PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	MAGNETOcardiography parameters to predict future Sudden Cardiac Death (MAGNETO-SCD) or ventricular events from implantable cardioverter defibrillators: study protocol, design and rationale
AUTHORS	Lachlan, Thomas; He, Hejie; Sharma, Kavi; Khan, Jamal; Rajappan, Kim; Morley-Davies, Adrian; Patwala, Ashish; Randeva, Harpal; Osman, Faizel

VERSION 1 – REVIEW

REVIEWER	Paari Dominic Center for Cardiovascular Diseases and Sciences at Louisiana State University Health Sciences Center Louisiana, United States
REVIEW RETURNED	03-May-2020

GENERAL COMMENTS	MAGNETO-SCD is a prospective study by Lachlan T et al proposed to evaluate the use of a easy-to-use, portable magnetocardiography, which can be used in an unshielded clinical environment to predict sudden cardiac death. The authors proposed to use a baseline pre-procedure MCG in patients undergoing primary or secondary prevention ICD to study the correlation between MCG parameters and future VA as evidenced by appropriate ICD therapy. In general it's a well thought out study with sound background, rigorous methods and adequate follow up. The manuscript itself is very well written. Here are some of my questions and concerns for the authors: 1) In the introduction the authors write "However, SCD remains a significant cause of death with the majority occurring in groups deemed to be low risk.". Continuing this thought in the discussion, they add "There are a group of patients who, based on current recommendations, do not qualify for an ICD, yet will go on to have a SCD event". These statements give the impression that the authors imply that the results of the current study may be extrapolated to help predict SCD in the general population. I'm sure that the authors understand that the population being studied in the protocol is a highly preselected group of patients that have the highest risk of SCD based on the currently available tools of prediction. The current selection criteria based on EF and previous h/o VT and resuscitated SCD appears to be the only ones that have stood the test of time despite signals from single studies regarding the utility of ECG criteria, evidence of fibrosis and others. Therefore, the findings from this study may help with predicting "patients who qualify for an ICD (by current guidelines), who never require them" as mentioned by the authors. Further studies will be needed to study predictors of SCD in the general population using this technology which should be

	clarified. 2) Have the authors thought about adding predicting Inappropriate ICD therapies as a secondary objective? Inappropriate shocks increase mortality as shown in many studies. As the study follows a population with devices, this information is readily available. If the study can identify patients that are not predicted to have SCD based on MCG parameters but are at increased risk of inappropriate ICD therapies, that may be a very important subgroup to avoid. 3) Inclusion criteria: Are patients with channelopathies getting a primary or secondary prevention ICDs included? This should be clarified as these patients are an entirely different population and the mechanisms of SCD in them are different. 4) MCG waveforms may be dynamic just like surface 12 lead ECGs in patients with an arrhythmogenic substrate and therefore a single ECG may miss critical information. Unfortunately the authors may not be able to obtain more MCGs after the device is implanted. If there was a way to obtain 2 pre-procedure ECGs, it may be beneficial. 5) The strength of the study is in the standardization of the ICD programming to the MADIT-RIT programming protocol. 6) The authors are using fQRS, , QT spatial dispersion and late QRS activity as parameters to predict SCD based on previous studies which showed promise. The authors do NOT describe in their methods their algorithm for machine learning. Is the machine learning- supervised, unsupervised or semi-supervised? I hope that the authors are considering employing unsupervised learning, so the machine learning can pick signals other than the ones explicitly explored in the protocol.

REVIEWER	Gianfranco Gensini IRCCS Multimedica, Sesto San Giovanni, Milan, Italy
REVIEW RETURNED	10-May-2020

GENERAL COMMENTS	In this manuscript Lachlan et al clearly showed the protocol of MAGNETO-SCD trial. The sudden cardiac death risk assessment is often imprecise because it has routinely performed only with ejection fraction, and other specific parameters are used only in limited cases for research purposes. This study investigated the role of magnetocardiography to better define the sudden cardiac death risk before ICD implantation, using a new device called VitalScan MCG. In this manuscript the authors illustrated exhaustively the study objectives, the study design with complete discussion and references. No conflict of interest were reported neither discrepancies by ethical protocol. Some minor observations: - study limitations should be better described - “blood tests for circulating vascular biomarkers“ should be explained in the main text and should be add also in the figure 4. - During the follow-up routine ICD interrogation and quality of life questionairre were scheduled in the study plan. In the text was not well explained if patients with ventricular arrhythmia will be assessed by clinical visit and biochemical exams. I congratulate authors for trial design hoping in positive and significant results.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Paari Dominic
Institution and Country: Center for Cardiovascular Diseases and Sciences at Louisiana State University Health Sciences Center Louisiana, United States Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below MAGNETO-SCD is a prospective study by Lachlan T et al proposed to evaluate the use of a easy-to-use, portable magnetocardiography, which can be used in an unshielded clinical environment to predict sudden cardiac death. The authors proposed to use a baseline pre-procedure MCG in patients undergoing primary or secondary prevention ICD to study the correlation between MCG parameters and future VA as evidenced by appropriate ICD therapy. In general it's a well thought out study with sound background, rigorous methods and adequate follow up. The manuscript itself is very well written. Here are some of my questions and concerns for the authors:

1) In the introduction the authors write "However, SCD remains a significant cause of death with the majority occurring in groups deemed to be low risk.". Continuing this thought in the discussion, they add "There are a group of patients who, based on current recommendations, do not qualify for an ICD, yet will go on to have a SCD event". These statements give the impression that the authors imply that the results of the current study may be extrapolated to help predict SCD in the general population. I'm sure that the authors understand that the population being studied in the protocol is a highly preselected group of patients that have the highest risk of SCD based on the currently available tools of prediction. The current selection criteria based on EF and previous h/o VT and resuscitated SCD appears to be the only ones that have stood the test of time despite signals from single studies regarding the utility of ECG criteria, evidence of fibrosis and others. Therefore, the findings from this study may help with predicting "patients who qualify for an ICD (by current guidelines), who never require them" as mentioned by the authors. Further studies will be needed to study predictors of SCD in the general population using this technology which should be clarified. This has now been addressed and is clarified in the discussion section (p 16) and added as a limitation (p 4)
2) Have the authors thought about adding predicting Inappropriate ICD therapies as a secondary objective? Inappropriate shocks increase mortality as shown in many studies. As the study follows a population with devices, this information is readily available. If the study can identify patients that are not predicted to have SCD based on MCG parameters but are at increased risk of inappropriate ICD therapies, that may be a very important subgroup to avoid. We would like to thank the reviewer for this helpful suggestion and have now included this (p 8)
3) Inclusion criteria: Are patients with channelopathies getting a primary or secondary prevention ICDs included? This should be clarified as these patients are an entirely different population and the mechanisms of SCD in them are different. This is now clarified (p 9) and have acknowledged this in the limitations section (p 4)
4) MCG waveforms may be dynamic just like surface 12 lead ECGs in patients with an arrhythmogenic substrate and therefore a single ECG may miss critical information. Unfortunately the authors may not be able to obtain more MCGs after the device is implanted. If there was a way to obtain 2 pre-procedure ECGs, it may be beneficial. We assume the reviewer is referring to MCG (rather than ECG). We now acknowledge MCG data may be dynamic and include this as a limitation (p 4)
5) The strength of the study is in the standardization of the ICD programming to the MADIT-RIT programming protocol. Thank you, we agree
6) The authors are using fQRS, , QT spatial dispersion and late QRS activity as parameters to predict SCD based on previous studies which showed promise. The authors do NOT describe in their

methods their algorithm for machine learning. Is the machine learning- supervised, unsupervised or semi-supervised? I hope that the authors are considering employing unsupervised learning, so the machine learning can pick signals other than the ones explicitly explored in the protocol. This is clarified on p 8; we are using an unsupervised algorithm

Reviewer: 2
Reviewer Name: Gianfranco Gensini
Institution and Country: IRCCS Multimedica, Sesto San Giovanni, Milan, Italy Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below In this manuscript Lachlan et al clearly showed the protocol of MAGNETO-SCD trial.
The sudden cardiac death risk assessment is often imprecise because it has routinely performed only with ejection fraction, and other specific parameters are used only in limited cases for research purposes. This study investigated the role of magnetocardiography to better define the sudden cardiac death risk before ICD implantation, using a new device called VitalScan MCG.
In this manuscript the authors illustrated exhaustively the study objectives, the study design with complete discussion and references. No conflict of interest were reported neither discrepancies by ethical protocol.
Some minor observations:
- study limitations should be better described This has now been expanded (p 4)
- "blood tests for circulating vascular biomarkers" should be explained in the main text and should be add also in the figure 4. This is now included (p 11 and p 22)
- During the follow-up routine ICD interrogation and quality of life questionairre were scheduled in the study plan. In the text was not well explained if patients with ventricular arrhythmia will be assessed by clinical visit and biochemical exams. This is now clarified on p 11
I congratulate authors for trial design hoping in positive and significant results. Thank you