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UNMASKING CONCEALED ARRHYTHMIA SYNDROMES

MAIN SPONSOR: Imperial College London
FUNDERS: British Heart Foundation, Imperial Biomedical Research Centre
STUDY COORDINATION CENTRE: Dr Keenan Saleh
IRAS Project ID: 330619

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Protocol authorised by:

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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:

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https://www.imperial.ac.uk/research-and-innovation/research-office/research-governance-and-integrity/

Funder

This study is funded by the Imperial Biomedical Research Centre.

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

AUC	Area under the curve
ARVC	Arrhythmogenic right ventricular cardiomyopathy
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
Echo	Echocardiogram
HCM	Hypertrophic cardiomyopathy
ICC	Inherited cardiac conditions
LQTS	Long QT syndrome
NN	Neural network
RASE	Rare Arrhythmia Syndrome Evaluation
RBBB	Right bundle branch block
UHF-ECG	Ultra-high frequency electrocardiography
VT	Ventricular tachycardia
VF	Ventricular fibrillation

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STUDY SUMMARY

TITLE	Unmasking Concealed Arrhythmia Syndromes
DESIGN	Proof-of-concept studies to develop ECG AI algorithms, followed by case-control diagnostic accuracy study and prospective cohort studies
AIMS	1. To develop machine learning algorithms for 12-lead ECGs to detect diagnostic features of Brugada syndrome. 2. To test and validate these algorithms prospectively in participants wearing ambulatory ECG recording devices. 3. To ascertain the role of UHF-ECG for risk stratification in patients with inherited arrhythmogenic conditions
OUTCOME MEASURES	• Brugada ECG algorithm sensitivity, specificity and AUC value for both 12 lead ECGs and 12 lead vest ECGs • Yield of extended duration multi-electrode ambulatory ECG monitoring to detect the Brugada ECG pattern in concealed Brugada syndrome • The utility of extended duration multi-electrode ambulatory ECG monitoring to detect a single case of underlying Brugada or LQTS manifestation in idiopathic VF
POPULATION	Healthy volunteer controls, patients with a diagnosis of Brugada syndrome, patients with a diagnosis of idiopathic VF syndrome and patients with other inherited arrhythmogenic conditions
ELIGIBILITY	Participant sets (Appendix 1): • Group A – healthy volunteers • Group B – concealed arrhythmia syndrome patients (patients with a normal ECG with a known underlying arrhythmic diagnosis) • Group C – manifest arrhythmia syndrome patients (patients with an arrhythmic syndrome with an abnormal ECG)
DURATION	November 2023 – November 2026 (3 years)

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1. INTRODUCTION

1.1 BACKGROUND

Sudden cardiac arrest is often the first clinical presentation of an inherited arrhythmia syndrome (1). In up to 37% of young sudden cardiac arrest survivors, no clear cause is identified despite comprehensive clinical evaluation (2). These patients and their relatives, who are likely to harbour a genetic predisposition for life-threatening arrhythmias, can remain undiagnosed for years as phenotypic changes may not be apparent at the time of their assessment. Patients with these concealed arrhythmia syndromes can also present with syncope or palpitations with apparently normal cardiac investigations at the time of presentation. If a diagnosis cannot be made, they cannot be protected from their potential risk of sudden arrhythmic death.

Concealed arrhythmia syndromes may manifest themselves transiently during day-to-day physiological provocations such as peaks, troughs and sudden changes in cardiac autonomic tone. For example, long QT syndrome can manifest immediately after exercise, while Brugada ECG patterns can emerge during fever and deep sleep (3). It is not currently practicable to conduct sufficiently prolonged and detailed ECG assessment to sensitively detect these transient electrical manifestations. Instead, we are currently obliged to conduct short term provocation tests, using exercise, orthostasis, and drugs, which have low diagnostic yield and (in the case of ajmaline) can induce fatal arrhythmias (4). Invasive electrophysiology studies and genetic testing can identify some rare cases but are most often non-contributory (5–7).

We postulate that novel non-invasive ECG-based diagnostic techniques and long term ambulatory monitoring may further augment our ability to detect these concealed arrhythmia syndromes.

