Remote Clinical Trial Operations:
Patient Education for Medical and Wearable Device Use

by

Carly Madeleine Smith

Bachelor of Science, Mechanical Engineering
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Submitted to the Department of Mechanical Engineering
in Partial Fulfillment of the Requirements for the Degree of

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Signatures of Authors.....
Carly Madeleine Smith
Department of Mechanical Engineering
August 5, 2022

Certified by.....
Brian W. Anthony
Principal Research Scientist of Mechanical Engineering
August 5, 2022

Accepted by.....
Nicolas Hadjiconstantinou
Professor of Mechanical Engineering
Chairman, Committee on Graduate Studies
August 5, 2022

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Abstract

Consumer wearable devices with the capability to remotely collect longitudinal physiological data used for machine learning and artificial intelligence are set to revolutionize healthcare, including enabling remote clinical trials. Yet, there is no regulatory framework in place to standardize their utilization. In traditional clinical studies, user-related error is minimized, as a designated clinician performs all physiological measurements on each subject. However, in remote clinical settings, this standardization is lost, as each participant becomes responsible to collect their own physiological data. Patient education materials for remote studies must be designed intentionally to minimize user-related factors such as misuse and nonuse of device, as these mistakes introduce heterogeneity into and devalue longitudinal physiological data sets. This thesis project addressed the current state of remote clinical trial operations and provides a framework for human-subjects researchers to establish their own standardized remote clinical trial operations. Specifically, it focuses on the creation of intentional patient education materials with respect to fundamental principles of human cognition to reduce user-related error in wearable device operation.

Thesis Supervisor: Brian W. Anthony
Title: Principal Research Scientist of Mechanical Engineering

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Most importantly, thank you to my family. To my dad, thank you for teaching me to be an engineer. And to my mom, thank you for showing me how to be a compassionate one. Matt, thank you for leading by example, teaching me to earn my place then exceed expectations. Grace, thank you for being my greatest source of light and love.

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Introduction

This thesis reviews key components in the design of remote clinical trial operations, focusing on the standardization of consumer wearable device use through the design of human-centered patient education materials. This project along with the work of Imane Ait Mbiriq, Ryan Lin, and Joyce Noh, was a collaborative effort of four Massachusetts Institute of Technology students to prepare Tufts Medical Center to conduct two upcoming clinical trials remotely. Each team member focused on individual components of the overarching 10-step framework for remote clinical trial operations.

This introduction is comprised of five sections. The first section provides a general understanding of current remote clinical trial operations and introduces two upcoming remote trials and one completed trial. These studies, conducted by Tufts Medical Center and MIT Lincoln Labs, represent an industry standard for remote clinical trial operations. The next two sections summarize the motivation for research in patient education and wearable device use as well as the problem statement of this project. The fourth section provides background for all contributors from the Massachusetts Institute of Technology Master of Engineering in Advanced Manufacturing and Design Program (MITamd), Massachusetts Institute of Technology Center for Clinical Translational Research (CCTR), Tufts Medical Center, Tufts Clinical Translation Science Institute (CTSI), and the Institute for Clinical Research and Health Policy Study (ICRHPS). The final section outlines the remaining thesis structure and includes overview of the subprojects completed by the MIT Advanced Manufacturing and Design team.

Remote Clinical Trials

Clinical trials are designed and conducted to test the effects of certain experimental treatments on human subjects. Traditionally, clinical trials are performed such that human data is collected at a research facility or hospital. Over the past few years, an increasing prevalence of telehealth technology and the isolation of the Covid-19 pandemic encouraged the consideration of remote operations for clinical trials. Objectives of remote clinical trials include increase in patient enrollment as well as racial and ethnic diversity in enrolled patients. According to the FDA's data, only 3% of the country's physicians and patients take part in clinical trial research that leads to new therapies (1). Remote clinical trials have high potential in reducing barriers, including patients' reluctance to participate in clinical trials and dropouts. These can be related to different factors:

- Occupation: Participants are concerned about losing pay or not getting leave and therefore refuse to participate in trials involving hospitalization as per the protocol requirements (2)
- Transportation: In person trials require participants to be present in the trial facility which can result in transportation difficulties and additional costs.
- Comprehension of Trial Requirement and Consent: participants with less advanced education background may have difficulties comprehending the trial's instructions which can lead to wrong expectations and eventually dropouts.

The remote operation of clinical trial may serve to diversify the population participating in clinical studies and improve subject monitoring with continuous physiological reporting from wearable devices. However, the lack of clear regulations and guidance for remote clinical testing remains an obstacle for clinical entities who wish to start transitioning their onsite trial operations to remote settings (Hirsch et al., 2017).

Detection and Risk Assessment in Post COVID-19 Infection – A Long COVID-19 Observational Pilot Study (Long COVID Trial)

In a partnership with MIT Lincoln Labs, Tufts Institute for Clinical Research and Health Policy Study (ICRHPS) will conduct a novel remote clinical study to better understand the challenges of remote physiological data acquisition using consumer wearables. The study employs Oura Ring wearable devices to build longitudinal data sets for Artificial Intelligence and Machine Learning model development.

Phase IIb Study to Evaluate the Clinical Efficacy of Niclosamide in Patients with Mild to Moderate Symptoms from SARS-CoV-2 infection (Niclosamide Phase 2b Trial)

In response to the growing need to investigate potential treatments of Covid-19, researchers at Tufts Medical Center and Tufts Clinical Translation Science Institute will conduct the second phase clinical trial remotely to evaluate the effect of Niclosamide on participants with mild to moderate Covid-19 symptoms. Patients will receive a remote trial kit with devices to measure oxygen saturation levels and temperature.

Industry Standards (Niclosamide Trial)

March 2020, a placebo controlled clinical trial was conducted using a telehealth platform to determine whether Niclosamide reduces SARS-CoV-2 shedding. The platform was used for study visits, symptoms monitoring, and coordination of participants-self-collected specimens. A Phase 2 randomized clinical trial opened to accrual on October 1, 2020 and the last participant enrolled on April 2021. The trial included 73 adults with mild to moderate Covid-19. At the conclusion of the remote trial, surveys and interviews with participants and researchers were conducted to further understand the barriers, facilitators, and benefits of remote clinical trials. Interviews revealed participants' appreciation for clear instructions. The participants wanted additional reminders for sample collection (3).

Research Motivation

Consumer wearable devices with the capability to remotely collect longitudinal physiological data are set to revolutionize healthcare, including the questions of remote clinical trials. Yet, there is no regulatory framework in place to standardize their utilization. The clinically-oriented value of wearable devices has yet to be established (4) as the majority of wearable devices lack FDA approval through the 510k process (5). Despite their lack of FDA approval, wearable devices continue to be employed in remote clinical trials to advance clinical understanding and create longitudinal data for artificial intelligence and machine learning (6).

There are three main factors affecting the quality or value of physiological data generated by wearable devices: technical-related, user-related, and data-governance related. This thesis focuses on user-related factors affecting physiological data quality—most notably, nonuse and misuse of wearable devices. Nonuse and misuse of devices at any degree can potentially devalue the longitudinal data collected as it introduces incompleteness and heterogeneity to data sets (6).

In traditional clinical studies, user-related error is minimized, as a designated clinician performs all physiological measurements on each subject. However, in remote clinical settings, this standardization is lost, as each participant becomes responsibly to collect their own data. In this way, heterogeneity is introduced on two levels: within personal as well as interpersonal physiological data sets (6).

