CatCam – Choroidal reflectance camera for the detection of congenital cataracts.

Clinical Study Protocol

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Protocol Number:	CatCam 2016
Study Title:	Assessment of a choroidal reflectance camera for the detection of congenital cataracts
Investigational Product:	Novel infra- red detection system: CatCam
Protocol Version:	Version 2.0

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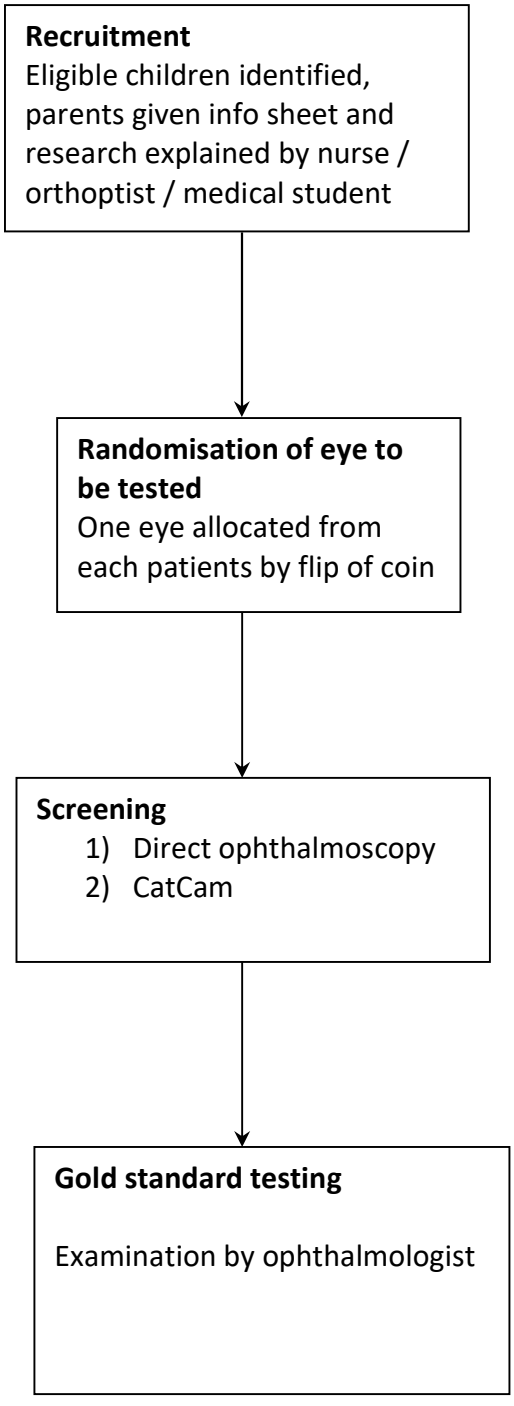
Study Sponsor:	Cambridge University Hospitals NHS FoundationTrust

1 Study Synopsis

Title of clinical trial	**Assessment of a choroidal reflectance camera for the diagnosis of congenital cataract**
Sponsor name	Cambridge University Hospitals NHS Foundation Trust
Medical condition or disease under investigation	Congenital and developmental cataracts
Purpose of clinical trial	Compare diagnostic sensitivity and specificity of i-Cam compared to current screening test
Primary objective	Evaluate sensitivity and specificity of CatCam compared to the currently available technique
Secondary objective (s)	To optimise and refine the CatCam to maximise it ease of use
Study Design	Comparison of the sensitivity and specificity of two diagnostic tests with binary outcomes with regards to gold standard (ophthalmic examination)
Study Endpoints	Completed testing on sufficient number of children to give good statistical power
Sample Size	Approximately 260 children
Summary of eligibility criteria	Children from birth to 5 years of age with or without congenital or developmental cataract waiting for an ophthalmology examination
Active comparator product(s)	"red reflex" screening with direct ophthalmoscope
Route(s) of administration	Non-contact photography
Maximum duration of treatment	20 minutes total
Procedures: Screening & enrolment	Eligible children will be recruited from the paediatric eye clinic waiting room
Baseline	At this same visit children will be examined using the current "red reflex" screening test with a direct ophthalmoscope and then examined with CatCam. Each test should take 5 minutes prior to seeing the ophthalmologist.
Treatment period	10 minutes total for both diagnostic tests
End of Study	Following ophthalmic consultation on the same day
Procedures for safety monitoring during trial	CatCam infra-red output will have been measured to be within acceptable international standards by the developing engineers and have been approved by the clinical engineering dept at Addenbrooke's.
Criteria for withdrawal of patients on safety grounds	n/a
Regulatory submissions on safety grounds	Registration as a Class IIa Medical Device

