Optimizing Biosensor-based Trials

A Parexel Pilot of Multiple Sensors in End-to-End Data Collection

Drug development is moving beyond the clinic into real-world therapeutic evaluation—and ever closer to the patient's daily life and medical needs. Applications of biosensors for remote data collection offer enormous opportunities to better engage patients in research and to deliver therapies that provide greater value for the patients who use them. In this report, Parexel shares insights on how to integrate multiple biosensors in a research approach that improves patient experience, delivers end-to-end remote data collection, and presages greater efficiencies that will ultimately reduce time to market.

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Multiple sensors, terabytes of data

With clinics locked down and industry racing to meet life-and-death needs for COVID-19 interventions, biosensors and devices proved their worth. But we can't harness their full value in clinical trials until we can integrate wearables for end-to-end data management. And not just one, but *multiple* sensors and devices, from multiple vendors, generating unprecedented volumes of data. Sponsors will need research partners who can help them meet new challenges—from teaching patients to use devices correctly to teasing out meaningful data from terabytes of data flow. Parexel has learned how best to design controls up front and how to engage patients in use of new mHealth technologies.

As the lingering COVID-19 pandemic accelerates adoption of decentralized trials, Parexel is working to further operationalize mHealth sensors and devices for remote data capture in clinical research. Our ongoing evaluations have three major goals:

> Assess the capabilities and integration of multiple biosensors and devices into end-to-end research platforms.

> Address the data management challenges posed by unprecedented volumes of data generated by wearable and connected devices.

> Engage patients in correct, compliant use of devices as the collection of accurate, quality data shifts from clinical sites to study participants.

By the time Parexel undertook this pilot study, we had experience from more than 150 decentralized trials. Initially, we partnered with Oracle early in the pandemic to assess the potential for clinical trial use of activity trackers (Apple Watch, ActiGraph Centrepoint Insight Watch, Withings Pulse HR). We then modeled successful end-to-end data capture from all devices and shared insights for best practices concerning logistical shipping, global implementation, and patient training.

Our most recent evaluation focused on the integration of two clinical-grade biosensors used together with eConsent and electronic clinical outcome assessment (eCOAs). The primary objective was to assess the capabilities of Medidata's Sensor Cloud platform in integrating new and existing devices for end-to-end data capture and analysis. In addition, we wanted to understand how this model would support patient-facing challenges posed by sensor-based trials, including training, compliance and monitoring.

Proof-of-Concept Assessment Design

Medidata's Sensor Cloud offers a platform for industry collaborations aimed at integrating sensors and standardizing sensor data. We worked with Medidata to assess the platform's performance in integrating a Medidata sensor (BioStamp nPoint) currently available through the Sensor Cloud with a second sensor (NuvoAir spirometer) from an external vendor. Both sensors were used together with eConsent and eCOA to model a decentralized trial with end-to-end data collection and data visualization.

Objectives

Study Objectives & Duration

> Evaluate device integration and use in an end-to-end, multiple-sensor model.

> Assess participants' ability to use and manage two wearable devices.

> Test the addition of common mHealth tools: eCOA and eConsent

> Duration: 14 days

To conduct the 14-day evaluation, Medidata shipped two biosensors—the **Medidata BioStamp nPoint** and the **NuvoAir Spirometer**—to 15 adult participants across the United States, the United Kingdom, Denmark and Lithuania. Two groups of 10 participants received either the NuvoAir or the BioStamp, with five individuals across the two groups receiving both devices.

Participant number	NuvoAir	BioStamp	Location
1	Y		US
2	Y		US
3	Y		US
4	Y		US
5	Y		US
6	Y	Y	US
7	Y	Y	US
8	Y	Y	US
9	Y	Y	US
10	Y	Y	US
11		Y	EU
12		Y	EU
13		Y	EU
14		Y	EU
15		Y	EU

* Distribution was based on country because Biostamp was only available for use in the US.

