophthalmologist members of the TSC will review:

- All images with an evaluation of "Abnormal" but no linkage to ICD-10 codes indicating cataract, this may indicate false positives or a different pathology
- All images with an evaluation of "Normal" with ICD-10 codes indicating cataract – these may be due to false negatives or due to subsequent cataract development.

18 Ethical & Regulatory considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html). The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research 2018, the applicable UK Statutory Instruments, which include the Data Protection Act 2018) and the ICH Guideline for Good Clinical Practice E6 (R2) .

18.1 Ethical committee review

Before the start of the trial or implementation of any amendment approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents

e.g., advertisements and posters, will be obtained from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the CI's responsibility to produce the annual reports as required.

18.2 Regulatory Compliance

The trial will not commence until approval from a REC and the HRA is received. The MHRA will also be notified of a clinical investigation for the medical device used in this study.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

18.3 Protocol Amendments

Protocol amendments must be reviewed, and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA and REC.

The only circumstance in which an amendment may be initiated prior to HRA and/or REC approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA and/or REC approval has been obtained.

An Urgent Safety Measure is extremely unlikely in this study given the lack of risk from the intervention and should be reported within 24 hours to the CI and the sponsor. Once reported the CI will telephone or email the site PIs within 24 hours to notify them of the measure.

18.4 Peer Review

This protocol has been peer reviewed by the NIHR EME and Sponsor's R&D department.

18.5 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.6 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking administrative responsibilities on this trial. Additionally, a GCP certified clinical staff member will be responsible for checking the study database to search for maternal consent under maternal NHS number and to document on the study database following completion of screening if Neocam screening was not completed (and reason), if the baby was referred and if the NIPE examination was abnormal. GCP training should be updated every 2 years or in accordance with the Trust's policy.
There is no requirement for the staff undertaking the intervention to have GCP certification although they must have attended live or virtual site training. This training will be repeated on request from sites virtually or in person to cover staff rotations.

19 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust. The trial is funded by the NIHR.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.
There are no costs to the mothers associated with trial participation and no implications for insurance cover.

20 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should a monitoring visit occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for all participating sites. Additionally, the assigned paediatric ophthalmologist will be undertaking quality of control by reviewing a random 10% of all site images on a monthly basis (10.2). Sites will receive monthly feedback, both in numbers recruited and in quality of imaging. Study sites will receive feedback on image quality and have retraining if considered necessary by the assessor.

21 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time but are not planned. For this study this particularly includes communication between screeners and mothers, or between screeners, which may lead to contamination of screening assessment. They must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately. The Sponsor will report all protocol deviations, non-compliance or breaches to the MHRA.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

The Sponsor is responsible for notifying the REC and MHRA of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify CCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Sites may be suspended from further recruitment in the event of serious and persistent noncompliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the sponsor, Trial Steering Committee, Data Monitoring Committee, MHRA and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

22 Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

No party will be entitled to submit any publicity material without prior approval from CCTU. Plans for publication will be outlined in a separate publication plan, which will include details of authorship. Results of this trial will be submitted for publication in a peer reviewed journal(s). The manuscript(s) will be prepared by the Chief Investigators and authorship will be determined by mutual agreement. Trial publications and conference abstracts will be submitted to the National Institute for Health Research (NIHR) for approval prior to submission to the event organisers or the editors. All publications will acknowledge the support of the NIHR in funding this trial. Neutral or negative results will not constitute a reasonable justification to delay publication. A lay summary of the results will be available for all mothers on the study website at the end of the trial. Participating Investigators will not have the rights to publish trial data separately.
Updates on the study's progress will be available on the public website (mothers will have a record of this on a sticker in their child's Personal Health Record). Once published, a summary of the study results with a link to open-source publications will be available via this website