To fully utilize the capability of wearable devices and maintain safety in remote clinical settings, user-related factors affecting physiological data quality must be considered at the stage of trial design. Health practitioners must understand the utilities and limitations of the wearable devices they employ (7) and take proactive measures to standardize remote wearable device use through intentional patient education.

Problem Statement

Patient education for wearable device use in remote clinical trials is often supported by device manufacturer's manuals and existing trial documentation in place of more intentionally designed participant-instruction (8). This method of participant instruction violates many of the fundamental laws of human cognition, as technical documentation is often written in small font sizes, fluttered with complex jargon, and organized unfamiliarly. The resulting fragmented educational experiences places an extra burden on participants, who've already taken on the responsibility to partake in remote clinical trials. The lack of intentional patient-education encumbers standardized use of wearable devices in remote settings. This insufficiency introduces user-related variation, negatively impacting the quality and homogeneity of the longitudinal physiological data set collected.

Team Background

Massachusetts Institute of Technology Master of Engineering in Advanced Manufacturing and Design (MITamd)

The Advanced Manufacturing and Design program is a 12-month accelerated graduate program which combines MIT's eminent engineering curriculum with a pragmatic, industry-based, thesis experience (9).

Massachusetts Institute of Technology Center for Clinical Translational Research (CCTR)

The Center for Clinical and Translational Research is an MIT facility dedicated to supporting human-subject investigations. The CCTR staff work with researcher to design and execute experiments at a clinical standard (10).

Tufts Medical Center

Tufts Medical Center is a large academic medical center located in Boston, Massachusetts. The Medical Center serves as a teaching hospital to Tufts University School of Medicine and supports a wide range of biomedical research activities (11). The Institute for Clinical Research and Health Policy Study (ICRHPS) is located within Tufts Medical Center. ICRHPS provides researchers with an environment to safely and effectively conduct human subjects experiments (12).

Tufts Clinical Translation Science Institute (CTSI)

Tufts CTSI was created in 2008 in response to a growing need for translational biomedical research facilities. The Institute supports various schools of Tufts University as well as other hospitals and universities across the North East (13).

Thesis Structure

A ten-step framework was designed designed to support the establishment and operations of remote clinical trials.

1. *Parameters and Timeline of Trial*
2. Participant Tracking System
3. Device Storage and Cleaning
4. *Instructions for Device Use*
5. Current Device Inventory
6. Device Inventory Tracking System
7. Box Design
8. Box Inventory Tracking System
9. Box Assembly Plans
10. Delivery Management and Returns

Each step within the framework includes generalized guidelines to establish remote clinical trial operations and uses one of the two clinical trials introduced in section one of the introduction to exemplify an application of those guidelines. The content here focuses specifically on initial trial parameterization and the standardization of wearable device use through human-centered patient education. Content in the remaining sections of the framework was supported by the collaborative efforts of Imane Ait Mbiriq (14), Ryan Lin (15), and Joyce Noh (16) of the Massachusetts Institute of Technology. Imane Ait Mbiriq's work includes guidelines for inventory evaluation, tracking system development, and kit tracking system design (14). Ryan Lin's work includes guidelines for participant tracking systems, device storage and cleaning, material kitting, and shipping management (15). Joyce Noh's work includes a case study evaluation for accessible clinical trial kit design (16).

Parameters and Timeline of Trial

Leverage Existing Trial Documentation

The Institutional Review Board (IRB) is a board established by an individual organization or institution that holds authority over all clinical testing in the United States. An IRB reviews human-subjects research requests, either approving, requesting modification, or disapproving of new clinical trials (Umscheid et al., 2011). Minimally, an IRB application must include Risk Anticipated Benefit Analysis, Informed Consent, Assent, Selection of Subjects, Privacy and Confidentiality, Research Plan for Collection, Storage, and Analysis of Data, and Research Design and Methods (17). One of the most significant documents reviewed by the IRB is known as the IRB Protocol. For any clinical trial this document includes a timeline of activities as seen in Figure 1, background and rationale, risks/benefit analysis, study design details, study population criteria, study preparation, product storage and stability, safety assessments, statistical considerations, etc. (8). In preparation for a remote clinical trial, one must leverage this existing IRB document to derive parameters which will be used to later establish an inventory and subject tracking system.

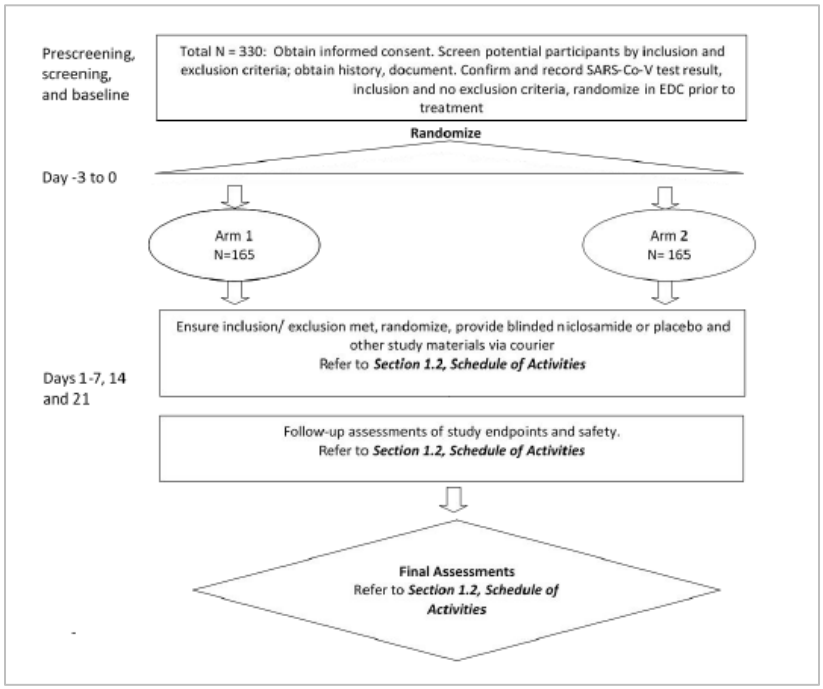


Figure 1. Timeline Schema from IRB Protocol for Niclosamide Phase 2b Trial

Key Parameters

The following three tables outline key parameters for the Niclosamide Phase 2b remote clinical trial. The expected number of participants and contents of each remote trial box were found in the IRB protocol for the study. These parameters will impact our approach to patient education. For example, from Table 1, the Niclosamide Phase 2b trial includes both children and adults. Instructions for participation and use of the medical devices listed in Tables 2 and 3 must be understood by diverse sample of individuals, varying by age and level of education.

minimum number of index children/adolescent participants	200
maximum number of index children/adolescent participants	400
minimum number of household contact participants	384
maximum number of household contact participants	768

Table 1. Expected Number of Participants in Future Niclosamide Phase 2b Trial

Index Children/Adolescent Trial Box		
Device	name/brand	Count
Pulse Oximeter	W.B Mason NWLPulsoximeter	200-400
Thermometer	Avantik GL4687	200-400
Test Sample Box	Cosmos ID sample box	200-400
Study Pills	Niclosamide or Placebo	200-400
Rapid PCR test	CUE health	7 x (200-400)

Table 2. Niclosamide Phase 2b Index Children/Adolescents' Trial Box Components

Household Contact Trial Box		
Device	name/brand	Count
Pulse Oximeter	W.B Mason NWLPulsoximeter	384-768
Thermometer	Avantik GL4687	384-768
Study Pills	Niclosamide or Placebo	384-768
Rapid PCR test	CUE health	8 x (384-768)

Table 3. Niclosamide Phase 2b Trial Household Contacts' Trial Box Components

Designing Patient Education for Wearable Device Use

Current Methods

Patient education for wearable device use in remote clinical trials is often supported by device manufacturer's manuals and existing trial documentation in place of more intentionally designed participant-instruction (8). Telehealth platforms allow clinicians and participants to meet and review their understandings of the device instructions. However, this help is offered on an as-needed basis.

