WHITE PAPER

# Optimizing continuous electrocardiography (ECG) monitoring in clinical trials

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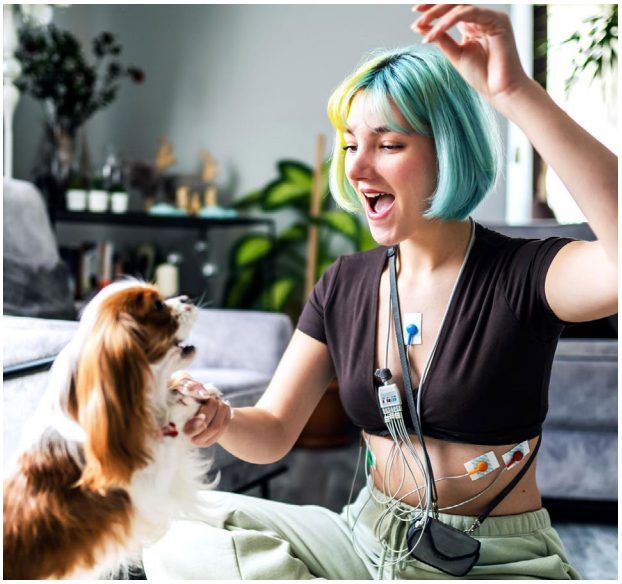
## Background

The electrocardiogram (ECG) is a vital tool to assess cardiac safety and efficacy in clinical trials. The standard 12-lead ECG assesses the heart's electrical activity for a duration that is typically 10 seconds. This "snapshot" of the heart's electrical rhythm will not capture any arrhythmias that occur outside of the 10-second window. Depending on the drug development program, longer duration and continuous ECG monitoring may be required to detect cardiac events that are infrequent and occur between study visits. Continuous ECG monitoring also facilitates the assessment of arrhythmia burden (e.g., arrhythmia frequency and arrhythmia duration), which is particularly useful for assessing the efficacy of an antiarrhythmic therapy. Continuous ECG monitoring devices are commonly used for the clinical care of patients. There are several guidelines from organizations such as the American College of Cardiology and the European Society of Cardiology about the appropriate use of these devices for clinical care.[1,2] However, there are no consensus guidelines published on the use of continuous ECG monitoring in clinical trials, which will be the focus of this paper.



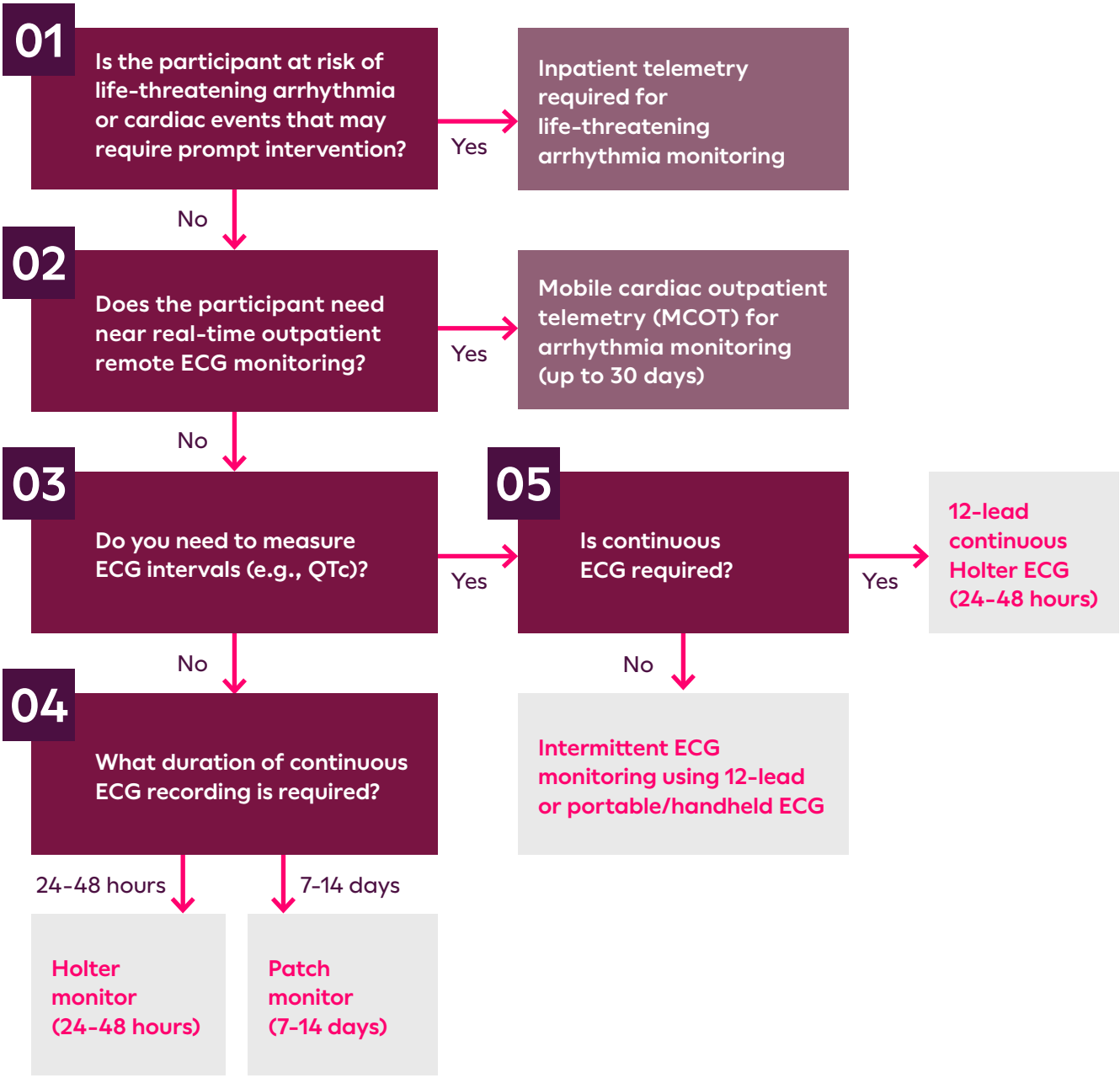
## Selection of a continuous ECG monitoring modality

