

NIRS Study Information

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Chapter 1

About

This study is being conducted in collaboration with the PrismaHealth Cancer Institute, Furman University Health Science Department, and University of South Carolina School of Medicine Greenville.

1.1 Contact Information

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Chapter 2

Literature

2.1 Near Infrared Spectroscopy

Continuous wave NIRS devices use the modified Beer-Lambert law to calculate the volume of oxygenated and deoxygenated hemoglobin.

Spatially resolved NIRS devices use multiple transmitters at different distances from a receiver to calculate a Tissue Saturation Index, or TSI.

The NIRS device utilized in this study is the PortaMon by Artinis Medical Systems. The PortaMon could be considered both a continuous wave and spatially resolved device. It uses three continuous-wave transmitters with a single receiver to calculate the TSI.

Each transmitter emits two wavelengths of infrared light. One wavelength is for oxygenated hemoglobin and one wavelength is for deoxygenated hemoglobin, therefore each transmitter measures both oxygenated and deoxygenated hemoglobin.

The transmitters emit light into tissue where the light waves bounce off structures in the tissue and return to the receiver.

The receiver measures the light that returns in Optical Densities. Calculations using several different parameters and assumptions convert OD into usable units.

Subcutaneous adipose tissue has different optical properties than muscle tissue. Most calculations do not account for two separate layers of tissue with different scattering and optical properties. There have been some papers within the last few years examining multi-layered tissues and the effects on NIRS measurements using computer modeling and phantom tissues. Most papers utilizing NIRS in exercise physiology assume a limited or negligible effect of adipose tissue thickness on measurements and report participants' adipose tissue thickness.

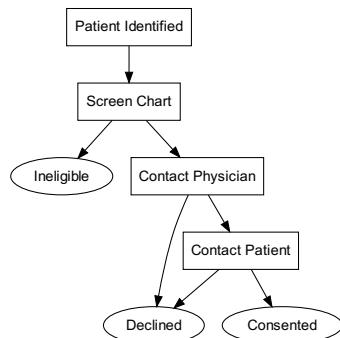
Different areas of the body have different types of tissue structure and this have different optical properties. Previous papers have reported the measurements of optical properties at various locations of the body. Consult with the device manufacturer and reports of these optical properties to determine the best settings for your device.

Most studies assume that the tissue structures have constant optical properties. This may not hold true, especially during activities like exercise where blood flow increases and the contents of blood fluctuate. Accounting for varying optical properties has led to the development of time-domain and other measurement techniques. These devices are more expensive than a continuous wave device. Therefore, most NIRS devices assume constant optical properties of the measured tissues.

The differential pathlength factor (dpf) is the measurement of the path that the light waves take through tissue. DPF values have been well researched and measured for multiple body locations and differing adipose tissue thicknesses. This parameter is used in calculating TSI.

Chapter 3

Patient Recruitment



3.1 Inclusion/Exclusion Criteria

To be eligible for the study, patients must:

- have primary breast or gynecological cancer
- non-metastatic
- that is being treated with chemotherapy
 - no immunotherapy or radiation at the same time or before chemotherapy
 - the chemotherapy regimen can be any regimen that is considered *standard of care*

- cannot have had chemotherapy within the past 5 years for any reason
- able to participate in moderate exercise on a stationary bike
- female patients only, male breast cancer patients are not eligible at this time

3.2 Screening the Electronic Medical Record

Prisma Health uses EPIC as their electronic medical record service. You can only access EPIC with permission from Prisma Health. The medical students may technically have access to EPIC but they have not had much training on how to use it and actually accessing it can be cumbersome and difficult for them. It is much easier for a Research Coordinator to do any work in EPIC.

Use the Production Environment of EPIC. In the Production Environment, you can create and run reports that you cannot in the Read Only Environment.

Log in with your Prisma Health log in information and select the department CANCER-FARIS ONCOLOGY [100224000].

3.2.1 Using a Report

Reports are very useful for gathering information about potential patients. I have created several reports with various uses.

3.2.1.1 Find Patients Eligible for NIRS by Treatment Plan

3.2.1.2 Find Upcoming New Consult Appointments with NIRS Providers

3.2.1.3 ‘

Go to My Reports.

I have a report named NIRS Eligibility by Stage that has the following parameters:

Select Patients in Registries

From

Registries:

Registry ID: CANCER POPULATION REGISTRY

Level of detail:

Patients

Where

Registry metrics: (1 OR 2 OR 3 OR 4 OR 5) AND 6

1 Metric Name or ID: DM TREATMENT PLAN
PROVIDER and Metric Value: Contains EDENFIELD,
WILLIAM JEFFERY

- 2 Metric Name or ID: DM TREATMENT PLAN PROVIDER and Metric Value: Contains ELDER, JEF-FERY WAYNE
- 3 Metric Name or ID: DM TREATMENT PLAN PROVIDER and Metric Value: Contains JORGENSEN, CARLA WALKER
- 4 Metric Name or ID: DM TREATMENT PLAN PROVIDER and Metric Value: Contains STEPHENSON JR, JOE JOHN
- 5 Metric Name or ID: DM TREATMENT PLAN PROVIDER and Metric Value: Contains PULS, LARRY EDWIN
- 6 Metric Name or ID: DM MED PATIENT RECIEVED CHEMOTHERAPY IN PAST YEAR and Metric Value: No

AND *Diagnosis in grouper:*

- Diagnosis Grouper (VCG): EDG ID CANCER BREAST OR
- Diagnosis Grouper (VCG): EDG ID CANCER FALLOP-IAN TUBE OR
- Diagnosis Grouper (VCG): EDG ID CANCER OVARY OR
- Diagnosis Grouper (VCG): EDG ID CANCER CERVIX OR
- Diagnosis Grouper (VCG): EDG ID CANCER VAGINA OR
- Diagnosis Grouper (VCG): EDG ID CANCER VULVA

AND *Treatment Plan Start Date:*

- Episode Types: Infusion Treatment and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Staatuses: Active and Treatment Plan Start Date: Greater than or equal to TODAY - 14 OR
- Episode Types: ONCOLOGY TREATMENT and Discontinue Reasons to Exlude: (none) and Plan Number: (none) and Plan Statuses: Active and Treatment Plan Start Date: Greater than or equal to TODAY - 14 OR
- Episode Types: ONCOLOGY TREATMENT and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: Future and Treatment Plan Start Date: Less than or equal to TODAY + 14 OR

Episode Types: Infusion Treatment and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: Future and Treatment Plan Start Date: Less than or equal to TODAY + 14

AND *Cancer Stage Distant Metastasis (M) Value:*

Stage Classifications: Clinical and Fallback Classifications: (none) and Signed Only?: (none) and SmartData Identifier: EPIC#42385 and Which Stage: Most Recent and Cancer Stage Distant Metastasis (M) Value: cM0 OR

Stage Classifications: Clinical and Fallback Classifications: (none) and Signed Only?: (none) and SmartData Identifier: EPIC#42385 and Which Stage: Most Recent and Cancer Stage Distant Metastasis (M) Value: cM0(i+) OR

Stage Classifications: Clinical and Fallback Classifications: (none) and Signed Only?: (none) and SmartData Identifier: EPIC#42385 and Which Stage: Most Recent and Cancer Stage Distant Metastasis (M) Value: M0 OR
Stage Classifications: Pathologic and Fallback Classifications: (none) and Signed Only?: (none) and SmartData Identifier: EPIC#42385 and Which Stage: Most Recent and Cancer Stage Distant Metastasis (M) Value: cM0 OR

Stage Classifications: Pathologic and Fallback Classifications: (none) and Signed Only?: (none) and SmartData Identifier: EPIC#42385 and Which Stage: Most Recent and Cancer Stage Distant Metastasis (M) Value: cM0(i+) OR

Stage Classifications: Pathologic and Fallback Classifications: (none) and Signed Only?: (none) and SmartData Identifier: EPIC#42385 and Which Stage: Most Recent and Cancer Stage Distant Metastasis (M) Value: M0

AND *Line of Treatment:*

Episode Types: ONCOLOGY TREATMENT and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: (none) and Line of Treatment: Not equal to Third Line OR

Episode Types: Infusion Treatment and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and

Plan Statuses: (none) and Line of Treatment: Not equal to Third Line

AND *Treatment Plan Goal:*

Episode Types: Infusion Treatment and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: Active and Treatment Plan Goal: Not equal to Palliative OR

Episode Types: Infusion Treatment and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: Future and Treatment Plan Goal: Not equal to Palliative OR

Episode Types: ONCOLOGY TREATMENT and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: Active and Treatment Plan Goal: Not equal to Palliative OR

Episode Types: IONCOLOGY TREATMENT and Discontinue Reasons to Exclude: (none) and Plan Number: (none) and Plan Statuses: Future and Treatment Plan Goal: Not equal to Palliative

This will return a list of potentially eligible patients who meet the parameters specified in the query above. I have the report settings such that the results table shows me their treatment plan start date, next oncology appointment date, name, MRN, clinical stage, diagnosis, and plan provider. When I select a patient from the list, it displays an Oncology Snapshot under the report results table. I take a quick look through the Oncolog Snapshot and if I need to take a closer look at their chart, I can open it up.

I have not figured out how to share this report or its results with other people. As it is, I look through the patients returned by the report and eliminate any definitively ineligible patients.

Sometimes metastatic disease is listed as a second diagnosis and therefore slips through the exclusion of metastatic disease. Vascular diseases and injuries that would preclude ability to exercise are other common exclusion criteria. Male patients with breast cancer are not eligible for this study. Take a quick look through the patient's problem list. If the patient does not have any immediate exclusionary problems, pass their name and MRN on to the research coordinators, Sydney Hackwell and Katie Banenas. They will conduct a full chart screening and contact the patient if they are eligible.

I include all patients returned by the report into the List. This is because, from day to day, the report returns different patients. If a patient is not in the List, I will assume that I have not yet looked at their chart. So, even if I look at a chart and immediately determine that a patient is not eligible, I write their information into the List and mark them ineligible so I don't forget that I already screened their chart. This also helps determine if there are new potentially eligible patients returned by the report. On average, the report will

return between 5 and 10 patients. Due to the month long limit on treatment plan start date, the report will return the same patients for many days in a row. If you don't keep track of everyone that the report returned, even the ineligible ones, you may get confused about which patients need to be screened and which ones you have already screened.

3.2.2 Using the Schedule

Open the Schedule tab.

If there is not a schedule view that you like, you can make your own by clicking the green plus sign above **My Schedule**.

Give it a name. I called mine **nirs providers**. Under **Selected Columns** you can choose what information you want to display about the appointment. Under **Configuration**, you can add the providers. I added all five oncologists.

Now when you select that schedule, you will only see the five oncologists that refer to the NIRS study. To take a closer look at an appointment, expand the schedule by clicking the gray triangle next to the name of the schedule. Click on the provider name whose schedule you are interested in. This will expand the schedule of only that provider, where you can see more details about their appointments. Use the calendar in the top left to select different days.

Click on an appointment you are interested in examining further. This should open up a panel to the right of the schedule. I have this set up to show **Snapshot** as the default view. You can rearrange the panels shown in the snapshot by clicking on the wrench in the top right of the snapshot panel.

I use the schedule to screen patients coming in to the Multidisciplinary Clinic (MDC).

Jorgensen has appointments in the MDC every other Monday. Stephenson has appointments in the MDC every other Thursday. Screen these appointments at least one day before. Many will not have a chemotherapy plan or a cancer staging activity yet. Look for major health problems that would disqualify them from participation. If there are no major problems, pass the appointment information on to Katie and Sydney. If a patient has triple negative or estrogen receptor and progesterone receptor negative breast cancer, they are likely to receive chemotherapy and Katie or Sydney can contact them as soon as the chemotherapy is prescribed. This gives us more time for recruitment into the study, as Katie and Sydney can be at the MDC appointment or at the appointment where they are told about the chemotherapy, which is a lot more time than waiting until the chemo teach appointment to approach a patient.

3.3 Potential Patient List

I use a Microsoft List, created in my PrismaHealth OneDrive, to share the patient information with Katie and Sydney rather than sending tons of emails. I update the list when I identify potentially eligible patients. I include the patient's MRN, first and last name, primary diagnosis (breast or gynecological), and which of the referring oncologists is on their treatment team. If they have an upcoming appointment that Katie or Sydney could go to and tell them about the study, I include the appointment information. If their first chemotherapy infusion is scheduled, I include that date so that we know how long we have to recruit and schedule them in the HPL.

Katie and Sydney look through the list and conduct a more in depth chart screening. If they determine that a patient is not eligible, they click the **Ineligible** tag in the List and include reasons that the patient is not eligible. The categories of ineligibility that I included as defaults are: metastatic disease, chemotherapy treatment within the last five years, lab values, treatment plan other than chemotherapy. You can type in any new category you need; you are not limited to just the default ineligibility values.

