Remote Clinical trials Operations: Supply Chain Management and Framework Development

by

Imane Ait Mbiriq

Bachelor of Science, Industrial Engineering
Arts et Métiers ParisTech, 2021

Submitted to the Department of Mechanical Engineering in
Partial Fulfillment of the Requirements for the Degree of
Master of Engineering in Advanced Manufacturing and
Design

at the

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Abstract

Remote clinical trials present the new approach of revolutionizing traditional clinical trials in order to decrease costs, accelerate the processes and improve the experience for participants and trial's staff. The Covid-19 pandemic has significantly encouraged the implementation of remote clinical trials, since it became harder to reach participants and patients. The Tufts Medical Center aims to adopt remote clinical trial practices for their future clinical trials. The future trials include (1) a phase 2b a clinical trial testing the effectiveness of niclosamide in the shortening the Covid-19 contagious period in children and adolescents and (2) a data collection trial with participants suffering from Long Covid symptoms.

Although clinical trials can have different parameters and processes, this thesis suggests a general framework that can guide Tufts Medical center in their planning of the future remote trials including the design of the trial, the participant's recruiting, the trial's supplies' inventory management and the data collection during and at the end of the trial. The thesis also includes limitations and points of failure of the generalized framework.

Thesis Supervisor: Dr. Brian W. Anthony

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Next, I would like to express my gratitude to Professor Brian Anthony for his continual guidance and insightful advice over the course of this thesis project.

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Furthermore, I would like to express my appreciation for all the great work of my team members, Carly Smith, Ryan Lin and Joyce Noh. They are great teammates and sources of feedback and support.

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1- Introduction

1.1- Thesis project overview

This thesis projects originates from Tufts Medical Center, based in downtown Boston, Massachusetts. It is a center for biomedical research and is the principal teaching hospital for Tufts University School of Medicine. The Institute for Clinical Research and Health Policy Study (ICRHPS) is located within Tufts Medical Center. ICRHPS provides researchers with an environment to conduct human subjects' experiments safely and effectively. Furthermore, they are pursuing a new form of clinical trial that won't require in-person contact, a remote trial system that can reduce the amount of traffic coming in and out of the medical center.

The research team is based at the Massachusetts Institute of Technology, a private land-grant research university. MIT is heading the project with the support of Tufts Medical Center, with the goal to develop and instate a framework with which any number of clinical trials could be performed remotely, regardless of location, number of participants, and with minimal necessary technological knowledge.

The MIT Lincoln Laboratory, the United States Department of Defense federally funded research and development center, will also be backing up this project. They have also had to run fully remote clinical trials and are invested in helping a framework be developed for future use.

Figure 1: Tufts Medical Center's logo

1.2- Project Motivation

The main objective of remote clinical trials is to revolutionize the clinical trials model and increase 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 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.
- Understanding of trial requirement and consent form: participants with less advanced education background may have difficulties comprehending the trial's instructions which can lead to wrong expectations and eventually dropouts.

In response to the need to investigate potential treatments of Covid-19, researchers and scientists started have been putting efforts to examine different drugs against the disease. Niclosamide (an oral anthelmintic drug), was found to be promising drug candidate to reduce SARS-CoV-2 shedding and duration of symptoms for participants with mild to moderate symptoms (3).

In some cases, patients experience symptoms for longer than 28 days after diagnosis. Long covid conditions can include a wide range of new, returning or ongoing health problems, these may include but are not limited to general fatigue symptoms, respiratory and heart

symptoms, neurological symptoms and digestive symptoms. There is no test to diagnose long-covid and it doesn't affect everyone the same way (4).

In order to study the effectiveness of Niclosamide and collect more data about the Long Covid condition, clinical trials involving participants exposed to the virus are conducted by research teams at the Tufts Clinical and Translational Science Institute. The institute's motivation is to organize remote studies and change the patient's experience of participating in a clinical trial, and therefore having access to the traditionally harder-to-reach communities to participate especially during the current sanitary situation.

The alarming world health situation and the clear need to conduct trials remotely, is our main incentive to work on the process of the design and implementation of remote clinical trials and apply it to the Niclosamide and Long Covid trials.

1.3- Review of Previous work

In March 2020, a placebo controlled clinical trial was conducted at Tufts Clinical and Translational Science Institute, using a telehealth platform to determine whether Niclosamide reduces SARS-CoV-2 shedding. The platform is 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. As a result, there was no effect of Niclosamide on decreasing the contagious period of SARS-CoV-2 infection.

After the trial, surveys and interviews with participants and researchers were deployed to further understand the barriers, facilitators, and benefits of remote clinical trials.

Results of interviews: key takeaway from the interviews is that participants appreciated having clear instructions and the trial box delivered. Other participants suggested sending reminders to participants on the day samples should be collected. There was also a difficulty enrolling African American and Hispanic participants.