The clinical trial characteristics and objectives for arrhythmia monitoring drive the selection of the most appropriate continuous ECG monitoring solution. ECG devices are useful for monitoring heart rate and rhythm, ST segment and T wave changes, interval duration measurements, waveform morphology and heart rate variability.

Continuous ECG monitoring provides enhanced identification and quantification of cardiac endpoints that include but are not limited to QT interval prolongation (with 12-lead ECGs extracted from the continuous ECG recordings), tachyarrhythmia and bradyarrhythmia events. Cardiac arrhythmia events are detected by continuous ECG monitoring even if the patient is asymptomatic. Other factors that influence the choice of continuous ECG monitoring in clinical trials include the need for real-time or near real-time reporting, participant compliance, device and data logistics, duration of monitoring, regional approvals and financial cost. Continuous ECG monitoring may use computerized real-time ECG data analysis. However, all review and interpretation of continuous ECG data should ultimately be performed by physicians and qualified health care professionals who are experienced at reviewing ECGs for clinical trials. The continuous ECG monitoring report should include information about the heart rate, arrhythmia diagnoses, frequency of common arrhythmic events (e.g., premature atrial contractions [PACs], premature ventricular contractions [PVCs], supraventricular tachycardia [SVT], ventricular tachycardia VT]) and representative ECG tracings of arrhythmia events.

Continuous ECG monitoring devices differ on the level of monitoring and surveillance, the precision of the ECG signal capture, duration of monitoring and the mode of delivering the ECG data from the study participant to the clinical team. A decision tree for the use of continuous ECG monitoring in clinical trials is illustrated in Figure 1.

**Figure 1. Decision tree for use of ambulatory ECG monitoring in clinical trials**



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## 01 Monitoring for cardiac safety risk

The first consideration for determining the type of continuous ECG monitoring centers on whether there is a high risk of life-threatening cardiac events that require continuous ECG monitoring and may require prompt clinical intervention. If the clinical trial involves the development of a drug that has unknown or potential high cardiac safety risk, then inpatient cardiac telemetry may be required especially when the cardiac safety of the drug has not yet been established. An example would be a clinical trial for a new anti-arrhythmic medication that has potential pro-arrhythmic effects or a clinical trial enrolling participants at high risk for life-threatening arrhythmias.

### Inpatient monitored telemetry

Inpatient monitored telemetry can be used in a clinical trial when there is potential for immediate, life-threatening cardiac arrhythmias that require prompt recognition and therapeutic intervention (i.e., advanced cardiac life support, cardiac defibrillation). Continuous ECG surveillance by trained personnel with the appropriate level of ECG rhythm interpretation certification is required for inpatient monitored telemetry. The cardiac telemetry monitoring system should have audible and visual alarms to alert site staff to cardiac safety events. There should be a memory storage capacity of at least 24 hours to enable review of a participant's ECG data. The ECG data must also be able to be uploaded to or printed for storage in the study participant's source data record. Inpatient monitored telemetry is expensive, inconvenient for study participants and a limited resource. Thus, inpatient telemetry is not appropriate when the cardiac safety risk is low.