If a patient is determined to be eligible, one of the Research Coordinators will contact their oncologist to get permission to approach the patient at their next appointment. If the provider declines the study for them, then the patient is marked as **Declined** in the List. If the provider consents for the patient to be approached about the study, then one of the Research Coordinators will approach the patient at their next appointment. The patient will then either sign a consent or decline the study. If they decline the study, click the **Declined** tag in the List. Include a reason that they declined, such as stress, not enough time, etc.

After contacting the patient, they will contact you if the patient signs the consent form. After the consent form is signed, we can begin contacting the patient to start scheduling for lab visits. Contact Dr. Julie Martin after obtaining the consent form and she will put all NIRS related blood draws into EPIC. If for some reason we are not able to get the NIRS draws done at the same time as the other pre-chemo blood draws, consult with the patient and schedule this through Dr. Julie Martin.

If a patient is not wearing shorts for a lab visit, there are disposable shorts in the lab for patient use. They are located in a box under the bed in the back corner.

3.4 Travel Expenses

If a patient lives more than 50 miles from the Cancer Institute, they are eligible for travel expenses to be reimbursed. Use a map service, such as Google Maps, to map the driving distance between their address and the Cancer Institute.

The Greenphire ClinCard is a re-loadable debit card that we use for reimbursement purposes. Have the patient fill out a W-9 if they qualify for the ClinCard.

Sara Biddle has access to the ClinCard Admin Portal. If you need to get access to the ClinCard Admin Portal, contact Jan Keuber at the Clinical Research Management Office for help.

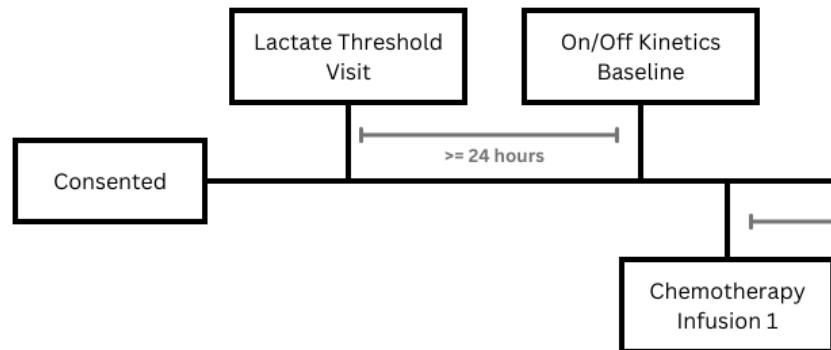
The ClinCard for the NIRS study is currently programmed for up to 10 visits to the lab. Each visit can reimburse up to \$125 for any travel or hotel expenses.

3.5 After a Consent

After a patient has signed the informed consent, the research coordinator will use the RedCap survey to fill out the basic information about a patient and assign the patient a study ID number.

Chapter 4

Data Collection



4.1 Lactate Threshold Visit (First Visit)

This protocol is the participant's first visit to the lab. Have any medical students helping out with testing arrive to the lab at least 30 minutes prior to the participant.

4.1.1 Preparation

At least an hour prior to the time the participant is scheduled to arrive, turn on the metabolic cart by flipping the power switch on the extension cord.

Print out the following forms:

- MMSE C.3
- Godin-Leisure Time Exercise Questionnaire C.2
- Physical Activity History C.4
- BFI C.1
- PROMIS Global Health C.5
- Lactate Threshold Data Collection Sheet
- Contact Information Form

Frankie keeps some forms already printed out in the file cabinet by his desk. If you cannot find them or need to print more, you can download the forms you need from the file repository in RedCap.

Write the patient's study ID number, visit ID, and the date in the upper left corner of each sheet in pen. For Lactate Threshold Visits, the visit ID is LT.

Place the MMSE, GLTEQ, and Lactate Threshold Data Collection Sheet on one clipboard. These will be filled out by laboratory staff.

Place the BFI, PROMIS Global Health, Contact Information Form, and Physical Activity History (Intake) forms on one clipboard. These will be filled out by the participant.

Assemble the VO₂ mask except for the blue rubber part as described in B.3.3. Place the assembled pieces in a sterile pink bucket.

Prepare the PortaMon as described in A.4 by putting in a charged battery, wrapping the PortaMon in plastic saran wrap, and placing the double sided taupe tape.

Calibrate the metabolic cart as described in B.3.1 if the metabolic cart has been on for at least 30 minutes. Before doing calibrations, remember to change the date and time on the computer to match the actual date and time, as the PARVO cart is not connected to the internet. Do both the Flowmeter Calibration and Gas Calibration. Remember, percent change must be less than 1% to save the calibration results. If you cannot get the percent change that low and don't have any more time, save the result and tell Frankie about it so he can fix it later.

Run lactate meter controls as described in D.2.1.1.

Everyone is required to wear a mask while the patient is in the lab. Prisma Health keeps a supply of masks in the hallway that connects to the parking garage. We wear masks since our patients are receiving chemotherapy and their immune systems will not be functioning well during chemotherapy treatment. Patients and any people they bring with them are not required to wear masks. If they wish to, you can direct them to the supply of masks in the hallway.

Approximately 10-15 minutes before the patient is supposed to arrive, send someone to the Cancer Institute lobby to meet them. They will walk the patient up to the Human Performance Lab.

4.1.2 Exclusion Criteria

There are three exclusion criteria that we must test before continuing with any data collection.

1. Adipose Tissue Thickness

In order for the PortaMon to collect useful data, the subcutaneous adipose tissue thickness above the vastus lateralis and directly under the device must be less than 2 centimeters.

Use the steps described in D.1.1 to measure the participant's subcutaneous adipose tissue thickness above their vastus lateralis. If ATT is less than 2 centimeters, the participant continues through the next steps.

Place the NIRS device over the area measured using ultrasound following the steps described in A.4.4.

2. Sufficient Physical Activity

Sedentary patients will be unable to complete the testing protocol and thus will be excluded from participation. To determine physical activity levels, administer the Godin-Leisure Time Exercise Questionnaire C.2. If the score is less than 14, the patient would be sedentary and will not be eligible to participate. Administer the GLTEQ to the patient and score it immediately.

3. Mental State

Patients must be aware of their situation and fully able to consent to participation. The Mini-Mental State Examination C.3 helps detect any underlying issues with memory that would render a patient unable to participate. If the patient scores less than ____, the patient will not be eligible to participate due to mental conditions. Administer the MMSE to the patient and score it immediately.

4.1.3 Data Collection

Have the subject complete the following instruments:

- Physical Activity History C.4
- BFI C.1
- PROMIS Global Health C.5

Review the completed Godin-Leisure Time Exercise Questionnaire and Physical Activity History instruments. Use your best judgement in collaboration with the other investigators to determine the wattage jumps. See E.1.2 for further information about deciding wattage jumps.

Measure the subject's face to determine mask size. Record mask size on data collection sheet. Finish assembling mask by attaching the blue rubber mask of the appropriate size to the assembled pieces.

Put the heart rate monitor on the patient.

Have the subject get on the stationary bike and make adjustments to the seat height, seat depth, pedal length, and handlebar placement to the comfort of the participant.

If the PortaMon has been on for at least 10 minutes, proceed.

Place the assembled mask on the participant's face and connect clear tubing to the mask.

Conduct Lactate Threshold Exercise Test as described in E.1.

4.1.4 After Data Collection

As soon as you click **End Test** on the PARVO and the software stops collecting data, take the VO₂ mask off the participant. The masks are very uncomfortable and we want them to have to wear it for as little time as possible.

Help the patient off the stationary bike. Offer them a chair and a towel. Remove the PortaMon from their leg and pull off all the tape. Take the heart rate monitor off of them.

Escort the patient to their next destination, which will normally be back down to the Cancer Institute lobby.

Pull the saran wrap and tape off of the PortaMon and throw it away. Remove the PortaMon battery and charge it. Wipe down the outside of the PortaMon case with antibacterial wipes.

Print out the 10-second report of the data collected by the PARVO and place with the other data collection sheets.

Measure the seat height, seat depth, and pedal length of the stationary bike and record on the data collection sheet.

Remove the button from the heart rate monitor. Wipe the button down with antibacterial wipes and put the heart rate monitor strap in the pink bucket to be cleaned with the PARVO mask parts.

Remove all dirty PARVO parts and place in pink bucket.

Take the pink bucket and put it on the blue cart. Follow the steps described in @ref() to clean and sanitize the pieces.

4.2 On/Off Kinetics Visit

4.2.1 Preparation

At least an hour prior to the time the participant is scheduled to arrive, turn on the metabolic cart by flipping the power switch on the extension cord.

Print out the following forms: - Physical Activity History (Follow Up) - BFI - PROMIS Global Health - On/Off Kinetics Data Collection Sheet

Write the patient's study ID number, visit ID, and the date in the upper left corner of each sheet in pen. The visit ID for an On/Off kinetics is the number corresponding to the cycle of treatment and "CYCLE". For the first On/Off Kinetics, which occurs prior to beginning chemotherapy treatment, the visit ID is 0CYCLE. For the next On/Off Kinetics, which occurs after the first cycle of chemotherapy and prior to beginning the second cycle of chemotherapy, the visit ID would be 1CYCLE.

Place the BFI, PROMIS Global Health, and Physical Activity History (Follow Up) forms on one clipboard. Place the On/Off Kinetics Data Collection Sheet on a different clipboard.

Assemble the VO₂ mask as described in B.3.3. Use the mask size recorded from the Lactate Threshold Visit to fully assemble the mask and place in a sterile pink bucket.

Prepare the PortaMon as described in A.4 by putting in a charged battery, wrapping the PortaMon in plastic saran wrap, and placing the double sided taupe tape.

Calibrate the metabolic cart as described in B.3.1 if the metabolic cart has been on for at least 30 minutes. Before doing calibrations, remember to change the date and time on the computer to match the actual date and time, as the PARVO cart is not connected to the internet. Do both the Flowmeter Calibration and Gas Calibration. Remember, percent change must be less than 1% to save the calibration results. If you cannot get the percent change that low and don't have any more time, save the result and tell Frankie about it so he can fix it later.

Refer to the stationary bike measurements recorded from the Lactate Threshold Visit. Set the bike seat and pedals to match those measurements.

4.2.2 Data Collection

Have the subject complete the following instruments:

- Physical Activity History C.4
- BFI C.1
- PROMIS Global Health C.5

If the PortaMon has been on for at least 10 minutes, proceed.

Place the assembled mask on the participant's face and connect clear tubing to the mask.

Conduct On/Off Kinetics Exercise Test as described in E.2.

Take the mask off the patient's face. Help the patient get off the bike. Remove the NIRS device and the heart rate monitor.

Chapter 5

Data Storage

Follow all appropriate data export instructions for PARVO and NIRS data.

All physical copies are stored in a locked filing cabinet in the Human Performance Lab.

The study RedCap stores all identifying patient information and digital copies of data.

After a patient is identified and signs a consent form for the study, the research coordinator will fill out the **New Patient** survey in RedCap. When this survey is completed, it automatically assigns a study ID number to the patient and sends an email to Frankie Bennett and Sara Biddle about the newly consented participant.

When a patient completes an HPL visit, go to the patient's record in RedCap.

5.1 Missing Data Codes

The following missing data codes are enabled in RedCap:

- INV, Invalid
- NA, Not Applicable
- OTH, Other
- NI, No Information

When inputting data into RedCap, use the following guidelines to determine which missing data code to use. You can input a missing data code by selecting the M next to the input field.

If the item is blank, as in not answered or no one wrote it down on the data collection sheet, use **NI, No Information**. If the item had an error during data collection, for example if the lactate meter shows **ERR**, use **INV, Invalid**.

If the item was not used during data collection, use NA, Not Applicable. If the reason does not fit into any of the above categories, use OTH, Other and record a comment by clicking on the text bubble icon and typing into the notes field.

5.1.1 Patient Information

After consenting the new patient, open up the patient's chart in Epic and fill out the forms under Patient Information.

5.1.2 Lactate Threshold Visit

Under the Lactate Threshold event in the appropriate patient record in RedCap, start filling out the data collection instruments for the event.

Fill out the following data collection instruments: HPL Visit, One-Time Measurements, Lactate Parvo, Godin Leisuretime Exercise Questionnaire, Mini-Mental State Examination, Brief Fatigue Inventory, PROMIS SF v1.1-Global Health, Physical Activity, and Data Files.

The information to fill out HPL Visit, One-Time Measurements, and Lactate Parvo will be found on the Lactate Threshold Data Collection Sheet that was filled out during the patient visit.

Chapter 6

Data Analysis

Be sure you have exported and stored all data appropriately.

6.1 Lactate Threshold

Take the lactate threshold data collection sheet.

Average the duplicate lactate measurements for each completed stage.

