OBSERVATION PLAN

LONGITUDINAL ASSESSMENT OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN OUT PATIENTS AT HIGH CARDIOVASCULAR RISK USING PORTABLE ECG DEVICE

Study Short Title	**INDIA ECG REGISTRY – LONG TERM (LT)**
Study No.	**ERIS/OS/22/001**
Version No.	**00**
Date	**January 2022**

Confidentiality Statement

INDIA ECG REGISTRY – LONG TERM

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Sponsor: Eris Lifesciences Ltd.
Plot No. 142/2, Ramdas Road, Off SBR, Near Swati Bungalows, Bodakdev, Ahmedabad – 380054, Gujarat.; Phone : +91-79-69661082; Fax: +91-79-30179404; Email : info@eris.co.in

Study Principal Investigator: Dr. Jamshed Dalal
(Details Awaited)

Disclaimer:
Please note that this exercise of real-world data collection is merely a non-interventional study (not a clinical study/trial or biomedical research) where prevalent practice patterns are observed in a naturalistic setting, the way it happens in routine/typical clinical practice, and the experiential data of such doctors is captured with his/her consent and later analyzed in a pooled, anonymised manner, respecting patient confidentiality (data privacy clause is signed by the patient). The remuneration to the doctor per patient is of nominal value and there is a cap on how many patients can be enrolled by each doctor. Hence it does not fall within the purview of the New Drugs and Clinical Trials Rules 2019 or the latest ICMR Biomedical Research guidelines. Clinical Trials Registry India (CTRI) registration will be done from a publication perspective, and in this way, the regulator will also be intimated.

Sponsor's Approval

I, on behalf of Eris Lifesciences Ltd, India, have read and understood this proposal and hereby approve the same. I agree to comply with all requirements regarding the obligations of the sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013) and ICH-GCP E6 (R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules (2019) and ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017).

_____ _____

Mr. V S Joshi (President, Medical)
Eris Lifesciences Ltd.,
Shivarth Ambit, Plot No. 142/2, Ramdas Road, Off SBR, Near Swati Bungalows, Bodakdev, Ahmedabad – 380054, Gujarat.

Dated

Principle Investigator's Approval

I, the undersigned, have read and understood this proposal and hereby agree to conduct the study in accordance with this complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013) and ICH-GCP E6 (R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules (2019) and ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017).

I understand that the information in this study observation plan is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the sponsor.

I understand that the sponsor/s may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.

_____

Name & Signature of Principal Investigator

_____

Date

Joint Principle Investigator's Approval

I, the undersigned, have read and understood this proposal and hereby agree to conduct the study in accordance with this complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013) and ICH-GCP E6 (R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules (2019) and ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017).

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_____

Name & Signature of Joint Principal Investigator

_____

Date

Co- Principle Investigator's Approval

I, the undersigned, have read and understood this proposal and hereby agree to conduct the study in accordance with this complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013) and ICH-GCP E6 (R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules (2019) and ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017).

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_____

Name & Signature of Co-Principal Investigator

_____

Date

Co-Investigator's Approval

I, the undersigned, have read and understood this proposal and hereby agree to conduct the study in accordance with this complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013) and ICH-GCP E6 (R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules (2019) and ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017).

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_____

Name & Signature of Co- Investigator

_____

Date

Investigator's Approval

I, the undersigned, have read and understood this proposal and hereby agree to conduct the study in accordance with this complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013) and ICH-GCP E6 (R2) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2004, CDSCO), New Drugs and Clinical Trial Rules (2019) and ICMR's National Ethical Guidelines for Biomedical and Health Research involving Human Participants (2017).

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_____

Name & Signature of Investigator

_____

Date

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LIST OF ABBREVIATIONS

Sr. No.	Abbreviation	Full Form
1.	ECG	Electrocardiogram/ Electrocardiography
2.	CVD	Cardiovascular Diseases
3.	ASCVD	Atherosclerotic Cardiovascular Diseases
4.	CAD	Coronary Artery Disease
5.	MI	Myocardial Infarction
6.	PAD	Peripheral Artery Disease
7.	OPD	Out Patient Department
8.	LVH	Left Ventricular Hypertrophy
9.	CRF	Case Record Form

OBSERVATION PLAN SYNOPSIS:

STUDY TITLE	LONGITUDINAL ASSESSMENT OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN OUT PATIENTS AT HIGH CARDIOVASCULAR RISK USING PORTABLE ECG DEVICE
STUDY SHORT TITLE	India ECG Registry – Long Term
STUDY RATIONALE	India is a rapidly developing country; this has led to a rapid change from reduction in burden of communicable diseases to an increase in burden of non-communicable diseases. In India, Cardiovascular diseases (CVDs) have become the major cause of mortality. When we compare the people of India with Caucasians, the CVD affects 10 year earlier.[2,3] Traditional risk factors which are responsible for such high CVD epidemic in India include dietary factors, smoking, obesity, diabetes, hypertension, aging population, sedentary lifestyle, family history of CVD etc.[1] The patients at high CV risk include at least 3 risk factors mentioned above.[4,5] Majority of patients at high CV risk have no symptoms until manifestation of first major cardiovascular event such as sudden cardiac arrest, myocardial infarction, or arrhythmia. Considering the silent progression of cardiovascular disease, early diagnosis and treatment is critical.[6,8] Besides biochemical and physiological factors, electrocardiogram [ECG] should be carried out not only in the cases of a fatal danger (e.g. Cardiac chest pain) but also in the cases of asymptomatic high risk patients with or without cardiovascular or heart disease. Early detection of ECG abnormalities is necessary in patients with high risk CVD and in patients without overt disease before occurrence of serious and irreversible damage. [9,10,11] Systematic global CVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, Familial Hypercholesterolemia, CVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing CVD risk) [12]. The 12-lead ECG remains the gold standard, however, it can be difficult to perform for a variety of reasons including dedicated and trained staff, a private clinic environment, time required, cleaning and setting up network of cables (4 limb electrodes and 6 pericardial electrodes) and busy OPD. [9] Thus, there is a need for an ECG device with good sensitivity and specificity, which is easy to use, less time consuming and less tedious.

	When discussed individually with physicians, each agreed that the cardio-metabolically deranged patients routinely should be subjected to ECG monitoring. Hence, we performed a survey among 1863 physicians in India in which they were asked about their current practices of using electrocardiographic (ECG) assessment in diagnosis and monitoring of their cardio metabolic patients. Outcome of the survey showed that while 90% of physicians agreed to the necessity of doing ECG of cardio-metabolically deranged patients, only 61% of all physicians could perform ECG screening in less than 40% of cardio-metabolic patients. According to them there was no availability of ECG device (35.8%), it was too time consuming (40.2%) and or there was lack of trained staff (27.5%). Majority of physicians (69.7%) agreed in use of point of care ECG device which can be a solution for more screening of cardio metabolically deranged patients whether symptomatic or asymptomatic. According to the survey 88.7% physicians would appreciate if such portable handheld ECG device was made available to facilitate screening in their practice. Kardia Mobile 6L (First and only FDA cleared device) is low-cost, compact and handheld ECG device is now used increasingly world over by physicians and patients for screening and diagnostic purpose. This device has been validated in clinical practice and showed a high level of agreement and strong co-relation with 12-lead ECG device.[8,15] For the purpose of the study, we make available Kardia Mobile 6L device to the study participating physicians to enable them to subject their cardio metabolically deranged patients to ECG in their clinical practice.
STUDY OBJECTIVE	To screen high CV risk patients (asymptomatic and symptomatic) at outpatient department (OPD) for ECG abnormalities using FDA approved portable ECG device and follow-up for 5 years.
INCLUSION CRITERIA	• Adult Men or Women aged ⩾ 40 years • Asymptomatic subjects with at least 3 CV risk factors visiting to the OPD for routine clinical checkup OR Symptomatic subjects with suspected CVD visiting to the OPD for further clinical assessment • Subjects willing to provide written informed consent form
EXCLUSION CRITERIA	• Subjects with implanted devices like pacemaker, external cardiac defibrillator • Subjects with known CVD (Arrhythmias on treatment, MI, Stroke, PAD, Heart failure, Post cardiac intervention (PCI, CABG, Ablation, Device implant etc.)