1.4- Team Introductions

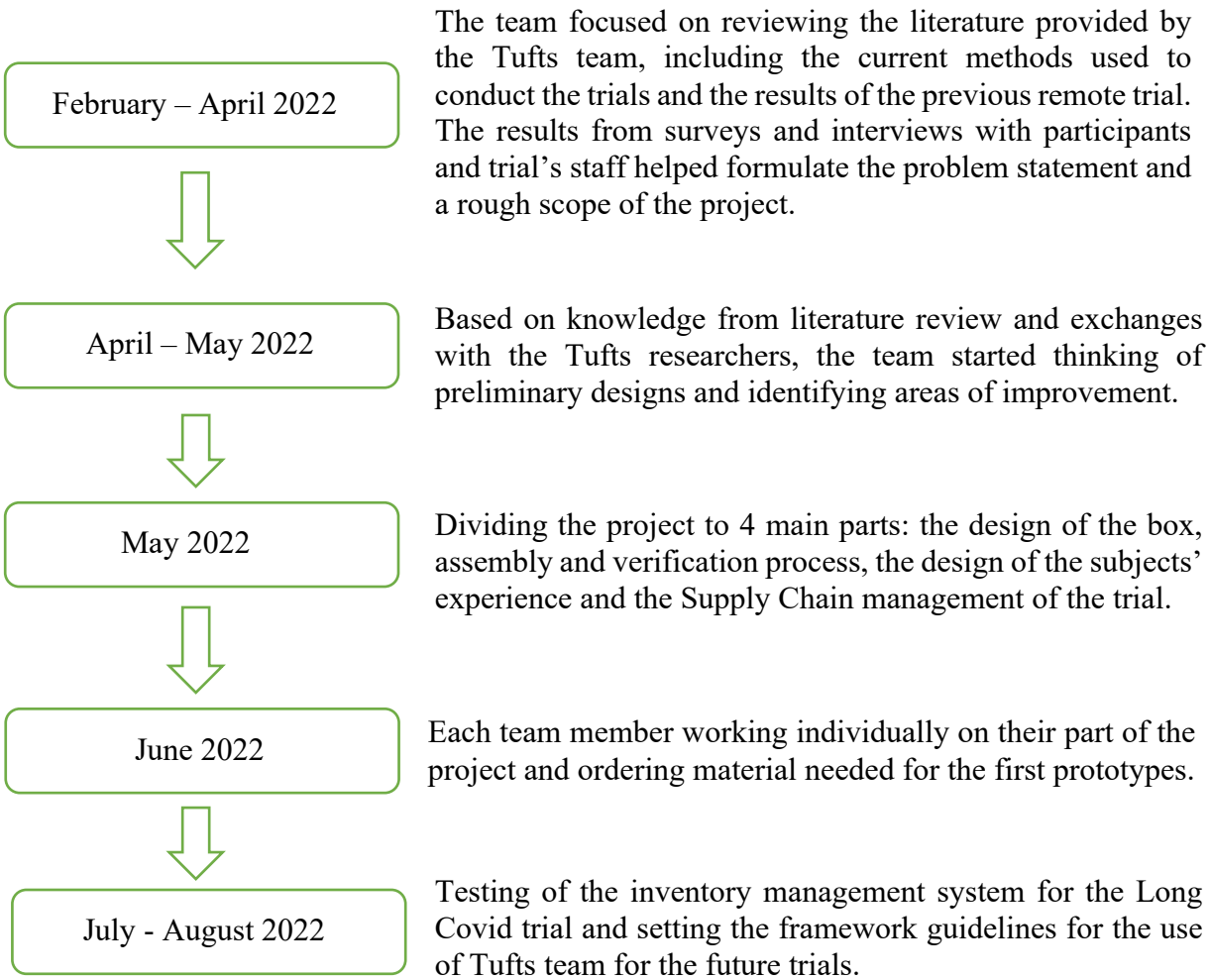
The working project team consisted of MIT's students and faculty and Tufts' researchers;

A. Ryan Lin, Imane Ait Mbiriq, Joyce Noh, and Carly Smith- four graduate students from MIT's Master of Engineering (M.Eng) in Advanced Manufacturing and Design program, responsible for development and delivery of the project.

B. Dorothy Dulko, Manlik Kwong, and Cortney Wieber- three research personnel from Tufts Medical Center who provided background information, project motivation, resources, and much guidance.

C. Brian Anthony, MIT M.Eng thesis advisor, and Xiang Zhang, Postdoctoral Associate at MIT, who helped define project specifications and helped the team through the thesis project process.

1.5- Project Timeline



1.6- Overview of Sub-projects:

The content is this thesis focuses specifically on guidelines for inventory evaluation, tracking system development, and kit tracking system design. Carly Smith's work includes the design of patients' education and instructions for successful participation in the remote trial (5). Ryan Lin's work includes guidelines for participant tracking systems, device storage and cleaning, material kitting, and shipping management (6). Joyce Noh's work includes a case study evaluation for accessible clinical trial kit design (7).

2- Overview of Clinical trials:

2.1- Clinical trials: definition and methods:

Clinical trials are studies to test new drugs, already approved drugs, devices, or other forms of treatments. Many clinical trials look at new ways to detect, diagnose, or measure the extent of disease. Some even look at ways to prevent diseases from happening (8).

A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials (also called interventional studies) and observational studies. ClinicalTrials.gov includes both interventional and observational studies (9).

Clinical trials:

In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. For example, investigators may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases (9).

Clinical trials used in drug development are sometimes described by phase. These phases are defined by the Food and Drug Administration (FDA).

Phase 0: helps researchers find out if the drugs do what they're expected to do. This may help save time and money that would have been spent on later phase trials.

Phase I: are done to find the highest dose of the new treatment that can be given safely without causing severe side effects. These studies also help to decide on the best way to give the new treatment.

Phase II: studies determine the effectiveness of an experimental drug on a particular disease or condition in approximately 100 to 300 volunteers. This phase may last from several months to two years. Most Phase II studies are randomized, which means that subjects are assigned randomly (by chance not by choice) to receive either the experimental drug, a standard treatment, or a placebo (harmless, inactive substance). Those who receive the standard treatment or placebo are called a control group (8).

Phase III: Phase III studies are conducted at multiple centers with several hundred to several thousand patients for whom the drug is intended. Massive testing of a drug provides continued generation of data on a drug's safety and efficacy. As in Phase II, most Phase III studies are randomized and blinded (10).

Observational Studies:

In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health (8).

2.2- Challenges facing clinical trials:

The challenges facing clinical trials vary from patient recruitment to adoption of technology, and regulatory requirements, to increasing costs.

