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1 Full / long title of study

To assess the accuracy of a machine learning tool, to diagnose a range of common external eye conditions

1.1 Short study title / acronym

Assessment of the EyeVdoc App

1.2 Research reference numbers

1.3 IRAS number

1.4 Sponsor EyeV Ltd

1.5 Protocol and version no/ date

Version 1.0

This protocol has been designed to ensure regard for the HRA guidance

1.6 Study website

www.eyevdoc.com

This is an open site but no recruitment to the study will occur before approval from the HRA and notification to the MHRA of a clinical device trial.

2 Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor.

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

For and on behalf of the Study Sponsor:

Signature:

Date:

22/07/2023

.....

Name (please print):

Cellan Griffiths

.....

Position: Director

Chief Investigator:

Signature:

Date:

22/07/2023

.....

Name: (please print):

Adam Holliday

.....

3 Key study contacts

Chief Investigator	Adam Holliday
Study Co-ordinator	Cellan Griffiths
Research team	Adam Holliday - Optometrist Cellan Griffiths - Software developer
Sponsor	EyeV Ltd
Joint-sponsor(s)/co-sponsor(s)	N/A
Funder(s)	EyeV Ltd
Key Protocol Contributors	As above
Committees	N/A

4 Study summary

Study Title	To assess the accuracy of a machine learning tool to diagnose a range of common eye conditions
Internal ref. no. (or short title)	Assessment of the EyeVdoc App
Study Design	Comparative accuracy
Study Participants	Patients with a limited range of eye conditions
Planned Size of Sample (if applicable)	Machine learning accuracy levels of 95% - see section 20.1
Follow up duration (if applicable)	n/a
Planned Study Period	Start tbc (1.10.23) for a max period of 12 months
Research Question/Aim(s)	Assess the accuracy of a machine learning tool to diagnose a range of common external eye conditions. To further train the machine learning tool, to increase accuracy. Contribute to the existing literature. Support the development of an patient facing APP

5 Funding and support in kind

Funder(s) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	Details of financial and non financial support given
EyeV Ltd	£ NIL

5.1 Role of study sponsor and funder

- The study sponsor will monitor the study conduct against applicable regulatory standards.
- The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results.
- The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study.

5.1.1 Declaration of conflict of interest

The CI (Adam Holliday) is also a director of EyeV Ltd.

6 Who we are

EyeV Ltd is a private company providing software solutions. Our software supports the NHS and private healthcare providers. We have designed and developed software to facilitate NHS patient referral processes, both within the NHS and private sectors; these are in use within the North East & Yorkshire and Milton Keynes, Bedfordshire and Luton regions. We have experience at providing patient facing software for ophthalmology services and have good relationships with ophthalmology healthcare providers.

7 Overview of the study

We are working to develop a low-cost machine learning based APP, to diagnose common external eye conditions.

A machine learning tool has been developed and tested, with positive outcomes but the accuracy of the App needs to be tested on a larger diverse population.

8 How will this be achieved:

1. Retrospective review of images collected from an existing NHS eyecare service.
2. Prospectively collect images from patients who present with eye problems.

9 Background

Common eye conditions account for a significant number of clinical visits, with health care clinicians – these maybe GP, optometrist, pharmacists, nurse, AHP or A&E departments. In some areas of the UK there are NHS funded services, for patients to present to a community optometrist (these are called Minor Eye Care services, or Optometry first) the outcome of these visits, for common external eye conditions, is often reassurance or advice on self-management. Where optometry services are not available, it can result in patients attending multiple visits with various clinicians. Considering the capacity and financial pressures on the NHS, this tool could help support capacity issues and reduce financial costs for the NHS.

The literature suggests that machine learning research has been focused on ocular retinal pathology, with a single paper looking at a single exterior condition with the aim of supporting clinical intervention (Abdani et al., 2022)

10 Participant journey

11 Aims / objectives of the study

i. Assess the accuracy of a machine learning tool to diagnose a range of common eye conditions.
ii. To further train the machine learning tool, to increase accuracy.
iii. Contribute to the existing literature.
iv. Support the development of an patient facing APP

11.1 What are the potential benefits of this study

i. Reduce patient anxiety.
ii. Support GRIFT.
iii. Reduce unnecessary clinical appointments.
iv. Increase clinical capacity.
v. Reduce costs to the NHS.