2 Study Flow Chart



3 Introduction

3.1 Background

All babies born in the UK undergo eye screening at birth and 6 weeks to enable the early diagnosis and management of congenital cataract, a treatable but potentially blinding condition affecting 1 in 2000 newborns. The current technique involves the assessment of the "red reflex" - the orange/red glow in the pupil seen during ophthalmoscopy (or flash photography) due to reflectance of light from the back of the eye. In reality, testing can be technically difficult because the pupil constricts to light during the examination and, particularly in babies of Asian and Afro-Caribbean ancestry, the red-reflex can be dim due to the effect of ocular pigmentation. As a result less than 50% of congenital cataracts are currently identified up by screening. [1] Early visual experience is required for good visual development and a delay in the surgical management of cataracts results in sub-optimal visual development and visual impairment. Additionally there are a large number of false positive referrals generated by neonatal congenital cataract screening. At CUHFT, every year we see approximately 25 infants urgent false positive referrals due to difficulty with the red reflex examination in primary care – extrapolating to the whole of the UK we would estimate 2,950 unnecessary examinations at a cost to the NHS of over £400,000 per year.[2]

The neonatal congenital cataract screening tests are performed by a range of healthcare professionals including nurses, midwives and doctors.

We have developed a new digital camera imaging system based on a modified mobile phone which improves the detection of choroidal reflectance, improving the pick up rate of cataract and other congenital eye malformations and allowing documentation of the examination. We predict that this will facilitate screening and improve the early detection of congenital cataract.

3.2 Data from non-clinical studies

CatCam has already been used in a number of adult volunteers and its components and photographic properties optimised to give the best image of choroidal reflectance. The device is comprised of a commercially available Nexus smart phone, on which the inbuilt camera incorporating an infra-red filter has been replaced with a model without the infra-red filter. There is an attached infra-red LED with a beam splitting lens which allows co-axial illumination.

Infra-red illumination is commonly utilised is ophthalmic photography. Commercially available photorefractors (such as Plusoptix) use eccentrically arranged infra-red diodes or laser to assess refractive error in children over 6 months, they require the child to look at the device when used a meter away. Although the wavelength and power output of the LED in CatCam is similar to these photorefractors, the difference lies in the coaxial nature of the illumination which enables choroidal reflectance to be assessed within a metre and without the compliance of the child.

3.3 Safety data

The prototype CatCam gives out infra-red radiation from a single light emitting diode well within the internationally accepted safety level (International Commission on Non-Ionizing radiation protection, see attached safety report).

4 Rationale for Study

If CatCam is found to be a more accurate diagnostic test than the current screening method, we hope that it will be accepted as the method of choice both in the UK as part of the Neonatal Infant Physical Examination screening process and internationally.

5 Trial objective and purpose

Primary objective: to compare the sensitivity and specificity of examination with CatCam compared to the current screening test of red reflex testing with a direct ophthalmoscope.

Secondary objective: to assess the ease of use and optimise the new device

5.1 Statement of design

This study is a comparison of the sensitivity and specificity of two diagnostic tests with a binary outcome. The gold standard for the diagnosis of congenital and developmental cataract is an examination by an ophthalmologist with the pupils dilated pharmacologically.
We will test one eye of each recruited child based on a flip of a coin.
It is estimated that the prevalence of cataract in the infants under 18 months in the paediatric eye clinic at Addenbrooke's is 20% and that in children between 18 months and 5 years of age is 10%. Previous studies have shown that the sensitivity of red reflex screening is 50% and the specificity is very low - in the region of 10%. We estimate that the sensitivity of CatCam will be approximately 85-90% and the specificity will be approximately 70%. With 95% CI levels and assuming accurate prevalence rates we expect to have to test 260 children.

The testing will take place at Addenbrooke's hospital.