Participants used MyMedidata, a single destination patient portal, to sign eConsent and complete an eCOA assessment. Medidata and NuvoAir conducted a remote training session with participants on how to correctly use the sensors and how long Medidata BioStamp nPoint should be worn. During the assessment period, the study leaders checked in on the portal to monitor daily compliance including data transmission and device usage.

Devices and Measurements

BioStamp is a wireless activity tracker currently available in Medidata's Sensor Cloud. BioStamp can be worn on multiple places on the body to collect physiological data on Vital Signs and movement.
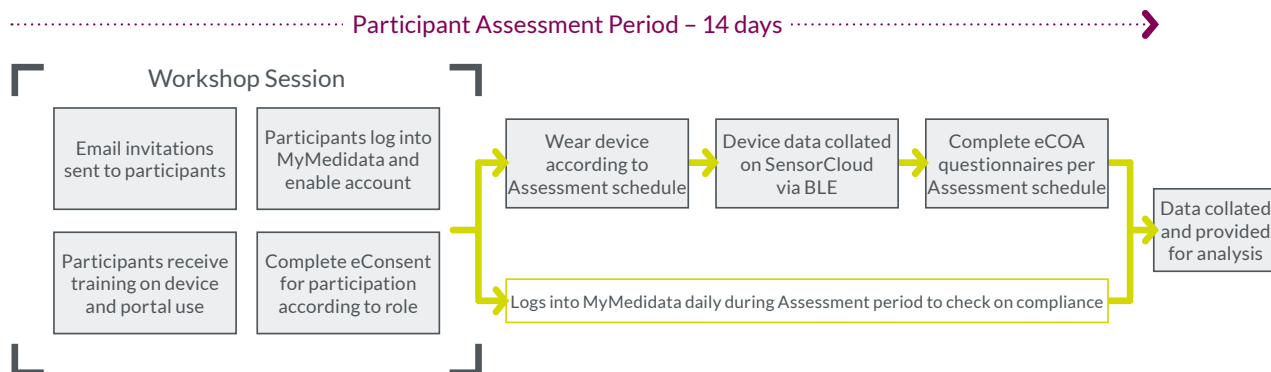
› Duration: typically worn up to 7 days for continuous measurement; for this study, participants were asked to wear the BioStamp sensors for 14 days.

› Key Measures: vital signs, activity/actigraphy and posture classification, electromyography (sEMG), and sleep metrics.

› Grade: medical grade; FDA 510K cleared.

› Data Transmission: to a paired cellular phone via Bluetooth Low Energy (BLE) transmission, then via cellular to Sensor Cloud.

› Charging: BioStamp sensors are recharged daily during which no data are collected.

NuvoAir is a wireless handheld device that combines a spirometer with mobile app and analytics to monitor and collect data on respiratory function. It is used clinically to help manage asthma, COPD and other respiratory symptoms/disorders. As part of this study, NuvoAir was integrated into the Sensor Cloud platform.

› Duration Used: 14 days; 2 measurements daily, a.m. and p.m.

› Key Measures: spirometry.

› Grade: medical grade; FDA cleared and CE marked.

› Data Transmission: to a paired cellular phone via BLE, then via cellular to SensorCloud.

› Charging: NuvoAir requires double A batteries which did not need replacement during the PoC assessment.

A myMedidata eCOA questionnaire was completed daily for five days to demonstrate that eCOA can be used alongside medical devices in a clinical trial.

Evaluation Design: Technology Data Flow

Participant Assessment Period – 14 days

Workshop Session

Email invitations sent to participants	Participants log into MyMedidata and enable account
Participants receive training on device and portal use	Complete eConsent for participation according to role

Wear device according to Assessment schedule → Device data collated on SensorCloud via BLE → Complete eCOA questionnaires per Assessment schedule → Data collated and provided for analysis

Logs into MyMedidata daily during Assessment period to check on compliance

Results and Lessons Learned

The BioStamp activity tracker and NuvoAir spirometer were successfully implemented for end-to-end data collection in this multiple sensor model, confirming Medidata's ability to integrate both a new and existing sensor in its Sensor Cloud platform. Participants reported that the devices were sufficiently easy and comfortable to use in our 14-day assessment. This proof-of-concept trial reinforced lessons learned in our previous evaluation of activity trackers. Here again, device shipping and importation posed challenges, and we saw the importance of prompts and compliance reminders for participants.