In the case of the Tufts Medical Center Niclosamide trial, an additional participant instruction manual was derived from the existing IRB documentation. The booklet includes an introduction to the trial, warnings, guidelines for participations, and a place for participants to record their temperature and oxygen saturation levels each day (8).

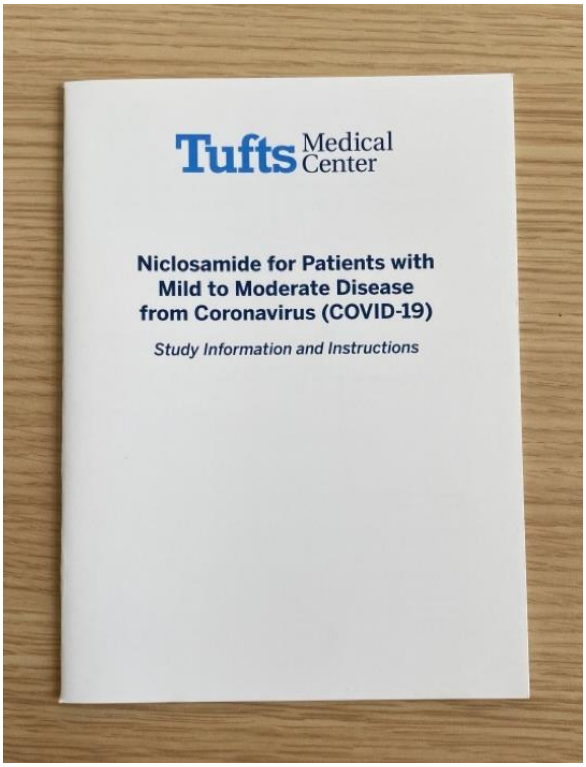
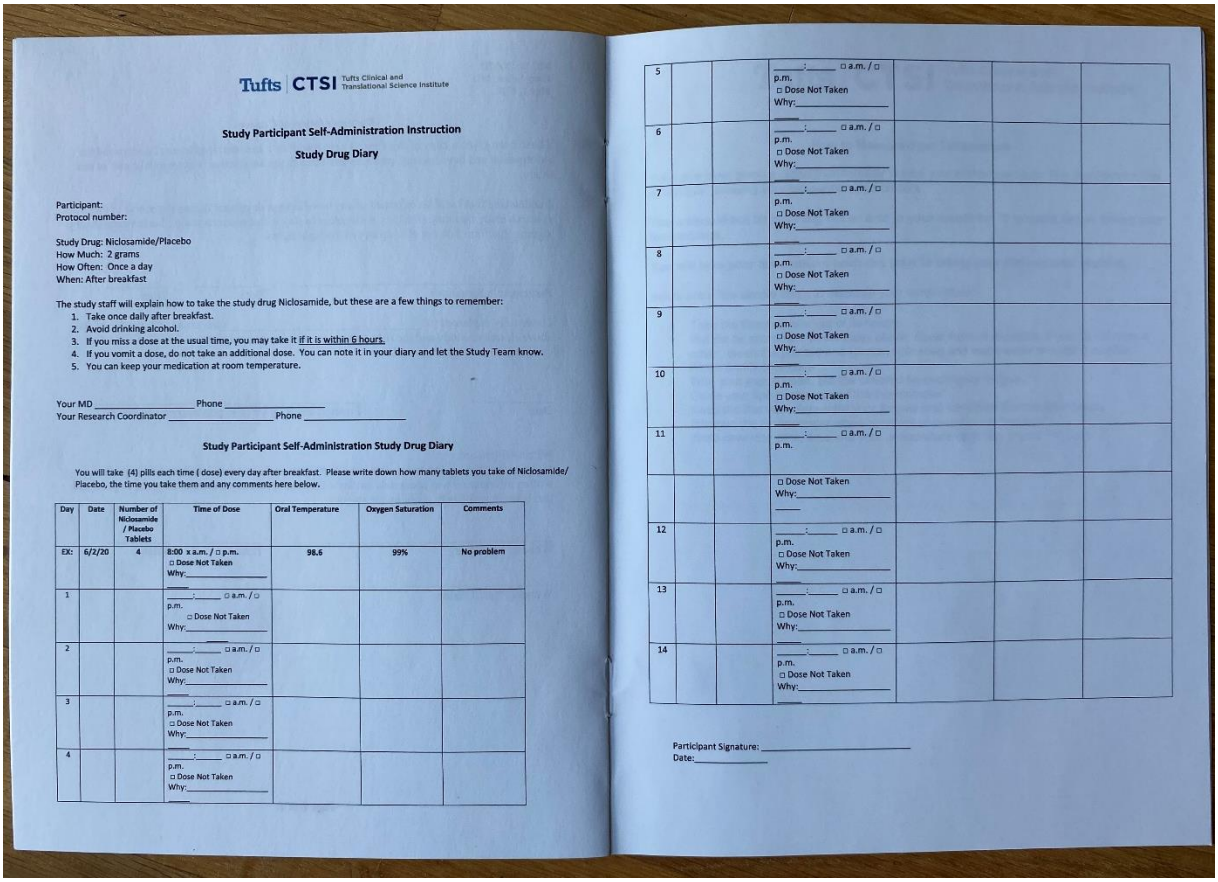


Figure 2. Niclosamide Phase 2b Trial, Study Information and Instructions Manual, Cover



Tufts | CTSI Tufts Clinical and Translational Science Institute

Study Participant Self-Administration Instruction

Study Drug Diary

Participant:
Protocol number:

Study Drug: Niclosamide/Placebo
How Much: 2 grams
How Often: Once a day
When: After breakfast

The study staff will explain how to take the study drug Niclosamide, but these are a few things to remember:

1. Take once daily after breakfast.
2. Avoid drinking alcohol.
3. If you miss a dose at the usual time, you may take it if it is within 6 hours.
4. If you vomit a dose, do not take an additional dose. You can note it in your diary and let the Study Team know.
5. You can keep your medication at room temperature.

Your MD _____ Phone _____
Your Research Coordinator _____ Phone _____

Study Participant Self-Administration Study Drug Diary

You will take (4) pills each time (dose) every day after breakfast. Please write down how many tablets you take of Niclosamide/ Placebo, the time you take them and any comments here below.

Day	Date	Number of Niclosamide / Placebo Tablets	Time of Dose	Oral Temperature	Oxygen Saturation	Comments
EX:	6/2/20	4	8:00 x a.m. / □ p.m. □ Dose Not Taken Why:_____	98.6	99%	No problem
1			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
2			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
3			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
4			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
5			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
6			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
7			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
8			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
9			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
10			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
11			_____:_____ □ a.m. / □ p.m.			
			□ Dose Not Taken Why:_____			
12			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
13			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
14			_____:_____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			

Participant Signature: _____
Date:_____

Figure 3. Niclosamide Phase 2b Trial, Study Information and Instructions Manual, Study Drug Diary

The Role of Human Factors

Human factors studies examine the interactions of people and technology. It considers innate human abilities and limitations. Figure 4 displays the cycle of human factors. The design of equipment, tasks, environment, selection, and training serve as inputs to the system and human. The output of this human-system interaction is some level of performance. By analyzing performance and identifying problems at point A, changes to the design inputs can be made at point B to improve output (18). The design of training with respect to human factors is particularly applicable in remote clinical trial settings, where a participant (human) interfaces with given instruction manuals (system).

