RESEARCH PROTOCOL

There's No Place like Home…Feasibility of Remote Physiological Monitoring in Childhood Heart Failure

Short title: WeRoaM: Wearable Remote Monitoring in Heart Failure

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1 Introduction and Background

Remote physiologic monitoring (RPM) refers to utilizing non-invasive medical devices to obtain physiologic data, such as pulse oximetry, blood pressure, weight, and electrocardiography at home. Recent advances in RPM have facilitated improved home-based care, reduced hospitalizations, and improved quality of life in adult heart failure populations[1–3]. Additionally, the integration of multiple physiologic variables acquired through remote physiologic monitoring into machine learning algorithms has been shown to predict hospitalization for heart failure[4]. Previous paediatric studies have demonstrated the utility of incorporating multiple physiologic variables into risk prediction algorithms[5] for cardiac events. This is particularly important in heart failure cohorts where limits of acceptability are often nuanced and patient specific. The use of multiple physiologic parameters creates a more comprehensive insight into the complex pathophysiologic changes in heart failure.

However, the use of RPM devices in children remains limited due to a lack of validated devices and uncertainty about the acceptability and uptake of such interventions. This is partly due to challenges developing devices that can be easily applied, and digital platforms suited to the wider range and variability in body sizes and physiologic parameters. Thus, care of children with heart failure continues to rely on hospital-based models, where tertiary heart failure centers serve large geographically and socio-economically diverse populations. A validated paediatric virtual home monitoring system using RPM to predict clinical deterioration could safely facilitate earlier discharge, reduce the need for outpatient hospital visits, and potentially improve outcomes while minimizing family social disruption and school absence.

The overarching goal of this project is to assess the feasibility of RPM in paediatrics and validate a RPM based risk prediction model for paediatric patients with or at-risk of heart failure, with a view to facilitating safe home-based care across geographically and socially diverse urban, rural, and remote communities. To achieve this goal, this study proposes to utilize a wearable Bluetooth enabled textile (Skiin Device) that can monitor heart rate and rhythm, respiratory rate and activity, together with additional home-based monitoring of blood pressure, oxygen saturations and weight. The textile, developed by Myant (Toronto, ON) has completed pilot[6] testing at SickKids to assess its validity in an outpatient setting (NCT04305340). The Skiin textile will be paired to its software solution, the Myant Health Platform (MHP), which comprises the Skiin Connected Life App (phone application), the Myant Back End (cloud storage of data) and the Myant Virtual Clinical Portal (internet browser visualization of data collected). The Skiin Connected Life App will be used for collection of ECG, heart rate, body temperature, and physical activity throughout the day, and can generate the following average metric for each night when the device is used: resting heart rate, respiratory rate, resting heart rate variability, sleep duration, body temperature.

The MHP will be paired with another RPM platform, Sphygmo™ (mmHG Inc). The Sphygmo™ platform consists of a smartphone App (Android, iOS), which can be linked with Bluetooth-compatible devices for automated uploading of measurements to a clinician portal. This platform, originally developed for adults, has the ability to connect with blood pressure, heart rate, weight, and oxygen saturation devices. This platform will be used for collection of additional physiologic data as above and is currently under study at Stollery Children's Hospital. The two systems will have a single-sign on feature allowing their integrated use by the patient, their families, and the research team. We will leverage descriptive and predictive analytics to augment clinician monitoring by defining trajectories and longitudinally predicting risk of key adverse outcomes.

2 Rationale

Advances in technology now offer opportunities for RPM of heart failure patients with a virtual platform. However, to date this technology remains untested in pediatrics and care continues to rely on a hospital-based model. This model presents challenges in providing equitable access to care particularly to those with lower socio-economic status or living in remote communities. For those with increased risk of life-threatening complications, frequent hospital visits are needed for monitoring, and are associated with a financial burden and negative impact on quality of life of both patient and family. Tools that predict clinical deterioration with heart failure using a virtual home monitoring system could facilitate safe care in the home irrespective of geographical location, fewer in-person outpatient visits, better communication with care providers and potentially improved outcomes. As a result, telemonitoring technology specifically tailored for pediatric populations with machine-based algorithms to predict deterioration is needed to take the vital next step towards the equitable provision of safe, home-based care.