11.2 Common eye conditions being considered

Condition identifier	Diagnosis
A	Ptosis
B	Dermatochalasis
C	Blepharochalasis
D	Allergic conjunctivitis
E	Bacterial conjunctivitis
F	Dry eye
G	Anterior uveitis
H	External hordeolum
I	Internal hordeolum
J	Entropion
K	Ectropion
L	Blepharitis
M	Pterygium
N	Pingquela
O	Anisocoria
P	Sub conjunctival haemorrhage
Q	Episcleritis

11.3 What does the MHRA say

The MHRA were contacted for advice.

"The answer to your question does depend on what market you intend to approach. For GB you can apply a UKCA mark but if you want to be on the NI/EU market you will need a CE mark.

We are updating the GB regulations and will accept a CE mark for a while to come though. See: https://www.gov.uk/government/news/impact-of-extension-of-medical-device-regulations-transitional-period-and-the-validity-of-certificates-in-the-eu

It does sound that the research you are planning would be considered to be a Clinical Investigation and you should look at guidance given here: https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device

David Grainger MSc MIPEM"

Plan

1. Apply to REC via IRAS.
2. Notify the MHRA 60 days in advance of conducting a clinical investigation of a medical device.

12 Study design

The study is based on a comparative accuracy design Bossuyt et al., (2006).

There are two arms to this study, for data collection.

12.1 Inclusion criteria

i. Age: 18 yrs and over
ii. Ability to consent
iii. Being diagnosed with one of the below external eye conditions

12.2 Exclusion criteria

i. No smartphone

12.3 Retrospective analysis of external eye images

From an existing clinical service (Leicestershire, COVID urgent eye service) using images which were provided by patients as part of their clinical care and which a diagnosis was made by a clinician. Consent to use images was given by patients, for use in their clinical care but not for research. A new consent process would be undertaken for use of the images for research process (section 15).

12.4 Prospective data collection

Patient presents to a community optometrists/ophthalmologist, who performs a clinical assessment, provides diagnosis, treatment and management. If the patient has one of the eye conditions being considered in section 10.2, the clinician will discuss study with the patient and if interested in participating, provides the participant with the PIS EyeVdoc leaflet. The clinician will indicate on the PIS EyeVdoc leaflet the clinical diagnosis(s). The participant can then enrol into the online study at a convenient time after the clinical visit.

The consenting process is outlined in Section 15 and the participant will then answer the following questions:

1. Age
2. Gender
3. Ethnicity
4. Condition identifier
5. Smartphone device being used
6. How long have they had the problem
7. Have you they been given any treatment

The participant will then take an image(s) of the eye and upload directly to the study website.

13 Machine learning algorithm & model

The study will use two open-source software programmes, for the development of the algorithm model and subsequent deployment of the model

