Imperial College London

AI-ECG Accessory Pathway Localisation Study

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STUDY COORDINATION CENTRE: Dr Ahran Arnold
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Protocol authorised by:

Name & Role	Date	Signature
Dr Ahran Arnold Investigator	07/08/2024	Dr Ahran Arnold

Study Management Group

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Study Coordination Centre

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Clinical Queries

Clinical queries should be directed to Dr Keenan Saleh who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Head Research Governance and Integrity
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
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https://www.imperial.ac.uk/research-and-innovation/research-office/research-governance-and-integrity/

Funder

This study is funded by Innovate UK.

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the **UK Policy Frame Work for Health and Social Care Research.** It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATION

AI	Artificial intelligence
ECG	Electrocardiogram
EPS	Electrophysiology study
PPG	Photoplethysmography
HCP	Healthcare professional

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STUDY SUMMARY

TITLE	AI-ECG Accessory Pathway Localisation Study
DESIGN	Prospective validation study
AIMS	1) To develop and finalise a machine learning algorithm to localise accessory pathways from the 12-lead ECG. 2) To prospectively validate machine learning algorithms for accessory pathway localisation through a clinical trial.
OUTCOME MEASURES	• **Key deliverable:** A prospectively validated AI algorithm for accessory pathway localisation, which can produce reliable, reproducible and accurate outputs **Outcome measures:** • Overall accuracy of the AI algorithm predictions, as compared to the operator assessment. • Overall accuracy of the AI algorithm predictions, as compared to the ground truth of successful ablation location determined by fluoroscopy ± 3D mapping. • Sensitivity, specificity, positive and negative predictive values, and F1 score of the ECG AI algorithm for accessory pathway localisation • Difference in accuracy between the AI algorithm prediction and human estimation from the 12-lead ECG. • Difference in accuracy between the AI algorithm and pre-specified, established manual localisation algorithms (Arruda, Milstein, Pambrun, Boersma, D'Avila and Chiang). • Correlation of accessory pathway localisation by human estimation, and manual algorithm output as compared to the true location on 3D mapping.
POPULATION	Patients referred for an EPS
ELIGIBILITY	Inclusion Criteria 1) Age 13 - 100 years old 2) Referred for invasive electrophysiological study as part of their usual clinical care 3) Manifest pre-excitation on their ECG any time prior to their procedure 4) Able to give consent Exclusion criteria 1) Patients with known location of their accessory pathway from a previous EPS 2) Age <13 years old 3) Age > 100 years old
DURATION	1st March 2025 – 1st March 2027

1. INTRODUCTION

1.1 BACKGROUND

Accessory pathways are congenital cardiac abnormalities that can enable electrical impulses to bypass normal atrioventricular nodal conduction. This leaves patients at risk of supraventricular tachycardias and even sudden death in the case of pre-excited atrial fibrillation. The location of an accessory pathway can be definitively established by successful ablation. It is desirable to localise a suspected accessory pathway prior to an invasive electrophysiological study both to guide procedure planning and to personalise the consent process: pathway location determines much of individual procedure risk.

Accessory pathway location can be estimated from the 12-lead ECG using either human expertise or manual localisation algorithms that rely on specific ECG features. These approaches are subject to inter-operator variability and are often time consuming and difficult to perform for inexperienced users, respectively. Validation studies of these algorithms have not shown high accuracy, or even reproducibility in some cases. These studies are also problematic due to being either retrospective, using strict eligibility criteria not representative of clinical practice, or validation cases being entirely non-external.

Artificial intelligence has been increasingly investigated for its role as a high-performance predictive tool in healthcare and beyond. Machine learning algorithms can reproducibly classify medical data with very high levels of accuracy. Within cardiology, AI has been successfully applied to ECG interpretation for several cardiac conditions. Our group has developed a proof-of-concept AI algorithm for accessory pathway localisation, which has demonstrated an accuracy of 93% when retrospectively applied to 156 12-lead ECGs (left vs septal vs right).

To formally validate the real-world accuracy of this AI algorithm for accessory pathway localisation, it is imperative that: 1. The algorithm is tested **prospectively**; 2. The algorithm is tested on **consecutive** cases, avoiding cherry-picking; 3. The tested algorithm is locked such that it cannot be influenced by any new data during testing. 4. The testing cohort must include **external** cases, to avoid AI overfitting and test generalisability. These standards are essential for robust validation and to provide a genuine assessment of the accuracy for the algorithm before real-world application and use in clinical practice.

2. STUDY OBJECTIVES

Primary objectives

1) To finalise a testable ECG AI algorithm for accessory pathway localisation.
2) To prospectively validate the accuracy of the ECG AI algorithm for accessory pathway localisation, as compared to the ground truth of successful ablation location (determined by fluoroscopy ± 3D mapping) through a prospective clinical trial on consecutive unseen cases.

Secondary objectives

1) To evaluate the relative performance of the AI algorithm compared to human interpretation and conventional manual algorithms.
2) To compare the accuracy of ground truth locations to complete annular maps from 3D electro-anatomical mapping.