3 Study Objectives

3.1 Primary Objectives

1. To investigate the feasibility of a remote physiological monitor using a textile smart garment (Skiin devices) using the Skiin Connected Life App along with additional standard home monitoring tools (BP monitor, weigh scales) that are paired with a Bluetooth enabled app (Sphygmo™)

2. To test the acceptability of a remote physiological monitor using a textile smart garment (Skiin devices) along with the acceptability of a Bluetooth enabled app (Sphygmo™)

3.2 Secondary Objectives

1. To leverage analytical methods to develop descriptive and predictive tools using RPM that augment detection of clinical deterioration in pediatric patients as measured by admission, adverse cardiac events and patient reported outcomes within 6-months post intervention.

4 Study Duration

Patients will be recruited over a 2-year period.

5 Study Design

We will conduct a prospective, longitudinal multi-centre observational study of feasibility of a virtual RPM system. We will then define population vital sign behavior in pediatric outpatients with heart failure syndromes or at-risk of heart failure. The use of normative vital sign ranges derived from healthy children in abnormal physiological states has limited utility when the relevant question is how unusual an individual patient's behavior is within a population of patients who all have abnormal vital signs. Longitudinal data collected in this study will generate a foundational dataset that will be stratified by age, sex and diagnosis to determine 'normative' patient behavior in the context of a compensated heart failure syndrome in pediatric outpatients. All of the data points sampled will be used to generate distributions of vital sign behavior both at the level of the individual patient and the population (cohort) as a whole utilizing a validated methodology we have previously applied to analyze similar inpatient vital signs[7].

6 Study Procedures

6.1 Study Population

This study will enroll 100 paediatric outpatients (8 to 18 years old) with diagnosis of cardiomyopathy (with systolic or diastolic dysfunction), subjects with congenital heart disease with biventricular or univentricular physiology plus systemic ventricular dysfunction from 4 tertiary heart failure care centres.

6.2 Eligibility Criteria

1. Patients from 8-18 years of age who are outpatients at time of study enrollment.
2. Patients with a chest size of at least 69.85 cm in perimeter/circumference (as measured under the pectoral muscles)
3. Patients at-risk for heart failure and with American Heart Association (AHA) Stage B-D Heart Failure will be included in this study irrespective of heart failure medication use.
4. HF etiologies include: congenital cardiac malformation with systemic ventricular systolic dysfunction, idiopathic cardiomyopathy, familial/inherited and/or genetic cardiomyopathy, history of myocarditis with persistent ventricular dysfunction, neuromuscular disorder, inborn error of metabolism, mitochondrial disorder, acquired (chemotherapy, iatrogenic, infection, rheumatic, or nutritional), ischemic (e.g., Kawasaki disease and post-operative HF), and left ventricular non-compaction, restrictive cardiomyopathy and HCM with systolic or diastolic dysfunction.

6.3 Exclusion Criteria

1. Patients within 3 months of a surgery.
2. Patients supported by ventricular assist device at study onset.
3. Inability to use technology due to physical or cognitive impairment in the patient or caregiver.
4. Non-English speaking.
5. Patients who have an implantable cardiac defibrillator or pacemaker
6. Patients whose chest size is too large or small to fit available sizes of the Skiin device.

Eligible patients will be identified by a study team member. Patients may be approached for consent in cardiology outpatient clinics or at time of discharge from inpatient stay. Written consent will be obtained from the participant or substitute decision maker prior to any study activities being performed on the patient.

6.4 Withdrawal Criteria

A participant can choose to withdraw from the study at any time by informing the study team. Data can be withdrawn from the study up until the point of statistical data analysis.