Patients' challenges: Patients may reside far from study centers; even the largest multicenter trials can pose geographic challenges for those wishing to participate. Moreover, depending on the number of clinic visits required by the study protocol, significant travel and time costs may be associated with participation. In addition, trials designed with narrow eligibility criteria for participation purposely eliminate many patients who might have the disease being studied but are ineligible because of other characteristics (e.g., age, level of disease progression, exposure to certain medicines).

In addition, trials often require patients to temporarily leave the care of their regular doctor and receive services from unfamiliar providers. In addition to confronting potentially undesirable interruptions in care, it is understandably difficult for many patients to justify the physical and emotional strain of leaving their regular provider to volunteer for a clinical trial (11).

Organizers' challenges: Trials and studies' have to manage locating funding, responding to multiple review cycles, obtaining Institutional Review Board (IRB) approvals, establishing clinical trial and material transfer agreements with sponsors and medical centers, recruiting patients, administering complicated informed consent agreements, securing protected research time from medical school departments, and completing large amounts of associated paperwork (11).

2.3- Remote clinical trials:

Remote clinical trials offer an alternative means to the traditional trials conducted in the medical centers and institutes. All trial procedures are conducted virtually, enabled by

digital technologies and devices and supply delivery at home. This shift in clinical trials has been enabled by a constellation of evolving technologies and services.

Patients who would otherwise face daunting challenges from centralized study trials may be able or willing to enroll in remote clinical trials, because remote monitoring and data collection minimize obstacles to participating, such as logistical difficulties in accessing the trial location e.g., travel costs, nonacceptance of job absences for study activities, and mobility challenges posed by medical comorbidities. A collateral effect is improvement of trial access for participant populations that are currently most underrepresented in current traditional trials: the elderly, the poor, those living in remote locations, and many ethnic minorities (12).

While there's no specific way to conduct remote trials, the following list includes activities that decentralize a traditional trial:

Digital Site engagement:

- Remote and central-site monitoring
- Digitized investigator engagement and payment

Patient online identification and recruitment:

- Patient identification
- Digital trial Marketing and patient activation
- Online-recruitment portals

Trial decentralization to homes:

- Direct to patient clinical supply from sites
- Remote patient monitoring
- Electronic clinical outcome assessment and electronic patient-reported outcome

Remote clinical trials existed before the pandemic, but Covid-19 accelerated the adoption of remote trials' techniques. With the rise of COVID-19, enrolling patients in traditional studies has become even more difficult using the traditional techniques (13).

2.4- Planned Remote trials at Tufts Medical Center:

After organizing the niclosamide phase 1b trial using remote techniques, Tufts Medical Center research team are planning 2 fully remote clinical trials:

Niclosamide Trial:

Phase II Adaptive Randomized Trial to Evaluate Niclosamide in Children and Adolescents with SARS-CoV-2 infection and Post-Exposure Prophylaxis in Their Household Contacts.

Information from the IRB protocol: Double-blind, randomized, placebo controlled, adaptive Phase II clinical trial to evaluate the effect of the anthelmintic drug niclosamide on viral shedding and symptoms in children and adolescents with SARS-CoV-2 infection (COVID-19) managed in an outpatient setting. This study will also evaluate the effect of niclosamide as post- exposure prophylaxis (PEP) in close household contacts. Niclosamide, which has potent antiviral activity against single-stranded RNA viruses including coronaviruses, was proposed as an antiviral during the SARS outbreak in 2002. We hypothesize that the antiviral activity of niclosamide may be extended to COVID-19 disease.

The primary objectif of the trial is to evaluate the safety and efficacy of the niclosamide and shortening the contagious period as determined by time to respiratory viral clearance and to evaluate the efficacy of Post Exposure Prophylaxis (PEP) with for the prevention of COVID-19 infection.

There are 2 categories of study participants:

- Outpatients aged 5-17 years old who are COVID-19 (SARS-CoV-2) positive by laboratory PCR or rapid POC PCR test within 3 days.
- Close household contacts of COVID-positive index child / adolescent who are 5 years of age or older currently living in the same home as the COVID-positive index case, testing negative by rapid POC PCR on day 1 of index case study participation.

The study is estimated to complete enrollment within 12 months of initiation of enrollment; however, enrollment will still be open until the goal of 200 index children/adolescents is reached. The duration of the entire project is anticipated to be a maximum of 18 months and the sample size will possibly be increased according to a pre-specified sample size adaptation rule, up to a maximum of 400 index children/adolescents.

Long Covid Trial:

The primary aim of this study, sponsored by and in collaboration between Tufts Medical Center and MIT's Lincoln Labs is to explore the practical use of consumer wearable devices like the Oura ring, thermometer, finger pulse oximeter, and Kardia Mobile devices to capture Long COVID-19 symptoms that the participant may or may not be readily aware of. Data collection will also include self-reporting of symptoms if and when experienced that may be related to Long COVID-19. Another purpose of the study is to learn more about the long-term effects of COVID-19 (Long COVID) on individual patient health and on the healthcare system.

The study will be conducted remotely outside the clinical setting and from the participants' homes. Minimum 30 subjects are expected to enroll for a duration of 4 months, first month to ship and setup data collection devices and 3 months of data collection.

At the completion of participation, the subject may keep the thermometer and finger pulse oximeter. All other devices and materials must be returned using a return box that will be shipped to the participant including a return shipping label.

3- Supply Chain Management for remote clinical trials:

3.1- Supply Chain and Inventory management overview:

Supply chain management covers the planning of all activities involved in sourcing and procurement, conversion, and all logistics management activities. Principally, it includes coordination and collaboration with channel partners, which can be suppliers, intermediaries, third party service providers, and customers. Essentially, supply chain management combines supply and demand management within and across companies (14).