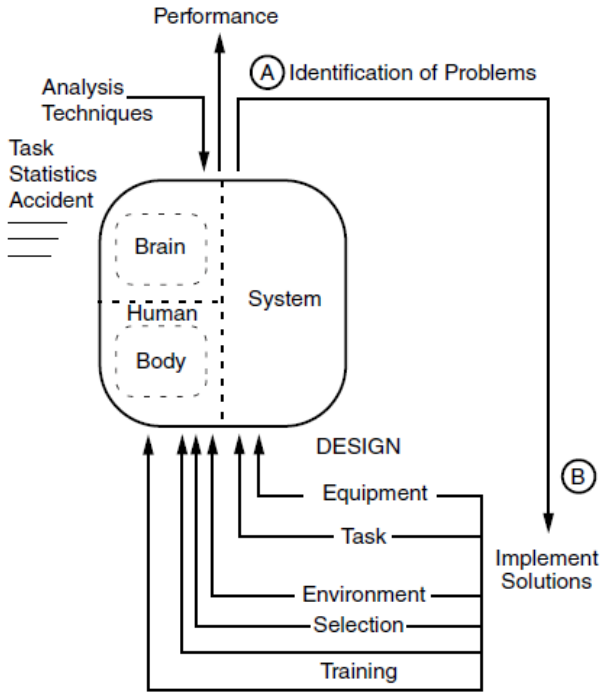


Figure 4. Cycle of Human Factors (18)

Human Cognition and Perception

There are known limitations to human cognition, as the brain has a limited pool of attentional resources to allocate to processing new information. Resource Theory states that as the mental effort required by an activity increases, one's ability to carry out that activity is degraded (18).

There are three main stages of human cognition. The first stage is perception, when information is collected from the environment through various senses. In stage two, central processing occurs, when that information is manipulated by our prior knowledge of familiar situations and as well as the context of the situation. The third phase acts as the feedback loops, where actions generate future processing (18).

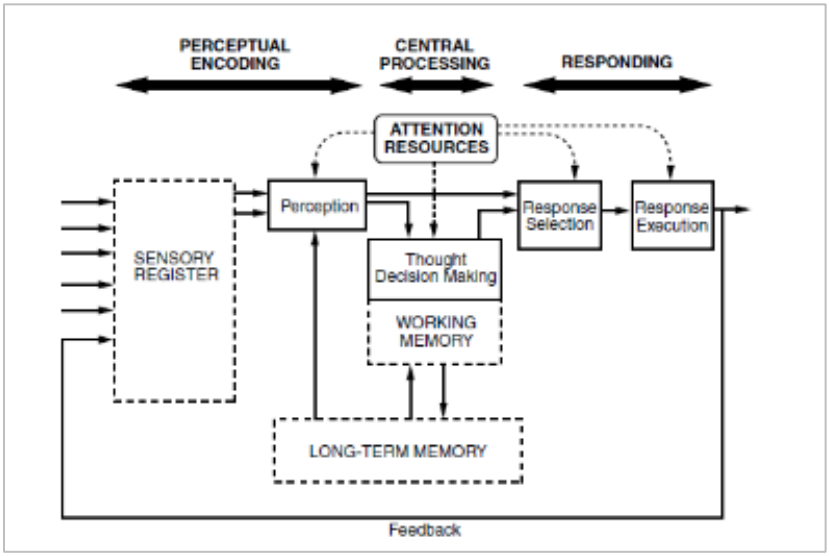


Figure 5. Human Information Processing (18)

Perception is the stage of human cognition where meaning is extracted from sensory inputs such as visual arrays or audio sequences (18). There are two main processes of perception: bottom-up and top-down. Figure 3 exemplifies the difference between bottom-up and top-down processing. Bottom-up processing assembles some truth or understand from sensory inputs whereas top-down processing uses model and expectations to understand sensory cues. Top-down processing is used when bottom-up processing because strenuous due to poor environmental conditions (18).

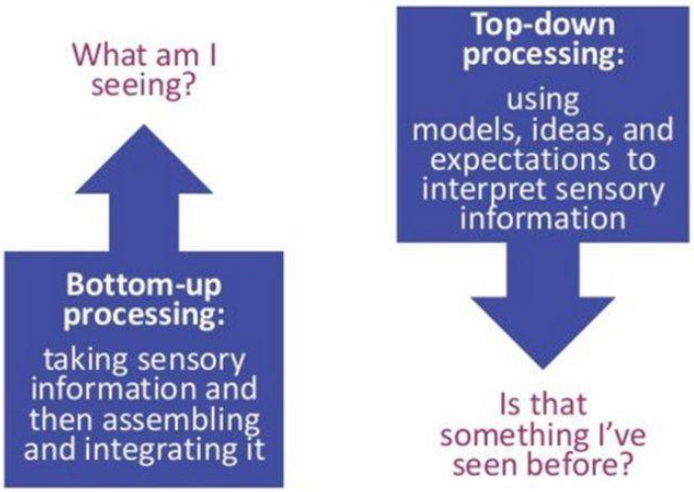


Figure 6. Two Methods of Human Perception
(aminlimpo.com/2016/06/the-concepts-of-top-down-and-bottom-up.html?m=1)

In the design of wearable devices and remote clinical trial instructions, small improvements to both top down and bottom-up processing can be leveraged to create greater compliance to study guidelines. Bottom-up processing can be maximized with organizational improvements to manuals, legible fonts, distinct message sets, etc. Top-down processing can be maximized through redundancy, mental models, highlight negation, etc. (18).

Patient Education and Human Memory

Working Memory

Working memory is the portion of human memory dedicated to holding temporary information. Information inside the working memory is always active, whether it was originally perceived from the environment or draw from long term memory. Working memory is limited both by capacity and length of time information can be held. Approximately five to nine units of working memory are available when processing new information. New information can be kept active through rehearsal. However, if too many units of information are presented at once, the time to rehearse all units will exceed the amount time the first unit can be held on to (18).

Long-Term Memory

Long-term memory is a more passive form of human memory and is activated only when needed to supplement working memory. Semantic memory is a specific type of long-term memory which related to facts and procedures (19). Semantic memory is the primary mechanism utilized in patient education.

Designing for Memory

As patient education tools are developed to support wearable device use in remote clinical trials careful consideration should be given to the capacity of human memory. Working memory function can be optimized through intentional instruction design. Strategies include chunking information into units, limits the number of units of information presented to nine, keeping sentences short. Strategies to improve long-term memory function include active reverbalization or note-taking. It is crucial that clinicians responsible for designing patient education materials do not overestimate participants ability to comprehend remote clinical trial instructions because of their own familiarity with the content.

Example: Oura Ring Charging Instructions

The Oura Ring is a consumer wearable device which will be used in an upcoming Long COVID remote clinical study at Tufts Medical Center. This ring comes packaged with three instruction manuals as seen in the figure below (20).