7 Assessments

7.1. Medical History

Medical records will be accessed to collect baseline characteristics including date of birth, sex, gender, postal code, diagnoses, surgeries, current heart failure medications, and procedures. The

number of pediatric cardiology clinic visits, hospitalisations, ED visits, and cardiac investigations in the last 2 years will be collected to describe the patients' requirements for access to cardiac care. To satisfy our secondary objective, we will collect data on patient outcomes 6-months post intervention. This data will include: admissions, adverse cardiac events and patient reported outcomes In addition, the family will be asked to complete a demographic form that compiles information about parents' ethnicity, education level, socio-economic status, access to Wi-Fi and iOS/Android devices in the home.

7.2 Anthropometric Measurements

These will consist of body weight, height/length, and body surface area obtained as per standard hospital policy.

Additional measurements may be obtained of the chest perimeter at the sub-pectoral level, to select the appropriate size of the Skiin chest band (Bluetooth enabled smart textiles device).

7.3 Comparator Data

Routine blood pressure, heart rate, average respiratory rate, body temperature, ECG at enrolment (if available) or within the preceding 6 months prior to enrolment, and oxygen saturation (if available) will be obtained at clinic visit prior to commencing study per the standard of care for comparison with measures obtained with the Skiin device.

7.4 Textile Style Selection and Placement

The Skiin comprises a textile chest band that will be appropriately sized for patient size. A Skiin biometric pod will be charged ahead of the visit and positioned in the garment. The family will be provided with equipment to reload the Skiin pod, and launder the smart textile, and be shown how to do so.

7.5 Skiin Connected Life App (SCLA)

Following consent families will be asked to download the Skiin Connected Life App (SCLA) onto their iOS (13+) or Android (9+) device using the Wi-Fi in the clinic. For patients that do not have access to one of these devices, a Samsung A Tablet will be provided for study purposes. The families will be shown how to register and pair the Skiin pod to the SCLA and a test run will be performed prior to leaving the clinic (e.g., report a mock symptom and check electrocardiogram signal).

The SCLA collects real time heart rate, body temperature, and ECG. It also collects resting heart rate, resting heart rate variability, resting respiratory rate and sleep duration over-night. Device real time results will be compared to vitals taken at the same time in the clinic setting. Discrepancies in measurements, including any reasons for the discrepancies will be documented. In addition, written instructions with pictures will be provided for the families to take home.

7.6 SphygmoTM App

Following consent families will be asked to download the SphygmoTM App onto their iOS or Android device using the Wi-Fi in clinic. For patients that do not have access to one of these devices, a Samsung A Tablet \will be provided for study purposes. The families will be shown how to pair the Bluetooth devices to the SphygmoTM App and a test run for each of the devices will be performed prior to leaving the clinic. Device results will be compared to vitals taken at the same time in the clinic setting. Discrepancies in measurements, including any reasons for the discrepancies will be documented. In addition, written instructions with pictures will be provided for the families to take home.

7.7 Patient-reported Outcomes

To assess quality of life, participants will complete the Pediatric Quality of Life (PedsQL) Quality of Life Module 4.0[8] as baseline, end of intervention (12 weeks) and post-intervention (6 months post intervention). This is a self-reporting instrument that consists of 23 items in four domains: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). It has been designed for multiple age groups, including a parent Proxy report if required. For participants 8-12 years of age, parents will complete the Parent Proxy report as well.

Participants will also complete at baseline, end of intervention (12 weeks) and post-intervention (6 months post intervention) the Patient Global Impression of Severity (PGIS). This instrument will be used to capture the patients' current health status relative to their heart failure over a 7-days recall period. This is a global index that is used to rate the severity of a specific condition. It is a simple, direct, and easy to use scale that is understandable to clinicians. The PGIS uses a 5-point patient evaluation scale (none, mild, moderate, severe, very severe) for patient self-report in those aged ≥7 years.