As a part of the overall supply chain, inventory management includes aspects such as controlling and overseeing purchases from suppliers as well as customer and activities of inventory, storage, deciding on the order quantity and timing of order. The main reason for holding inventory is to smooth operations in the case of uncertain demand and supply. Inventory management helps in establishing the required stock levels.

Inventory management and visibility contributes to cost reduction, fulfilment optimization, better customer service and prevention of theft, spoilage and returns (15).

3.2- Supply Chain Management for remote clinical trials:

Remote clinical trial supply chains ensures that supplies needed to conduct a clinical trial are ordered, manufactured, shipped and received, so that the trial implementation is not disrupted.

Clinical trial can have various parameters and take different population sizes. Therefore, a different supply chain strategy is needed to manage each and every trial ensuring that the complex elements in every trial and at every environment work seamlessly.

The most direct impact of supply chain management on trial participants relates to ensuring a continuous supply of all the supplies needed for the enrolled participants to start on the day the trial is supposed to start.

Planning and end-to-end clinical supply chain also requires responsive forecasting and planning. Advanced analytics for patient forecasting allows visibility on the number of patients expected to participate in the trial and therefore the order quantities are determined in advance and delayed orders situations can be avoided. A tool used to support this planning and management is an interactive response technology (16).

Interactive Response Technology (IRT) is also called randomization and trial supply management. It helps clinical trial sponsors and sites manage the patient and drug supply logistics throughout a clinical trial. Because of its ability to offer control and flexibility while increasing efficiency, it has served a vital role in helping pharmaceutical and biotechnology companies organize data to mitigate risk and to reduce time and costs in their trials (17).

The technology system includes a patient management part that randomizes patients into treatment arms to make sure they receive the drug, combination of drugs, or placebo based on that treatment arm. It also helps schedule patient visits during the trial and maintain patients' blinding.
IRT enables clinical supply staff to call for shipments on supplies and devices needed for the trial, it also provides accountability for when a supply is sent to the use of the participants or returned (17).

3.3- Inventory management:

3.3.1- Problem statement:

The transition to remote clinical trials raises new challenges around inventory management. Traditional trials are often conducted in the same facility where the different devices and tools needed for the trial are stored. For remote trials, each participant is sent the trial's supplies in a box that was prepared by the trial's staff; this format makes it hard to keep track of all equipment without using an inventory management system.

An important aspect behind the design of remote clinical trials is cost reduction, the trial's participant will be asked to send back some of the supplies or the devices at the end of the trial. These supplies may be expensive like wearables, physiological monitors, and other medical devices. This is where it's important to have a centralized inventory management system that the study staff can have access to in real time to update the inventory log with the correct information.

Once information about the trial's supplies and participants count is determined, a major next step is to assess the current device inventory and determine the counts and locations. It is common that a device or other clinical trials supplies are used in more than one clinical trial. Keeping track of all the devices inventory ensures that costs are optimized by not having to make device purchases for each trial. In the case where box trials are sent to participants, highly priced devices are returned at the end of the trial and other devices with a lower value can be kept.

3.3.2- Data collection and Inventory audit:

In order to organize the trial's supply chain, the first step was to collect data about all of the supplies that can be used in future remote trials. This ensures that existing devices are

considered and that no unnecessary purchases are made. This step is also crucial to build and organize an inventory tracker.

Tufts' team has been conducting trials on site in the past years and the supplies used were stored in both Tufts medical center and Lincoln Lab.

First step: Building a list of all the existing supplies than can be used in future trials.

Device	name/brand
Pulse Oximeter	W.B Mason NWLPulsoximeter
Thermometer	Avantik GL4687
Electrocardiogram	Alivecor Kardia mobile 6L
Oura ring	Oure gen 2
Garmin watch	Garmin Venu Sq
FitBit health tracker	Fitbit Inspire 2
Samsung Watch	Samsung Galaxy Watch 3
Covid-19 Testing Kit	CUE health rapid PCR test
Test Sample Box	Cosmos ID sample box

Table 1: Examples of existing supplies at Tufts Medical center

Second step: Collecting characteristics and parameters of each of the supplies:

- Count: number of units of each item in the different storage locations, including the items currently used in a trial and that will be returned to Tufts.

- Description: concise explanation of the device and its usage.

- Storage location: current placement of the units at the time the inventory audit is done.

- Price: the price at which each unit was purchased from the supplier. The price is included to determine which item will be kept by the participant at the end of the remote trial. High-priced items are returned to be used in future trials, while other items with a lower value can be kept by the participants and can be considered as a reward.

- Supplier: the company or organization that the items were sourced from.

- Dimensions: the exact measurement of each item is needed for the design of the trial's box.

- Lead time: the period it takes to receive an order of an item from the suppliers, the lead time is needed for planning orders ahead of the trial's start and avoiding delays of trial's supplies.

- Restock level: the minimum reorder stock level is the level of inventory at which a new purchase order should be placed. It is generally higher than the minimum level to cover any emergencies that may arise as a result of unexpected delays. The restock level is most important in the case of items that are often used in every trial or that have a high lead time.

- Minimum order quantity: the lowest order level of an item imposed by the supplier.

Third step: Verification of all information in the inventory log by the trial's staff and the rest of the team in order to validate the information about each item.

3.3.3- Trial's description and parameters

For every potential clinical trial, the Institutional Review Boards (IRB) requests a protocol and consent documents that serve as the recipe for the conduct of the research activity. It needs to communicate all of the information that the following groups need to conduct their part of the study the investigator and the investigative team, the data manager, the statistician and the IRB or other review body. Therefore, the protocol must include the study population, a full description of the study's design and procedures, and the supplies and devices that will be used to conduct the study (18).

The IRB protocol document is used as a reference to build the list of supplies needed to conduct the study and the exact quantities needed of each device.