2. STUDY OBJECTIVES

Primary objective: To combine novel non-invasive ECG techniques and long term ambulatory ECG monitoring to unmask concealed arrhythmia syndromes

Secondary objective: To explore the utility of non-invasive ECG techniques for arrhythmic risk stratification

3. STUDY DESIGN

3.1 RECRUITMENT

Brugada ECG AI training
We will collate anonymised Brugada ECG data from UK and international centres. We will collaborate with site-specific representatives to coordinate secure ECG data transmission and acquisition. All ECG data will be anonymised at the point of collection. Consent will not be sought as only anonymised ECGs will be obtained. There will be no access to patient-identifiable data from the research team and all data will be fully anonymised prior to transfer. These ECGs will be acquired from pre-existing hospital digital infrastructure, namely the electronic health record or ECG data management system. Data will be transmitted securely through trusted secure data transfer systems where available. Where this option is not available, ECG data will be physically retrieved via a researcher visiting the centre and copying anonymised data onto an encrypted hard drive.

We will acquire digital ECG recordings as well as scanned paper ECGs of patients with established Brugada syndrome. Paper ECGs will be scanned and imported onto local secure storage. We will also gather anonymised ECG data from Imperial College Healthcare NHS Trust patients. We aim to acquire around 3000 patient ECGs in total for AI training. Where available, corresponding clinical data will also be collected alongside participants' ECGs, including results of any relevant genetic testing and other investigations including ajmaline provocation testing.

Prospective studies
200 patients will be recruited in total. The direct care team will screen the records and identify patients followed up at Imperial College Healthcare Trust that are suitable for the study. Patients will also be identified at several national ICC centres, via our collaborators, and invited to attend the Imperial College London Pert Rose Research Unit for recruitment into our study.

We will recruit 3 groups of participants:

- Group A – healthy volunteers
- Group B – patients with a normal ECG and an underlying inherited arrhythmic syndrome
- Group C – patients with an arrhythmic syndrome with an abnormal ECG

We will be aiming for an approximately even distribution of participants to be recruited to each group.

The direct care team will obtain consent to share their 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. Written consent will be gained prior to any tests taking place.

3.2 SPECIFIC TECHNIQUES USED IN STUDY

Ambulatory ECG monitoring: Participants will be fitted with various ECG monitoring devices to capture prolonged ECG recordings. These will include commercially used Holter monitors up to 12-leads, research grade CE-marked cardiac monitoring devices and wearable ECGs which can be applied for days to weeks at a time to capture long term rhythm recordings.

Ultra High Frequency ECG: Our centre is a pioneer in using Ultra-High Frequency ECG (UHF-ECG) to detect, isolate and amplify high frequency components that are filtered out in conventional ECGs. These frequencies (1-2kHz) do not travel far: each chest lead measures only activation of its nearest ventricular wall. We will perform UHF-ECG recordings in our participants to better characterise changes in QRS morphology and activation for diagnosis and risk stratification of arrhythmia syndromes. The UHF-ECG machine is CE-marked.

3.3 METHODOLOGY

Study A: Brugada ECG AI development
The research team will collate at least 3000 ECGs, representing the 3 different categories previously mentioned. All ECGs will be either digital or converted to a digital format using in-house developed software. ECGs will subsequently be processed to enable direct extraction of the ECG complexes from the recordings. The resulting ECG data will be segmented to enable labelling by experts in Brugada ECG analysis.

The anonymous ECG data will be reviewed and annotated by experts. Each ECG will be labelled by 5 individual experts from a larger pool of experts, who will collectively share the task of ECG labelling for our entire training set. Experts will be comprised from the ICC specialists at Imperial College Healthcare NHS Trust, as well as our research collaborators within the UK and internationally. The categorisation of each case will be determined by expert majority agreement.

The labelled ECG data will be divided into the training set (75% of ECG data) and a separate hold-out validation set (25% of ECG data). The training set will be used to train separate neural networks (Appendix 2). Once the neural networks have been developed, they will be tested for their accuracy against a hold-out validation dataset.

Study B: Remote arrhythmia diagnostics
In this study, we will undertake validation studies to assess the robustness, accuracy and applicability of the aforementioned AI algorithms (i.e. neural networks) on ECG recordings from several different ambulatory monitoring modalities. This protocol will encompass participants recruited in Groups A-C.