At the end of the study, participants will complete the MedTech 20[9,10] which is a standardized tool measuring how medical devices affect people's general well-being and assess users' experiences of benefits of any medical technology product used by patients with disability/disease. The Questionnaire consists of 20 statements of attributes of patient benefit of medical devices. The statements are grouped into 4 domains as follows: sense of security, social participation, integrity, and convenience, with each domain including five attributes. When answering the questionnaire, participants are asked to select to what extent they agree with statement, for the product in question, on a 7-point scale; from (disagree) to (completely agree). In addition, participants can choose a not relevant response if the attribute is of no relevance for the product in question. Hence, there are 8 answer options. Based on the responses, an index (0-1) describing the product's benefit can be calculated, with an index closer to 1 representing a larger general patient-reported benefit from the product of concern

New York Heart Association Failure class will be completed at baseline, end of intervention (12 weeks) and post-intervention (6 months post intervention) to assess extent of limitation in physical activity due to heart failure symptoms[11].

7.8 Data Collection

7.8.1 Data collection with the Skiin devices

Data will be collected during a 12-week period. Study participants will be asked to wear the Skiin chest band daily and to keep in proximity their Bluetooth enabled device (smartphone or tablet).

Participants will wear the Skiin chest band continuously for the first 48 hours of study participation. Following that and for the remaining duration while in the study participants will be asked to only wear the device for a 12-hour period between 8pm and 8am keeping their bluetooth enabled devices (smartphone or tablet) in close proximity (e.g., in pocket or backpack during the day, in the bedroom during the night) to capture a maximum of real-world situations. This will provide continuous data and for the research team to understand the feasibility and value of the continuous remote monitoring of this population through the Skiin garments.

The biometric pod within the Skiin chest band is designed to transfer data continuously to a paired Bluetooth enabled device with SCLA. When not connected (e.g., when too far from the smartphone or tablet), the Skiin pod can store ECG data for up-to 45-minutes.

7.8.2 Data collection with the Sphygmo devices

Additional physiologic parameters will be collected daily through devices compatible with the SphygmoTM App (BP, oxygen saturation, weight). These devices will include:

- Blood Pressure: A&D Life Sciences BP Monitor: UA-615BLE – License #94858
- Oxygen Saturation: Nonin SpO2: Model 3230 – License #68959 **or** Contec SpO2: Model CMS50D-BT - License #90629.
- Weigh Scale: A&D Medical/LifeSource UC-352BLE – This is not represented or used as a medical device

Transmission of data to the clinical portal designed for the SphygmoTM App and SCLA will be monitored by the study coordinator and a secure message will be sent at the six-week mark to remind families that they are at the mid-way point of the study and how to contact the study coordinator if they are having any difficulties. Study personnel will be available throughout the duration of the study for troubleshooting. Participants will be asked to transmit data daily. Pre-paid packages will be provided to courier back the equipment at the end of the 12-week period including tablets.

7.9 Data Handling and Storage

All paper case report forms will be kept in a locked filing cabinet in a locked office, only accessible by the study team. De-identified data will be entered and stored on a REDCap database hosted on a secure server through the Women and Children's Health Research Institute at the University of Alberta. Only study team members and authorized personnel will have access to this database.

Data generated by the Skiin device will be housed on the Myant Backend, which is part of the Myant Health Platform (MHP, Class 2 software medical device) platform and data from other clinical devices (weights, saturations, BP) will be housed on the physician portal of the Sphygmo™ platforms and can be uploaded to redcap or downloaded to a CSV file. The Collaborator, Mazwi, has developed a novel time series database that will facilitate archival and retrieval of higher frequency patient physiological recordings[12].

Study data will be stored for up to 10 years in accordance with Health Canada policies for device studies.

7.10 Confidentiality

The study team will take all necessary precautions to ensure the confidentiality of participants. Participants in this study will be assigned a study specific ID that will be linked to their personal identifying information, maintained on a password protected and encrypted master list, stored on a secure AHS server. Identifying data is required to verify participant information, accessed only by members of the research team. De-identified data will be extracted from the REDCap database for analysis.

Specific study team members will have access to the Participants' identifying information and Skiin data (ECG, heart rate, steps, posture, overnight average metrics) through the Myant Virtual Clinic Portal (MVCP, part of the MHP). The MHP is hosted on a secure server that implements

HIPAA compliant data security procedures throughout the clinical workflow process from data collection to server storage and viewing.