3. STUDY DESIGN

3.1 RECRUITMENT

We aim to recruit 100 patients for a prospective validation study of our AI algorithm for accessory pathway localisation. The direct care team will screen the records and identify patients followed up at Imperial College Healthcare Trust.

Patients will be contacted by members of their direct care team. This will occur either when they attend for routine appointments or during inpatient admission. The direct care team will obtain consent to share patients' information with the research care team. Once the patient has consented to their information being shared, a member of the research team will contact the patient and explain the details of the research study. The patient information leaflet will be provided to the patient via post or electronically via email with the patient's permission.

If the patient is agreeable, they will be formally consented on the day of their clinical EP study procedure by a member of the research team. Written consent will be gained prior to any data being collected or participation in the research protocol.

All patients recruited to this study must have had an ECG demonstrating manifest pre-excitation at any time prior to their EPS.

3.2 METHODOLOGY

Data collection
All data will pseudonymised at the point of collection by the direct care team. Pseudonymised and anonymised data will be securely held password protected computers at Imperial College London (Sponsor). Pseudonymised data will be kept separately from the key that identifies it and separately from data with the patients name, hospital number, address and NHS number. With the consent of the patient and clinical care team medical information such as procedure reports will be obtained. These data will be kept separate from identifiable personal data. All identifiable information will be securely held in NHS Trust computers and will be held in strict compliance to NHS Data Protection and Confidentiality regulation. Patient identifiable information will not be shared from external institutions.

AI algorithm testing
The AI algorithm has been trained using raw, digital 12-lead ECG data from patients with manifest accessory pathways who underwent successful ablation. The training data was labelled using associated procedure reports, fluoroscopy and electro-anatomical map data. The algorithm will output the location of an accessory pathway (left vs right, anterior vs posterior, septal vs lateral).

At commencement of the prospective validation study, the final AI accessory pathway localisation algorithm will be locked so that it cannot be trained on any new input data. This will be confirmed by an independent researcher. Using a digital 12-lead ECG as the input, the algorithm will output the categorical location of the pathway; this will be provided as a transverse axis location (left, septal, right) and a vertical axis location (anterior, mid, posterior).

Participants who agree to be recruited to the prospective validation study will undergo 12-lead ECG recordings via conventional digital ECG machines and EP recording systems during their EP study. These ECGs will be analysed at Imperial College London, where the AI algorithm will be applied to determine the AI-predicted location. At the time of their EP study, the successful ablation location will be recorded by the operating physician (estimated

from fluoroscopy). The proportion of ECGs correctly predicted by the AI algorithm, matching the operator assessment, will be the primary outcome measure of AI accuracy.

Data separation
AI processing of participant ECG data will be undertaken on Imperial College London computers. All linked procedural data from the EP study (i.e. 3D electroanatomical mapping data, human operator prediction, procedure report and fluoroscopy frames) will be strictly separated from the AI algorithm. The AI algorithm will be applied by a researcher, blinded to the true accessory pathway location, and the resulting output will be stored separately. We will maintain strict division of data so that researchers inputting ECG data into the AI algorithms and analysing its outputs are analysed independently of the operator predictions, thus minimising any performance bias. An independent researcher will act as a monitor for the research protocol. Finally, the human operators and team performing the ablation will have no access to the outcome of the AI prediction at any point.

Operator workflow
Using the patient's 12-lead ECG, the operator will be asked to make a prediction of the accessory pathway location within the case report form prior to the start of the procedure, which can be performed using their own analysis or via a manual algorithm (such as Arruda), according to their preference.

All patients will undergo their planned EP study. There will be no change to their clinical treatment. As part of the procedure, operators will be able to perform their usual procedural workflow for accessory pathway identification and ablation, whether that be using electroanatomical mapping, fluoroscopy or electrograms or a combination of these. As part of the data collection during the case, we request operators to collect the following data to determine the true accessory pathway location:

- The electroanatomical location of the final ablation lesion which resulted in loss of pathway conduction, which should be tagged.
- Sufficient electroanatomical geometry to produce a complete annular map on the side of the accessory pathway, to accurately assess the true location of the accessory pathway on the annulus
- The fluoroscopy image demonstrating the catheter position on pathway ablation.

Burdens/Risks:

Patients will be subject to the small risk of their EPS procedure. The risk of this procedure includes a < 1% risk of bleeding / vascular injury, bleeding around the heart, heart attack and death. No additional risk will be conferred as part of this study as the patients will not require any additional instrumentation, monitoring or manoeuvres beyond usual routine clinical care.

Furthermore, ionising radiation will be used as part of the procedure through the use of fluoroscopy to site catheters in the correct location and change their position. We expect around 1 minute total fluoroscopy time. Appropriate radiation regulations will be followed.

Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer is estimated as 0.006% (Risk coefficient for adult population is 5x10-5 per mSv, HPA-CRCE-028) and the risk of the additional radiation to routine care is about 0.00015%. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

3.4 STUDY OUTCOME MEASURES

Primary Outcome Measures

- A prospectively validated AI algorithm for accessory pathway localisation, which can produce reliable, reproducible and accurate outputs.
- Overall accuracy of the AI algorithm predictions, as compared to the operator assessment.

