# HREC Project ID 88239 – Research Protocol

# Title

The Syncope-Stopper study: comparison of upfront pacing with standard care for high-risk patients with unexplained syncope.

# Project Team Roles & Responsibilities

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Research sites for this project

Alfred Health  
Cabrini Health

Western Health

Melbourne Health

# Resources

* The two treatment groups are considered acceptable standards of care (i.e. there is equipoise), thus additional funding for pacemakers or loop recorders as part of this study will not be required.
* The principal investigator Dr Jeremy William has sought scholarship funding from the NHMRC, RACP, CSANZ and Monash University.

# Background

* 1. Literature review

Syncope is defined as transient loss of consciousness due to cerebral hypoperfusion, characterised by rapid onset, short duration and spontaneous complete recovery (1). Unexplained syncope poses a significant diagnostic challenge to clinicians. Although syncope accounts for approximately 1-2% of emergency department (ED) presentations and 3% of hospital admissions (2, 3), approximately half of patients admitted for investigation of syncope are discharged without a clear diagnosis (4). Both patients with identifiable cardiac causes of syncope and those with syncope of unknown cause are at increased risk of serious injury from recurrent syncope as well as higher mortality (5).

Up to 20% of patients with implantable loop recorders (ILR) for unexplained syncope require subsequent permanent pacemaker (PPM) insertion for bradyarrhythmia (6). While ILRs are frequently inserted for further diagnostic evaluation, they are costly and do not prevent further syncopal episodes.

Several scores have been developed for use in the emergenc y department for identifying patients with syncope at risk of ‘adverse events’, including the Evaluation of Guidelines in Syncope Study (EGSYS) Score, Canadian Syncope Risk Score and the San Francisco Syncope Rule (7-9). However, these scores have not been validated for use beyond the ED, are cumbersome to use and include variables (e.g., haematocrit, breathlessness, hypotension) that are unable to guide cardiologists evaluating the potential for future bradycardia and the utility of PPM implantation.

*The ’DROP’ score – preliminary data*

Our group has developed a novel risk score to predict patients at highest risk of bradycardic syncope. This was derived from a cohort study of 100 patients (50 consecutive patients from each group) presenting to three centres with syncope or pre-syncope who underwent ILR insertion between 2013 and 2020 (10). Group 1 (n=50) underwent PPM insertion due to severe bradyarrhythmia detected on ILR. Group 2 (n=50) demonstrated no bradyarrhythmia on ILR over >3 years follow-up. Each patient’s medical record was assessed to identify baseline clinical characteristics, medication history, syncope history, electrocardiographic and echocardiographic parameters.

The average time from ILR implant to subsequent PPM insertion was 213 days. No patients had ventricular arrhythmias requiring insertion of cardiac defibrillation device. Main indications for PPM implant were sinus node dysfunction / sick sinus syndrome (79%) and high-grade AV-block (21%). Univariate analysis revealed age >65 years (p=0.001), first degree AV nodal block (p=0.003), absence of predisposing factors (p=0.004) and distal conduction disease (p=0.007) as significant univariate predictors of future PPM requirement. A time-to-event analysis (time to PPM implant) was performed to assess the predictive value of each of these four predictors, and each of these were highly significant (p<0.01). These were subsequently incorporated into the novel ‘DROP’ score:

|  |  |
| --- | --- |
| **D** | **D**istal conduction disease (any of RBBB, LAFB, LPFB and LBBB) |
| **R** | **R**elated historical precipitating factors absent (e.g. overheating, posture, exercise) |
| **O** | **O**lder age (>65 years) |
| **P** | **P**rolonged PR interval (>200ms) |

*\*1 point for each, range 0 – 4. Abbreviations: LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block.*

Patients with a high DROP score (3-4) were more likely to require earlier PPM implantation compared to patients with lower scores (1-2) while no patients with a DROP score of zero subsequently required pacing (log-rank p<0.001), as shown in the figure below:

**Chart, line chart

Description automatically generated**

The components of the DROP score are consistent with previously identified predictors of bradycardic syncope. A study by Palmisano et al showed that while age >75 years was a significant predictor for pacemaker insertion, prodrome preceding syncope was non-significant (11).