Myant staff will not have access to the MVCP nor to any identified health information. Myant staff may have access to de-identified dataset without any Personal Identifying information if the study team shares with them the Skiin pod number and time of usage. The study team may share with Myant non-identifying health information such as sex, BMI, medical history, and age which may be required for algorithm development and validation. Access to these research datasets will be limited to Clinical and Data Sciences team members involved in this study (i.e., on a need-to-access basis).

The Sphygmo platform implements HIPAA compliant data security procedures throughout the clinical workflow process from data collection to server storage and viewing. After the patient transmits their blood pressure and vitals readings into the app, the data is stored locally on the smartphone using 256-bit advanced encryption standard (AES) protocol. Next, the data is transmitted to the server using hypertext transfer protocol secure (HTTPS) transport layer security (TLS) as the encryption protocol where it is stored securely on the server using 256-bit AES protocol and is visualized by clinical users via HTTPS.

All data that is collected is region specific, and in Canada is stored on Server Cloud Canada servers, which acts as the cloud server storage center for the Sphygmo remote patient monitoring platform. Data does not leave Canada. Server Cloud Canada is SOC 2, and 3 compliant.

7.11 Device Storage and Use

Devices provided by Myant will be stored in a secure location to which only team members have access. Myant textiles are designed to be used multiple times by/for the same individual and sustain between 30 and 50 washes at their commercial stage**.** For the purpose of the present study, each device will be used by a single patient. All devices will be returned to Myant at the end of the study.

8 Analysis Plan

8.1 Study Endpoints

Primary Outcomes: Feasibility will be assessed by recruitment rates (the number of participants recruited; retention rate (the number of participants who complete measures at baseline and at follow up post intervention), percentage of people with access to Wi-Fi and smart devices,

Acceptability will be assessed by compliance defined as >80% of the physiologic monitoring requested has been captured twice daily for a period of 12 weeks; Medtech 20 will also inform on acceptability.

Secondary Outcomes: For the secondary outcome we will use a composite end-point. Given the low prevalence and rarity of events such as death or transplant from chronic heart failure in paediatrics, there is limited potential for large outcome trials. As a result, we have elected to use a composite end-point designed for the PANORAMA-HF study and based on Packer's composite score which has been extensively used in adult heart failure studies[13–15].

Patients will be ranked within 5 categories from worst to best based on heart failure events such as death, transplant listing, need for mechanical circulatory supports, as well as progression of heart failure symptoms by NYHA or Ross Class and patient reported outcomes as assessed by the PedsQL and PGIS.

Patients who experience a clinical event during follow up will be classified into category 1 and 2 as described in Table 1. Patients without a clinical event during follow up will be divided into 3, 4 and 5 based on change from baseline symptoms and functional capacity (Table 1).

Table 1

Category	Sub-Category	Description	
1	A	Death, listing for transplant, mechanical circulatory support, mechanical ventilation required for life support at study end-point	
2	B	Worsening heart failure with ICU admission	
	C	Worsening heart failure with hospital admission (no ICU)	
	D	Worsening heart failure with no hospital admission	
3	E	Worsened NYHA/Ross or P-GIS on last available assessment compared to baseline	If no change in NYHA/ROSS or PGIS, further rank by PedsQL
4	F	Unchanged NYHA/Ross or P-GIS on last available assessment compared to baseline	If no change in NYHA/ROSS or PGIS, further rank by PedsQL
5	G	Improved NYHA/Ross or P-GIS improved (neither can be worse) based on last available assessment compared to baseline	If no change in NYHA/ROSS or PGIS, further rank by PedsQL

ICU, intensive care unit; NYHA, New York Heart Association; PedsQL, Pediatric Quality of Life Inventory; PGIS, Patient Global Impression of Severity

8.2 Statistical Analysis

Baseline and demographic characteristics will be analyzed using descriptive statistics. Adherence with the protocol will be determined by the mean number of requested assessments performed and the proportion of patients who completed >80% of measurements.

