MEDPACE

EXPERT INSIGHTS: Q&A ON THE EVOLUTION AND INTEGRATION OF ECG WEARABLES IN CLINICAL TRIALS

Tell us a little bit about your clinical development background with electrocardiograms (ECGs) and wearables.

Swapneel Shete, BHMS

I started my career 20 years ago as a resident medical officer managing cardiac patients in an Intensive Cardiac Care Unit. A year later, I joined an ECG core lab as a central ECG reader, eventually moving into different roles managing ECG core lab operations, projects, and customer accounts; I am currently in a scientific advisory role. Over time, I have seen a wide range of devices collecting ECG endpoint data for clinical trials. To provide Sponsors, sites, and patients with relevant device solutions that meet protocol objectives and regulatory expectations, my role involves determining and adopting fit to purpose devices/wearables for ECG data collection, as well as analysis approach across different study requirements, trial phases, therapeutic areas, and drug indications. I work closely with Sponsors, device manufacturers, medical monitors, and industry experts in designing, developing, and integrating these solutions.

Sal Zabbatino, MD

I have over 35 years of experience in pharmaceutical and device clinical research and have been a part of the Medpace leadership team since its founding in 1992, serving as Director in key departments. I have extensive experience with imaging, cardiac safety, and connected devices in clinical trials, including DXA (BMD and TBC), Cardiac Echo, Cardiac SPECT, Ultrasound, MR, CT, endoscopy, photography, Biopsy Read Management, ECG, Holter, ABPM, CGM, Actigraphy, and other remote biosensors. My focus is on the medical, technical, and operational integration of these modalities into the overall conduct of these studies.

How has the use of ECGs in clinical trials evolved over time?

Over the years, devices used to collect ECG endpoint data within clinical trials have evolved significantly, offering more advanced solutions to meet trial and patient needs. The standard 12-lead ECG was sufficient for years, allowing for the collection of bedside 10-second printouts and continuous rhythm printouts for manual measurements and site investigator review. The demand for extended continuous recording of heart rhythm that allowed for patient mobility led to the implementation of the 12-lead Holter. The 12-lead Holter has since become key in satisfying the ICH E14 guidelines, which pushed for greater safety measures in clinical trials, including the consideration of replicate ECGs time-matched to PK assessments, routinely completed by extracting 10-sec, 12-lead ECGs from the Holter recording. Advancements in the standardization of ECG file structures and the development of digital tools for more precise fiducial point placement have also contributed to the feasibility of this solution.

As concerns over capturing hard-to-detect arrhythmias have grown, there has been increased interest in recording rhythm data for durations beyond the standard 24-48-hour Holter. To meet evolving trial needs, devices must be wearable for longer durations while optimizing the collection of high-quality data with minimal impact on patients' day-to-day activities, leading to the evolution of wearable devices.

The implementation of decentralized trials has required core labs to provide sites, affiliated home health nurses, and patients with innovative solutions to support remote ECG data collection while seamlessly meeting protocol objectives and regulatory requirements. Medpace Core Labs (MCL) understands this very well and integrates these solutions, thereby providing Sponsors with viable options that suit their trial needs.

Tell us a little about the integration of the CRO, core lab, Sponsor, sites, and patients in trials with ECGs.

The goal of a core lab is to provide Sponsors, sites, and patients with the most suitable device solutions for centralized ECG data collection, ensuring alignment with the protocol endpoint objectives and adherence to regulatory expectations. The core lab selects and implements the most suitable data analysis approaches across various clinical trial phases, therapeutic areas, and drug indications to best meet protocol endpoints.

The core lab plays an important role in seamlessly integrating all trial elements. They collaborate with device vendors to offer tailored device solutions, support sites, manage data workflows, and ensure central analysis, reporting, cleaning, and transfer of data. Thus, a core lab ensures standardization, data privacy, security, and regulatory compliance, resulting in reliable data outcomes for clinical trials.

While working closely with Sponsors and patients, the core lab prioritizes the integrity of data. This involves identifying solutions that meet the needs of the Sponsor while keeping patient comfort in mind — a key factor for ensuring patient compliance throughout a trial. Decentralized trials offer greater flexibility while enhancing patient comfort and compliance.

With a comprehensive understanding of available devices, MCL is well equipped to help Sponsors identify the best solutions for both trial and patient needs, while overcoming the challenges of integrating wearable devices into the trial.

What are some of the unique challenges faced in clinical trials with ECG wearables? What are strategies to overcome these challenges to ensure a successful trial?