Figure 7. Oura Ring Unboxing

(Oura Ring indicated by red arrow)

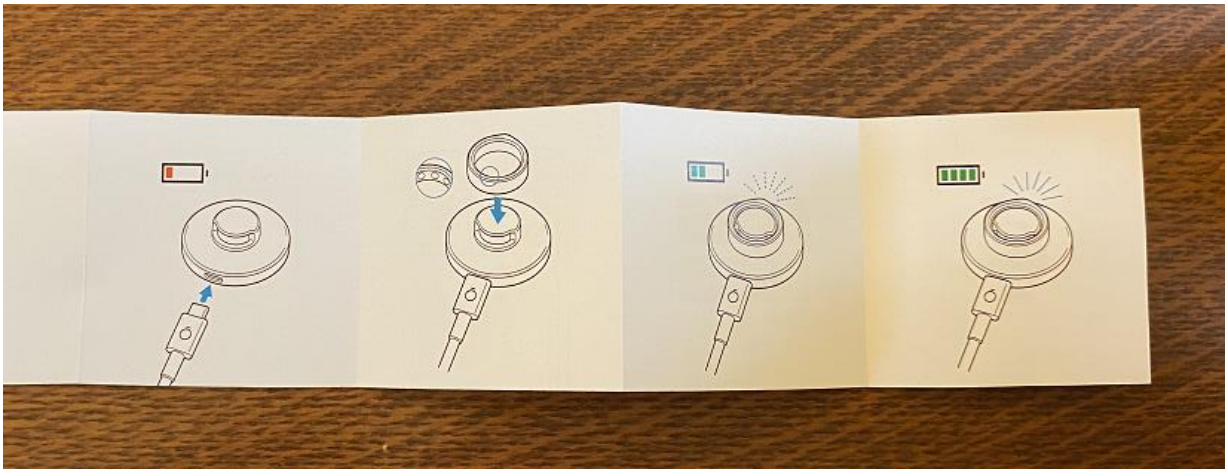


Figure 8. Manufacturer's Charging Instructions for Oura Ring

The charging instructions for the Oura Ring are shown in Figure 5. The four images in the instructions are vague and unsupported by text or audio. This lack of context place additional mental strain on the participant. They must decipher the drawings, relying on long-term memory to access familiar situations.

To minimize the mental effort required and maximize standardization of wearable device operation the existing visual Oura Ring charging instructions shown in Figure 5 can be supplemented with images of the actual Oura Ring device, which mimic the drawings as seen in Figure 6. This image gives the participant a realistic mental model of the Oura Ring to work with. This provides the participant with a reference model in their working memory, minimizing the mental effort required to access long-term memories involving similar device charging.

Figure 9. Oura Ring on Charger

Patient Education and Human Decision Making

Decision-making

Decision making is required when one options must be selected as opposed to a number of alternative options. Decisions are often constrained by limited context and time. Decision making begins with perception when information and cues are gathered from the environment. Various hypotheses are then generate guessing the meaning of the information gathered. The future states relevant to each hypothesis are considered along with their inferred state, cost, and values (18).

As the systems and environments human beings interact with become more complex, decision-making becomes more cumbersome and erroneous. Humans often do not consider rationalizing all factors in each decision they make. Rather, they follow a description decision model, which provides a simpler but less complete means of decision-making (18).

One decision making technique that is often used by human beings is heuristics. Heuristics play a role in natural decision-making processes, as they provide general rules, shortcuts, or rules-of-thumb when the information perceived within the decision-making process exceeds one's cognitive capacity. Shifting to the use of heuristics is more efficient in terms of processing but can dangerously lead to bias and mistakes (18).

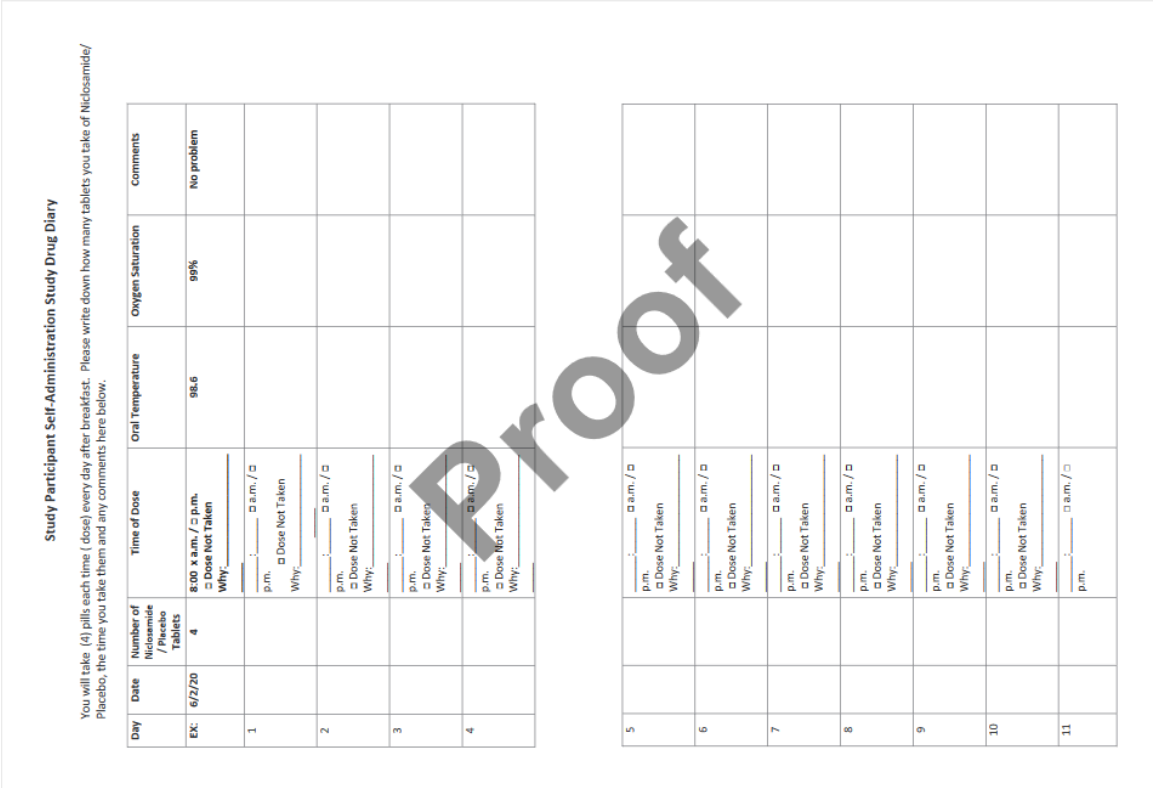
Personal heuristics will play a role in the decision-making processes of remote clinical trial participants as they are cognitively overloaded with new information at the start of the trial. Use of heuristics introduces variation into the physiological measurement process as each participant strays from the standardized instructions. To minimize the use of harmful heuristics in remote clinical trials, patient education materials should be intentionally designed to minimize the cognitive effort required to comply.

Design for Decision-Making

Heuristics can also be strategically employed to improve decision-making through useful defaults, data visualization, and proceduralization (18). An example of a useful default is the turn signals cars, which automatically switch off once a turn has been completed. Remembering to turn off the signal would have required additional cognitive resources by the driver so in this case a heuristic has minimized error.

Example: Tufts Niclosamide Study Drug Diary

Consider the Study Participant Self-Administration Study Drug Diary from the first phase Niclosamide trial (21).



Study Participant Self-Administration Study Drug Diary

You will take (4) pills each time (dose) every day after breakfast. Please write down how many tablets you take of Niclosamide/ Placebo, the time you take them and any comments here below.