Physiological data will be analyzed as discussed in the study plan. Descriptive statistics including mean, variance, median and quartiles will then be used to characterize the population distribution in a manner that facilitates detection of outlier behaviour in individual patients. Correlation of

outlier behavior with outcomes of interest allows identification of 'undesirable' trajectories associated with adverse events and 'desirable' trajectories that can become targets for goal directed management. This approach permits mapping vital sign behaviour to categories of specific risk of adverse events as well as other actionable clinical outcomes, such as the need to titrate medical therapy.

We intend to augment this risk monitoring approach by incorporating change point detection for both individual vital signs and patient trajectory to facilitate earlier detection of deterioration and individualize risk stratification further. Finally, as the cohort grows in size we will probabilistically forecast the vital sign time series by leveraging neural networks (RNN) to learn the temporal dependence of the data and Long Short-Term Memory (LSTM) to deal with missing or irregularly sampled data. For patients with multiple vital sign observations for each timepoint multivariate Multi-Layer Perceptron (MLP) models will be employed to forecast a vector (magnitude and direction) of patient behavior. study duration, study methods, analysis plan, and timelines)

8.3 Enrolment Justification for Aim 2:

Based on the preliminary unpublished data from the Panorama study as described above: Category 1: 13.6%; Category 2: 9.07%; Category 3-5: 77.34%

We set statistical power at 80% and p-value <0.05, and a prevalence of ~20% for Category 1 and 2, a sample size of 100 would be able to detect a change in sensitivity between 80-90% and a specificity of 70-90%. As this is a screening test for worsening HF, we will prioritize sensitivity over specificity[16].

9 Study Devices

9.1 Skiin Textile Device

The Skiin chest band and biometric pod (electronics for recording and sending signals) are approved as a Class II medical device by Health Canada (License Number 106352).

Skiin devices collect real time ECG, heart rate, and body temperature and overnight average resting heart rate, resting heart rate variability, and sleep duration. The Skiin textile will be paired to its software solution, the Myant Health Platform (MHP), which comprises the Skiin Connected Life App (phone application), the Myant Back End (cloud storage of data) and the Myant Virtual Clinical Portal (internet browser visualization of data collected).