	• Pregnant women
STUDY DESIGN	Multicenter, Observational, Prospective, Longitudinal, Non-Interventional Study
NUMBER OF SUBJECTS	N=30,000
STUDY DURATION	5 Years
STUDY ENDPOINTS	**Primary Endpoints:** • Prevalence and type of ECG abnormalities in high risk symptomatic and asymptomatic outpatients • Prevalence of high CV risk patients developing Fresh ECG abnormalities during 5 years follow-up and its co-relation with their cardiovascular risk profile **Secondary Endpoints:** • Sensitivity, specificity, positive and negative predictive values of ECG screening in high-risk out patients • Development of Risk prediction model for Indian patients using ECG to find out most important CVD risk predictors for cardiac abnormalities • Association of cardiac abnormalities with CVD risk predictors. • To evaluate the regional differences in prevalence and types cardiac abnormalities
DATA AND SAFETY MONITORING PLAN	Because of the observational design of the study, the subject will remain under control of their treating physician. All the data generated during the study will be captured directly into the electronic case records form (i.e. e-CRF) to prevent data entry errors. Data quality management will be the responsibility of Eris Lifesciences Limited. The principal investigator (PI)/Co-PIs will have access to all data during the study. There will be regional co-investigators who will have access to the data from all subjects in their respective region. The 5000 participating investigators will have access to the data of their own subjects (6 subjects/ Investigator)
Statistical analysis	For direct detection We will verify the findings of the physician with the electrophysiologist/cardiologist for the following cardiac abnormalities. (All inconclusive results will be treated as positive in our analysis (because in the clinical situation these participants with cardiac abnormality cannot be ruled out and need to have a 12-lead

	ECG). We will calculate sensitivity, specificity, likelihood ratios and 95% CIs for each test (for all cardiac abnormalities together). Analyses for both single-lead ECGs will be carried out per physician and transmitted to the cardiologist. We will analyse the agreement between the cardiologist and physician within each pair together with the κ value. Next to the prevalence of abnormality findings we will verify the follow-up (change of) treatment Survival curve We will use sex-specific Cox proportional-hazards regressions to relate risk factors to the incidence of a first CVD event during a maximum follow-up period of 5 years after the moment of the first ECG. In addition, we will use sex-specific Cox proportional-hazards regressions to relate risk factors to the first time occurring of an ECG abnormality in patients who had no abnormality at the first screening but developed this during the 5-year follow-up period. We will aim at establishing prediction model from which CVD risk can be mathematically estimated The aim is to estimate 5-year absolute CVD risk. For this the following covariates will be considered age, total cholesterol, waist circumference, BMI, LDL-C, HDL-C, HBA1c, systolic and diastolic blood pressure, antihypertensive medication use, current smoking, and diabetes status, diet (veg/non-veg). If the covariates have a significant influence these will be included in the model, otherwise excluded. (All continuous variables will be naturally logarithmically transformed to improve discrimination and calibration of the models and to minimize the influence of extreme observations. We shall adjust for the use of antihypertensive/ anti-diabetes medication by modeling the impact of a participant's systolic blood pressure, anti-diabetes medication differently on the basis of use of such medications.)

1. STUDY INFORMATION

1.1. INTRODUCTION:

Cardiovascular disease (CVD) remains the leading cause of death and premature death worldwide, despite advances in the availability of effective and safe prevention strategies around the world. Of the 18.6 million CVD deaths globally in 2019, 58% have been in Asia.[1]

India is a rapidly developing country; this has led to a rapid change from reduction in communicable diseases to an increase in non-communicable diseases. In India, Cardiovascular diseases (CVDs) have become the major cause of mortality. When we compare the people of India with Europeans, the CVD affects 10 year earlier[2,3]. For example, before the age of 70 years 52% death occurs in India as compared to only 23% in Western populations.[2] Traditional risk factors which are responsible for such high CVD epidemic in India include dietary factors, smoking, obesity, diabetes, hypertension, aging population, sedentary lifestyle, family history of CVD etc.[1] The patients at high CV risk include at least 3 risk factors mentioned above.[4,5]Results from the Global Burden of Disease study show an age-standardized CVD death rate of 272 per 100,000 population in India, which is well above the global average of 235.[3]