1. Google AutoML
2.

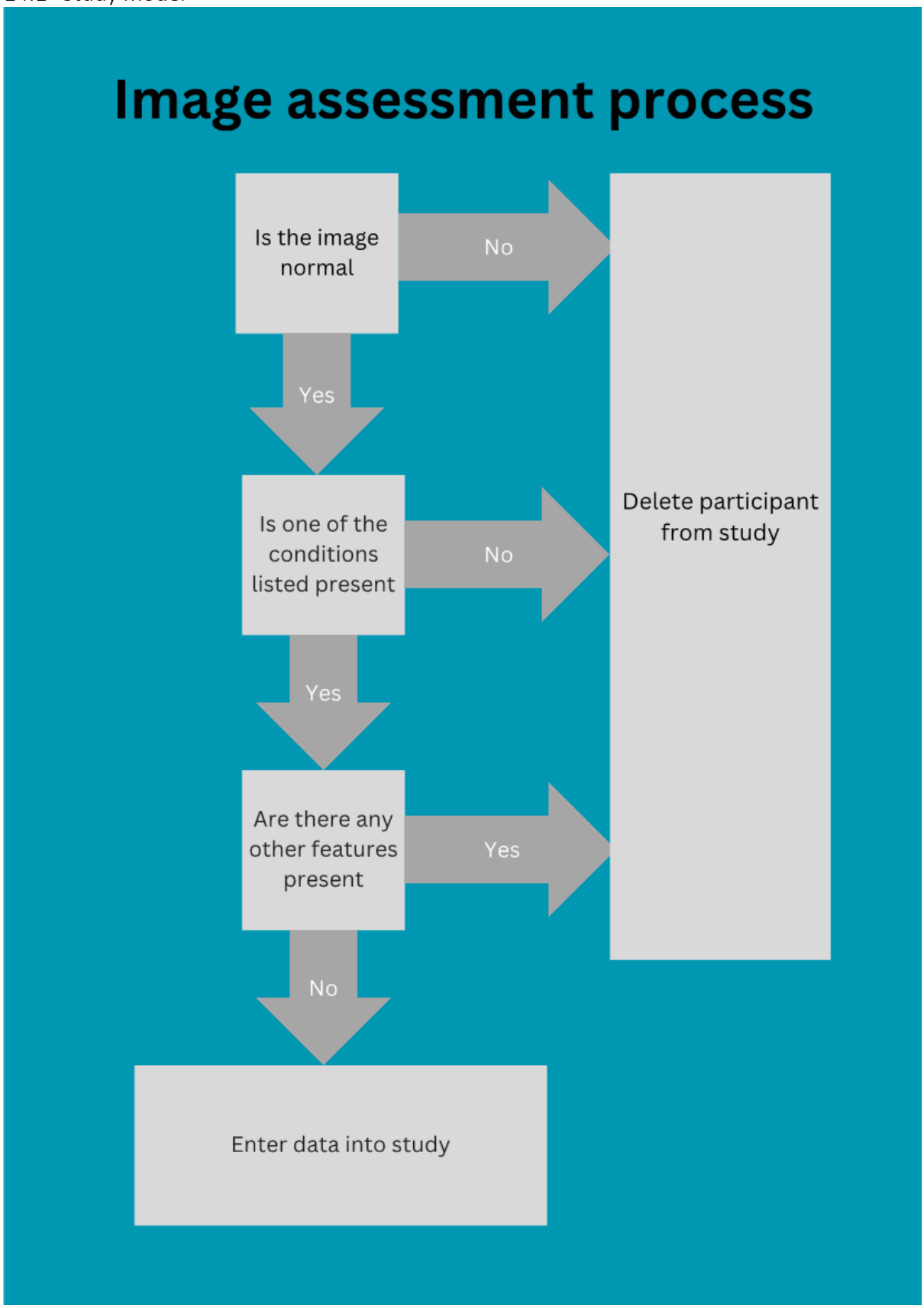
- This will use a supervised ML model.
- It is a cloud-based programme which will be stored locally within our own infrastructure on AWS.
- Images will enter Google AutoML along with a clinical diagnosis(s).
- ND software will ensure that the image is of an eye.
- Linear will label all features, using support vector and decision-making algorithms.
- Within Google AutoML there is an iterative process of train / validation / re train.