## 02 Near real-time outpatient or remote monitoring

If inpatient monitored telemetry (i.e., real-time continuous ECG monitoring) is not required, the next consideration is whether near real-time monitoring of cardiac telemetry should be implemented remotely. For a clinical trial, near real-time continuous ECG monitoring can be implemented in the outpatient ambulatory setting. For this use case, there should not be a high risk of life-threatening arrhythmias. Near real-time continuous ECG monitoring should be used when there is a risk for non-life-threatening arrhythmias that can be treated with interventions such as adjusting medications and directing the participant to seek urgent medical care. An example could be atrial fibrillation that could benefit from the participant using an anti-arrhythmic medication or going to the hospital for evaluation and treatment.

### Mobile outpatient cardiac telemetry

Mobile cardiac outpatient telemetry (MCOT) or mobile cardiac telemetry (MCT) can be used when there is a need to monitor cardiac safety at home. MCOT is a small ECG sensor or cardiac patch that records the cardiac electrical activity using external electrodes on the chest wall. The ECG recordings are transmitted and reviewed by a central monitoring center for near real-time analysis. The MCOT device has preprogrammed computer algorithms to auto-detect and auto-send cardiac arrhythmia event data automatically to the central monitoring center.

The study participant can also trigger the MCOT device to send ECG data corresponding to the symptomatic episode to the central monitoring center. The MCOT rechargeable battery and data transfer capabilities enable monitoring for 1 month in duration or more. There is continuous attended surveillance by the Central Monitoring Center staff who can notify the responsible physician for pre-specified alert conditions. The responsible physician could, for example, (a) request transportation of the participant to the hospital or (b) speak with the participant and adjust medications (such as initiation of anti-arrhythmic drug treatment, for example). There may be a delay between the time of the arrhythmic event, review of the ECG and contacting the participant. Thus, the continuous ECG monitoring is considered near real-time as opposed to real-time.

## 03 ECG interval measurements

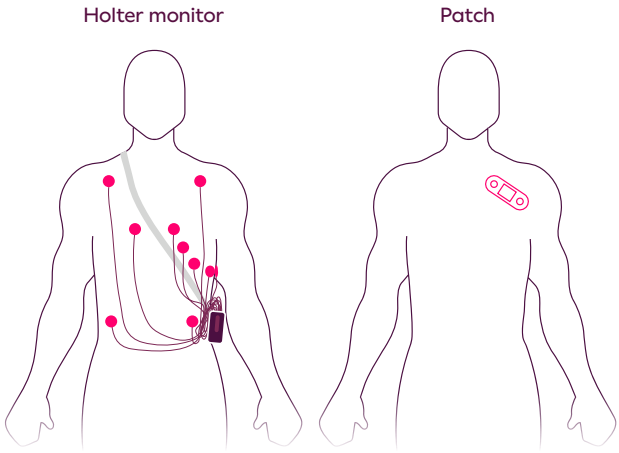
Another consideration is the need to obtain ECG data for QT interval analysis. If ECG QT interval duration measurements are required for intensive or thorough QT analysis, this is best performed using the traditional 12-lead ECG device or Holter ECG device from which individual, 10-second ECGs can be extracted for later analysis. This is because QT interval analysis using a higher ECG sampling rate with multiple leads provides more precise ECG interval duration measurement. The MCOT and other patch cardiac monitors are not appropriate for intensive QT analysis if the ECG sampling rate is too low.

## 04 Duration of continuous ECG monitoring

When continuous or frequent ECG monitoring and QT interval analysis are required in a clinical trial, the 12-lead Holter ECG monitor is recommended for monitoring durations of 24 hours to 48 hours.

If the duration of continuous cardiac monitoring in a clinical trial needs to be greater than 24 to 48 hours, the cardiac patch is a convenient device that can be worn by the study participant for a duration lasting up to 14 days.

**Figure 2. Holter and Patch monitors**




### Holter monitor

The Holter monitor was developed in the 1940s and is a commonly used continuous ECG device for evaluating arrhythmias in clinical care. The Holter monitor has a battery life and data storage that can typically operate for 24 hours to 48 hours. The Holter ECG can be used as a 3-lead or 12-lead ECG by changing the participant cable and electrode setup. Holter ECG devices are available that have measurement fidelity with a sampling rate up to 1000 samples/second. Holter ECG devices can use a standard SD data storage card and can also transmit data via Bluetooth to a computer



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laptop or electronic tablet. The larger size of the device and the shorter battery life limit the use of the Holter monitor. Other limitations of the Holter monitor that limit extended use in the outpatient setting include frequent electrode detachment, signal quality issues due to poor adherence of lead electrode to skin, tangled lead wires, skin sensitivity to lead electrode adhesive and poor participant acceptance of extended durations of Holter monitoring. Additionally, it should be noted that, for a Holter monitor to detect a cardiac arrhythmia of interest, it must occur during the 24- to 48-hour monitoring period.