Make a plot of lactate by power (Watts). Find the power at which lactate would have been 4.00. That is the power at which lactate threshold occurred.

Multiply this power by 1.1 to calculate the power at which the patient will conduct subsequent on/off kinetics testing.

6.2 On/Off Kinetics

6.2.1 Using the App

Use the exported .txt file. Upload this file into the Shiny app.

Refer to the data collection sheet and find the time on the NIRS that the exercise test started. Input this time.

Look at the graph of the data. Make sure that the transitions are at the appropriate times on the graph. The graph should end on a rest stage. The transitions between stages should occur at the labelled vertical lines on the graph. If the graph seems a little off, you can adjust the start time by a few seconds to align the timing of the transitions as close as possible to the labelled lines on the graph.

Once the graph of the raw data looks correct, look at the plotted regressions. The gray is the raw data and the red is the regression line. The red should

follow the gray raw data as closely as possible. If the regression does not seem to follow this at all, you can try adjusting the `transition time` variable. This will remove a few seconds from the beginning and end of the stage, where the patient may have been moving around on the bike or adjusting from the previous stage. Check to make sure that removing the time made a beneficial difference. Sometimes removing the transition time is helpful and sometimes it makes things worse so try several values and check the regression lines each time.

Once you are content with the regressions, check the final table of regression coefficients.

When you are okay with the results obtained from the app, you can download the report as a `.pdf`. The report shows the parameters used for the analysis, graphs, and results tables from the analysis. Save this `.pdf` with the raw `.txt` file and name is appropriately.

```
knitr::include_app('https://saragracebiddle.shinyapps.io/DataAnalysis/')
```

Upload the report into RedCap.

6.2.2 By Hand

Use the exported `.txt` file.

Read in the exported PortaMon data.

I have written a custom file reader for exported PortaMon files. Oxysoft allows you to add in ‘Events’ to the measurements, kind of like time markers. However, when you export the measurements after adding an ‘Event’, Oxysoft adds an extra column that is mostly empty except for where the ‘Event’ was added in. Most read functions do not like this and will throw an error when you try to read in the data. The function I wrote will take the file and throw out the extra ‘Event’ column. Oxysoft also adds metadata to the header of the file. Most read in functions do not like this either, as they will look to the top of the file to figure out what the rest of the file looks like. `read_nirs` will parse the metadata for the information we would like to keep. Then it reads the actual data as a data frame. The useful metadata pieces are passed on to the user as attributes of the raw data frame.

The PortaMon does not record in increments of time, it records the sample number. The PortaMon records data at a rate of 10 hz, so it takes 10 samples a second. The time in seconds from the start of the test is the sample number divided by 10.

The PortaMon was on and collecting data from the time the device was placed until the end of the exercise test. We aren’t interested in the data from before the start of the exercise test, so that can be removed. The best way to do this is to create a new column, named something like `zeroed_time` or `time_aligned`, and calculate it such that time = 0 in the `zeroed_time` column is the start time

of the test. Everything before that is a negative time and everything after is positive. Then you can filter on `zeroed_time > 0`. Why not just filter on `time > start_time`? If the start time written on the data collection sheet was off by a few seconds (which it often is), you cannot go back and readjust it, especially not if the time needs to be adjusted backwards. You can easily re-calculate the `zeroed_time` column based on the original time column, using the same data frame.

And you don't have to remember the start times of every data frame. If every data frame has been read in and time adjusted, then every data frame just needs to be filtered on `zeroed_time > 0`.

Plot the raw data to be sure that you removed all extraneous data from the beginning of the data frame. Make adjustments to the start time as needed.

Next, find the time chunks for each section of the test. An on/off kinetics consists of the following sections, each 2 minutes (120 seconds) in duration: Baseline Rest, Warm Up, Work 1, Rest 1, Work 2, Rest 2, Work 3, and Rest 3.

Plot the exercise test. On the x axis, use time in seconds. Have dual y axes, one with hemoglobin arbitrary units and one with percentages. Plot all signals (O_2Hb and HHb for all exported transmitters and TSI) over time and check that the transitions between sections line up with the expected times. Adjust slightly as necessary, as the start time recorded for the test may be slightly off due to human error / time taken for the PARVO to begin the test.

Use the plot and notes from the test to examine the data for movement artifacts that need to be removed before analysis. Remove as necessary.

The oxyhemoglobin and deoxyhemoglobin measurements have arbitrary units—they are change in oxy and deoxyhemoglobin. This means that we cannot use the amounts of oxyhemoglobin and deoxyhemoglobin and compare those over time. For example, the average oxyhemoglobin at rest could be measured as 4 for one test and 6 at the next test. This does not mean that at the second test, the amount of oxyhemoglobin in the blood was actually higher than at the first test.

Average the O_2Hb and HHb across the transmitters.

Calculate the steady state at the end of each non-baseline and non-warm up section (6 sections in total- 3 work sections and 3 rest sections) by averaging the last 30 seconds of the section for each signal type (O_2Hb , HHb , and TSI).

There are 18 steady state values: 3 signal types and 6 sections.

Calculate the delta steady state for each transition. Subtract the rest steady state from the corresponding work steady state. I.e. subtract rest 1 steady state from work 1 steady state.

There are 9 delta steady state values: 3 signal types and 3 transitions.

We use the following equation to describe an asymptotic or monoexponential curve:

$$y = (Asym - B_0) - (Asym - B_0) * e^{-t/\tau}$$

Where *Asym* is the asymptote (or Steady State), B_0 is the value at time 0, t is the time (in seconds), and τ is the time constant.

Calculate the coefficients for the monoexponential curve for each transition. There are 9 monoexponential curve equations: 3 signal types and 3 transitions.

When you are satisfied with the results obtained from the app, download the report and upload it into the RedCap.

Appendix A

PortaMon

A.1 Specifications

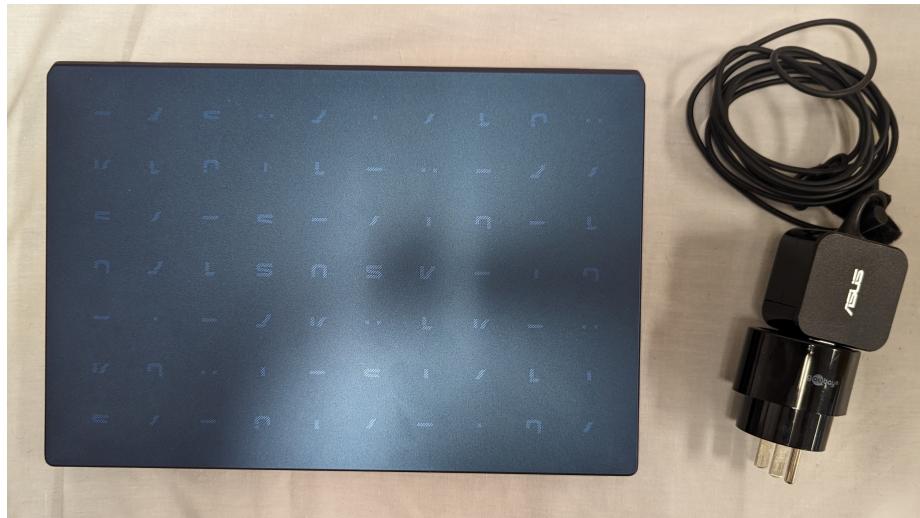
The PortaMon by Artinis Medical Systems is a spatial-resolved near-infrared resonance spectroscopy device. It uses one receiver with three infrared transmitters. Each transmitter is 5 millimeters further from the receiver. This allows the application of mathematical formulas to calculate an absolute tissue hemoglobin saturation, which Artinis Medical Systems refers to as the Tissue Saturation Index, or TSI. In the literature, this is referred to by various acronyms, such as TOI (Tissue Oxygenation Index). A full examination of the mathematics and physics behind the calculation of TSI was published as part of the SPIE Conference on Optical Tomography and Spectroscopy of Tissue III in 1999 [?].

The yellow case is one unit.



It contains the following:

- ASUS laptop
- laptop charging chord with European to American outlet converter



- yellow Artinis Oxysoft USB - Bluetooth dongle - ROCKEY4ND license key



- PortaMon device



- two batteries - battery charging dock - micro-USB chord for battery charging dock



A.2 Oysoft

Oxysoft is the software created by Artinis Medical Systems to connect with the PortaMon, collect, and analyze data.

Oxysoft is installed on the ASUS laptops that go with the yellow cases. These laptops do not have any PrismaHealth or USC SoMG software on them. If someone should want to install Oxysoft on a PrismaHealth or USC SoMG computer, Oxysoft will have to be approved by the respective organization's IT team.

Oxysoft has been approved to be on Sara Biddle's PrismaHealth desktop computer by PrismaHealth's IT. No other PrismaHealth or USC SoMG computers have Oxysoft installed.

If you wish to install Oxysoft on a personal computer or have been approved to install Oxysoft on an organization's computer, plug the yellow Artinis Oxysoft USB into the computer and run the installer.

- Oxysoft uses a legacy Bluetooth dongle to connect to the PortaMon. This makes using Oxysoft on a computer with the most up to date Windows difficult. It is easier to collect data on the ASUS laptops, which are default configured to use the Bluetooth dongle, and then export the data for analysis.
- Oxysoft creates files with the extension .oxy4 for every new measurement.

A.3 Batteries

The PortaMon batteries can hold up to 8 hours of power for the device. Make sure they are fully charged prior to a patient's visit.

Plug the micro-USB into the battery charging dock. Plug this into an outlet. Place the battery into the dock, sticker side down. The three metal connectors on the narrow side of the battery must be touching the three metal connectors on the charging dock. If the battery is correctly placed in the dock, an LED will light up. When the battery is fully charged, the LED will be green.



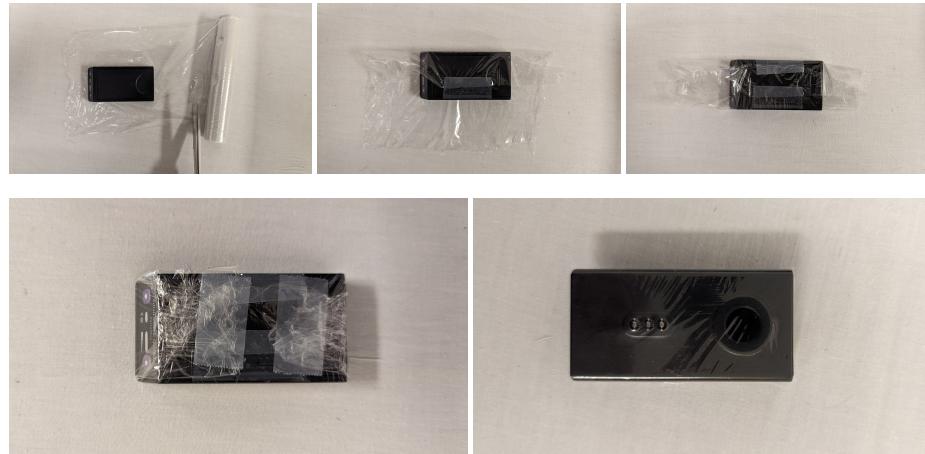
A.4 Before Data Collection

A.4.1 Instrument Preparation for Data Collection

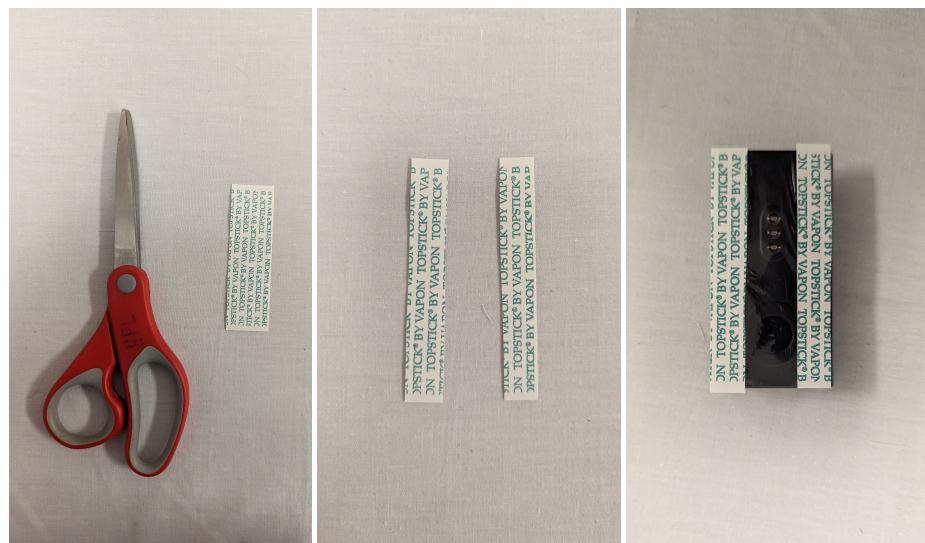
- Place a fully charged battery in the PortaMon, with the three connectors on the battery touching the three connectors in the PortaMon.
- Slide the top of the PortaMon back in until it clicks into place. If the battery is charged and placed correctly, LEDs on the bottom of the PortaMon will light up.