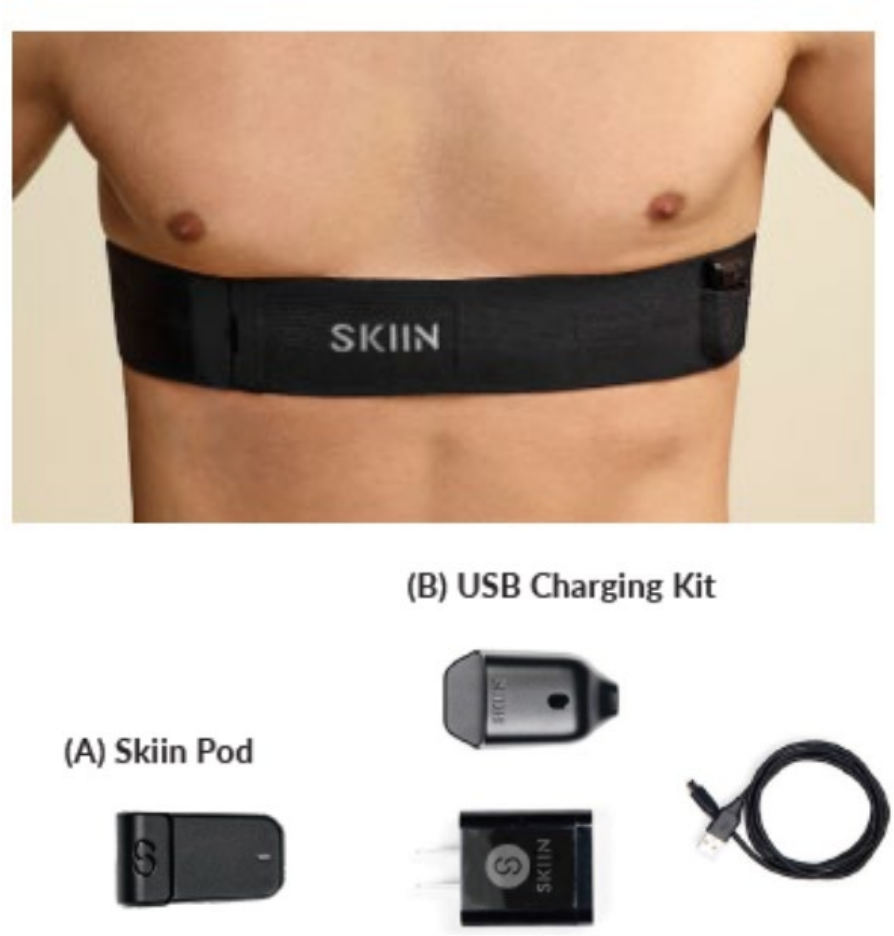
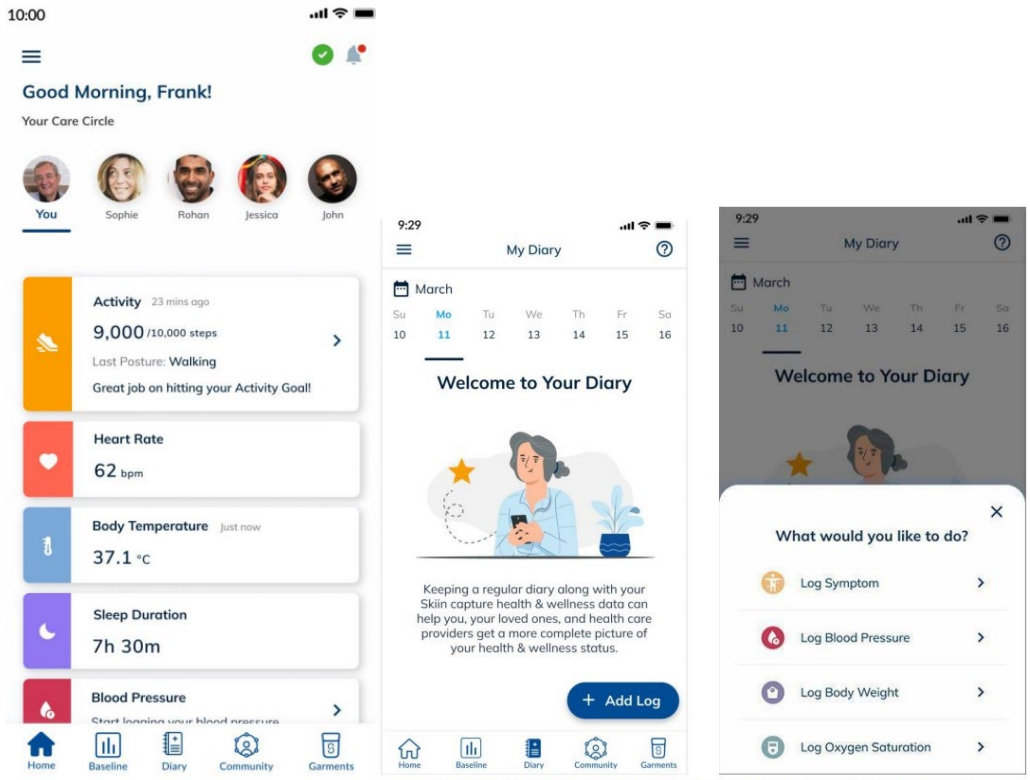
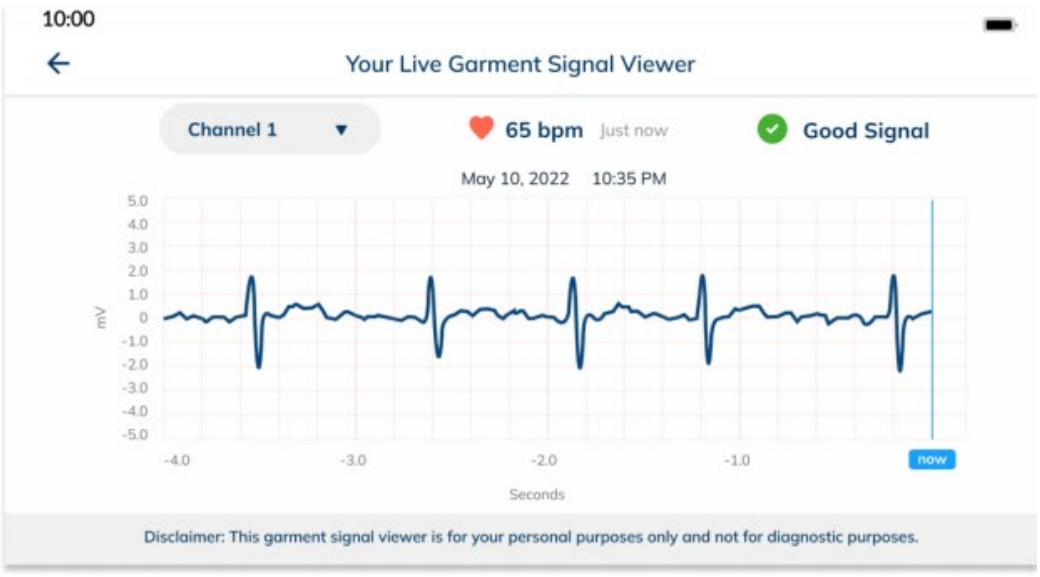