Niclosamide trial:

For the Niclosamide study, the number of index children/adolescents is set to 200, with 1.92 co-habitants per index case, we expect about 100 households and approximately 192 co-habitants to be allocated to each group (niclosamide and placebo). The trial employs the constrained promising zone design: based on the conditional power at an interim analysis, the sample size will possibly be increased according to a pre-specified sample size adaptation rule, up to a maximum of 400 index children/adolescents and a maximum 768 household contacts participants.

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

Table 2: Expected number of participants in the future Niclosamide trial

For this trial, the kit sent to the index children/adolescent is different than the one sent to the household contacts. Therefore, we will need 2 different inventory lists.

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 3: Niclosamide trial: 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 4:Niclosamide trial: Household contacts' trial box components

Long Covid trial:

For the Long Covid data collection trial, the number of participants is set to 30 minimum and the study will be 3 months long. All participants will be sent the same kit box.

Device	name/brand	Count
Pulse Oximeter	W.B Mason NWLPulsoximeter	30
Thermometer	Avantik GL4687	30
Electrocardiogram	Alivecor Kardia mobile 6L	30
Oura ring	Oura ring gen 2	30
Sizing kit	Oura sizing kit	30

Table 5: Long Covid trial: Participants' trial box components

2.3.4- Building inventory for new trial

For each trial, a management system will be created using App sheet or another Inventory management system platform. The system helps create an accessible inventory log that includes all the information collected previously for each device and allows quick data input and real time analysis of the stock level of each device. We will be demonstrating the use of Google's App Sheet (19) for the Long covid study as an application case.

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. It can also include some or all of the data about each device included in *the paragraph 3.3.2*.

Step 2: QR codes/IDing individual boxes

For each box, it should be tagged with the participants name, as well as a personalized QR code which will send an email to the Twilio server (20), affirming that the participant received the correct box. Each participant should be assigned a box number which will be encoded into the QR code, a machine-readable code consisting of an array of black and white squares. Alternatively, the kit can just be labeled "Kit 01" and the patient can confirm they got that specific box during the remote telehealth conference with the physician.

Step 2: Creating the App

Once the Google Sheets (21) document is in the right format, Tools>AppSheet>Create an App, will convert the data into an AppSheet app.

For the long Covid trial case, the app will look like following figures:

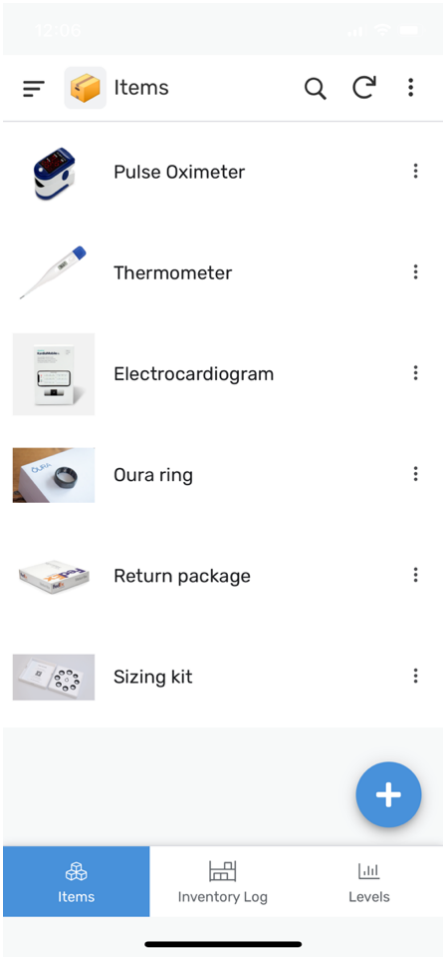


Figure 2: Long Covid Trial's App interface, items tab

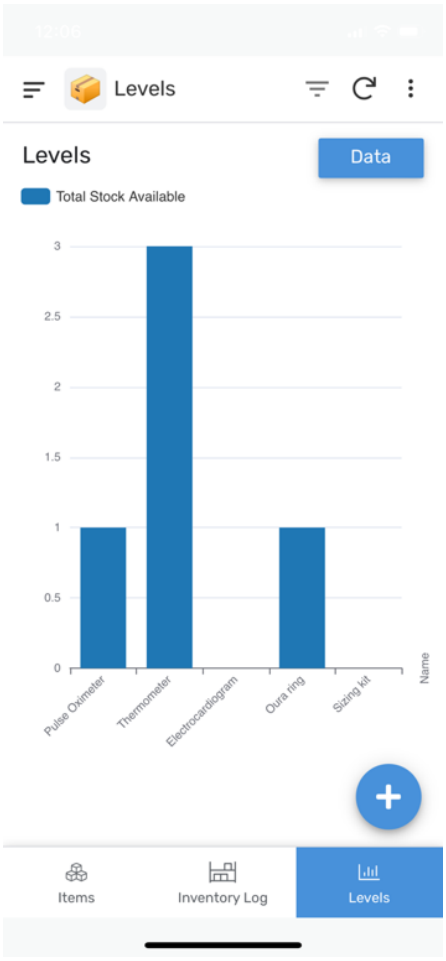


Figure 3: Long Covid Trial's App interface, levels tab

For each device, the inventory levels can be either updated on the Google Sheets or directly on the app. Appsheet can use the camera on the mobile device to capture barcoded data, which can be used to record any movement, whether it is stock in or stock out.