2. Tensor flow

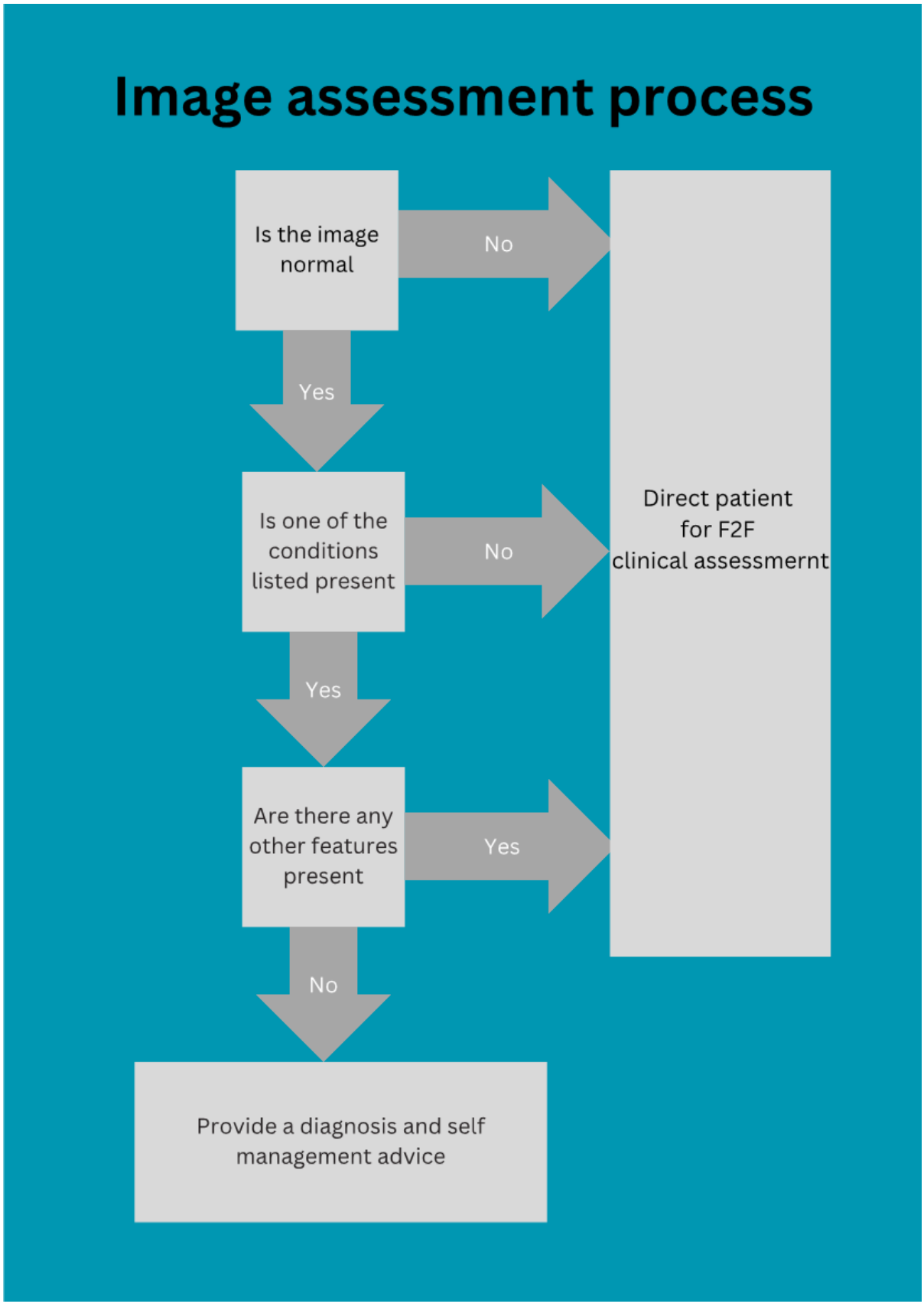
- When the AI model has been fully trained/ developed, it will be exported to Tensor flow.
- This programme will be used in the deployment process.
- Tensorflow allows image assessment at scale.
- This is a cloud-based programme but it will be stored locally within our own infrastructure on AWS

14 Image assessment process flowcharts

14.1 Study model



14.2 Trained model



15 Data collection

1. Review of data base.
2. By community optometrists / ophthalmologists.

16 Study setting

I. Using an existing clinical database of patients – some with images of external conditions outlined in sec 5.2.
II. Community optometry practices.
III. NHS clinical venues; hospital departments, community outreach clinics.

17 Recruitment

17.1 Patient eligibility criteria

i. Over 18 yrs old.
ii. Ability to consent.
iii. Being diagnosed with one of the conditions in sec 10.2.

17.2 Clinician recruitment

Ophthalmologists. Direct communication with colleagues and through a snowballing effect.

Optometrists. An invitation to participate into the study will be sent to clinicians, within the NEY region, Nottinghamshire, Leicestershire, Bedfordshire, Luton and Milton Keynes area.

Calderdale and Huddersfield NHS Foundation Trust's ophthalmology department have agreed to participate in the study

We would seek to recruit as many colleagues as possible to achieve adequate levels of patient participation.