- Wrap the PortaMon in clear saran wrap and tape the saran wrap in place. This prevents sweat and other moisture from getting in to the PortaMon. Since the PortaMon has electronic parts, it cannot be sterilized using liquids and the saran wrap means we do not have to sterilize the device itself. When testing is complete, pull saran wrap and tape off the PortaMon and throw it away.



- Cut the double-sided taupe tape length-wise into two long strips.
- Place one strip to the left of the transmitters and receiver and one strip to the right of the transmitters and receiver. Leave the exterior side of the double-sided tape covered until the placement on the thigh is complete.



A.4.2 Bluetooth Troubleshooting

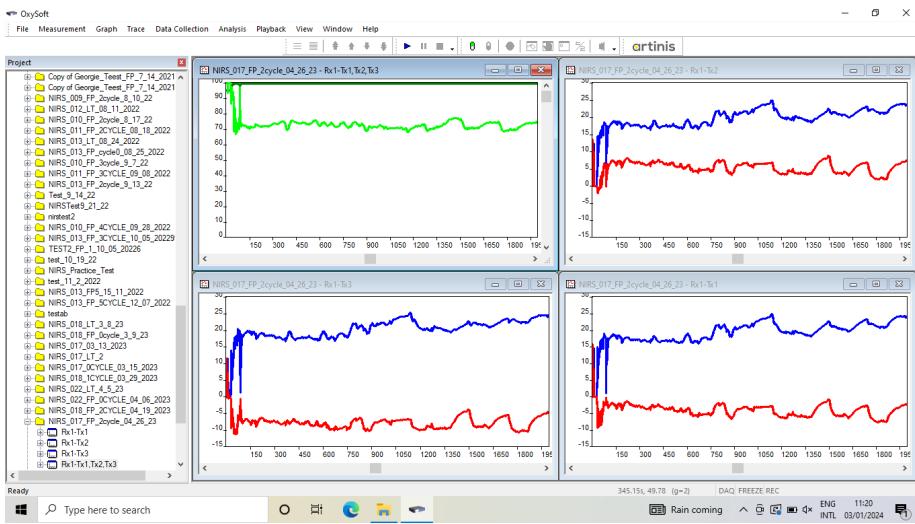
A.4.3 Start a Measurement

- Turn on the ASUS laptop.
- Ensure the bluetooth dongle and the Rockey dongle are plugged in to the laptop.

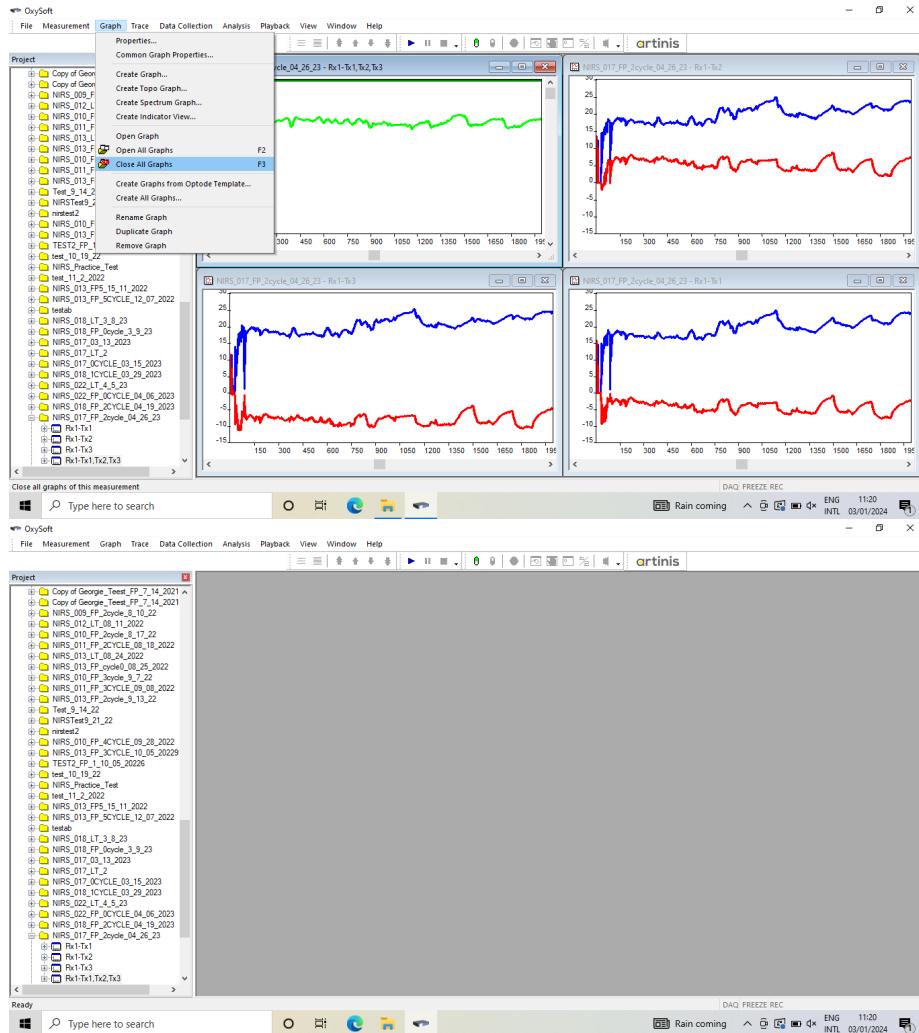
- The Rockey license key must say ‘ROCKEY4ND’ and NOT ‘ROCKEY4’. The ‘ROCKEY4’ is from an older Artinis device and is not the current license key. You will not be able to use the most up to date Oxysoft software with the incorrect license key.



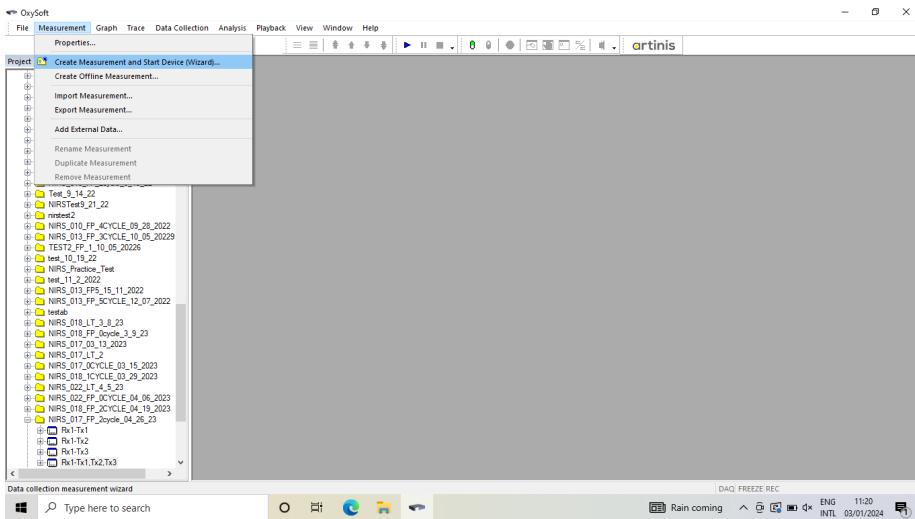
- Open Oxysoft.



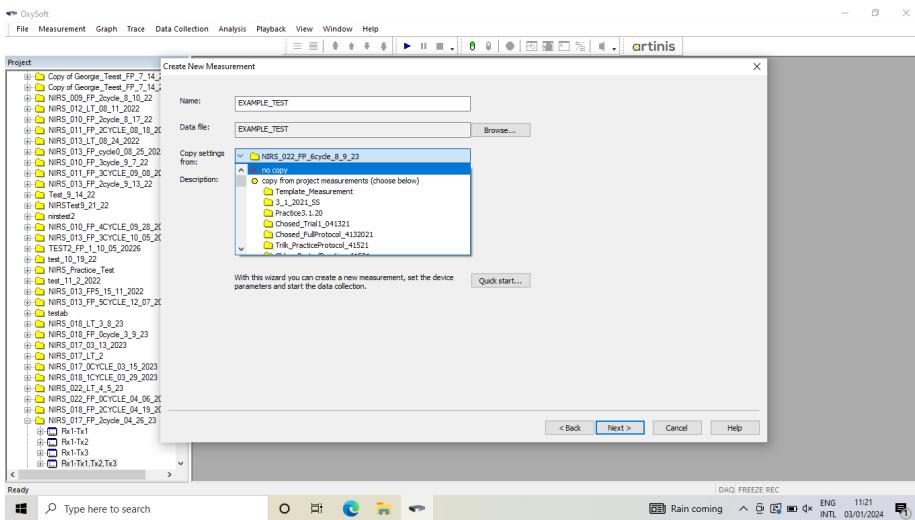
- Close any open graphs in the main panel.
 - Select **Graphs** in the top bar.
 - Select **Close all graphs**. There should be no open graphs in the main panel.



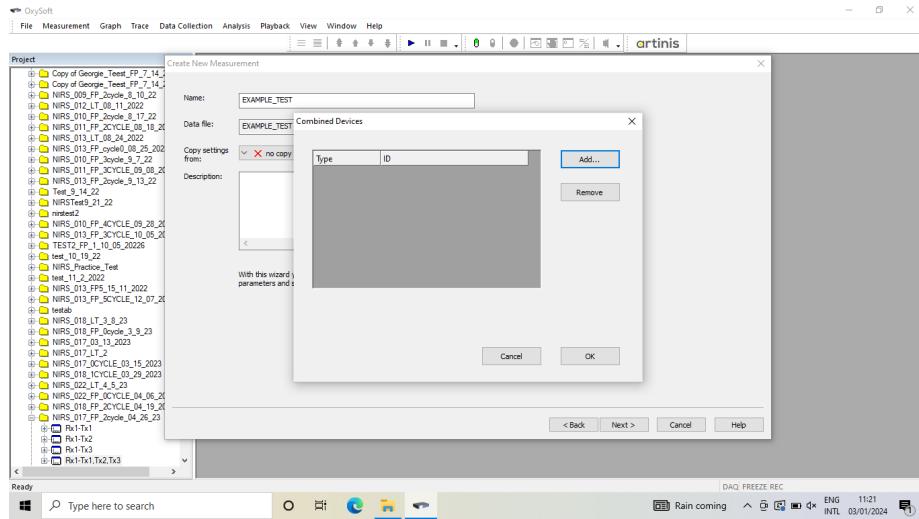
- Select Measurement in the top bar.
- Select Create Measurement and Start Device (Wizard)... from drop down.



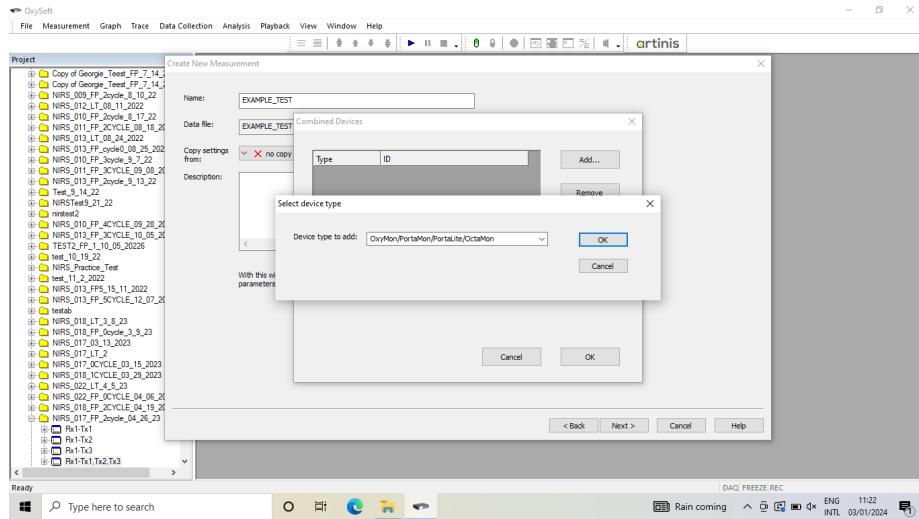
- Name the measurement appropriately.
- Select the **Copy settings from:** drop down.
- Scroll to the top of the drop down and select **no copy**.