Integrating ECG wearables into clinical trial design presents several challenges that must be addressed to ensure the fulfillment of device benefits and the success of the clinical trial.

Identifying the Right Device

Device selection must align with the goal of the trial, and sites must be capable of understanding and implementing the chosen device. Sites serve as the bridge between the Sponsor and patients, helping to ensure the validity of the data being collected. Educating the site on the device is essential, as the site staff will be instructing patients on how to use it. MCL works alongside our clinical colleagues overseeing other aspects of the study to support sites by providing patient guidelines for device usage, ensuring proper acquisition and submission of study data, making sure that patient support is available, and helping troubleshoot if issues arise.

It is necessary to determine which type of remote data is required and then identify the devices best suited for the trial endpoints. The selection of these devices is influenced by the number of ECG leads needed to support safety endpoints. For example, the initial phase of the studies may require a 12-lead, while a 6-lead ECG may be adequate for a study focusing on safety endpoints, and a post-marketing study for subject safety may be adequately managed using a single-lead continuous monitor.

Considering Geographical Location

The approval of the devices is contingent on geographical location and patient population, requiring careful consideration of regulatory factors. It is important to confirm that a device is suitable for clinical trial use by verifying the country-specific regulatory approvals from the manufacturer prior to selecting the device. Additionally, while wearables present opportunities for decentralized monitoring, some wearables that utilize mobile devices for data transfer require either a cellular signal or an internet connection, which some patients may not have. To address these challenges, MCL leverages partnerships with logistical vendors to satisfy these requirements by supplying hotspots or mobile devices for which the necessary wearable application can be utilized, regardless of patient location.

Capturing Quality Data and Ensuring Patient Compliance

The incorporation of new technologies to capture trial endpoints, such as those around ECG and rhythm monitoring, requires careful consideration to reduce variability. Patients must be familiar with mobile devices and receive proper training from site staff to ensure they capture quality data at the correct time points and transmit the data through the proper means for review. Ideally, wearables should allow patients to view the ECG, provide feedback on sufficient signal quality, and provide guidance on resolving connectivity issues. Comprehensive documentation and training for site personnel are the first steps in ensuring patients are equipped with the necessary information for

proper device wear and data collection. A well-crafted patient guideline, detailing steps for collecting optimal data, can further improve patient engagement and compliance. MCL regularly drafts such documents to support sites in maintaining data integrity.

Efforts to improve patient compliance should prioritize user comfort and hassle-free integration of wearables into daily life. Compliance becomes a challenge for some wearable ECGs due to skin irritation and discomfort of bulky chest-strap monitors and ECG patches over long-term wear. However, a properly chosen wearable can often be preferred over conventional devices, improving compliance and resulting in more complete data. MCL considers the needs of each patient population when recommending wearable devices.

Data Review

The time between data collection and review of wearable data, particularly in decentralized trials, is important when identifying and following up on rhythm disturbances that may manifest during the trial. Several patch devices require patients to return the device to the vendor by mail, where the data is uploaded for review. This process is highly dependent on device packing and shipping timelines, placing burden on the patient to properly package and ship the device on time. Shipping complications can further delay the diagnosis of rhythms that may progress to life-threatening arrhythmias. Further, there is a risk of data loss due to misplaced or damaged shipments.

Fortunately, as wearable devices have matured, many have the capability to connect to mobile phones and tablets via Bluetooth connections. ECG wearable data can be sent to an app on a mobile device, which then transmits data to a vendor platform for regular review. Mobile apps also provide an opportunity to view the ECG during the patient preparation stages, allowing clinicians to verify proper waveform capture to support trial endpoints. Devices can now be easily attached to patients globally to monitor and collect data remotely for several days with minimum discomfort and ongoing compliance checks. This reduces the number of clinic visits needed and helps improve patient recruitment, retention, and engagement.

Summarization of Data

As wearables become increasingly capable of collecting high-frequency data over long durations, the challenge of reviewing and summarizing this data arises. ECG patch data can routinely last 14 days and require the identification of arrhythmias. MCL utilizes novel methods and automated algorithms integrated with device vendor platforms for seamless review and reporting of continuous ECG data. MCL has trained ECG Readers who are experienced in reviewing continuous ECG data from such wearables.

Tell us a little about the integration of ECG wearables with other sensors.

Advances in wearable devices have led to size reduction and the digitization of various vital signs and health metric collection beyond the ECG monitors mentioned so far. It is now possible to integrate biosensors, such accelerometers and thermometers, into the same wearable device used for ECG rhythm collection. Wearable device vendors have already integrated sensors to provide indices of activity, skin temperature, and respiration rate. This integration offers a more comprehensive, time-synced dataset, providing a greater understanding of the patient's condition and enabling better clinical determinations.