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Protocol
Participants will undergo the consent process and testing during a single research visit. The steps will include the following:

- Participants will be counselled regarding the research study and written informed consent will be obtained.
- All participants will undergo a 12-lead ECG and ultra-high-frequency ECG recording.
- Group A participants will additionally undergo an echocardiogram to ensure that they have a structurally and electrically normal heart.
- All participants will undergo testing with different ambulatory ECG modalities, depending on availability and resources. This will include Holter monitoring up to 12 leads, wearable cardiac monitoring devices (namely the Boston Scientific BodyGuardian MINI) and other wearable ECG technologies. These devices will be fitted by a member of the research team.
- Participants will be instructed how to maintain continuous ambulatory ECG recording via their device as far as possible, including during day-to-day life and including during sleep. Provisions of additional adhesive patches and devices may be required to facilitate long term monitoring up to 3 months.
- Participants will be provided with a digital symptom and activity diary via email to record their daily activity diary, the occurrence of any arrhythmia-related symptoms and gather real-time feedback on tolerability of their monitoring device. In patients who do not have an email, a paper symptom/activity diary will be provided.
- Data will be remotely uploaded onto the cloud via secure digital infrastructure or housed securely on the cardiac monitoring device.
- Participants will be provided with pre-paid parcels with courier collection for retrieval of the ambulatory ECG devices and wearable ECGs at the end of the 3 month study period.

Application of ECG AI to ECG recordings
ECG recordings will be downloaded onto local storage. The digital ECGs will be processed and denoised using specialized algorithms developed by the research team. The previously developed ECG AI algorithms for Brugada syndrome will subsequently be applied to the cleaned ECG recordings for all patient groups.

We will establish the sensitivity for the Brugada classification algorithms on recordings from patients with manifest Brugada syndrome (Group C) and their specificity using the recordings from the healthy volunteers (Group A). The algorithms will also be applied to

patients with concealed arrhythmia syndromes (Group B) to determine the diagnostic yield of different ambulatory ECG recording modalities for different time durations. We will apply both the in-house developed Brugada ECG AI algorithms as well as existing ECG AI algorithms developed by external academic or industry collaborators, to investigate for underlying concealed arrhythmias.

Ultra-high-frequency ECG analysis
High frequency bandwidth ECG data obtained via ambulatory ECG recordings will also be processed to extract high frequency components for signal averaged UHF-ECG analysis. This will be used to investigate for characteristic UHF-ECG profiles synonymous with underlying Brugada syndrome.

Manual ECG review with physiological and activity data
We will also manually analyse ECG recordings coinciding with day to day physiological stressors using activity diaries to look for transient manifestations of concealed arrhythmia syndromes.

Study C: Arrhythmic risk stratification using UHF-ECG
This protocol will encompass participants recruited to Groups A-C

Protocol
Participants will undergo the consent process and testing during their initial research visit. The steps will include the following:

- Participants will be counselled regarding the research study and written informed consent will be obtained.
- All participants will undergo a 12-lead ECG and ultra-high-frequency ECG recording for up to 5 minutes in duration.
- Patients will be followed up prospectively for instances of ventricular arrhythmias, aborted cardiac arrest or sudden cardiac death.

Ultra-high-frequency ECG analysis
We will utilise computational modelling to determine the degree of QRS fractionation within the UHF-ECG profile. We will also investigate the role of other metrics and parameters to analyse UHF-ECG fragmentation. These data will be used to assess the value of QRS fractionation as a surrogate for arrhythmic risk in patients with underlying inherited arrhythmic or arrhythmogenic conditions.

Burdens/Risks:

There are no significant risks entailed within this non-invasive study. A potential burden will be the requirement to wear an ambulatory ECG monitor semi-continuously over a 3 month period, as participants must remain motivated and engaged. We expect that participants will not always be wearing the monitoring devices and as part of the study, we will be assessing acceptability, user-friendliness, practicality and participant comfort using feedback from research participants. The adhesives used for the ECG electrodes can cause skin irritation or redness in some participants and non-allergic adhesive preparations may be required.

3.4 STUDY OUTCOME MEASURES

Primary Outcome Measures

- Sensitivity, specificity and AUC value for neural networks 1 and 2 to detect the Brugada ECG pattern in 12-lead ECGs.