### Patch

A Patch monitor is a small sensor that is held by adhesive on the study participant's chest wall. The Patch has good participant compliance since it is low profile and water resistant. Study participants can wear the Patch during their daily activities. The Patch monitor has a battery life and data storage capacity of 7 days to 14 days, which is much longer than the Holter monitor's 24- to 48-hour duration. The Patch is useful for assessing heart rate, heart rhythm and atrio-ventricular conduction abnormalities. The Patch is typically a 1- or 2-lead ECG device and does not require external lead wires. A limitation is the closely spaced electrodes, which may limit the ability to diagnose certain arrhythmias and prohibits the ability to detect ischemic changes. The closely spaced electrodes can also result in inconsistent ECG quality, particularly with larger body habitus. The Patch is contraindicated when the individual has a skin allergy or sensitivity to the adhesive. The patch is also not suitable for intensive QT assessment given the lower sampling rate and limited leads compared with the standard 12-lead ECG. Thus, the Patch cannot replace the role of the standard 12-lead ECG performed at screening and study visits in a clinical trial.

## 05 Intermittent ECG monitoring

If continuous cardiac monitoring in a clinical trial is not required, a traditional 12-lead ECG device or portable/handheld ECG can be used to monitor cardiac safety and assess the effects of investigational products on the heart.

### AliveCor KardiaMobile

The AliveCor KardiaMobile 6L is a wireless pocket-sized handheld ECG device paired with a smartphone that collects a 30-second ECG, recording the six standard limb leads. There are two dry electrodes on top of the device (for the left and right thumbs) and one dry electrode on the back of the device (for the left knee or ankle). No disposable adhesive electrodes or wires are needed. The KardiaMobile 6L ECG can be easily used by participants independently at home to supplement the scheduled clinical visits where standard 12-lead safety ECGs are collected. This approach is suitable for QT safety monitoring and can reduce the frequency of required clinic visits without compromising QT safety monitoring needs. In addition, the KardiaMobile 6L device is suitable for intermittent assessment of arrhythmias, either with scheduled time points (i.e., daily or weekly) for 30-second recordings or unscheduled/on-demand to record an ECG when symptoms develop.

## Additional considerations

The modalities described in this paper should fulfill the continuous ECG monitoring needs of most clinical trials. There are other types of continuous ECG monitors (e.g., cardiac event monitors, implantable loop recorder) used in clinical care that are not commonly used in clinical trials, and these devices are beyond the scope of this white paper. The decision tree in Figure 1 is a simple and practical guide for determining which type of continuous ECG monitoring should be implemented in a clinical trial. The first branch of the decision tree involves whether the study participants are at high risk for life-threatening cardiac arrhythmias. It is important to emphasize that inpatient monitored telemetry is only indicated for participants that are at a high risk of life-threatening cardiac arrhythmias and is not a substitute for close clinical observation. Like inpatient monitored telemetry, MCOT also uses attended surveillance by a central monitoring center. MCOT provides an additional safeguard than the Patch because of the near real-time cardiac arrhythmia monitoring. However, whether MCOT improves participant outcomes (reduces cardiac events and mortality) compared with the Patch has not been demonstrated and is not known. If a study participant is having a life-threatening cardiac arrhythmia at home, the near real-time arrhythmia monitoring provided by MCOT may be inadequate to urgently implement life-saving measures.

For precise QT duration interval measurement, ECGs extracted at specific time points from a 12-lead Holter ECG should be used rather than the Patch, as the Holter's multiple leads and higher sampling rate offer greater precision. Additionally, intensive QT analysis is typically performed in the inpatient setting, when extrinsic factors that influence the QT interval can be controlled. If continuous ECG monitoring is not required and intermittent remote or home ECG QT interval safety monitoring is required, the portable handheld KardiaMobile 6L ECG can be used.

Patch monitoring is typically reserved for the outpatient setting. The advantage of the 7- to 14-day Patch over the 24- to 48-hour Holter ECG monitor is the ability to detect an increased number of arrhythmia events because of the increased duration of ECG monitoring. The single lead adhesive electrode used in the Patch and MCOT monitors have good participant acceptance and compliance.

## Trial objectives drive the choice of ECG monitoring modality

The choice of which continuous ECG monitoring modality to use in a clinical trial is dependent on the objectives of the trial. The attributes and limitations for each type of continuous ECG monitoring assessment must be considered to choose the most appropriate ECG device for the clinical trial. Advances in technology will continue to improve our ability to assess cardiac arrhythmias and improve the cardiac safety of participants in clinical trials. Early input and guidance from cardiac safety experts familiar with the attributes and limitations of each of these monitoring modalities can be very beneficial when designing a clinical trial.

## References

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## About Clario

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