5.2 Study duration

Study duration will be between 6-9 months, aiming to start testing on 01/12/16 and finish by 03/07/17.

5.3 Study objectives

5.3.1 Primary objective

Primary objective: to compare the sensitivity and specificity of examination with CatCam compared to the current screening test of red reflex testing with a direct ophthalmoscope.

5.3.2 Secondary objective

Secondary objective: to assess the ease of use and optimise the new device

5.4 Study endpoints

5.4.1 Primary endpoint

Clinical testing will cease once sufficient children have been recruited to enable adequate statistical power.

5.5 Criteria for Discontinuation

5.5.1 Individual subject

Request of the child or parent to withdraw from study or cease testing.

6 Selection and withdrawal of subjects

6.1 Inclusion Criteria

- Children 5 years and under who are being seen in the eye clinic and who are due to have a full ophthalmic examination

6.2 Exclusion Criteria

- Children whose parents do not have conversant English
- Children with structural eye abnormalities such as microphthalmia and anophthalmia

6.3 Assignment and Randomisation Number

Since the two eyes of a child cannot be counted as independent, we will use a flip of a coin to determine which eye will undergo testing.

6.4 Method of Blinding

The nurse / medical student or orthoptist recruiting and performing the screening tests will not have read the child's referral letter or be aware of the child's ocular history.

6.5 Emergency Unblinding

Not applicable

6.6 Subject withdrawal criteria

The child will be withdrawn from the study if it he/she is unable to cooperate with the testing.

7 Study procedure and assessments

7.1 Informed consent

Parents/carers of children identified as fitting the inclusion criteria for testing will be given the information leaflet and the consent form to read. The nurse / medical student / midwife will then be able to discuss the study with the parent and take informed consent.

7.2 Screening evaluation

The child will undergo the full range of tests which they require as a result of their referral during the same clinic visit, including a full eye examination by an ophthalmologist.

7.3 Baseline data

All patients will have a full medical history taken and a clinical examination .The following are to be recorded:

a) Age and date of birth
b) Any significant past medical or ophthalmic history
c) Family history of early onset cataract
d) Family ethnicity

7.4 Study assessments

7.4.1 Timing of assessments

The diagnostic tests under study and the gold standard investigation will take place at the same clinic visit and the child will not need to attend subsequently for the trial. Further follow ups will be given depending on the child's ophthalmic diagnosis.

8 Evaluation of Results

At the time of testing the nurse / medical student / midwife will make an assessment of whether a cataract was seen either during the red eye screening with a direct

ophthalmoscope and on the basis of the digital photo from the CatCam. The results will be compared to the gold standard examination once the required number of children has been seen.

9 Assessment of Safety

9.1 Definitions

9.1.1 Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product

9.1.2 Adverse reaction of an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship

9.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).
When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

9.1.4 Serious adverse event or serious adverse reaction

Any untoward medical occurrence or effect that:

- 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.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject 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.

9.2 Expected adverse drug reactions

In order to minimise unnecessary work, it is recommended that all expected adverse drug reactions and all expected serious adverse events are listed in the protocol (otherwise they will have to be reported as SUSARs).
Sometimes, unexpected adverse drug reactions and unexpected serious adverse events become 'expected' during the trial, in which case the protocol should be amended and such events would not need reporting. The Chief Investigator and Data Monitoring Committee (if applicable), should determine whether any events become 'expected' during the course of the trial and apply for MHRA and Ethics Committee approval for a substantial amendment.

9.3 Expected Serious Adverse Events

In order to minimise unnecessary work, it is recommended that all expected adverse drug reactions and all expected serious adverse events are listed in the protocol (otherwise they will have to be reported as SUSARs).

9.4 Recording and evaluation of adverse events

Individual adverse events should be evaluated by the investigator and, where indicated, they should be reported to the sponsor. This includes the evaluation of its seriousness, causality and expectedness and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.
The sponsor has to keep detailed records of all SAEs reported to him by the study team.

Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4.This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

Assessment of severity

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate: The subject 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 subject's life is at risk from the event.