Secondary Outcome Measures

- Sensitivity, specificity, positive and negative predictive values, and F1 score of the ECG AI algorithm for accessory pathway localisation.
- Difference in accuracy between the AI algorithm prediction and human estimation from the 12-lead ECG.
- Difference in accuracy between the AI algorithm and pre-specified, established manual localisation algorithms (Arruda, Milstein, Pambrun, Boersma, D'Avila and Chiang).
- Overall accuracy of the AI algorithm predictions, as compared to the ground truth of successful ablation location determined by fluoroscopy ± 3D mapping.
- Correlation of accessory pathway localisation by human estimation, and manual algorithm output as compared to the true location on 3D mapping

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Subjects will be recruited at the research site.

4.2 INCLUSION CRITERIA

FOR STUDY A:

1. Referred for EPS procedure as part of their clinical care, with a finding of pre-excitation on their ECG
2. Manifest pre-excitation on their ECG any time prior to their procedure
3. Able to give consent
4. Minimum age 13 years old
5. Maximum age 100 years old

4.3 EXCLUSION CRITERIA

- Unable to give consent
- Adults > 100 years old
- Children < 13 years old
- Patients with known location of their accessory pathway from a previous EP study

4.4 WITHDRAWAL CRITERIA

The research protocol will be terminated early if:

1. Patients lose their capacity to consent or become clinically unstable
2. The patient chooses to withdraw from the study
3. The sponsor, the chief investigator or the research team review the data and decide to stop the study

4.5 CONSENT

Patients will be identified by members of their direct care team when they attend clinic appointments or are admitted to the hospital. Patient records may be reviewed to assess suitability and this will be performed by members of the direct care team. Participation in the

study will be discussed with the patients by their direct care team and information will only be passed on to the research team with the patients consent. Verbal consent will be gained by the direct care team for personal contact information to be shared with the research team. This will be documented in the patient notes. The direct care team will make patients aware that participation is voluntary and that if they do not wish to participate it will not affect their usual care.

Written consent for the study will be obtained by a member of the research team, this will be a physician who is experienced in performing electrophysiology study procedures. Patients will have details of the study discussed with them and any family members or friends the patients wish to be present. They will also be provided with written information (patient information sheets). Patients will be given as much time as they wish, with a minimum of at least 24 hours, to decide whether they wish to participate in the study and will be offered additional visits to further discuss the study if they wish. Patients are able to withdraw their consent from the study at any time. Patients will be made aware that their participation is voluntary and that if they do not want to take part it will not affect their usual care. Patients who agree to take part in the study will sign a consent form, a copy of the form will be given to the patients and a second copy will be kept in their study record file. A copy will also be kept in the site file.

Conflicts of Interest:
There are no conflicts of interest to report.

Dissemination of Results:
The results will be disseminated to the scientific community through peer reviewed journal publications, internal reporting, publication on website and conference presentations. Identifiable information will not be included in the publication. Depending on patients' preferences we will either write, telephone or arrange to meet participants after the analysis has been completed. We will summarise the findings and details of how the results are relevant to them.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non-serious AEs

All such events, whether expected or not, should be recorded.

5.2.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Scotland B REC (25/SS/0034) where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
Dr Ahran Arnold email: ahran.arnold@imperial.ac.uk
Please send SAE forms to: Hammersmith Hospital, Du Cane road, London W12 0HS.
Tel: 020 8383 4967 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT & FOLLOW UP

Patients will not be followed up beyond the time of their EPS procedure, as all the required data will be available at that time. The study end point will thus be at the completion of their EPS procedure. The study will end after 100 patients have been recruited or by the study end date.

As the study protocol does not deviate from routine clinical care, no incidental findings are expected related specifically to clinical research. While incidental findings can be seen in the context of the routine clinical EPS procedure, these will actioned by the clinical care team as is usual practice.

7. STATISTICS AND DATA ANALYSIS

We aim to recruit 100 patients to undergo the AI algorithm prospective validation study. Based on retrospective pilot data of our accessory pathway localisation AI algorithm, we determined the accuracy of the AI algorithm to be 93% accurate and the next best manual algorithm prediction to be 77% accurate. Assuming the same accuracy in the prospective study, using a one-way two sample t-test, 91 participants would be needed to provide 90% power at the 5% significance level.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Scotland B REC (25/SS/0034) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Children from 13 to 17 years old will also be recruited as part of this study. Separate patient information sheets and consent forms will be provided to children depending on their age to meet their language comprehension level. One will be aimed for 13-15 year olds, and one for 16-17 year olds. Children aged 13-15 years old will be provided a tailored information sheet with simpler language. They will be consented with their parental guardian present, who will be able to consent on the behalf of the child. Children aged 16-17 years old will be provided with a separate tailored information sheet but will be able to consent for themselves.

8.3 CONFIDENTIALITY OF RECORDS:

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London hold negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

Innovate UK are funding this study.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research

9. STUDY MANAGEMENT

The clinical day-to-day management of the study will be co-ordinated by Dr Keenan Saleh.

10. PUBLICATION POLICY

Our aim to publish in a major international cardiology journal and present at international cardiology conferences.