Figure 1: Skiin textile chest band, Pod and USB charging kit.



SCLA Home Page

Diary page - Adding a log (symptom, blood pressure, body weight, oxygen saturation) slide out



SCLA Heart Rate - Signal Garment Viewer - Example of a good signal

Figure 2: Skiin Connected Life app

9.2 Spyhgmo™

This RPM system was developed by mmHg Inc, a local physician led, digital health company. The Sphygmo™ platform consists of a smartphone App (Android, iOS), which can be linked with Bluetooth-compatible devices for automated uploading of measurements to a clinician portal. This platform, originally developed for adults, has the ability to monitor blood pressure, heart rate, weight, and oxygen saturations. Sphygmo™ has multiple features that lends its applicability to a broad patient population including those with limited resources.

10 Infection Control Measures

Sensors which are disposable will be removed from the participants immediately after testing and disposed of as per institutional approach to disposal of personal healthcare products (e.g., gel electrodes).

The textile equipment made by Myant (providing the innovative measurement being evaluated against reference device) will be single-use and returned to Myant in a sealed bag to be returned to Myant. The electronic pod placed in the textile, which does not come in direct contact with the participant, can easily be sanitized using a standard disinfecting wipe.

11 Assessment of Safety and Adverse Events

11.1 Risk Assessment

There is no known risk of any harm directly from the measurement or the outlined protocol. Subjects or their guardians will reserve the right to withdraw from the study at any time should they feel uncomfortable or believe that the protocol is unmanageable in their physical state – which will also be noted by researchers when determining subject participation. Slight skin irritation may be experienced at sites of electrode placement from skin preparation or adhesives used to attach. Participants and/or their guardians will be asked about any possible allergies to adhesives to prevent reactions from occurring.

Note that the use of adhesive is related to the routine hemodynamic and physiologic assessment of the vital signs, while the innovative devices developed by Myant will be simply worn, strapped on, or laid on without using adhesives.

11.2 Safety Monitoring

Clinical treating team will be instructed to contact the study team if they feel the device is disrupting clinical care or causing irritation to the patient. Each reported event will be reviewed by Study Investigator within 24 hours. Notes contained in the electronic medical record will also be reviewed for the study period to assess important developmental and clinical activities.

11.2 Documentation and Reporting of Adverse Events and Reactions

The study participants will be monitored for adverse events by the study team and by the treating clinical team which may be unaffiliated with the study while the study device is in contact with the patient. When the Skiin device has been removed from the participant, adverse event monitoring for study purposes will cease. Adverse events that may be attributable to the Skiin Device will be monitored until resolved.

Only adverse events that, in the opinion of the treating clinical team, may be attributable to the Skiin Device as documented in clinical recorded in the study participant adverse events log. These

events will then be reassessed by a physician on the study team for relatedness to the Skiin Device, severity, and seriousness.

12 References

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