Insights and recommendations are shared below.

Device Selection: Make it a unified experience

> Regardless of the number of devices used, the essential point is managing the integration and complexity of "more than one" to enable end-to-end data collection, visualization and analysis. Rigorous mapping of devices to research goals is even more essential in this context.

> Actigraphy is complex-- it's important to know what type of data a given device will generate. Device data are not necessarily comparable. For example, the BioStamp records a wide array of data with nearly 50 different parameters measured across sleeping, moving, and resting, while the Fitbit Charge 5 claims to measure only 10 parameters. Another factor to consider is that the controlled environment for data integrity afforded by a medical grade device is superior to that of commercial grade devices. Updated algorithms which occur during software updates may introduce inconsistency to data collection: sponsors cannot control the release of software updates by commercial device manufacturers, which may change the measurements collected.

Devices may seem simple, but every patient has a different level of skill and experience. Training has to cover everything, from how to change device batteries to how to reach the Help Desk.

> Sensors should be validated and backed by technical specifications as well as supported by evidence-based research. While FDA clearances and CE marks give a measure of assurance, they do not guarantee that devices will perform as manufacturers claim. When onboarding new devices, and especially when multiple devices are being implemented, technical specifications function as a blueprint to manage complexity and ensure quality. Supporting research for device performance also should be evaluated, and research submitted to support the application should be reviewed. A literature search can identify peer-reviewed manuscripts for review and evaluation of the supporting research. Most device manufacturers will provide supporting research upon request. Much of this documentation is available for sponsor review by the device manufacturer.

> Therapeutic area expertise is critical. Medical directors who understand the relevant disease condition should be central to the device selection process to provide insight into issues related to form factor, data consistency and reliability. Physicians can provide a medical perspective on whether the measures obtained from a device will contribute to endpoint and outcome determination. Based on their deep knowledge of the patient journey, physicians can recognize device form factors that may not suit patients with certain

medical conditions—for example, a thin layer of muslin cloth might be used under an activity tracker to protect sensitive skin in cases of dermatitis, or one brand of a continuous glucose monitor may be more suitable for some body types than others.

› Device certification, import restrictions and approval conditions vary considerably across countries. This variability is often underappreciated in the planning of global studies. Regulatory approval and CE marks are major considerations in device selection; regulatory status determines whether a device can be imported, which in turn impacts site selection. For example, Japan requires a Giteki mark to certify compliance with radio law specifications with additional restrictions on devices that transmit radio signals. Shipping challenges include the need to adapt to changing conditions in local environments which can result in considerable delays. Constantly changing COVID restrictions introduced major delays in our evaluation. Following COVID outbreaks, some countries required waiting periods of two to three weeks before devices could be released.

Data Deluge: Make it meaningful

› Have clear, upfront requirements for data needed to demonstrate study objectives and collect only what is essential. Sensor data can be voluminous. The BioStamp, for example, has the ability to measure vital signs, activity/actigraphy and posture classification, sEMG, and sleep metrics. Fewer devices and fewer measurements support better compliance and a more comfortable experience for the patient.

› Avoid "noise"—an excess of data can obscure meaningful results. The vast capabilities of wearables will challenge researchers to identify meaningful findings in a sea of information. In this study, data retrieved from the BioStamp exceeded what an excel spreadsheet can hold. Managing terabytes of data poses myriad questions: where will data be stored; what will be used in real time; will it be reported daily, weekly or monthly? Multiple sensors add to this complexity; however, analytical tools offered by device platforms can make it efficient to look for important correlations in volumes of sensor data. Another example is combining electronic patient-reported outcome (ePRO) data and sensor data in visualizations to show relationships between patient-reported outcomes and objectively measured data from medical-grade sensors

› Don't break the blind! Consider how sensor data reported to sponsors, sites, research teams and patients will be used and whether a given type of data might break study blinding. For example, BioStamp shows heart rate over time. How might a site use that data? What kind of actigraphy might be used for safety signals? To protect the blind, the clinical data from the device should not be shared with the site; however, wear time and compliance data should as it allows site operations to intervene when compliance issues arise related to sensor usage.