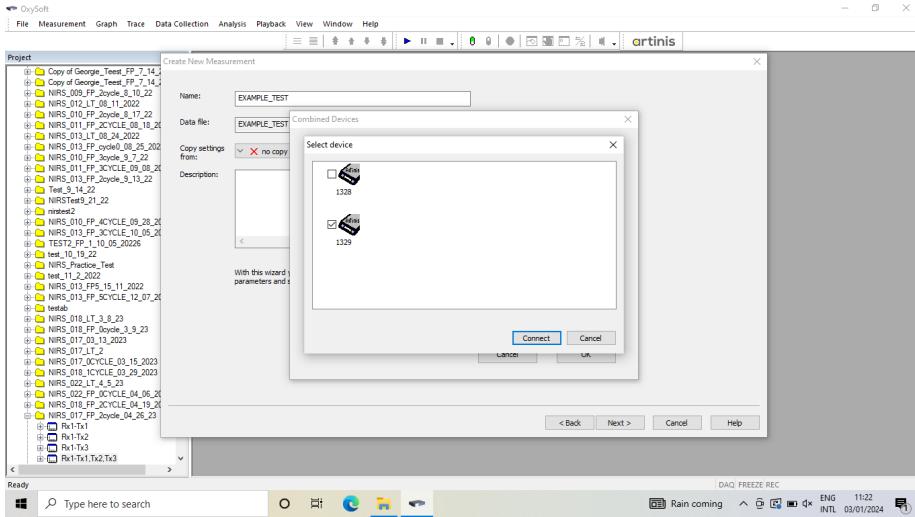
- Click **Next**. Pop up will open to add a bluetooth device.



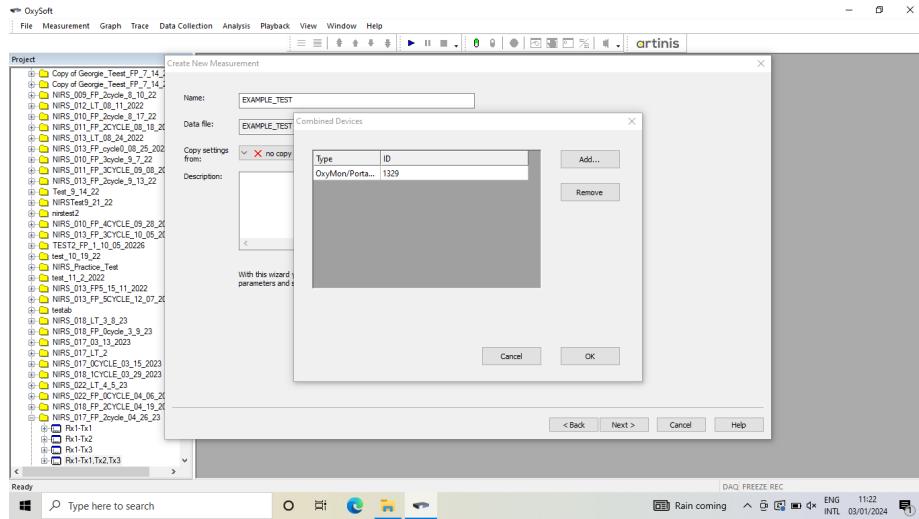
- Click Add. Pop up will open to select type of device.
- Select OxyMon/PortaMon/PortaLite/OctaMon, which should be auto filled.



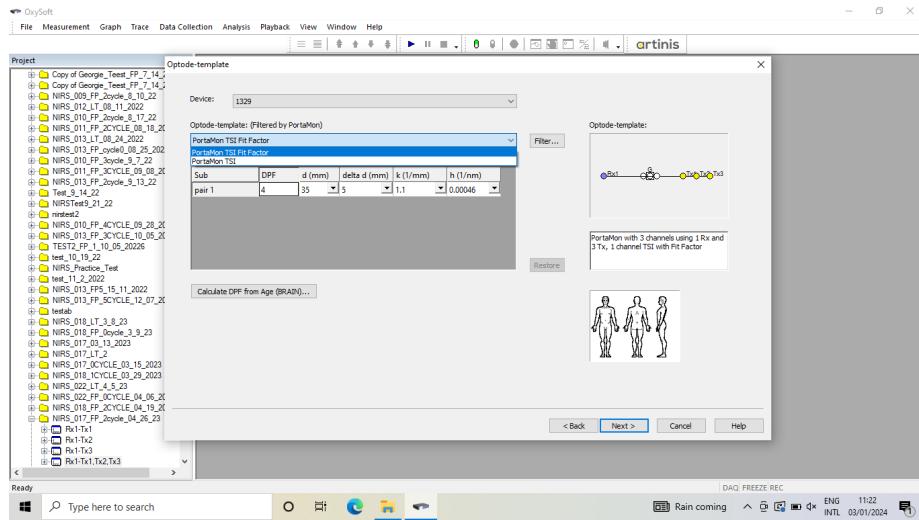
- Click OK.
- Select correct device number, this should match the number on the top of the Portamon.



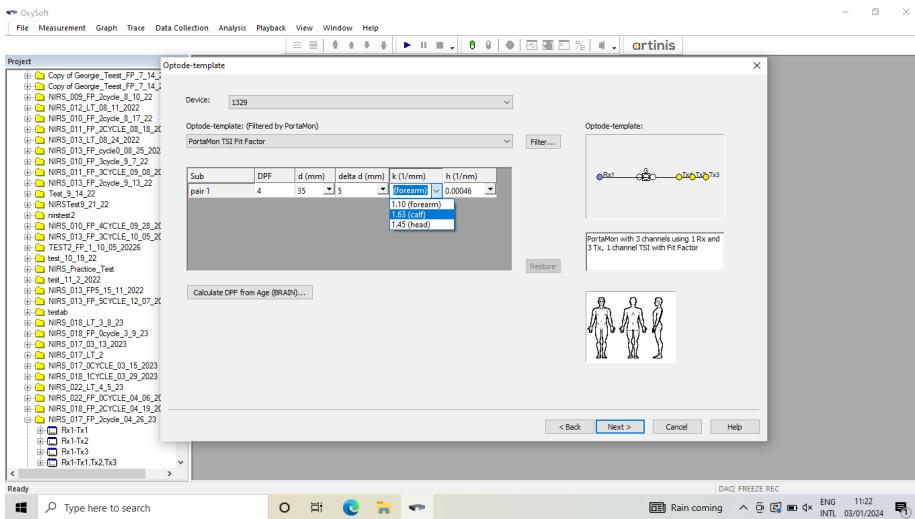
- Click **Connect**.
- Device should pair with the computer. If it does not, try the following steps:
 - Check the device is on. The green LED light should be on. If not, turn on by holding down the button on the left until the lights come on (about three seconds).
 - Hold the bluetooth button down for about three seconds while you click **connect** on the computer.
 - Unpair the device with the computer in the computer's bluetooth settings, then re-pair.
 - Restart the computer.
 - Try using the other Portamon.
- When successfully connected, a blue LED will turn on on the Portamon and the device type and number will be listed in the **Combined Devices** pop up.



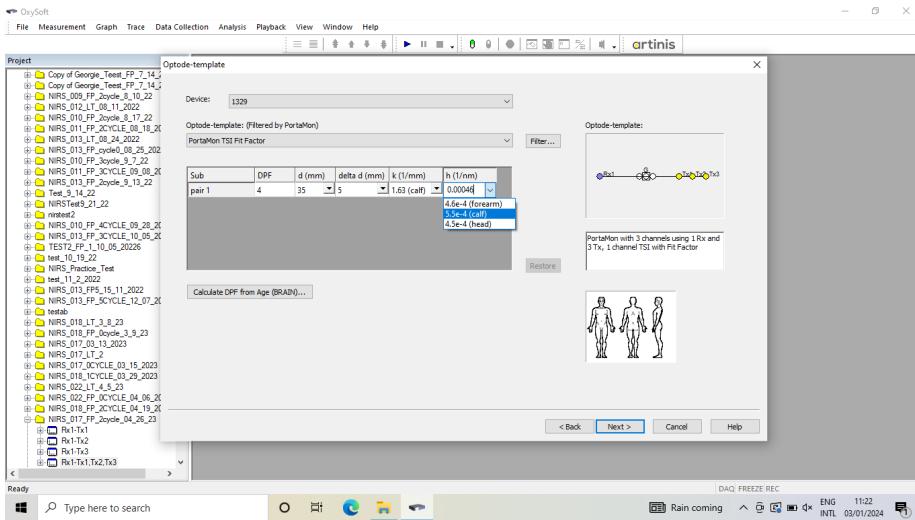
- Click OK.
- The Optode-template window will now be open.
- Under Optode-template: (Filtered by PortaMon) click the drop down.
- Select Portamon TSI Fit Factor.



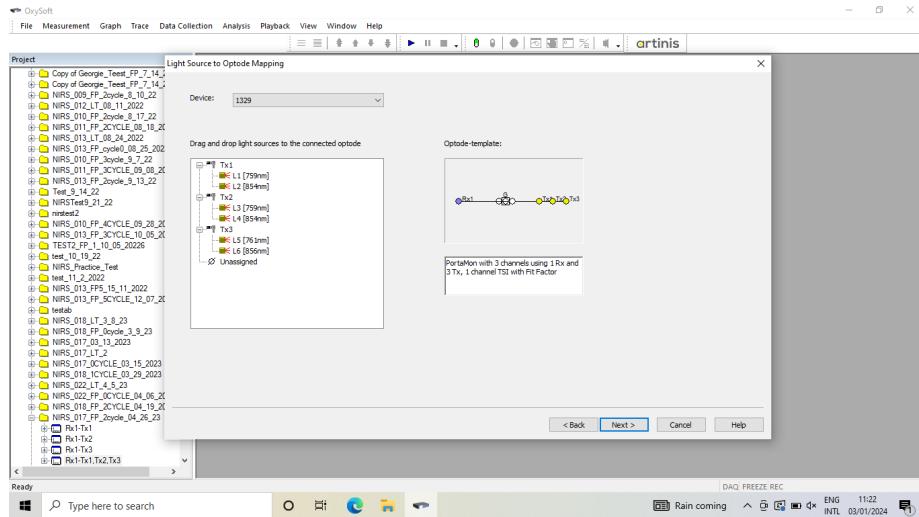
- Under k (1/mm) click the drop down.
- Select 1.63 (calf).



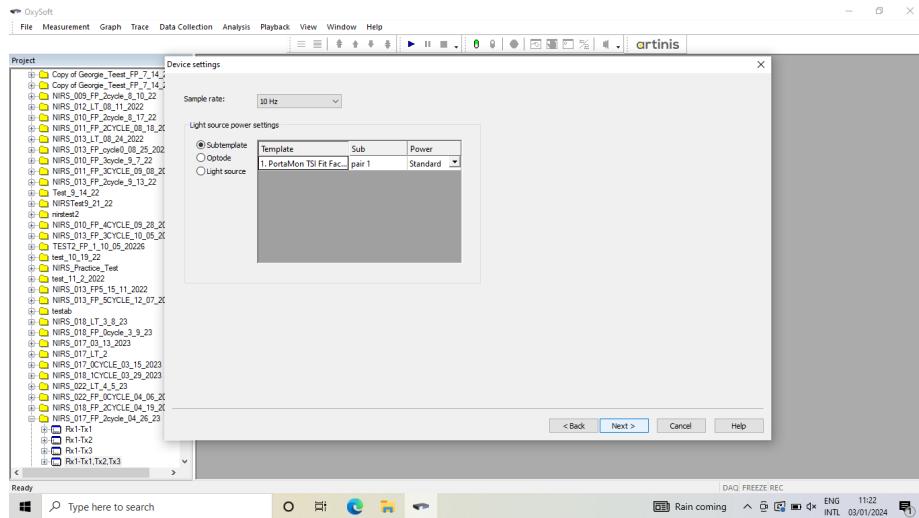
- Under h ($1/\text{mm}$) click the drop down.
- Select $5.5\text{e-}4$ (calf).



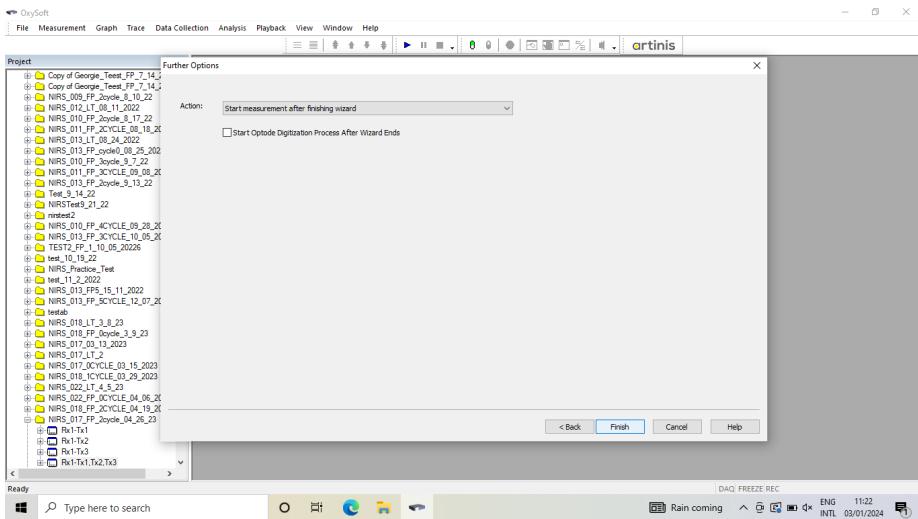
- Click **Next**.
- The Light Source to Optode Mapping window will now be open. Leave all settings as is and click **Next**.