Majority of patients have no symptoms until a first major cardiovascular event such as sudden cardiac arrest, myocardial infarction, or arrhythmia. A major contributing factor appears to be the inability to detect these cardiac disorders until the end of their natural history, thus missing therapeutic window where maximum benefit could be offered with early intervention. Assessment of aforementioned traditional risk factors may help to predict CV disease, but cannot detect who is at the risk, [6] for instance in the elderly population, the prediction of coronary heart disease (CHD) by traditional risk factors is less accurate than in middle-aged adults.[7] Considering the silent progression of cardiovascular disease, early diagnosis and treatment is critical.[8]

Besides biochemical and physiological factors, electrocardiogram [ECG] should be carried out not only in the cases of a fatal danger (e.g. Cardiac chest pain) but also in the cases of asymptomatic high risk patients with or without cardiovascular or heart disease.[9] Screening proactively with ECG may reveal unrecognized ECG abnormalities in large number of patients. Early detection of ECG abnormalities is necessary in patients with high risk CVD and in patients without overt disease before occurrence of serious and irreversible damage.[10, 11] Systematic global CVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, Familial Hypercholesterolemia, CVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing CVD risk (2021 ESC guideline).[12]

As per prospective registry study done at UK, a high prevalence of ECG abnormalities (31.8%) was present from the selected population (n=4739). Thus, ECG gives the capacity to become aware of those abnormalities and offers in advance intervention and treatment, and in all likelihood improve cardiovascular outcome.[6, 9]

The 12-lead ECG remains the gold standard, however, it can be difficult to perform for a variety of reasons including dedicated and trained staff, a private clinic environment, time required, cleaning and setting up network of cables (4 limb electrodes and 6 pericardial electrodes) and busy OPD.[13] Thus, there is a need for an ECG device with good sensitivity and specificity, which is easy to use, less time consuming and less tedious.

When discussed individually with physicians, each agreed that the cardio-metabolically deranged patients routinely should be subjected to ECG monitoring. Hence, we performed a survey among 1863 physicians in India in which they were asked about their current practices

of using electrocardiographic (ECG) assessment in diagnosis and monitoring of their cardio metabolic patients.

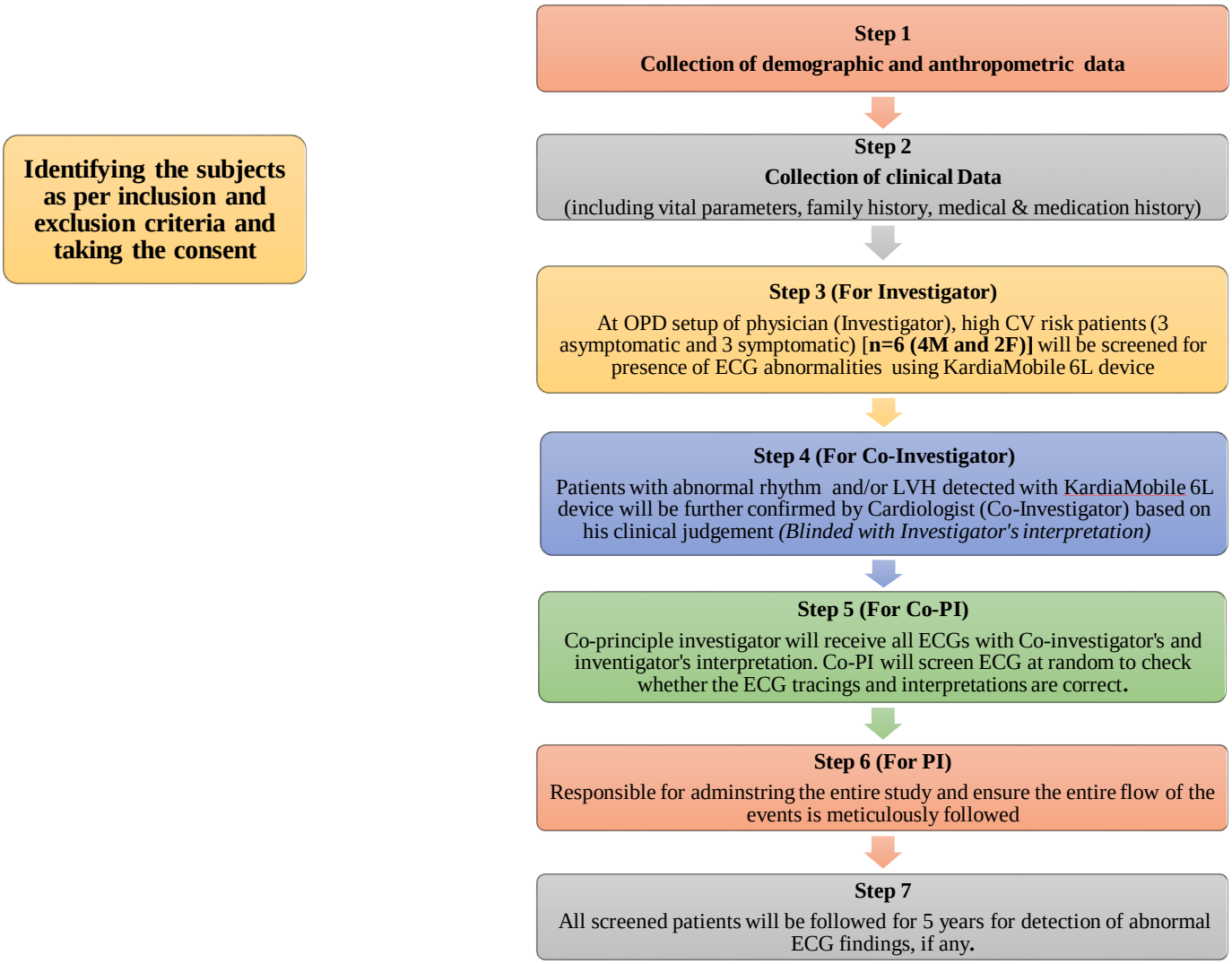
Outcome of the survey showed that while 90% of physicians agreed to the necessity of doing ECG of cardio-metabolically deranged patients, only 61% of all physicians could perform ECG screening in less than 40% of cardio-metabolic patients. According to them there was no availability of ECG device (35.8%), it was too time consuming (40.2%) and or there was lack of trained staff (27.5%). Majority of physicians (69.7%) agreed in use of point of care ECG device which can be a solution for more screening of cardio metabolically deranged patients whether symptomatic or asymptomatic. According to the survey 88.7% physicians would appreciate if such portable handheld ECG device was made available to facilitate screening in their practice.[14]