Syncope secondary to bradyarrhythmia is five times more prevalent in patients ≥65 years (12), due to physiologic changes with ageing, co-morbidities and increased vulnerability to adverse effects of therapies (13, 14). Furthermore, Sud et al identified syncope without warning, ECG feature of LBBB, structural heart disease and history of ischaemic heart disease as significant risk factors for syncope secondary to primary cardiac arrhythmia (15). In our cohort, absence of prodromal symptoms and structural or ischemic heart disease did not however predict pacing requirement.

The DROP score is simple, easy-to-use clinical tool. It uses variables that are easily quantified from a bedside evaluation. We hypothesise that implementation of the DROP score to facilitate upfront pacemaker implantation can reduce the need for lengthy inpatient monitoring and potentially prevent further syncopal episodes in high-risk patients. Furthermore, upfront pacemaker implantation compared with ILR implantation may be favourable from a cost perspective, as ILRs are on average 3-4 times more expensive than pacemaker devices (16).

* 1. Research aim

We aim to perform a multicentre, randomised controlled trial of 200 patients presenting with ‘high-risk’ unexplained syncope (DROP score ≥2) to determine whether early upfront pacing reduces future syncope and hospitalisation.

* 1. Overall study hypothesis

Early pacemaker implantation (a ‘Syncope-Stopper’) is the safest and most cost-effective strategy for managing high-risk patients with unexplained syncope, with the novel DROP score able to identify patients at highest risk of bradycardia.

# Project Design

* 1. Population

We aim to recruit 200 patients (see power calculation below) through Alfred Health, Melbourne Health, Western Health and Cabrini Health. Patients will be screened for eligibility at time of presentation to ED or admission to the hospital under the Cardiology or General Medicine teams.

* 1. Inclusion criteria:
* At least 1 ‘unexplained’ syncopal episode within 1 year prior to enrollment
* Age ≥ 55 years;
* DROP score ≥ 2
  1. Exclusion criteria (any of the following):
* Likely neurocardiogenic or vasovagal cause of syncope, defined as postural BP drop >30 mmHg, carotid sinus hypersensitivity, history of micturition, defecation or cough syncope)
* Left ventricular ejection fraction <40%
* Previous PPM, ICD, or ILR implant
* Existing ACC/AHA/HRS/ESC Class I indication for PPM or ICD implantation
* Contraindication to insertion of a transvenous cardiac pacing device
* Comorbidity precluding 12 months follow-up
* DROP score 0-1: these patients will be monitored in an additional observational arm
  1. Randomisation:

The primary investigator will coordinate a strategy of 1:1 block randomisation. Randomisation envelopes will be created using computer-generated code into blocks of ten, numbered externally, and then sealed within an opaque envelope that conceals the treatment designation. Neither the patient nor the researchers will be blinded to group allocation.

* 1. Intervention:
* Treatment group (n=100): Pacemaker implantation within 1 month of enrolment (a ‘syncope stopper’, single or dual chamber device at discretion of the operator).
* Control group (n=100): standard care without direct pacemaker implant. May include Holter monitoring or ILR, based on clinician discretion.
  1. Outcomes:

The primary outcome for this study is a composite of the four following outcomes at 12 months:

* Cardiovascular death
* Recurrent syncope
* Bradycardia resulting in pacemaker implantation
* Device-related complications

Secondary outcomes will include:

* The individual outcomes that make up the primary composite outcome above
* Recurrent cardiovascular hospitalisation
* All-cause mortality
* Quality of life and syncope symptom score
* Total length of hospital admission over the 12-month follow-up
* Cost to healthcare system
* Acute and chronic device-related complications
* Subsequent pacemaker implant (control group)
* Incidence and prevalence of tachyarrhythmia or bradyarrhythmia
* Percent pacing burden in those patients receiving pacemakers
  1. Power Calculation

We anticipate that 47% of patients will have recurrent syncope at 12 months. To detect a difference of 20%, 90 patients will be required in each group to provide a power of 0.8 at an α of 0.05. To account for cross-overs and drop-outs, we would increase sample by ~10% and aim to include 100 patients per group yielding a total study population of 200 patients.