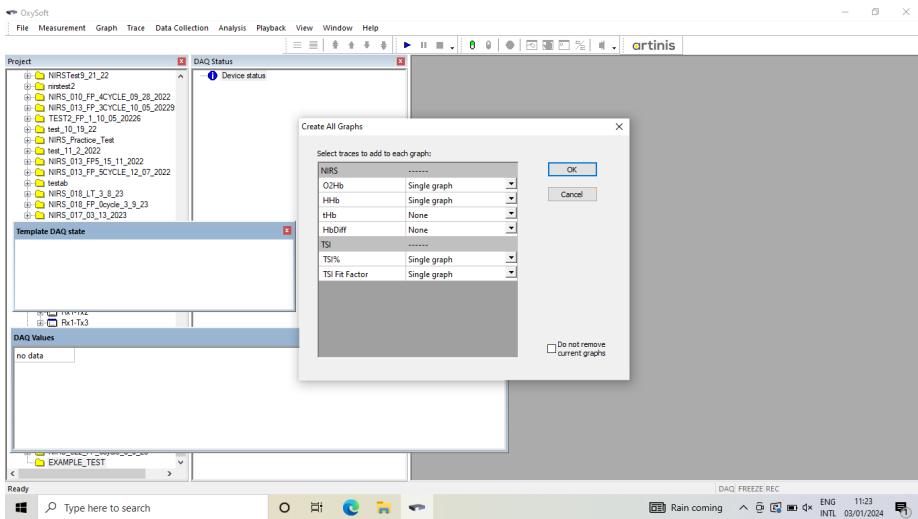
- The Device settings window will now be open. Leave all settings as is and click **Next**.



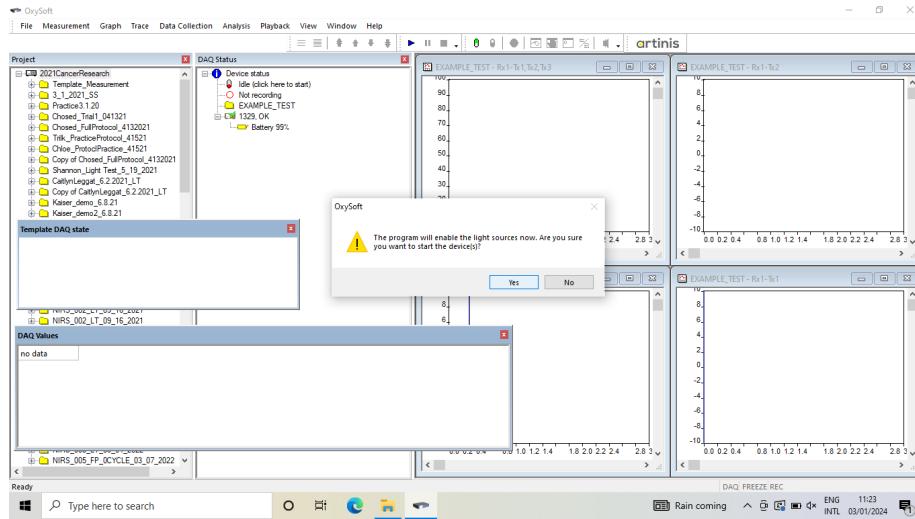
- The Further Options window will now be open. The Action drop down should have **Start measurement after finishing wizard** selected.



- Click Finish.
- The Create All Graphs window will pop up. Leave settings as is and click OK.



- There will be an Oxysoft pop up. It says 'The program will enable the light sources now. Are you sure you want to start the device(s)?' DO NOT click yes yet. Wait until device has been placed correctly. Follow the steps described in A.4.4.



A.4.4 Instrument Placement on Vastus Lateralis

The PortaMon can measure up to 2 centimeters depth into tissue. Since we are interested in muscle oxygenation, the muscle belly has to be within 2 centimeters from the surface of the skin. Otherwise, the device is not measuring muscle oxygenation but adipose tissue oxygenation. Therefore, we use an ultrasound to measure the subcutaneous adipose tissue thickness.

Place the device over the location measured by ultrasound.

Connect the NIRs by following the steps under A.4.3.

Click ‘yes’ to enable light sources and begin data collection. Wait approximately 10 seconds. Check the DAQ (Data Acquisition) values to determine whether the NIRS is receiving good data. If one or more of the DAQ values show as red, then make small adjustments to the placement of the device to attempt to get better DAQ values. If the small adjustments add up to a large difference from the original ultrasound measurement location, re-measure adipose tissue thickness using the ultrasound in the new location.

When all three DAQ values remain white when the subject moves around their leg, then the device is in the best location. If one of the DAQ values turns red during movement, that can be okay but only ONE. If two of the DAQ values are red, then TSI cannot be calculated so we do our best to have at least two good signals, three if at all possible.

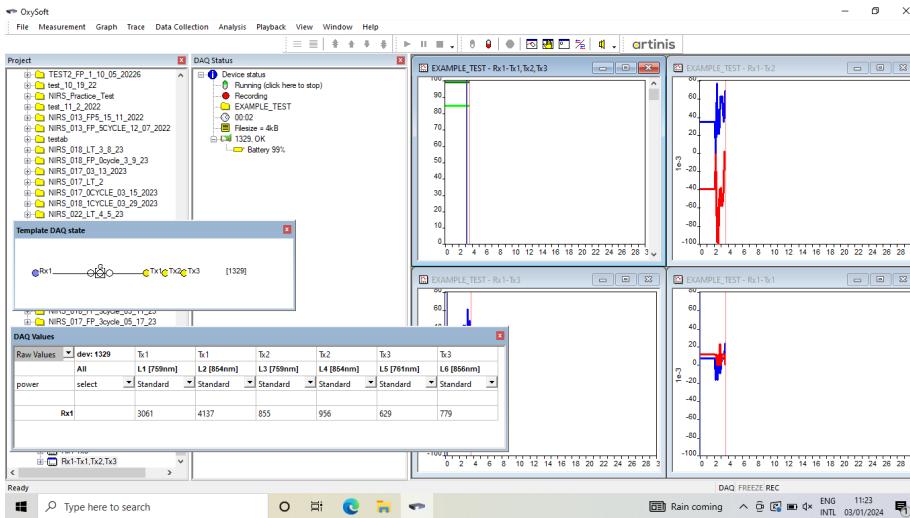
Rock the device laterally and remove the tape cover on the exposed side. Rock the device back into place and stick the tape to the subject's skin. Repeat on the other side. Double check that the DAQ values remain consistent.

Take a picture of the placement. Use a measuring tape to show the distance

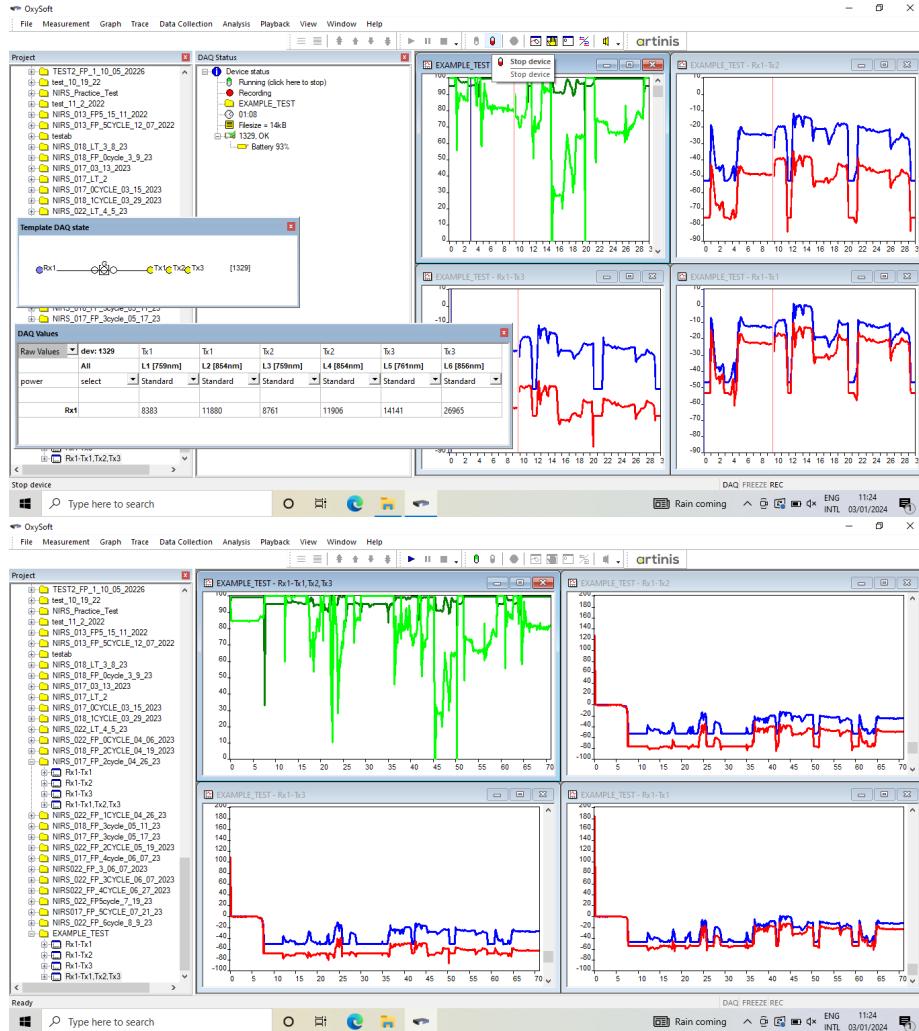
from the top of the kneecap to the bottom of the device and use a perpendicular measuring tape to show the distance from the center of the thigh to the right edge of the device. Print the picture and place in the participant's physical file. Upload a .png of the picture into the RedCap.

A.5 During Data Collection

- When the device is placed correctly, click yes. The new measurement will begin.



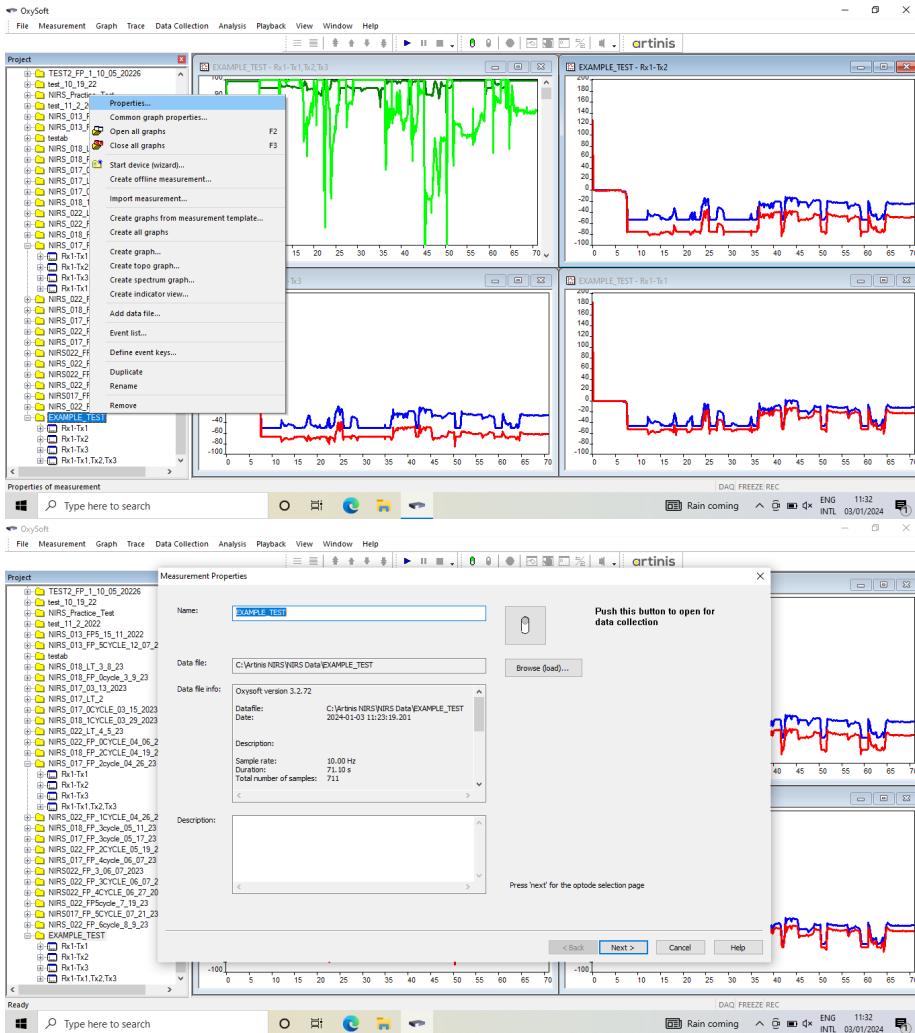
- When you are done with the measurement, click the red pill in the top bar to stop the light sources. Oxysoft will stop the rolling every 30 seconds view and you will be able to see the whole measurement in the panes.