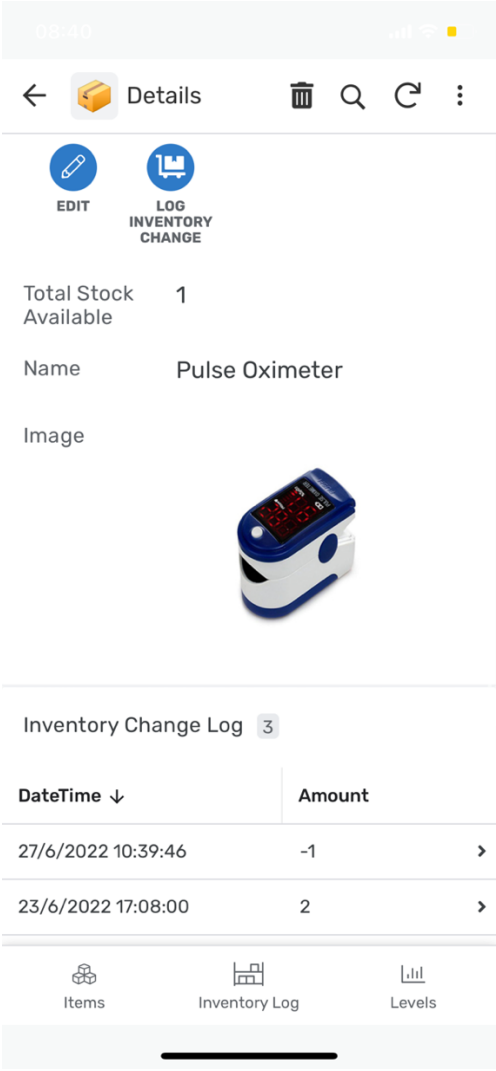


Figure 4: Details of the Pulse Oximeter inventory log on AppSheet

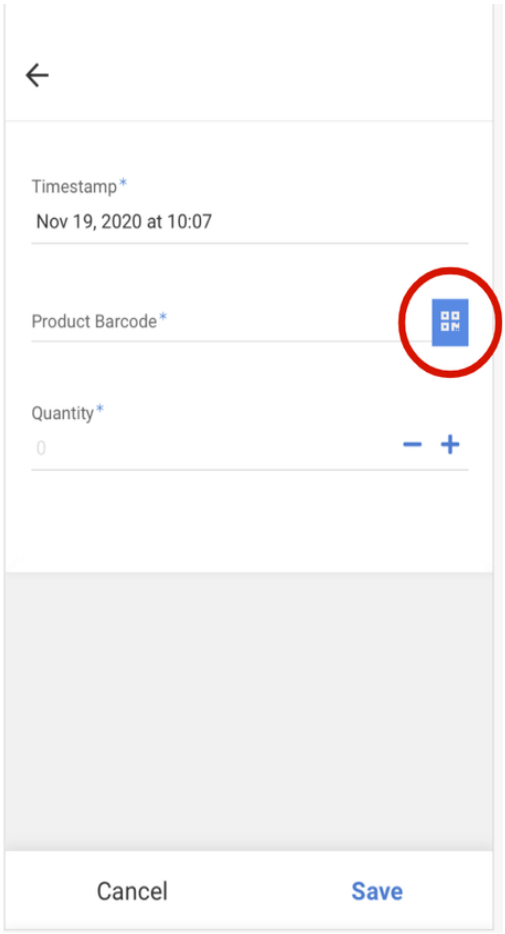


Figure 5: Use of barcode to update inventory log on Appsheet

Step 3: Setting restock levels

When the enrollment for the study starts, the trial's staff needs to make sure that all devices needed are in stock in the quantities needed. Setting a restock level for each device allows the staff to receive email alerts when a device is running out of stock and a replenishment is needed.

The stock level is dependent on other variables like the lead time and the minimum order quantity.

3.4- Possible Points of failure:

Planning uncertainties: remote clinical trials include a lot of parameters and details that are used in the overall planning. There can be numerous uncertainties in these parameters that may have an influence on the application of the trials. These uncertainties can be around the predicted number of participants, the duration of the trial, the count of supplies needed.

Manufacturing delays: Before the start day of the remote trial, the trial boxes should be ready to be shipped to participants containing all the necessary supplies. Therefore, delays in Manufacturing one or more of the supplies can delay the start of the trial.

Enrollment delays: The supplies used for a remote trial can also be used in a future trial, the delay in enrollment may result in delating the end of the trial and therefore affecting other trials and phases.

Shipment delays: Similar consequences as manufacturing delays, shipment delays has consequences on the remote trial timeline.

Return and Destruction: Since the participants are required to return some of the trial's box components, there's a risk of the participants losing and damaging these devices.

Box assembly errors: The assembly process of the remote trials s manual which gives place to human error, the use of the checklist can be helpful in this case but there's always chance for error.

4- Generalized Framework to support remote clinical trials:

In order to assist Tufts Medical Center team with the future remote trials, a generalized framework was developed to support the trial's planning and day to day operations. The framework consists of eleven individual processes and five databases.

Databases:

Patients, Devices, Boxes, Shipments, Samples

Process Outline:

1. Parameters and Timeline of Trial
2. Participant Tracking System
3. Device Storage and Cleaning
4. Device Setup (prior to packing/shipping)
5. Current Device Inventory
6. Device Inventory Tracking System
7. Box Design
8. Box Inventory Tracking System
9. Box Assembly Plans
10. Shipping and Delivery Management
11. Returns

The following sections explain each of these processes in details. The processes current device inventory, device inventory Tracking System and Box Inventory Tracking System are explained in sections 3.3.2, 3.3.3 and 3.3.4.

4.1- Parameters and Timeline of Trial

An Institutional Review Board (IRB) processes and structures all clinical testing in the United States. The IRB reviews 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 (*45 CFR Part 46 (2018-07-19) -- Protection of Human Subjects*, n.d.). 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, background and rationale, risks/benefit analysis, study design details, study population criteria, study preparation, product storage and stability, safety assessments, statistical considerations, etc. 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.