"The video training and the prompt responses from the Medidata team when I had minor issues with the app made the experience easy and understandable. Before taking part in this study, I had never used a spirometer, or a skin sensor. These interactions helped me understand the importance of data and compliance for study conclusions. As a result, I was more thoughtful and precise with the daily assessments."
(Study Participant)

> Data on compliance monitoring and device health are essential. This information is as critical to study quality as device-generated clinical data. During assessments, is the participant wearing the device? Wearing it as directed? Is the battery charged? In our evaluation, we found that some participants would forget to reapply the BioStamp sensors after charging. It is important for sites to reinforce the message that device data are part of the protocol, are being monitored, and are critical to the study. Participant-friendly communication tools can emphasize this message together with instructions for device use. Sites can be given access to compliance data so that they can send reminders to participants when necessary. Devices can be set up with in-built reminders in the form of notifications on participants' phones. Gamification is another tool on the horizon to better engage participants. Some device platforms also provide operational dashboards to sites that convey quality and amount of expected sensor data, an early indicator of compliance and performance in the study.

Simplify the Patient Experience

> Multiple sensors can multiply research burden for patients. Using multiple sensors means that patients must learn to use and maintain several devices and must wear sensors, day and night, on multiple places on the body. Sponsors need to ask, are we just shifting research operations from sites to patients? The goal is to obtain essential data using the fewest devices for the shortest amount of time—make it seamless for study participants.

> Multiple devices also increase the training burden on patients. In this proof-of-concept trial we used live video for training and monitoring. Participants were observed using their devices in real time by the manufacturers to assess their understanding and ability to use devices as required by the study. Video training proved to be an excellent model, and participants indicated it gave them a measure of comfort with respect to applying the BioStamp patches and to measuring lung function with the spirometer. We recommend that when using multiple sensors, it is best to use one, single guide for all the devices.

> Form factor—the way the device is fit to the body—is an important consideration when writing a protocol. A post study survey confirmed that BioStamp was generally comfortable to wear and that NuvoAir was easy to use, but some participants reported that sensor adhesive (for Biostamp) was irritating at times. Devices like BioStamp may need to be moved to different places on the body to minimize irritation. This possibility should be built into the study protocol and training information.

Recommendations for better communication and overall patient experience

> Talk to patients about the importance of the data and their role in data collection.

> Measure compliance using one of several approaches: at the device level, at the site level, or by a third party.

> Provide a global help desk for both sites and patients.

> Let patients know their data have been received.

> If possible, report some data back to patients —for example, report their compliance versus the total study compliance.

Biosensor Advances; More Data, More Objectivity

Sensors and wearables can collect data previously inaccessible to sponsors, sites, and patients.

> Actigraphy data are being collected to measure activity in Phase I-IV studies involving neurological conditions such as depression and Parkinson's disease, as well as respiratory, cardiology, rheumatology and oncology indications among others.

> Spirometry readings outside the clinical setting can provide a more holistic view of the health status of study participants.

Sensors and wearables can enhance objective measurements.

> Provide more objective measurement in central nervous system and other indications that lack strong classical biomarkers and rely on subjective tools for outcome assessment.

> Enrich and complement eCOA data and patient diaries with objective sensor data and insights that self-reports and clinician reports cannot provide.

> Eliminate some intra-site and episodic variability in measurements, such as vital signs, lung function, and walk tests.

> Offer new opportunities to validate digital measurements to improve scientific endpoints.

With Heart™

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for a conversation

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