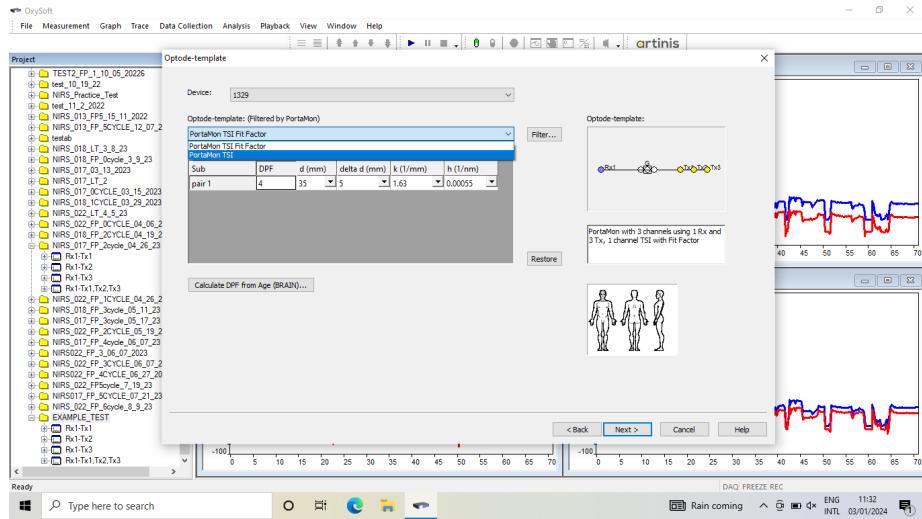
A.6 After Data Collection

A.6.1 Change Measurement Properties

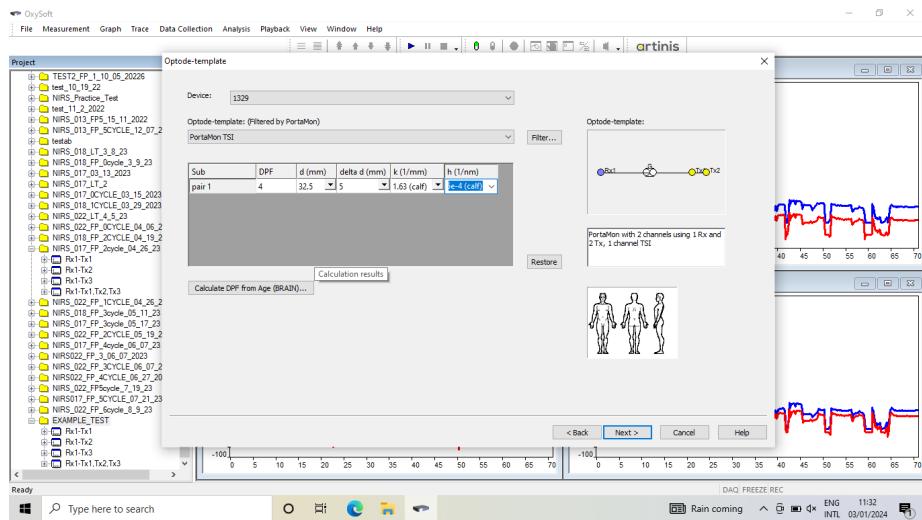
- Right click on the name of the measurement in the Project panel on the left.
- Select Properties.... This will open up a new panel.



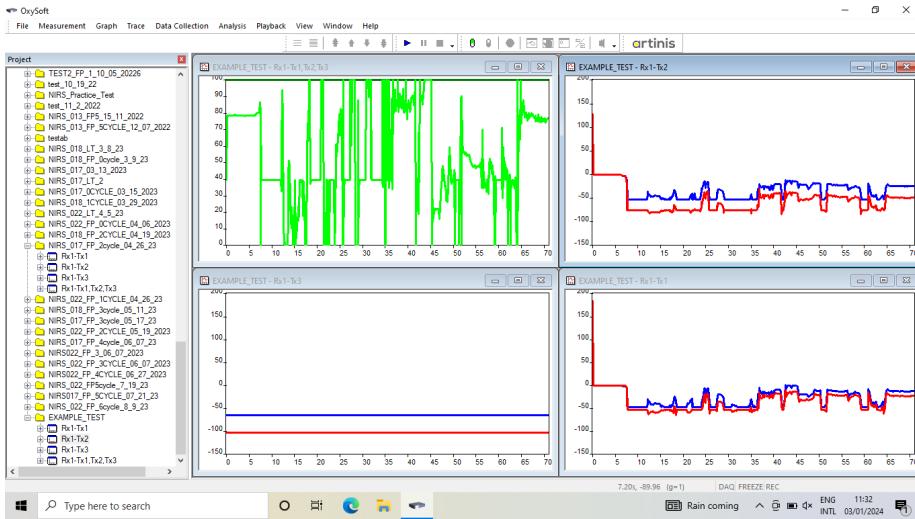
- Leave the measurement name and data file as is.
 - Click Next.
 - Under Optode -template: select PortaMon TSI instead of PortaMon TSI Fit Factor.



- Change the settings as follows:
 - Under d (mm) type 32.5.
 - Under δd (mm) type 5.
 - Ensure k (1/mm) is 1.63 (calf). and h (1/mm) is $5e-4$ (calf).



- Click Next.
- When Tx3 has been removed from the TSI calculations, the graph panels will look different. The Rx1-Tx3 panel will have two flat lines, one blue and one red. The TSIFF panel will still have a green line for TSI, and will no longer have a TSIFF line in that panel.



To undo these changes and revert to the original measurement with Tx3 included in the TSI calculations, right click on the file name and open up the **Properties** panel again. Click **Next**.

Next to the **Optode-template** settings table, there is a button on the bottom right that says **Restore**. Click **Restore**. Click **Next**.

The graphs are now restored to their original state.

A.6.2 Data Export

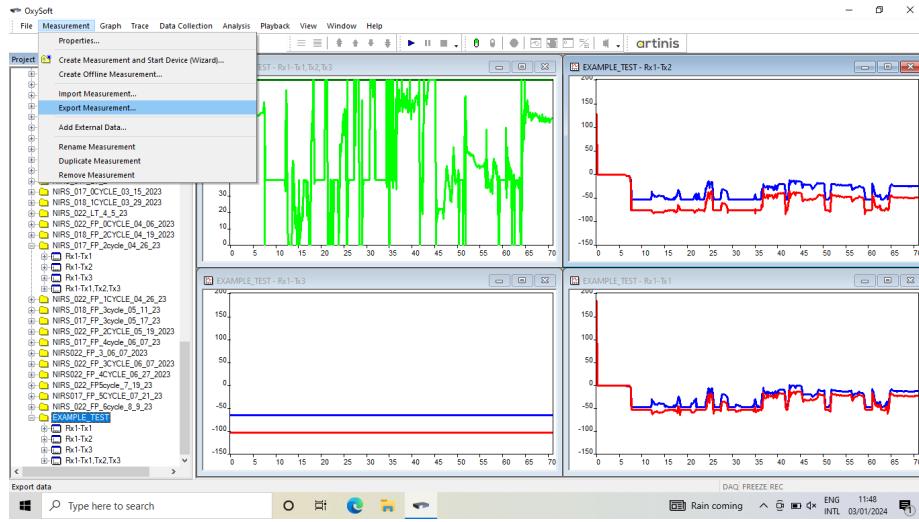
Ensure that only one measurement is open in the Oxysoft graph panels. Do this by closing all graphs, then selecting the name of the measurement you want to open in the file pane on the left.

If you are not sure or cannot tell, under the **Graph** drop down of the header bar, select **Close all graphs**. There should be no visible graphs in the main panel.

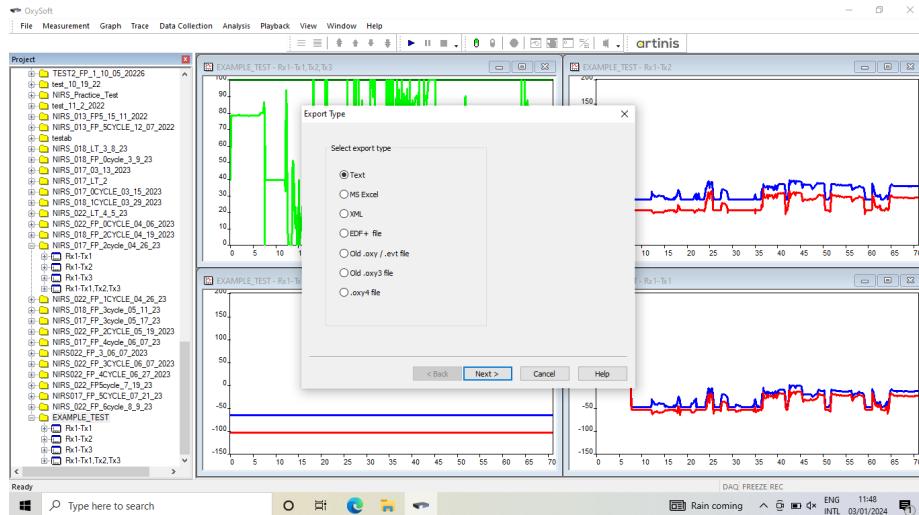
Select the name of the measurement you want to export in the **Project** panel on the left. Click **Open all graphs** under the **Measurement** drop down while the name of the file is highlighted. There should be four panels open, one titled **Tx1-Rx1**, **Tx2-Rx1**, **Tx3-Rx1**, and one **TSIFF**.

If all three transmitters had good DAQ values during data collection and never dropped into red, skip the next steps. If there were issues with only Tx3, follow the steps described in ??.

Select **Export measurement** under the **Measurement** dropdown.

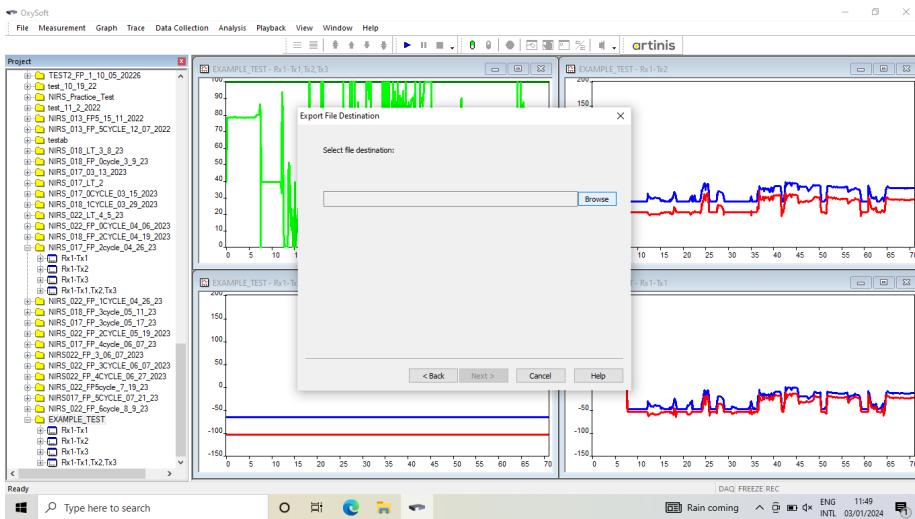


A new panel will open. Select the type of file you wish to export as. The automatic selection is text (.txt), which is the preferred type of export.

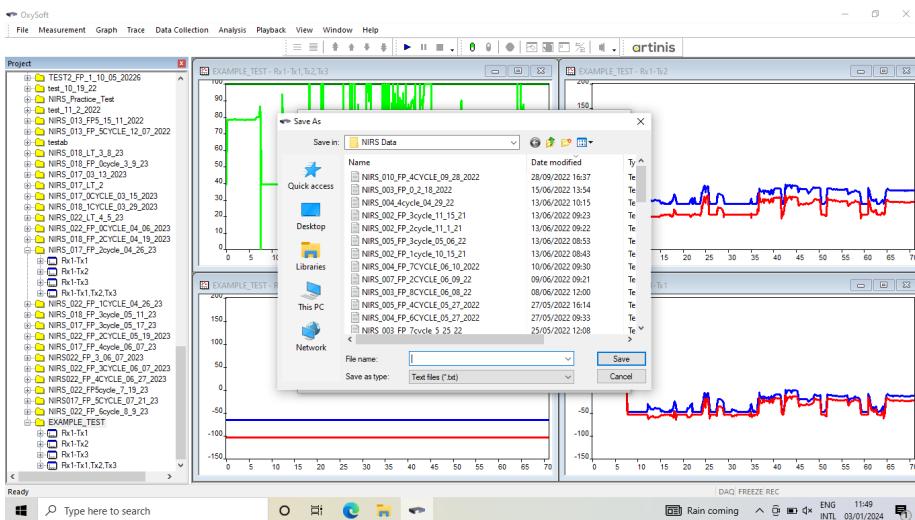


Click Next.