Day	Date	Number of Niclosamide / Placebo Tablets	Time of Dose	Oral Temperature	Oxygen Saturation	Comments
EX:	6/2/20	4	8:00 x a.m. / □ p.m. □ Dose Not Taken Why:_____	98.6	99%	No problem
1			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
2			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
3			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
4			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
5			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
6			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
7			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
8			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
9			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
10			____ : ____ □ a.m. / □ p.m. □ Dose Not Taken Why:_____			
11			____ : ____ □ a.m. / □ p.m.			

Figure 10. Niclosamide Information and Instructions - Study Participant Drug Diary (oriented as shown in diary design)

The figure shows the diary each remote clinical trial participant is expected to complete daily. Each participant must record the trial day, date, time of does, quantity of tablets taken, oral temperature, oxygen saturation, and additional comments. Immediately, the small font and rotated orientation imposes a cognitive strain on participants, making them more likely to default to heuristics in comprehending the table. As a participant reaches the second, third, and fourth pages of the table the boxes become further away from the row of titles. Remembering the seven column headings in order over the course of a two-week trial is highly unlikely due to the limitations of working and long-term memory. In this case, a participant is likely to naturally shift their decision-making to use heuristics, guessing which order the columns occur in and promoting error in physiological measurement reporting.

To minimize the use of personal-heuristics by participants and maximize standardization the table can be redesigned to reduce cognitive effort required.

Study Participant Drug Diary **Day of Trial:** ______

Date: _____ / _____ / _____
Time of Dose: _______ : _______ am/pm
Number of Tablets: _______

Oral Temperature: ________ °F
Oxygen Saturation: _________ %

Comments: ____

Study Participant Drug Diary **Day of Trial:** ______

Date: _____ / _____ / _____
Time of Dose: _______ : _______ am/pm
Number of Tablets: _______

Oral Temperature: ________ °F
Oxygen Saturation: _________ %

Comments: ____

Study Participant Drug Diary **Day of Trial:** ______

Date: _____ / _____ / _____
Time of Dose: _______ : _______ am/pm
Number of Tablets: _______

Oral Temperature: ________ °F
Oxygen Saturation: _________ %

Comments: ____

Study Participant Drug Diary **Day of Trial:** ______

Date: _____ / _____ / _____
Time of Dose: _______ : _______ am/pm
Number of Tablets: _______

Oral Temperature: ________ °F
Oxygen Saturation: _________ %

Comments: ____

Figure 11. Redesigned Study Drug Diary

The figure above displays the redesigned study participant drug diary. The entry fields have been reoriented upright and limited to two entries per page. Each entry space includes the titles of the information required by the participant and is clearly sectioned from the next. By simplifying the organization of the diary entries to the point of obviousness, bottom-up processing is maximized. Additionally in the case of oral temperature and oxygen saturation reporting useful defaults were employed to list the units of each measurement. The participant need not consider Celsius temperature or guess units for oxygen saturation. The alternative layout to the study participant drug diary also provides greater visual feedback to participants for each entry. The larger entry spaces reinforce the significance of each day of the remote clinical trial, the measurements collected, and comments provided. Each completed entry acts as a placeholder for the next in the day-to-day reporting.

Supporting Work

Participant Tracking System

As patients sign up for each trial they should be entered along with any relevant information into a database. Most simply, this can be an excel spreadsheet (14) with columns for patient's first and last name, account information for any medical devices, product number for each device sent to the patient, individual box deployment status, device replacement status if necessary, and telehealth visit information. An example of the participant tracking system for the Long COVID trial is shown below.

A	B	C	D	E	F	G	H	I	J	K	L
Patient #	**First**	**Last**	**Ring size**	**Oura Ring ID**	**Oura account ID**	**email**	**Account connected?**	**Box sent?**	**Box received?**	**Requires replacement:**	**First telehealth visit**
1	Ryan	Lin	9	2ac37ebh33	000041251	mit0369@mit.edu	Yes	Yes	Yes	Pulse Oximeter - on route	Complete
2	Imane	Mbiriq	Not received	Not sent	000034123	mit0370@mit.edu	No	No	No	NA	Not complete

Figure 12. Long COVID Participant Tracking System

Prior to registration, screening should be done consistently and with a script, so there are no statistical biases when enrolling new participants. Because the aim is to produce a clinical trial that can be done completely remotely, screening should be scripted for both phone call and email recruitment, as well as voicemail. An example of a voicemail script is provided below (obtained from the Long Covid case study trial):

This message is for (name of potential participant). My name is …… I am calling from Tufts Medical Center to provide you with information about a research study being conducted here at Tufts Medical Center. I will try you again later today/tomorrow. If you would like to reach me in the meantime, my number is …. Thank you and have a good day.

Device Storage and Cleaning

Regardless of whether the assembly of the trial kits is done onsite or offsite the medical center, incoming inventory must be received and stored properly. An estimate of the storage volume can be given by obtaining the number of participants, multiplied by the amount of volume each of their necessary materials will take up (for devices this can be obtained from the product website, and trial box dimensions can be obtained from the manufacturer. For ease of assembly and access, a “factory on wheels” should be built, or mobile storage racks that can be taken out of storage to an assembly area. These racks should contain all the necessary components for each trial kit, as well as any materials needed to clean or otherwise set up the devices. For example, our Long Covid case study trial shelves (purchased from Uline and assembled onsite) were required to store the following:

30x Trial box
30x Pulse oximeter
60x AAA Batteries
30x Electronic thermometer
30x Electrocardiogram
30x Oura ring
30x Oura ring sizing kits
30x Patient instruction pamphlets

A space should also be set aside for returning medical devices, where they are labeled as returned and used, or cleaned and ready to be shipped back out. Devices which are returned and need to have their data cleaned out should undergo a consistent cleaning process. This process may vary but will likely include using sanitary wipes to wipe down the device, and resetting the device back to factory settings. Placing the device into a bag and tagging it with the device ID number can also help improve inventory management (15).

Device Inventory Tracking System

For each trial, a management system will be created using a Google App Sheet (14) or another inventory management system platform. The system helps create an accessible inventory log that includes information each device utilized in a given remote clinical trial and allows quick data input and real time analysis of stock levels for each type of device. The following four steps summarize Google App Sheet setup for the Long COVID upcoming remote clinical trial.

Step 1: Organize the data collected about the devices in a Google Sheets.
The spreadsheet should include for each device, the bar code, the initial stock level and the restock level.

Step 2: Creating the App
Once a Google Sheet of device inventory has been created, Tools>AppSheet>Create an App. This converts the data table into an application. The following figures are from the Long COVID application.