18 Consent

EyeV Ltd have sought the advice of an external data privacy company when considering the consent process. The consenting process is remote or online (Wood, 2011; Wilbanks, 2018)

Retrospective

i. Patients would be contacted either by email or SMS and asked for their consent to use the images which they provided for research processes. This requires a positive responsive from the patient before any data will be incorporated into the study.
ii. If there is no response after 24hrs, a second SMS / email will be sent. If there is no response the patient will be excluded from the study and not contacted again.
iii. To comply with UK GDPR requirements, patients are also able to excise their right to withdraw from any further contact; and this is made available on the email / SMS message.
iv. For any patient to be incorporated into the study, a positive response will be required and we will forward a PIS providing information about the study

Prospective

I. Optometrists / ophthalmologists, will be invited to participate into the study.
II. After the clinical consultation, the clinician will provide potential participants a copy of the PIS with the diagnosis(s) circulated.
III. Potential participants can visit the study website and complete the online consenting process.

19 Data management

This Data Retention Statement outlines the policies and practices for the collection, use, storage, and deletion of data used in the development and training of our machine learning image model. Our commitment is to handle the data responsibly and transparently while ensuring data security and compliance with applicable data protection regulations.

19.1 Types of data

I. Images of the eyes(s)
II. Participant age, gender, ethnicity, email or mobile phone number
III. IP address
IV. Email address – voluntary

19.2 Data format

Electronic only

19.3 Collection

This is provided by the participant.

19.4 Access to study dataset

Only the research team will have access to the participant data.

19.5 Storge

Images and application databases will be stored in the United Kingdom, European Economic Area or United States, providing that the jurisdiction has adequate data security standards, maintains adequacy agreements between territories or is subject to contractual clauses with comparable information governance standards.

We will only store data in data centres with ISO27001 accreditation. We are also accredited to Cyber Essentials Plus standard, which is a scheme operated by the National Cyber Security Centre to ensure good practice in data security.

19.6 Data Collection and Usage

During the development and training of our machine learning image model, we collect a diverse range of images from various sources. This data is essential for the effective performance and functionality of the model. We use the collected data exclusively for the purposes of training, testing, and refining the machine learning model to deliver optimal results.

19.7 Data Storage and Security

We retain the collected data and images for the duration of the machine learning model's development and training process; this will be for a maximum of 5 years. All data is securely stored in accordance with industry best practices, and we take appropriate technical and organizational measures to protect the data from unauthorized access, alteration, disclosure, or destruction.

The data and images collected for our machine learning image model are securely stored on cloud services that are accredited to ISO27001. This internationally recognized standard ensures the implementation of information security management systems to protect the data from unauthorized access, disclosure, alteration, or destruction.

19.8 Data Deletion

Upon the completion of the machine learning model's training, we commit to deleting the data and images from our systems within 12 months. This deletion process will be carried out in a secure and irreversible manner, ensuring that no traces of the data are retained. We continuously review and improve our data deletion processes to ensure full compliance with data protection regulations and industry best practices.

19.9 Data Protection and Compliance

Our data retention practices are designed to be in full compliance with applicable data protection laws and regulations. We take our responsibility to protect user data very seriously and maintain a strong commitment to data security, privacy, and transparency.

19.10 Destruction

19.10.1 Process

This Data Destruction Statement provides an overview of the methods and procedures we employ to securely destroy the data and images used in our machine learning image model. We are committed to ensuring the proper disposal of data in compliance with the highest industry standards and regulations, including ISO27001.

Upon completion of the machine learning model's training, we initiate a secure data destruction process within 12 months. Our data destruction procedures adhere to the following principles:

19.10.2 Secure Deletion

We use advanced data wiping techniques to overwrite the stored data multiple times, ensuring that the original data is rendered unrecoverable.

19.10.3 Cryptographic Erasure

If applicable, we employ cryptographic erasure to delete encryption keys associated with the data, rendering the data unreadable and unrecoverable.

19.10.4 Physical Destruction

For any data that may be stored on physical media, we use secure methods of physical destruction, such as degaussing or shredding, to ensure the data is irretrievably destroyed.

19.10.5 Documentation and Verification

We maintain detailed records of our data destruction process, including dates, methods, and the responsible parties involved. Regular audits and assessments are conducted to verify that our data destruction methods are effective and compliant with ISO27001 and other relevant standards.

19.10.6 Third-Party Services

When working with third-party cloud services, we require them to adhere to our strict data destruction policies and verify their compliance with ISO27001 standards.

19.10.7 Data Destruction Compliance and Commitment

Our data destruction practices are designed to be in full compliance with applicable data protection laws, regulations, and industry best practices, including ISO27001. We take our responsibility to protect user data very seriously and maintain a strong commitment to data security, privacy, and transparency.