Kardia Mobile 6L (First and only FDA cleared device) is low-cost, compact and handheld ECG device is now used increasingly world over by physicians and patients for screening and diagnostic purpose. This device has been validated in clinical practice and showed a high level of agreement and strong co-relation with 12-lead ECG device.[13, 15, 16]. The same is also been validated for AF in India.[17] For the purpose of the study, we make available Kardia Mobile 6L device to the study participating physicians to enable them to subject their cardio metabolically deranged patients to ECG in their clinical practice

2. **STUDY OBJECTIVES:** To screen high CV risk patients (asymptomatic and symptomatic) at outpatient department (OPD) for ECG abnormalities using FDA approved portable ECG device and follow-up for 5 years.

3. **METHODOLOGY**

Study Design: Multicenter, Observational, Prospective, Longitudinal, Non-Interventional Study



4. CONSENT OF THE INVESTIGATOR:

A written consent of the subject/participant will be taken before the initiation of the study. If the participant is incapable of giving an informed consent, the participant's legally acceptable representative will sign the consent. If the participant or his legally acceptable representative is unable to read/write, an impartial witness will be required who will be present during the entire informed consent discussion and will also sign the consent form. The formal consent of a participant, using the IEC approved consent form, will be obtained before that participant undergoes screening or any study procedure.

Before requesting such consent, the investigator will provide all essential information for participants to make an informed decision about their participation in a language that is non-technical and understandable by the participant and/or his/her legally acceptable representative.

5. INCLUSION & EXCLUSION CRITERIA:

5.1 INCLUSION CRITERIA:

- Adult men or women aged ⩾ 40 years
- Asymptomatic subjects with at least 3 CV risk factors visiting to the OPD for routine clinical checkup OR Symptomatic subjects with suspected CVD visiting to the OPD for further clinical assessment
- Subjects willing to provide written informed consent form

5.2 EXCLUSION CRITERIA:

- Subjects with implanted devices like pacemaker, external cardiac defibrillator
- Subjects with known CVD (Arrhythmias on treatment, MI, Stroke, PAD, Heart failure, Post cardiac intervention (PCI, CABG, Ablation, Device implant etc.)
- Pregnant women