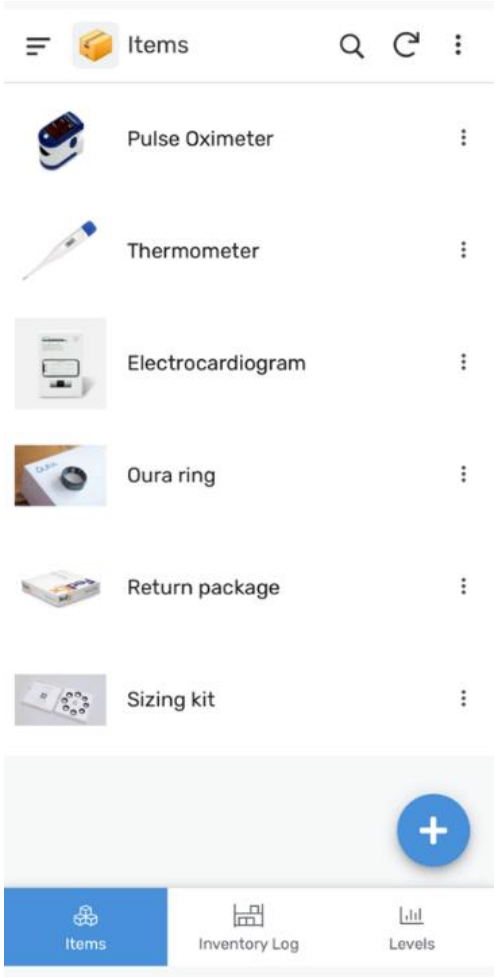


Figure 13. Long COVID Trial Application Interface, Items Tab

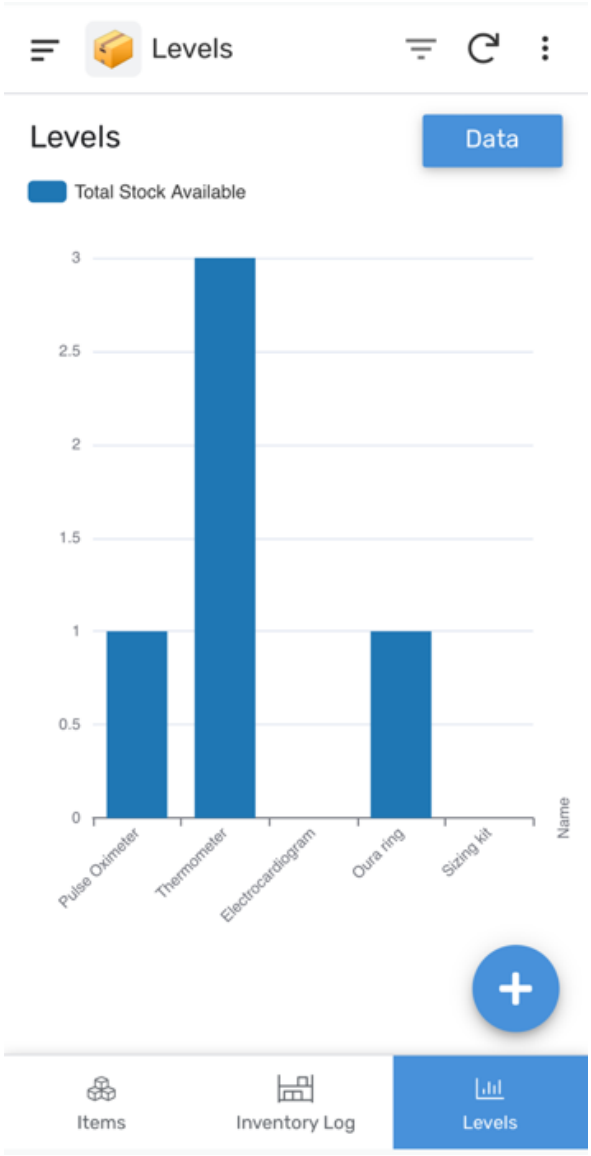


Figure 14. Long COVID Trial Application, Levels Tab

Step 3: Update Device Inventory Levels

The inventory levels for each device are updated from Google Sheets or within the application. A mobile phone camera can be used to capture and automatically upload barcode data from wearable devices.

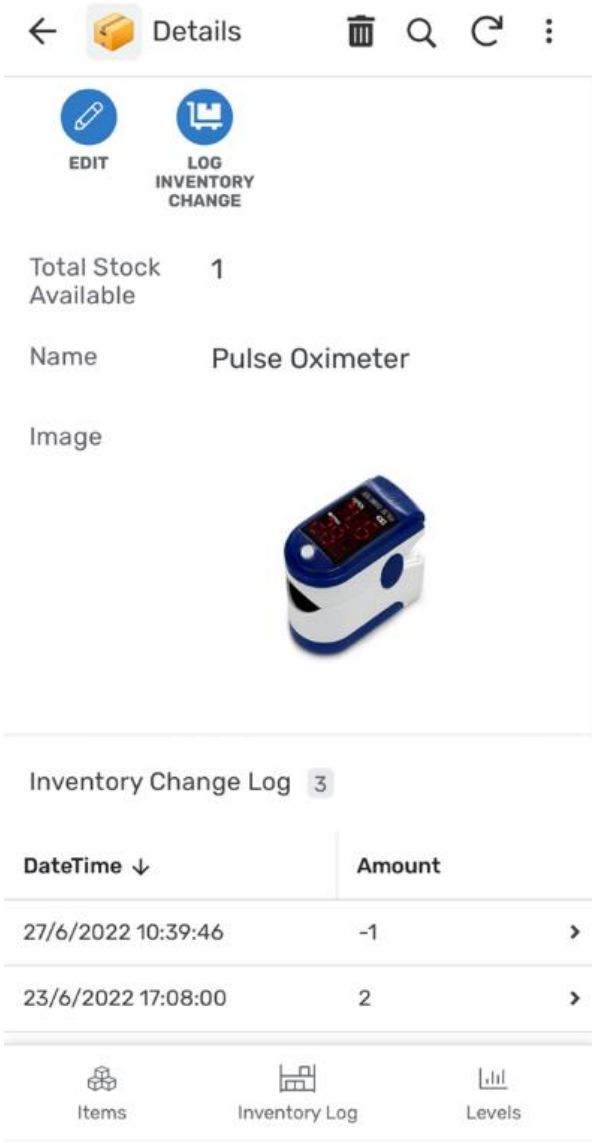


Figure 15. Long COVID Trial Application Interface, Device Details

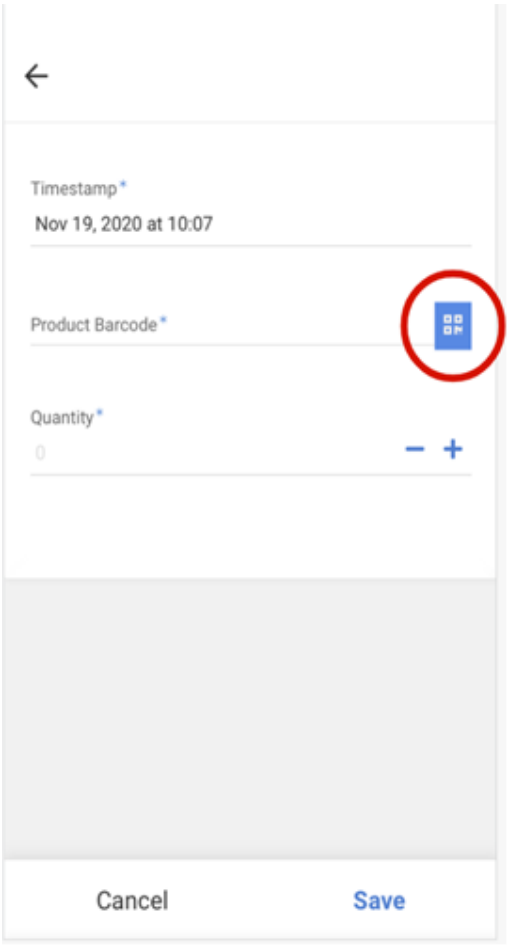


Figure 16. Long COVID Application Interface, Barcode Scan Capability

Step 4: Set Restock Levels

At the initiation of trial enrollment, trial staff should first validate device inventory to assure the quantity of available device will suffice for the target participant sample size, summarized in Tables 1, 2, and 3. A restock level should be intentionally chosen for each device. When the restock level is reached, an automated email alert will be sent to trial staff to indicate low device supply (14).