19.11 Data protection and patient confidentiality

AH is an experienced DPO and clinical safety officer and CG is the privacy officer for EyeV Ltd.

19.12 Indemnity insurance

This is provided by Cyber Essentials Plus Accreditation.

20 Data analysis

The aim of the project is to assess the accuracy of a machine learning tool to diagnose common external eye conditions, using smartphone cameras. Accuracy, quantifies how near the outcomes are to the natural or known value and in this study compares the clinical diagnosis provided by the clinician to the diagnosis given by the machine learning tool. The accuracy is quantified as a percentage value and the accuracy will be calculated for each combination of variables in Table 20-1 Statistical analysis will be performed and used for publication and the development of the APP. External statistical advice will be obtained.

Table 20-1 Collected data for each participant

Participant number	Condition number	Multiple conditions	Accurate	Smartphone device	Age	Gender	Ethnicity

20.1 Sample size

It is difficult to estimate sample sizes and measurable effect sizes for machine- learning based studies and the literature suggests that the standard approach to sample size calculations are not applicable but the sample size is considered suitable when it has appropriate effect sizes (≥0.5) and machine learning (ML) accuracy (≥80%). However, due to the paucity of literature our aim to obtain 95% ML accuracy, for all the conditions list in 10.2. We estimate that 10 participants will be required for each condition to achieve this.

In the closely related field of medical decision support systems, a commonly adopted rule of thumb for determining sample size is to require two participants, per feature in the model. It is speculated (Riley, 2020) that ML models will require larger sample sizes compared to simpler statistical models; to facilitate this we intend to use previous collected images to facilitate training of the ML model (sec 11).

21 Ethical and regulatory considerations

1. Regulatory considerations: Notify the MHRA 60 days in advance of conducting a clinical investigation into the medical device.
2. Ethical: There are potentially 2 ethical considerations associated with image collection and these are:

I. Biometric recognition. Some of the images may contain pictures of the iris, which have been used in biometric recognition. This could potentially enable patient identification from the image of an iris. Currently there are no national databases containing this information and so this is a theoretical risk.

II. Facial recognition. Some images may contain facial features which enable identification.

22 Data management

1) All data is only available to the study team – data is managed as per the data management protocol.
2) There are no iris biometric recognition databases.
3) Facial recognition is potentially possible, but data is managed per the data management protocol.

23 Research Ethics Committee (REC) and other Regulatory review & reports

The study has been reviewed by:

i. R&D team at Calderdale and Huddersfield Foundation Trust
ii. HRA ethic committee

The study will be registered with

i. MHRA
ii. ISRCTN

24 Peer review

This study has been reviewed by clinical colleagues: optometrists and ophthalmologists.

25 PPI

No PPI involvement has been sought. However, the participant facing website, PIS and protocols have been reviewed by:

i. Clinical colleagues
ii. Non clinical colleagues
iii. R&D team at Calderdale & Huddersfield hospital
iv. Research fellow in health data science

26 Complaints

Any complaints should be addressed to the chief investigator

27 Outcome & dissemination

1) The data will be published in peer reviewed journals
2) Participants will be sent a copy of the paper if they have indicated at consent they would like to be sent a copy – participants will need to supply an email address.

27.1 Glossary

Optometrist	Optometrists are trained to examine the eyes to detect defects in vision, signs of injury, ocular diseases or abnormality
Ophthalmologist	Surgical and medical specialists able to perform operations on eyes
Ptosis	Drooping of the upper eyelid
Dermatochalasis	Excess eyelid skin
Blepharochalasis	Active stage of recurrent episodes of upper lid swelling
Allergic conjunctivitis	An inflammatory response of the conjunctiva to an allergen
Bacterial conjunctivitis	An infection of the eye in which one or both eyes become red, watery and sticky, often with discomfort but not pain
Dry eye	Inflammation of the conjunctiva and cornea of the eye, due to inadequate tear secretion.
Anterior uveitis	Inflammation of the iris and/or ciliary body
Stye (External hordeolum)	Blockage of the sebaceous (Zeiss) glands or sweat (Moll) glands
Chalazion (Internal hordeolum)	Chronic sterile Lipogranuloma
Entropion	Inward turning of the eyelid margin
Ectropion	Outward turning of the eyelid margin
Blepharitis	Inflammation of the eyelid.
Pterygium	Ocular surface lesion originating in the limbal conjunctiva, extending over the cornea
Pingquela	Ocular surface lesion originating in the limbal conjunctiva
Anisocoria	Unequal pupil size.
Sub conjunctival haemorrhage	Small amount of bleeding takes place beneath the conjunctiva
Episcleritis	Unilateral or bilateral inflammation of the episclera, the thin layer of tissue between the conjunctiva and sclera