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- Yield of extended duration ambulatory ECG monitoring to detect the Brugada ECG pattern in patients with concealed Brugada syndrome, using neural networks 1 and 2.
- Sensitivity, specificity and AUC value for neural network 3 to diagnose concealed Brugada syndrome from 12-lead ECGs
- Sensitivity, specificity and AUC value for neural network 4 to diagnose an SCN5a mutation from 12-lead ECGs.
- Yield of extended duration ambulatory ECG monitoring to detect the Brugada ECG pattern (neural networks 1 and 2) and LQTS manifestation in patients with idiopathic VF.

Secondary Outcome Measures

- Yield of UHF-ECG to detect underlying Brugada syndrome in patients with a concealed ECG phenotype.
- Utility of UHF-ECG for arrhythmia risk stratification in patients with inherited arrhythmogenic conditions
- Beta angle value with highest predictive accuracy for Brugada syndrome based on expert consensus, using regression modelling.
- Identification of novel electrical manifestations that may represent underlying concealed arrhythmia syndromes during day-to-day physiological stressors.
- Clinical endpoints such as ICD therapies, all cause mortality and any clinical events such as hospitalisations or clinical deteriorations.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Participants will be recruited at Imperial College Healthcare NHS Trust. Participants may be based at other institutions and will be identified via research collaborators.

4.2 INCLUSION CRITERIA

FOR ALL PARTICIPANTS:

1. Adults willing to take part (ages 18 – 100 years old)
2. Able to give consent

SPECIFIC CRITERIA BY PARTICIPANT SET:

- Group A – healthy volunteers
- Group B – patients with a normal ECG and an underlying inherited arrhythmic syndrome
- Group C – patients with an arrhythmic syndrome with an abnormal ECG

Further details in Appendix 1.

4.3 EXCLUSION CRITERIA

- Unable to give consent
- Children age < 18 years and adults > 100 years old

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

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Study A
ECG data will be obtained from the host institution (Imperial College Healthcare NHS Trust) as well as external centres both in the UK and internationally. This data will derive from patients identified by the site-specific representatives, who will coordinate secure ECG data transmission and acquisition. All ECG data will be collected anonymously or anonymised at the point of collection. Consent will not be sought as only anonymised ECGs will be obtained. There will be no access to patient-identifiable data from the research team and all data will be fully anonymised prior to transfer.

Studies B and C
Patients will be identified by members of their direct care team. They may be identified when they attend clinic appointments. Patient records will 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 who discussed the study will make patients aware that participation is voluntary and that if they do not want to participate it will not affect their usual care.

Consent for the study of the prospectively recruited patients will be obtained by a member of the research team. 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.

5. ADVERSE EVENTS

5.1 DEFINITIONS

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

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 participant 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 participant 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 faxed 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 West of Scotland (REC 5) 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 Zachary Whinnett email: z.whinnett@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 be followed up over a 3 month period remotely while wearing their ambulatory ECG. 12-lead ECG and UHF-ECG data will be collected at the index visit. Symptom diaries and ambulatory ECG recordings will be collected at the end of the study interval. Any incidental findings that we identify during the study will be reviewed by the research team and reported to the GP and also the cardiology team normally looking after the patient. We will continue to follow up all patients after their last contact with the research team through review of the electronic health record and any clinical cardiac device checks up until the end of the study on 1st April 2027, at which time all follow up will cease. The prospective studies

will end after 200 patients have undergone the 3 month interval of follow up or by the study end date of 1st April 2027.

7. STATISTICS AND DATA ANALYSIS

We expect to have access to over 3000 patients' worth of ECG data to train and validate our neural networks, comprising a similar proportion of Brugada and non-Brugada ECGs. Our group has published extensively regarding applications of AI to ECG data (13–17) and includes experienced, independently-funded clinician scientists and engineers with expertise in machine learning. They will guide me in developing neural networks for ECG classification tasks and signal processing. As we will be employing a very similar methodology to our previous successful ECG AI projects in this experiment, we are confident that this quantity of ECG data will be sufficient to develop highly accurate neural networks.