Box Design

There will be one universal box that will have dimensions that fit all the contents of both the Niclosamide and the Long-COVID trials. Within the box will be foam inserts that will have cutouts where the specific devices will be placed. This design was mostly inspired by the Pelican case as shown in Figure 2 for the following reasons:

1. The larger polypropylene hard-shell case makes the packaging durable to stand against most damages from external factors experienced during shipping and handling as well as while in the patient's personal environment.
2. The foam inserts safely secure all components.
3. The cutouts in the foam make it easy for the patient to identify where devices need to be placed.
4. Both the outer hard-shell case and the foam inserts inside can be reused for future trials.

The following shows the assembled models of the box for each trial:

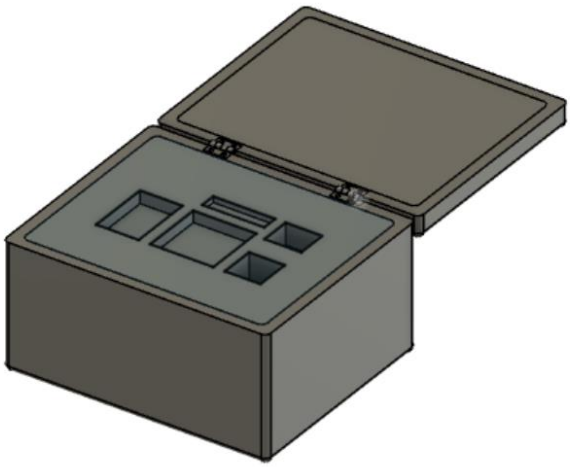


Figure 17. Box for Long-COVID Remote Clinical Trial

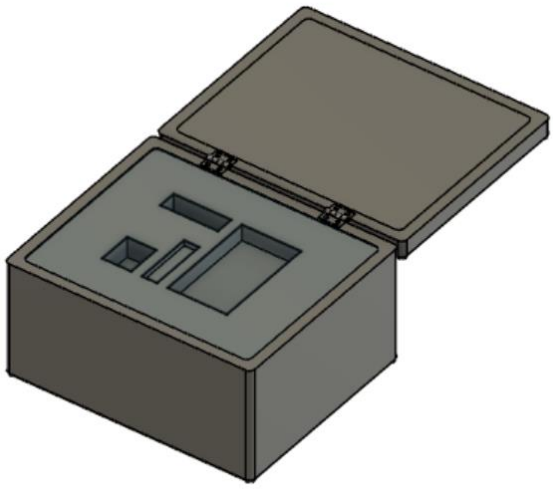


Figure 18. Box for Long-COVID Remote Clinical Trial

The following figures show models of the foam inserts for the Niclosamide remote clinical trial. The foam inserts and its cutouts are designed to snugly fit each of the devices as well as leave at least one inch of space between any two edges or surfaces. This includes between device cutouts and between the cutouts and all sides of the outer casing (16).

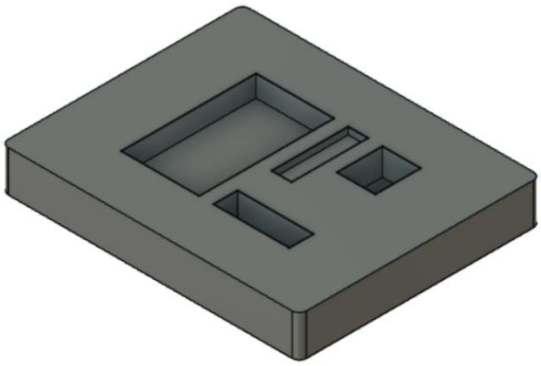


Figure 19. Top Foam Layer of the Niclosamide Trial Box

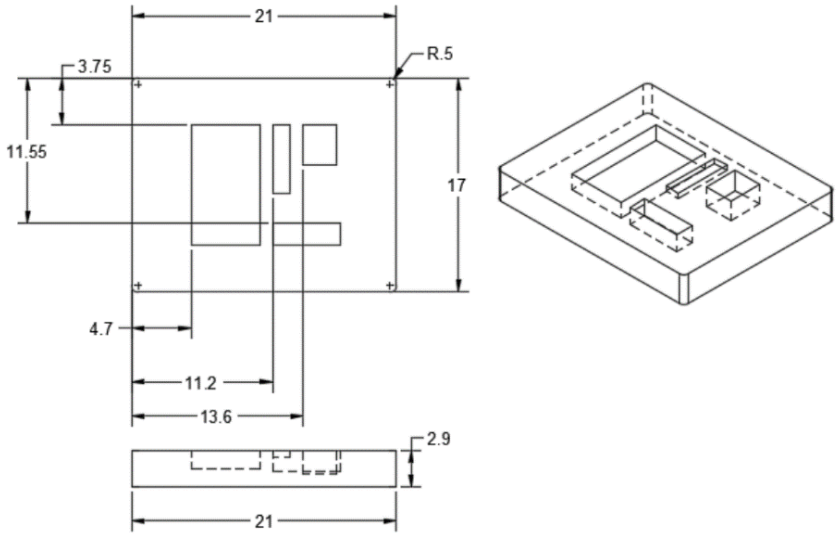


Figure 20. Top Foam Layer of the Niclosamide Trial Box Drawing in cm (1/2)

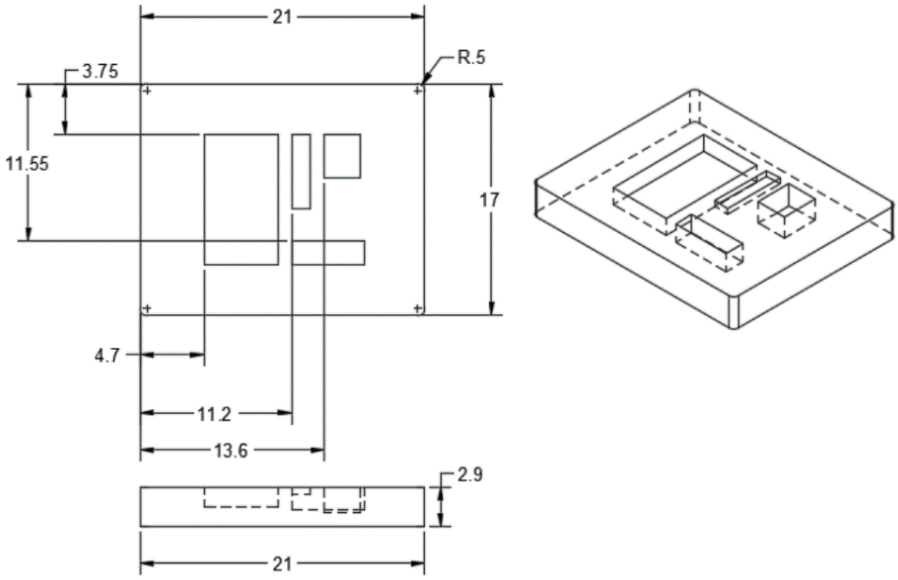


Figure 21. Top Foam Layer of the Niclosamide Trial Box Drawing in cm (2/2)

Conclusion

Consumer wearable devices are set to revolutionize healthcare, initially through their deployment in remote clinical trials. However, the lack of regulatory framework and standardization of use introduces potentially hazardous biases in longitudinal physiological data sets collected. To fully utilize wearable devices and maintain safety in remote clinical settings, patient education materials must be designed intentionally to minimize user-related factors such as misuse and nonuse of devices without imposing an additional burden on clinical trial participants. With an understanding of how human factor impact the interface of humans and technology, instructions for remote use of wearable and medical devices can be designed to enhance the quality of physiological data sets collected and increase participant-safety.

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