28 Version control

Date	Modification	Date completed	Person responsible
20.5.23	2 additional questions added to website Sec 12.2 amended	20.5.23	AH
07.07.23	Inclusion Sec 13 Machine learning algorithm & model	07.07.23	AH
07.07.23	Inclusion Sec 14 Image assessment process	07.07.23	AH
07.07.23	Sec 20.1 Sample size – details amended	07.07.23	AH
10.07.23	Sec 13.1 Change from Linair.ai to Google Auto ML	10.07.23	AH
10.07.23	Sec 3. Karnesh Patel Consultant ophthalmologist removed	10.07.23	AH
11.7.23	Sec 21 i) addition to regulatory considerations	11.07.23	AH
11.7.23	Sec 23. Amendments to text	11.07.23	AH
11.7.23	Sec 20.3 Sample size text amended	11.7.23	AH

Date	Modification	Date completed	Person responsible
21.7.23	Sec 18. Prospective consenting process wording changed from "After the consultation and data has been uploaded the patient will sent a copy of the consent form (see consent form document) by SMS or email. For their data to be used in the study a positive response will be required. If a positive response is not received within 72hrs then the patient data will deleted from the study website. "	21.7.23	AH
21.7.23	Sec 25. PPI updated	21.7.23	AH
21.7.23	Sec 5.1.1 Added – COI	21.7.23	AH
21.7.23	Sec 14.1 flow chart added	21.7.23	AH

29 References

Abdani, S.R., Zulkifley, M.A., Shahrimin, M,I. and Zulkifley, N,H. (2022) Computer-Assisted Pterygium Screening System: A Review. Diagnostics (Basel).Mar 5;12(3):639.

Arnold, S.L, Arnold, A.W, Sprano, J.H, and Arnold, R.W. (2019) Performance of the 2WIN Photoscreener With "CR" Strabismus Estimation in High-Risk Patients, Am. J. Ophthalmol. , 207, 195–203

Aslam, T.M, Tan, S.Z, and Dhillon, B. (2009) Iris recognition in the presence of ocular disease. J R Soc Interface, May 6;6(34):489-93.

Biometrics institute. Ethical principles for biometrics

Bossuyt, P.M, Irwig, L, Craig, J. and Glasziou, P. (2006) Comparative accuracy: assessing new tests against existing diagnostic pathways, BMJ, May 6;332(7549):1089-92.

Daniyal, R, Wei-Jen, W, and Chun-Chuan, C.(2023) BMC Bioinformatics, 24:48. Available from:

Han, J.H. (2022) Artificial Intelligence in Eye Disease: Recent Developments, Applications, and Surveys, Diagnostics (Basel), Aug 10;12(8):1927.

NEC AI principles

Raudys, S.J, Jain, A.K. (1991) Small sample size effects in statistical pattern recognition: recommendations for practitioners. IEEE Trans Pattern Anal Mach Intell 1991;13:252–64

Riley, R.D, Ensor,J, Snell, K.I, Harrell, F.E, Martin, G,P, Reitsma, J,B, Moons, K,G, Collins G and Van Smeden, M.(2020) Calculating the sample size required for developing a clinical prediction model, *Bmj,* Mar 18;368.

Wilbanks, J. (2018) Design issues in E-consent, *The Journal of Law, Medicine & Ethics,* 46 (1), pp. 110-118.

Wood, F, Kowalczuk, J, Elwyn, G, Mitchell, C. and Gallacher, J. (2011) Achieving online consent to participation in large-scale gene-environment studies: A tangible destination, *Journal of Medical Ethics,* 37 (8), pp. 487-492. https://www.locsu.co.uk/what-we-do/pathways/minor-eye-conditions-service-2/