6. STUDY PROCEDURES

6.1.1 Reasons of ECG monitoring:

Reason for recommendation of ECG	**<u>Asymptomatic patients with High CV risk (Presence of atleast 3 risk factors given below)</u> (Please mark √ in the relevant boxes)** 1. Age ≥40years ☐ 2. Hypertension ☐ 3. Diabetes☐ 4. Tobacco Use (Chewing/Smoking)☐ 5. Obesity (BMI ≥25kg/m^2)☐ 6. Dyslipidaemia☐ 7. CKD☐ 8. Family History of ASCVD (MI, Stroke, CAD, PAD)☐ 9. Waist Circumference (≥ 90 cm in male & ≥80 cm in female) 10. Any others ☐ **<u>Symptomatic patients with suspected CVD:</u> (Please mark √ in the relevant boxes)** 1. Chest Pain ☐ 2. Syncope ☐ 3. Palpitation ☐ 4. Shortness of breath☐ 5. Dizziness or Light headedness ☐ 6. Weakness or Fatigue☐ 7. Nocturnal Symptoms (Palpitation, Shortness of Breath, Chest Pain) ☐ 8. Post Prandial symptoms like chest pain ☐

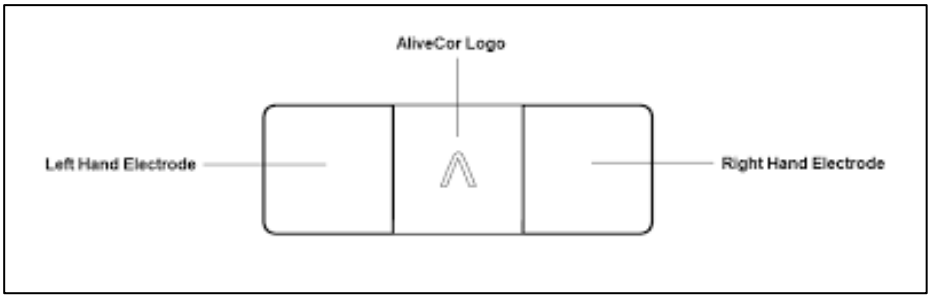
	9. Diaphoresis (excessive sweating) ☐ **10.** Any other if investigator thinks _____

6.1.2 Device

- KardiaMobile 6L is the world's 1st FDA-cleared six-lead personal ECG device.
- Detects the most common heart arrhythmias: atrial fibrillation, bradycardia, tachycardia and 28 different types of ECG abnormalities using EK-12 GE algorithms (as shown in table below)

EK12 Diagnostic Outputs	
1. Sinus Rhythm with 1st degree AV block	15. Consecutive PACs
2. Sinus Rhythm with 2nd degree AV block	16. Ventricular Bigeminy
3. Marked Sinus Bradycardia	17. Atrial Bigeminy
4. Juctional Rhythm	18. Inverted T-wave
5. Atrial Fibrillation with Rapid Ventriular Response	19. Normal QRS Frontal Axis**
6. Atrial Flutter (with AV Block)**	20. Left Axis Deviation**
7. Ectopic Atrial Rhythm	21. Right Axis Deviation**
8. Idioventricular Rhythm	22. RBBB**
9. Wide QRS Tachycardia**	23. LBBB**
10. Occasional PVCs	24. Hemiblocks**
11. Occasional PACs	25. Incomplete LBBB**
12. Frequent PVCs	26. Incomlete LBBB**
13. Frequent PACs	27. WPW
14. Consecutive PVCs	28. Inferior Ischemia/Infarction**
**** Possible only with 6L**	

- Gives more detailed heart information



6.1.3 Rules of monitoring

- Login to Kardia station on your android or apple device
- Signup with the details.
- Touch the lefthand and right hand electrode to activate the device and connect with Bluetooth of your phone/tablet/laptop.
- Place your phone or tablet on a table in front of you.
- Hold the KardiaMobile 6L in your hands with the "A" symbol facing you and pointing up.
- Now you need to tale 3 readings each of 30s as described in the annexure.
- Recorded ECG will be saved with the patient's history for clinician's interpretation

6.1.4 What not to do?

- Do not us the electrode on the portion of the body with too much body fat, body hair or very dry skin, as successful recording may not be possible.
- Do no store in extremely hot, cold, wet or bright conditions.
- Do not take recordings if electrodes are dirty. Clean them first
- Do not expose the device to excessive liquid
- Do not use it while charging your phone
- Do not drop or bump with excessive force
- Do not use with cardiac pacemaker, ICDs, or other implanted electronic device.
- Do not use in close proximity with other electrical and electronic equipment.