9.4.1 Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the

investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

9.5 Reporting adverse events

The Chief Investigator is responsible for the prompt notification to all concerned investigator(s), the Research Ethics Committee and competent authority (eg MHRA) of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

9.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

9.6.1 Who should report and whom to report to?

The Chief Investigator should report all the relevant safety information previously described, to the Sponsor, concerned competent authorities and to the Ethics Committee concerned. The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

9.6.2 When to report?

9.6.2.1 Fatal or life-threatening SUSARs

The MHRA and the Research Ethics Committee should be notified as soon as possible but no later than 7 calendar days after the study team and sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the MHRA and the Ethics Committee within an additional eight calendar days.

9.6.2.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

9.6.3 How to report?

9.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected investigational medicinal product,
b) an identifiable subject (e.g. study subject code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source,
and, when available and applicable:
- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

9.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

9.6.3.3 Format of the SUSARs reports

Electronic reporting should be the expected method for expedited reporting of SUSARs to the MHRA. In that case, the format and content as defined by the Guidance 1 should be adhered to.
The CIOMS-I form is a widely accepted standard for expedited adverse reactions reporting. However, no matter what the form or format used, it is important that the basic information/data elements described in annex 3 of the EU directive, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances).

10 Statistics

10.1 Study statistician

An independent statistician has given advice with regards to the statistical tests required and the approximate number of patients required to power the statistics.

10.2 Statistical methods to be employed

This study is a comparison of the sensitivity and specificity of two diagnostic tests with a binary outcome. The gold standard for the diagnosis of congenital and developmental cataract is an examination by an ophthalmologist with the pupils dilated pharmacologically.

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10.3 Interim analyses

Data will be reviewed once half the planned number of children has been examined in order to check estimated prevalence rates of congenital correct are correct.

10.4 Number of Subjects to be enrolled

See 10.1 and 10.2

10.5 Criteria for the termination of the trial

Technical failure of CatCam protoype, although simplicity of technical design makes this unlikely and the technology company which designed it have spare components to creat another prototype within a week.

10.6 Procedure to account for missing or spurious data

Children on whom none or only one of the diagnostic screening tests is possible will be excluded. Subjects unable to complete the testing will be excluded.

10.7 Definition of the end of the trial

The trial will be terminated once sufficient numbers of children have been tested to give sufficient statistical power to the comparison of sensitivity and specificity between diagnostic tests.

The sponsor must notify the MHRA of the end of a clinical trial within 90 days of its completion. The definition of the end of the trial must be provided in the protocol. Any change to this definition for whatever reason should be notified as a substantial amendment. In most cases, the end of the trial will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this should be justified in the protocol.

11 Direct access to source data / documents

The sponsor should ensure that it is specified in the protocol that the investigators will permit trial related monitoring, audits, REC review, regulatory inspections.

12 Ethical considerations

12.1 Consent

All patients will freely give their informed consent to participate in the study. A patient may decide to withdraw from the study at any time without prejudice to their future care

12.2 Ethical committee review

The study protocol is to be seen and approved by the appropriate ethical review committee(s) of any participating hospital. Copies of the letters of approval are to be filed in the study file

12.3 Declaration of Helsinki and ICH Good Clinical Practise

The study is to be carried out in conformation with the spirit and the letter of the declaration of Helsinki, and in accord with the ICH Good Clinical Practice Guidelines

13 Data handling and record keeping

The data will be kept on a CD and as a file on a hospital computer at Addenbrooke's for a period of 15 years by Miss Allen.

14 Financial and Insurance

This trial has been funded by Addenbrooke's Charitable Trust Innovation for Patient benefit grant. The investigators will be working within Cambridge University Hospitals NHS Trust and will be indemnified by the NHS.

15 Publications policy

Publications arising from the trial will be authored by Miss Allen. If the investigators demonstrate significantly improved sensitivity and specificity of the device compared to current methods we will seek to commercialise the device with an ophthalmic device manufacturer.

16 Supplements

Safety testing results: Appendix 1

References

1: Rahi JS, Dezateux C and the British Congenital Cataract Interest Group. *National cross sectional study of detection of congenital and infantile cataract in the UK: role of childhood screening and surveillance.* BMJ 1999;3(18) 362-5

2: te Water Naude A, Allen L, *Congenital cataract screening : the burden of false positives*. Poster BIPOSA 2016