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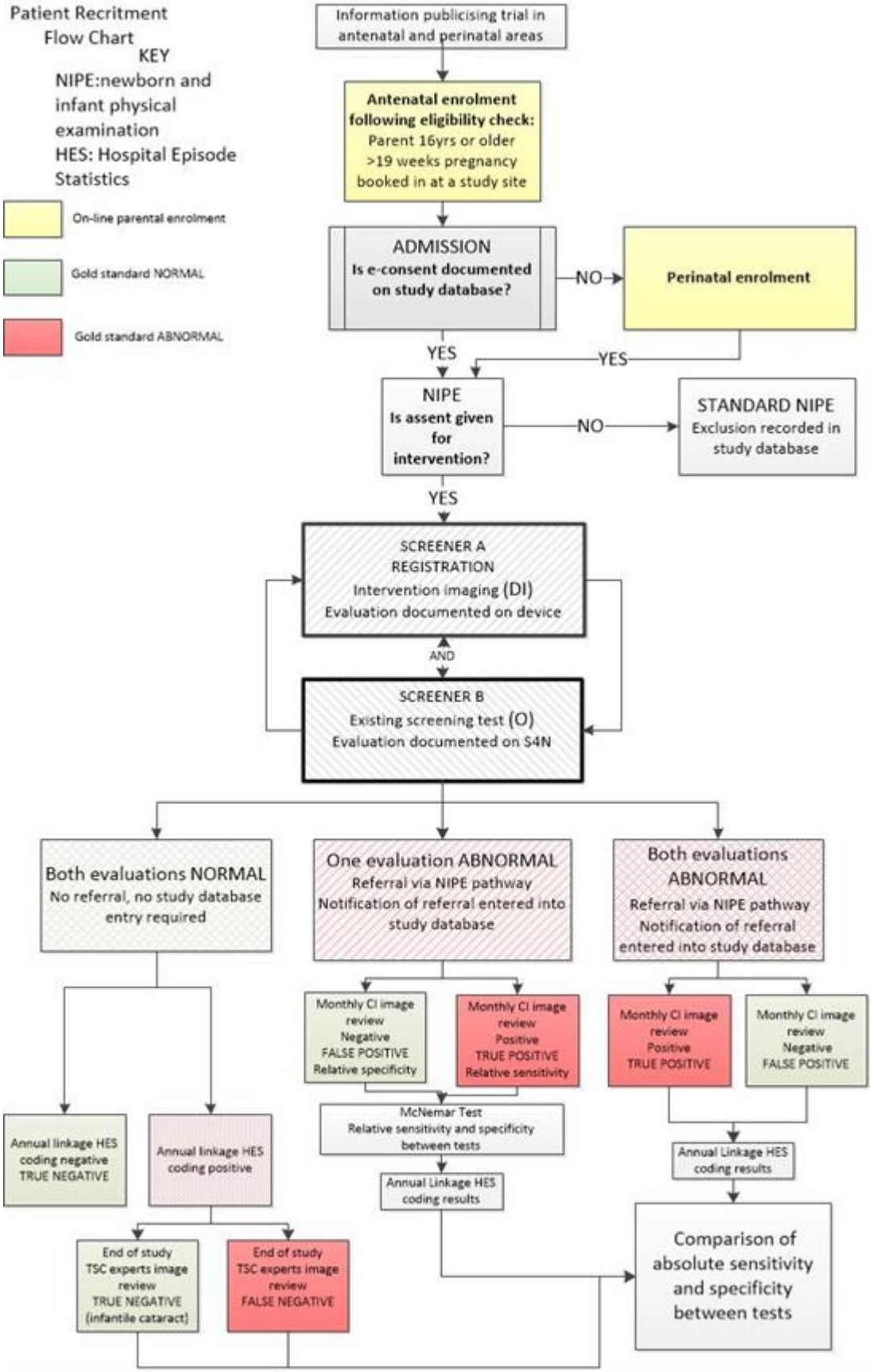
24 Appendices

24.1 Trial flow chart



25 Safety Reporting Flow Chart