7. STUDY EVALUATIONS AND MEASUREMENTS

7.1 PARAMETERS

The parameters like patient's demographic details, vital parameters, life style factors, family history, medical history, medication history, ECG and whatever the investigator captures as part of routine clinical practice will be recorded.

7.2 LABORATORY INVESTIGATION

Complete Lipid Profile

7.3 SCREENING AND MONITORING EVALUATIONS

It must be aimed to obtain the following subject data -

- Patients' demographic data, medical record review, medication history, etc.

7.4 STUDY DURATION: 5 years

7.5 INVESTIGATOR'S / CO-INVESTIGATOR'S INTERPRETATION:

Investigator's Interpretation					
Timeline	**ECG Record Date**	**ECG Abnormality (Yes/No) (Please mark √ in the relevant boxes)**		**If yes, please describe the abnormalities**	**Occurrence of any event (please specify) *(Stable Angina, MI, Stroke, Left Ventricular Dysfunction, Any other)***
1. Baseline		Yes[ ]	No [ ]		
2. At 12 month (1st year)		Yes[ ]	No [ ]		
3. At 24 month (2nd year)		Yes[ ]	No [ ]		
4. At 36 month (3rd year)		Yes[ ]	No [ ]		
5. At 48 month (4th year)		Yes[ ]	No [ ]		
6. At 60 month (5th year)		Yes[ ]	No [ ]		

ECG reports to be uploaded individually in pdf during each timeline:
Recorded by Investigator (Name with Dated Sign): _____

Co-Investigator's Interpretation*				
Timeline	**ECG Abnormality (Yes/No) (Please mark √ in the relevant boxes)**		**If yes, please describe**	**Intervention based on ECG abnormality**
1. Baseline	Yes[ ]	No [ ]		
2. At 12 month (1st year)	Yes[ ]	No [ ]		
3. At 24 month (2nd year)	Yes[ ]	No [ ]		
4. At 36 month (3rd year)	Yes[ ]	No [ ]		
5. At 48 month (4th year)	Yes[ ]	No [ ]		
6. At 60 month (5th year)	Yes[ ]	No [ ]		

***Co-investigator will be blinded with Investigator's interpretation**
Reviewed and approved by Co-investigator (Name with Dated Sign): _____

7.6 STUDY ENDPOINTS:

Primary Endpoints:

- Prevalence and type of ECG abnormalities in high risk symptomatic and asymptomatic outpatients

- Prevalence of high CV risk patients developing ECG abnormalities during 5 years follow-up and its co-relation with their cardiovascular risk profile

Secondary Endpoints:

- Sensitivity, specificity positive and negative predictive values of ECG screening in high-risk out patients
- Development of Risk prediction model for Indian patients using ECG to find out most important CVD risk predictors for cardiac abnormalities
- Association of cardiac abnormalities with CVD risk predictors.
- To evaluate the regional differences in prevalence and types cardiac abnormalities

8. STATISTICAL CONSIDERATIONS

For direct detection

We will verify the findings of the physicians with the electrophysiologist/cardiologist for the following cardiac abnormalities. (All inconclusive results will be treated as positive in our analysis (because in the clinical situation these participants with cardiac abnormality cannot be ruled out and need to have a 12-lead ECG). We will calculate sensitivity, specificity, likelihood ratios and 95% CIs for each test (for all cardiac abnormalities together).

Analyses for both single-lead ECGs will be carried out per physician and transmitted to the cardiologist. We will analyse the agreement between the cardiologist and physician within each pair together with the κ value. Next to the prevalence of abnormality findings we will verify the follow-up (change of) treatment.

Survival curve

We will use sex-specific Cox proportional-hazards regressions to relate risk factors to the incidence of a first CVD event during a maximum follow-up period of 5 years after the moment of the first ECG.

In addition, we will use sex-specific Cox proportional-hazards regressions to relate risk factors to the first time occurring of an ECG abnormality in patients who had no abnormality at the first screening but developed this during the 5-year follow-up period.

We will aim at establishing prediction model from which CVD risk can be mathematically estimated.