4.2- Participant Tracking System

As patients sign up for each trial they should be entered along with any relevant information into a database. At its most basic, this can be an excel spreadsheet with columns for the patient information. This should include the patient's first and last name, account information for any medical devices that need to be sent, IDs or product number for each device sent to the patient, individual box deployment status, device replacement status if necessary, and telehealth visit information (as applicable). A very basic example from the Long Covid trial case study 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 6: Long Covid participant tracking system

This data can be obtained by initial patient registration, as well as utilizing the telehealth visits to confirm delivery and account completion. Any special requirements or accommodations should also be taken careful note of and entered the database.

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.

4.3- 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.

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.

- storage volume estimate
- order racks and build
- new manuals from device manufacturers for each trial
- cleaning supplies for devices and boxes
- resetting devices

4.4- Device Setup Prior to Kitting and Shipment:

The devices should be ready to go out of the box for the participants, to make the trials as accessible as possible. As each device has a different setup, there should be documentation written for each device and given to each assembler to make sure the devices are all set up in a consistent manner. Some might be as simple as follows:

Pulse oximeter setup:

1- Unbox the pulse oximeter carefully
2- Remove the battery cap by applying gentle pressure and pushing away from the device
3- Install two AAA batteries and replace the battery cap
4- Return the pulse oximeter to the original package and ensure the instructions remain inside

This way each participant can take their own measurements (as instructed) without any difficulty.

This includes tailoring the necessary devices and services to each enrolled participant. If the study includes wearables or garments that require sizing, first acquire accurate sizing information. For example, for the Oura Ring (22) this step involves sending each participant a ring sizing kit, which will inform the medical center which size ring to send to them. This kit can be sent back and cleaned for reuse or disposed of if applicable. The data collected through either a telehealth visit, or other means should be recorded next to the patient in the database.

4.5- Box Design

After considering the tradeoffs of each of the existing boxes researched and detailed above as well as each trial's contents and their dimensions, the box was modeled using Autodesk Fusion (23).

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 (24) 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:

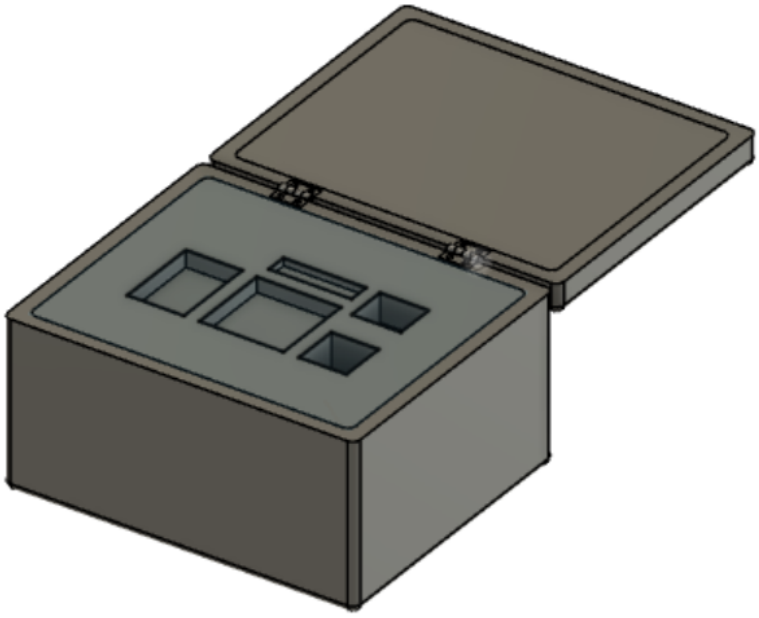


Figure 7: Complete assembled packaging for Long-COVID trial

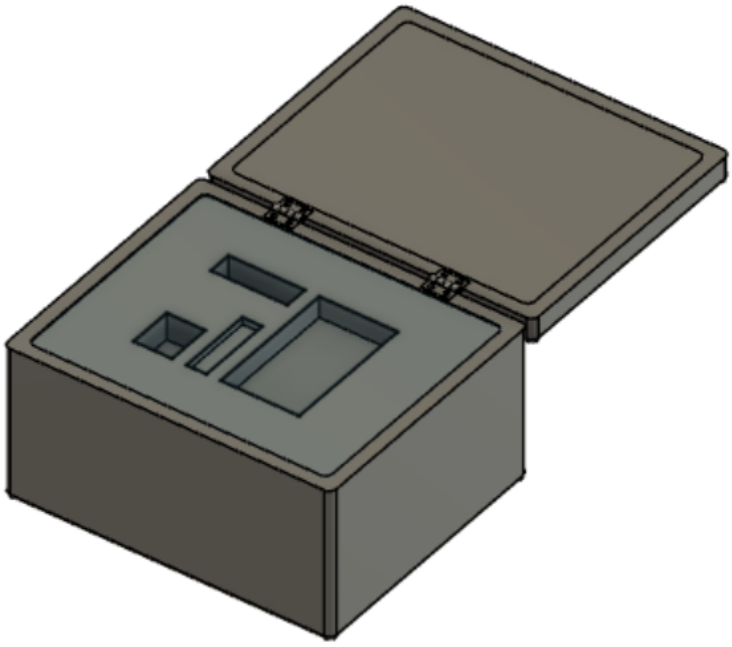


Figure 8: Complete assembled packaging for Niclosamide trial

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.