* 1. Approach to provision of information to participants and consent
* Consultation and consent will be performed by the principal investigator, Dr Jeremy William, across all recruitment sites.
* Written consent from the participant will be required for enrolment in the study. A detailed consent package containing the pertinent risks and complications of pacemaker insertion will be performed. This consent package will be adapted from a template supplied by the Alfred Health Research Ethics Committee.
* From the time of the screening consultation, patients will be provided up to 30 days to consider their decision to proceed with the trial.
* Patients will be provided a mobile phone number and email address that they can utilise to ask questions pertaining to the trial, including re-negotiating or rescinding their consent.
  1. Data Collection and sources

We intend to initially enrol patients through Alfred Health, Melbourne Health, Western Health and Cabrini Health. Currently, there is equipoise between the two groups with both strategies considered acceptable standards of care. Clinical research co-ordinators and post-doctorate researchers will assist investigators with recruitment and 3-monthly follow up:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Baseline** | **3 months** | **6 months** | **9 months** | **12 months** |
| 12-lead ECG | X |  |  |  | X |
| BP measurement: lying & standing | X |  |  |  | X |
| Basic demographics / clinical history / medications / health record review | X |  |  |  | X |
| Health questionnaire (inc. QOL, hospital admissions, syncope) | X | X | X | X | X |
| Basic bloods (glucose, FBE, UEC) | X |  |  |  |  |
| Transthoracic echocardiogram | X |  |  |  |  |
| Rhythm review  (inc. pacemaker check / Holter / loop recorder interrogation) | X | X | X | X | X |

* 1. Data Management:
* Each participant will be provided a codified de-identified label on enrolment to the trial. A password encrypted Excel (.xls) file will link these de-identified labels back to individual participants. This file will contain personal information including date of birth and contact information, for the purpose of co-ordinating follow-up.
* The health information described in section 5.10 above will be collected and stored in a separate password-encrypted Excel (.xls) file. This file will not containing any identifying information and will only reference each participant by their de-identified codified label.
* Statistical analysis by Stata Version 16.0 will generate statistics (.dta) files. These files will contain only de-identified health information
* All files will be stored on a single external solid-state drive stored in the Alfred Hospital Cardiology Department. The drive itself will be password-encrypted. No cloud backups will be kept. The file will not be kept on a public network drive.
* Patients will be consented for their health information to be utilised for this trial as well as future trials pertaining to the same research space (i.e. management of high-risk syncope, utility of the DROP score).
* Both the file containing personal information and health information will be stored for up to 10 years (until February 2033), at which time both files will be erased from the external hard-drive.
  1. Data Analysis:
* Data will be analysed using Stata Version 16.0.
* Descriptive statistics will be presented as frequencies and proportions, with comparisons across groups using the chi square test. Normally distributed variables will be presented as means and standard deviations, and non-normally distributed variables will be presented as medians and interquartile range. Statistical significance will be defined as p<0.05, two tailed.
* With respect to primary endpoints, analysis of ‘time to syncope’ will be performed using time-to-event methods according to the intention-to-treat principle, with outcomes in the two study groups to be compared with the use of hazard ratios and 95% confidence intervals using a univariate and multivariate Cox proportional-hazards regression model with adjustment for clinical variables included in baseline characteristics.
* The Data Safety Monitoring Board will meet every six months.
  1. Data Linkage
* No Data linkage is planned for this study.