The aim is to estimate 5-year absolute CVD risk. For this the following covariates will be considered age, total cholesterol, waist circumference, BMI, LDL-C, HDL-C, HBA1c, systolic and diastolic blood pressure, antihypertensive medication use, current smoking, and diabetes status, diet (veg/non-veg).

If the covariates have a significant influence these will be included in the model, otherwise excluded. (All continuous variables will be naturally logarithmically transformed to improve discrimination and calibration of the models and to minimize the influence of extreme observations. We shall adjust for the use of antihypertensive/ anti-diabetes medication by modeling the impact of a participant's systolic blood pressure, anti-diabetes medication differently on the basis of use of such medications.)

9. DROPUOUTS IF ANY:

Months	No. of patients	Reason of drop out
1. 12 month (1st year)		
2. At 24 month (2nd year)		
3. At 36 month (3rd year)		
4. At 48 month (4th year)		
5. At 60 month (5th year)		

10. CLINICAL ADVERSE EVENTS

The present proposal entails an observational, non-interventional study which means that AEs are most unlikely caused by the design of the study.

11. STUDYADMINISTRATION

11.1 DATA COLLECTION AND MANAGEMENT

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. Electronic form of case report forms (e-CRFs) will be used as and when required.

11.2 DATA SOURCES (IF APPLICABLE, FOR EXISTING RECORDS)

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study, Source data are contained in source documents. Examples of these original documents, and data records includes (but not limited to): hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the non-interventional study.

11.3 CONFIDENTIALITY

Information that can identify study subjects will be kept confidential and managed according to the requirements of the applicable law(s). Subject authorization to collect protected health information (PHI) will be a part of informed consent process. Data privacy clause will be the main aspect of such real world study ICFs.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least safety information at the end of their scheduled study period.

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1 DATA SAFETY MONITORING PLAN

This study will be monitored sufficiently to ensure that study is conducted, recorded and reported in accordance to approved observation plan, GCP, institutional policies and locally applicable regulatory requirements. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents.

12.2 RISK ASSESSMENT

Since the study is designed as observational, non-interventional study, the estimated risk for participants is not greater than minimal risk.

12.2.1 POTENTIAL BENEFITS OF STUDY PARTICIPATION

As this is an observational study using ECG, there will be direct benefits to the study participants for early detection of CVD, if any. Further it will be confirmed with expert in the field of cardiology. Additionally, data generated will be useful to the physicians too in early screening and further management of such subjects.

12.2.2 RISK-BENEFIT ASSESSMENT

Since the study is designed as observational study, estimated risk for participants is not greater than minimal risk.

12.3 RECRUITMENT STRATEGY

Participating study investigators will primarily be responsible for recruitment from the patients visiting them.

12.4 INFORMED CONSENT

The Investigator shall obtain a freely given, informed and written consent by the subject. If the subject is incapable of giving an informed consent, the subject's legally acceptable representative will sign the consent. If the subject or his legally acceptable representative is unable to read/ write, an impartial witness will be required who will be present during the entire informed consent discussion and will also sign the consent form. The formal consent of a subject, using the IEC-approved consent form, will be obtained before that subject undergoes any study procedure.

Before requesting such consent, Investigator will provide all essential information for subjects to make an informed decision about their participation (as required by current regulatory norms) in a language that is non-technical and understandable by subject and/or his legally acceptable representative.

12.5 PAYMENT TO SUBJECTS/FAMILIES

Since the study is designed as an observational, real world, non-interventional study in the naturalistic setting of routine or typical clinical practice, no payment will be made to subjects for participation in this study. Compensation also does not apply to such studies.

13. ANNEXURE

13.1 Detection Criteria

Detection of ECG Abnormalities	**Method**
Types of Arrhythmias (Kardia 6L)	EK-12 (GE- algorithm)
Left Ventricular Hypertrophy (LVH) (Kardia6L- Single Lead)	**Sokolow-Lyon Criteria:** Add the S wave in V1 plus the R wave in V5 or V6. If the sum is greater than 35 mm, LVH is present.

13.2 How to take ECG readings using Kardia 6L device

Reading 1: Normal 6L ECG	30s each (Total 90 seconds)
Reading 2: Single lead ECG at V1	
Reading 3: Single lead ECG at V6	

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