Case Study: MCL recently provided several data collection solutions to a Sponsor, leveraging the integration of ECG rhythm and activity in patch devices. To meet the Sponsor's request, an activity monitor solution utilizing a watch was provided, along with a patch device for extended ECG rhythm collection. Additionally, MCL provided a second solution in which both activity and ECG rhythm could be collected simultaneously on the same patch device. This reduced the number of vendors involved, the trial costs, and the number of devices the patient would be required to wear.

What do you see in the future for trends in wearables and ECG monitoring in clinical trials?

The landscape of wearable ECG monitoring in clinical trials is evolving quickly, driven by advances in technology and increased demand for data collection. Core labs must stay current on trends by reviewing new patches and wearables to assess their potential use.

Wearable devices continue to evolve, including improvements in acquisition time, the number of leads captured, data resolution, and longer battery life without interruptions. The size of wearable ECGs is becoming smaller and more discreet, making them easier to wear for patients. Many wearable ECGs are becoming more integrated into other everyday wearable devices like watches and rings. This leads to better comfort and patient compliance. The trend is shifting toward single devices with multiple sensors, such as activity, respiration, sleep, CGM, blood pressure, and more. This allows for more comprehensive monitoring, which is valuable for clinical trials requiring multifaceted data collection. These advancements will make wearable ECG devices more reliable and effective in clinical trials.

Additionally, there is greater prevalence of real-time review and alerts with the adoption of wearable ECG devices. These devices can now send immediate alerts of irregularities, making real-time review possible, while also providing real-time compliance indicators for the patient, site, and Sponsor. Artificial intelligence enhances data analysis by identifying patterns in data and providing insights, which reduces the need for manual interpretation and improves accuracy.

Furthermore, new innovative technology is now available to perform standard 12-lead at home, reducing the need for patients to travel to sites while still providing quality data with ease. Two notable advancements in this area come from Alivecor and QT Medical. Alivecor developed a remote 12-lead ECG data collection device with limited wires, progressing from a 6-lead to a 12-lead, offering the potential benefits of decentralized trials. QT Medical designed a device to capture 12-lead ECG data remotely while preventing data quality issues such as lead reversal by using pre-positioned leads available based on patient chest size and easy to choose options based on a sizing guide. This self-sticking, pre-positioned lead set connects seamlessly with the recorder and transmits the data via mobile application with an option to accept or reject the recording based on review of quality of waveforms on mobile device.

MCL remains at the forefront of innovations in the industry by exploring new ways to leverage advancements in ECG technology and seamlessly integrate them into clinical trials. Through ongoing collaboration with device vendors, MCL develops tailored solutions that meet the demands of the ever-evolving decentralized clinical trial landscape.

How do core labs play a key role in clinical trials integrating wearable ECGs?

A core lab seamlessly integrates advanced device solutions into the trial, helping Sponsors identify the best options for both the trial and the patient. While wearable ECG devices are sometimes seen as a very simple implementation, their integration into clinical trials is quite complex. This is where a core lab comes in. The clinical team manages patient recruitment, data monitoring, data collection, safety, and other aspects. When remote monitors are involved, it is necessary to make sure the site and patient are knowledgeable, patients remain compliant, data is accurately collected, and it aligns with trial objectives. Even when vendors supply the device, having a core lab dedicated to overseeing the execution and integration of these devices adds significant value.

Why should Sponsor's consider a partnership with MCL?

Sponsors need a core lab partner that can identify a wearable that meets the needs of the trial, is approved for the patient population, and that can be integrated for data collection. MCL has extensive experience supporting Sponsors through the integration of wearable ECGs into the complex structure of the overall trial. Medpace can leverage our relationships with vendors and assist Sponsors in identifying a wearable that is appropriate for their trial.

Medpace collects, harmonizes, and integrates data from wearables and remote devices into clinical trials as part of our full-service offering. As a full-service CRO, Medpace can execute clinical trials seamlessly with a corporate structure that is streamlined for execution, cohesive study teams, integrated services, and global resources to scale with a compound through all stages of clinical development.

In an increasingly complex drug development environment, direct access to scientific expertise is indispensable. At Medpace, our scientists are embedded in your projects and collaborate directly with your team to map out the best course of action. This drives quality and avoids missteps that could cost you time and money, ultimately accelerating your path to approval.