# Results, Outcomes and Future Plans

* 1. Plans for return of results of research to participants

The research is likely to generate findings or results of significance to the participants. In particular, if the trial demonstrates a favourable outcome for the intervention group (i.e.if patients with unexplained syncope and DROP score ≥2 demonstrate lower risk of syncope, hospital admission and all-mortality following pacemaker insertion compared with conservative care), this would imply that the control group would benefit from pacemaker insertion.

At the conclusion of the data analysis of the trial (expected to be Q4 2025), the results of the trial will be communicated to all participants in the form of a letter. Patients will be offered a face-to-face or telehealth consultation to discuss what this means for the healthcare moving forward.

* 1. Plans for dissemination and publication of project outcomes

The results of this project are intended for publication in a peer-reviewed journal and presentation at both national and international conferences.

* 1. Other potential uses of the data at the end of the project

Participants will be consented for the use of their health information data for use in follow-on future projects related to high-risk unexplained syncope and validation of the DROP score. We will limit the use of this health information data to 10 years from the beginning of the study (estimated Feb 2032) at which point the data containing the participants health information will be deleted/destroyed.

# Project timeline

The trial is expected to take three years to complete and publish:

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Year** | **2022** | | | | **2023** | | | | **2024** | | | | **2025** | | | |
| Quarter | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| Ethics approval |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Recruit |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 12 month  Follow-up |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Analysis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Publication |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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**Appendix 1: Conformity with the latest COVID-19 restrictions**

The authors of this protocol have reviewed the ‘Updated Alfred Health COVID-19 Guidance on Clinical Trials and Other Research (dated July 2022). This project falls under the category of a non-COVID-19 clinical trial.

This project is expected to commence in February 2023 and continue until February 2026. We expect that there will be ongoing restrictions related COVID-19 for part or all of this research period. The two key reasons we do not wish to defer the research project until COVID-19 restrictions cease include:

* We will be exclusively recruiting patients who have already attended hospital and been admitted under either a cardiology or general medical team. Therefore, our research will opportunistically approach these patients when they are already inpatients.
* We do not anticipate that our research will place participants at a significantly higher risk of contracting COVID-19
* There is no clear timeline for when COVID-19 restrictions will be fully lifted.
* At time of writing (September 2022), current COVID-19 cases in hospital are at the lowest level this calendar year (currently 332) and are on a significant down-trend.

We propose the following steps to conform with the advice provided in this guideline.

1. Where possible, we will conduct the consent process for participants during their inpatient stay. This is possible given the pool of participants recruited for this trial will be those admitted under cardiology or general medical teams to the hospital with an episode of syncope. This minimizes the need to return to the hospital for an outpatient visit for the purposes of consent and enrollment in the trial.
2. In situations where consent and enrollment during the participant’s inpatient stay is not feasible, we will give participants the option of a video telehealth service for consent only. If there are challenges with this telehealth software (e.g. poor internet connection, inability for participants to independently use the required technology) we will prefer a face-to-face appointment for consent.
3. For participants who are consented via telehealth, they will be required to attend a research site in-person for enrollment in order to complete the necessary investigations that are part of enrollment. The specific aspects that cannot be completed over telehealth will include physical examination and both lying/standing blood pressure measurement for all participants and a rhythm review (12-lead ECG, Holter monitor). Some participants will require baseline blood tests and echocardiography which will also be completed in-person on that same day.
4. For the follow-up appointments at 3, 6 and 9 months, we will preferentially book these as telehealth appointments for patients who have received a PPM. This will be possible as participants implanted with PPM routinely receive remote monitors from the device manufacturer on discharge, which allow for rhythm review remotely. For participants randomized to standard care (not receiving pacemakers) they will need to attend a research site for the follow-up appointments at 3, 6 and 9 months as a rhythm review (e.g. 12-lead ECG or holter monitor) will need to be completed.
5. All research staff (principal investigator, co-investigators, monitors) will be required to have had a minimum of two doses of an approved COVID-19 vaccine and wear and N95 mask whenever located at a clinical research site.