The accuracy of the prolonged duration ambulatory ECG recordings will be calculated using a binomial distribution. Assuming an actual accuracy of 95% and a target accuracy of >85% for ECG analysis discriminating between healthy normal participants and manifest Brugada patients, 90 patients will provide greater than 80% power in demonstrating that the measured accuracy is significantly greater than 85% at the two-tailed 5% significance level. To achieve 90 patients with some loss to follow up, I will recruit 50 healthy volunteers and 50 manifest Brugada patients.

McNemar's test will be used for paired analysis of 24-hour 12 lead Holter and prolonged ambulatory ECG recordings in the concealed arrhythmia patient set. Historical data report 20 to 34% sensitivity for 24-hour Holter for detection of the Brugada ECG pattern in patients with concealed Brugada syndrome (5,6). Assuming 25% sensitivity for 24-hour Holter and 60% for prolonged ambulatory ECG recordings beyond 24 hours, with the prolonged ambulatory ECG recordings being able to identify 80% of 24-hour Holter-identified cases, 35 patients would be needed to provide 90% power at the 5% significance level. I will recruit 50 patients.

We are also seeking to identify at least one extra patient with Long QT or Brugada syndrome by performing extended duration monitoring beyond standard 12 lead 24-hour Holter. Registry data (7–9) suggests that between 3-4% of idiopathic VF patients eventually receive a specific diagnosis of Brugada syndrome through conventional diagnostic testing and routine clinical follow up. A similar proportion are diagnosed with long QT syndrome. If extended duration monitoring can identify half of these (4%), then 50 patients will provide 87% power to detect at least one extra case (simulated through repeat sampling of a binomial distribution).

We also plan to recruit 100 patients with other inherited arrhythmic conditions, who can be subdivided into high and low arrhythmic risk groups. We believe that these cohort sizes will be adequate to gather sufficient pilot data to enable identification of subtle changes in UHF-ECG profiles.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the by the North of Scotland (1) Research Ethics Committee 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 participants 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.

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. All data will be analysed pseudoanonymously.

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

The Imperial Biomedical Research Centre and British Heart Foundation 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 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.

11. REFERENCES

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12. APPENDICES

Appendix 1 – Arrhythmic syndromes

Group B (concealed arrhythmia syndromes):

- Concealed Brugada syndrome
- Early repolarisation syndrome
- Idiopathic VF
- Purkinje-related arrhythmic syndrome
- Concealed pre-excitation

Group C (manifest arrhythmia syndromes):

- Manifest Brugada syndrome
- Manifest Long QT syndrome
- Manifest short QT syndrome
- Manifest pre-excitation / Wolff-Parkinson-White syndrome

- Catecholaminergic polymorphic VT (CPVT)
- Arrhythmic cardiomyopathy (ACM)
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Arrhythmogenic left ventricular cardiomyopathy (ALVC)
- Hypertrophic cardiomopathy
- Dilated cardiomyopathy
- Hypokinetic non-dilated cardiomyopathy
- Lamin-related cardiomyopathy
- Desmoplakin-related cardiomyopathy
- Titin-related cardiomyopathy
- Filamin C-related cardiomyopathy

Appendix 2 – ECG AI algorithms / neural networks that will be developed

- NN1 - Direct classification of the Brugada ECG pattern: This neural network will be trained to output whether a Brugada ECG pattern is detected based on the expert consensus classification. We will pool phenotype positive Brugada ECGs and non-Brugada ECGs within our ECG dataset.
- NN2 - Measurement-based classification of the Brugada ECG pattern: This neural network will be trained to establish the beta angle of the QRS (between the upslope of the S wave and downslope of the R' wave). The beta angle can be used to discriminate the Brugada pattern from Brugada mimics. Experts will be tasked with performing manual measurements on the ECG and the consensus measurement will be used. We will pool ECGs from all 3 groups within our ECG dataset.
- NN3 - Deep learning of concealed Brugada syndrome: This neural network will be trained to output whether an ECG represents underlying concealed Brugada syndrome. We will pool phenotype negative Brugada ECGs with a confirmed clinical diagnosis of Brugada syndrome alongside non-Brugada ECGs within our ECG dataset.
- NN4 - Deep learning of an SCN5a mutation from the 12-lead ECG: This neural network will be trained to detect changes in the ECG which indicate an underlying SCN5a mutation. In ECGs for patients who have already had SCN5a genetic testing, these ECGs will be divided into two groups based on their SCN5a status and used to train the neural network.