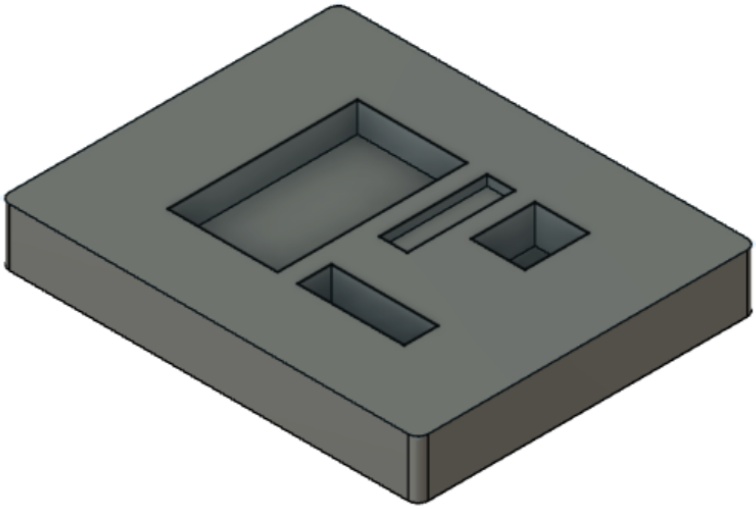


Figure 9: Top foam layer of the Niclosamide Trial Box

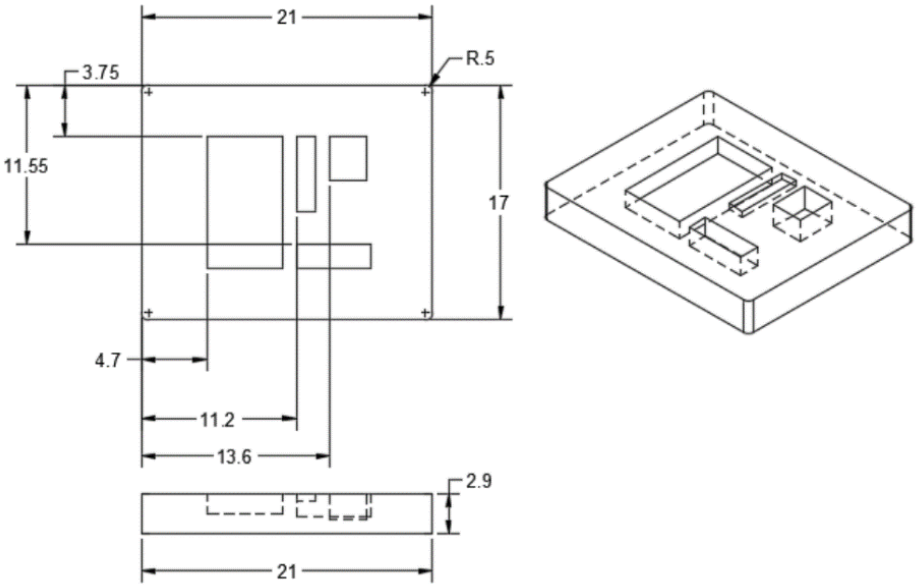


Figure 10: Top Foam Layer of the Niclosamide Trial Box Drawing

The dimensions are in inches.

The following is the material breakdown of each of the major parts of the box with additional detail as to their advantages:

Part	Material	Advantage
Outer Casing (Lid + Body)	Polypropylene	- Durable: resistant to external damages - Can be reused for future trials - Allows for easy return shipping
Foam Inserts	Polyethylene (Kaizen Foam)	- Known to be shock absorbant, vibration dampening, insulating, and cushioning in packaging applications - Multi-layered foam: easy to cut out the placement holes for the devices
Hinge	Polypropylene	- Durable - Smooth open and close
Latch Closure	Acrylonitrile butadiene styrene (ABS)	- Durable: withstands heavy use and adverse environmental conditions - Easy injection molding
Handle	Acrylonitrile butadiene styrene (ABS)	- Durable: withstands heavy use and adverse environmental conditions - Easy injection molding

Table 6: Materials' list

4.6- Box Assembly Plans

Assembly checklist

The boxes will need an assembly checklist for each individual clinical trial. The list of tasks will vary from trial to trial and should be tailored to the specific needs of the current trial. This most likely includes making sure all the necessary materials and devices have been received, device setup to make data gathering as easy for the patient as possible, verifying

all materials are in the box, marking the box with a nametag or writing the participants name on it, and sealing it. A simple example is shown below:

42.9%

#	Activities / Tasks / Items	Priority	Completed
1	~~Obtain all materials on the material list~~	High	✓
2	~~Setup pulse oximeter~~	High	✓
3	~~Setup electrocardiogram~~	High	✓
4	Setup Oura ring	High	
5	Add each item carefully to the box	High	
6	Take the specific QR code for this box and apply it to the lid	High	
7	Take nametag for this box and apply it to the lid	High	
8			
9			
10			

Figure 11: Sample checklist for the Long Covid trial

A second checklist should keep track of which boxes you have completed, and thus will let you know which box you're currently working on, and which will still need to be done.

24.0%

#	Activities / Tasks / Items	Priority	Completed
1	~~Box 01~~	High	✓
2	~~Box 02~~	High	✓
3	~~Box 03~~	High	✓
4	~~Box 04~~	High	✓
5	~~Box 05~~	High	✓
6	~~Box 06~~	High	✓
7	Box 07	High	
8	Box 08	High	
9	Box 09	High	
10	Box 10	High	
11	Box 11	High	
12	Box 12	High	
13	Box 13	High	
14	Box 14	High	

Figure 12:Example of actions checklist for the Long Covid trial

The details of each trial will differ from case to case, so an accurate checklist is pivotal to be obtained by working with the trial project owners.

4.7- Shipping and Delivery Management

Every participant ID will be connected to a shipping ID and the shipping will be done using a shipping company.

4.8- Returns

For both trials, some parts must be returned. The cutouts in the foam inserts for the specific devices that need to be returned will be colored and labeled. This will allow the patient to easily determine not only which items need to be returned but how to place them back into the box. The box will come with a set of instructions for how to proceed with the trial as well as instructions on how to return the package and a return shipping label

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