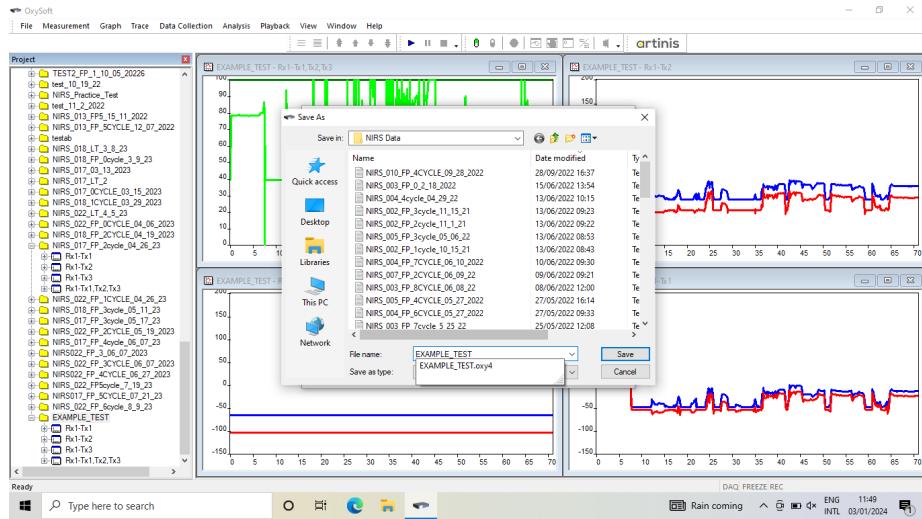
A new popup will prompt you to choose a location for the exported file.



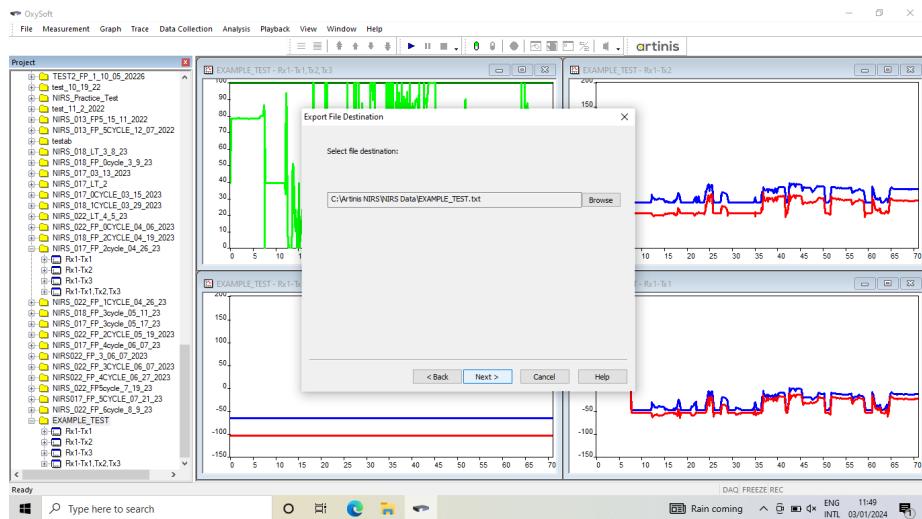
Click **Browse**.



There is a folder on the desktop for all data for the NIRS study. Select that folder as the destination. In the file name bar, type in the name of the measurement. I prefer for the exported file and the name of the measurement in Oxysoft to match for consistency. When you type in the name of the measurement in oxysoft, it will prompt you to select `nameofthefile.oxy4`. Do not select this. Just type the name of the measurement with no file extension.



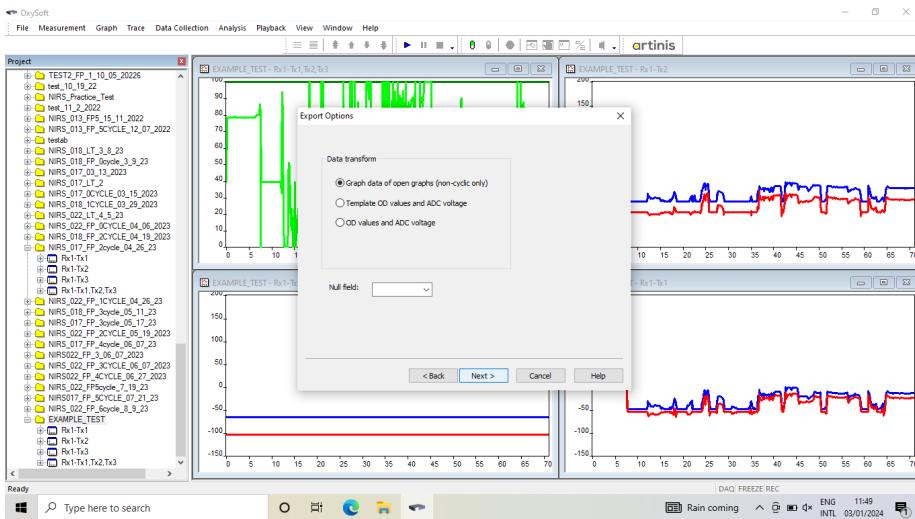
Click Save.



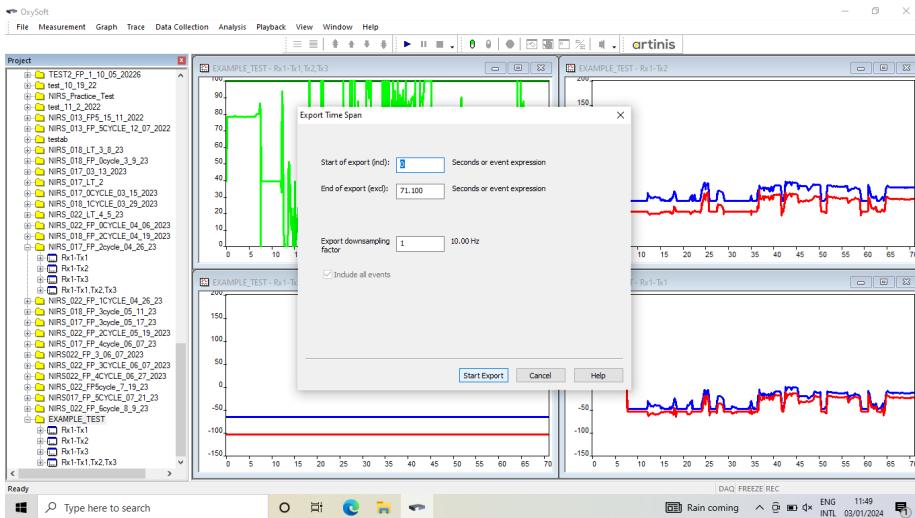
The file path should be to the NIRS data folder and should be named the same as the measurement with a .txt extension.

Click Next.

The Export Options popup will have several selections for the type of data to export. Leave the default selection, Graph data of open graphs. Click Next.



The **Export Time Span** pop up will have the option to remove data from the beginning or end of the measurement. Leave the time span as it is and export the full measurement. Click **Start Export**.



Appendix B

ParvoMedics TrueOne 2400

B.1 Specifications

The TrueOne Metabolic Cart by ParvoMedics measures maximal O₂ consumption, indirect calorimetry, and other metabolic conditions.

The computer that has the ParvoMedics software installed is not connected to the internet in any way. It has Windows 7. **Never connect this computer to the internet or update Windows.** This would require attaining approval to install the ParvoMedics software on PrismaHealth computers, which would take several months. The ParvoMedics software is not frequently updated and Windows updates could break the installation. Everything works as it is, and if it ain't broke, don't fix it.

B.2 Software

B.3 Before Data Collection

B.3.1 Calibration

In order to conduct calibration, the cart must have been powered on for *at least 30 minutes*. Turn on the cart by flipping the switch on the power strip on the back of the cart.

Log in using the password taped to the cart under the keyboard.

The computer on the cart is not connected to the internet. After logging in, you need to manually set the date and time to today's date and time. If you do not manually set the date and time, the data collection software will use the incorrect date and time and will save the data as such, which will make it difficult to locate later.

Open the ParvoMedics software.

Ensure the filter and other pieces are connected to the gas analyzer as shown below:

TODO add picture

B.3.1.1 Flowmeter Calibration

Select ‘Flowmeter Calibration’ from the software home page.

Enter room temperature (Celcius), barometric pressure (mmHg), and room humidity (%) from the Davis Vantage Vue on Sara Biddle’s desk.

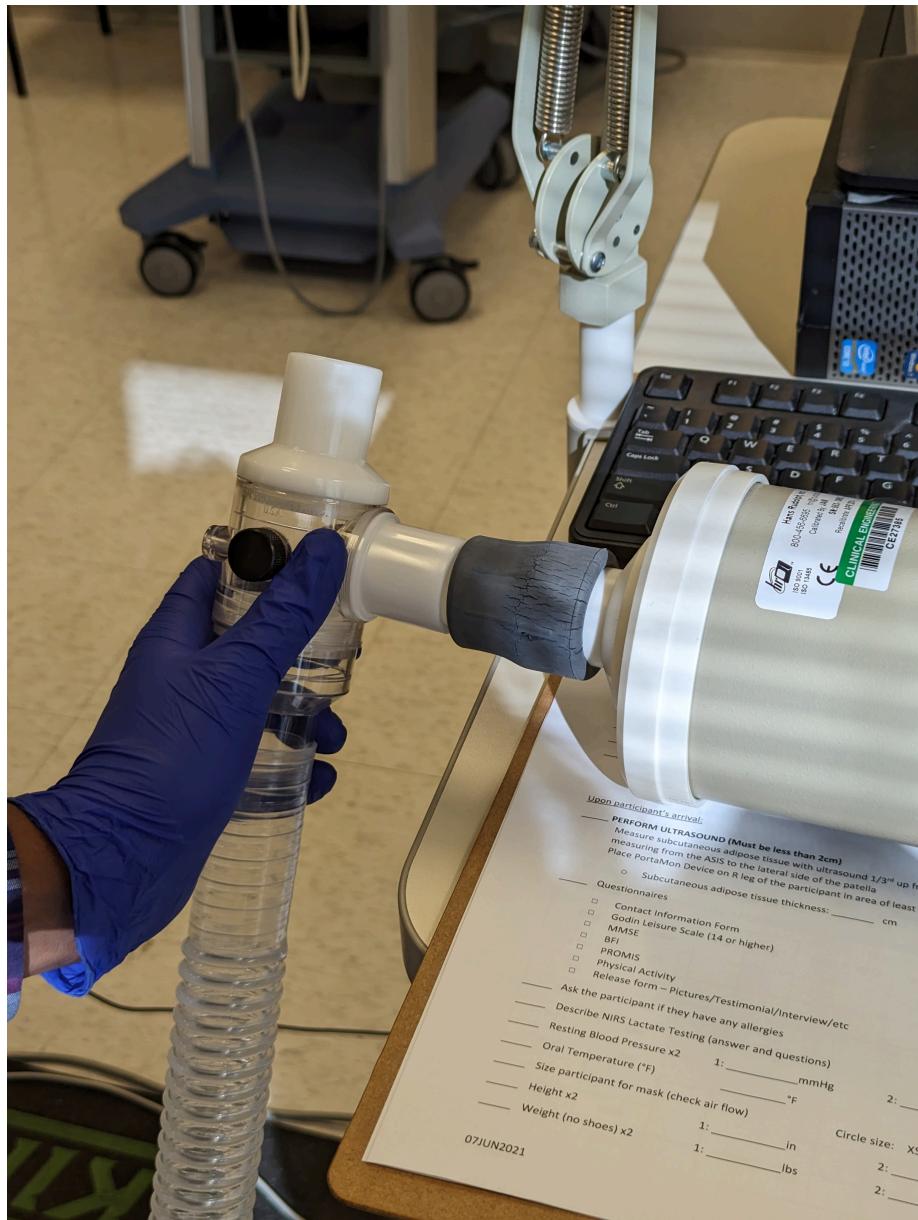
Get a piece of long clear tubing from Parvo equipment cabinet behind the door. The calibration syringe and connection piece are located in the third shelf on the Parvo cart.

Connect one end of the tubing to the clear end of the connection piece.



Connect the other end of the tubing into the gas analyzer module.

Connect the white end of the connection piece to the mouth of the calibration syringe.



Get Frankie Bennett to help with the actual flowmeter calibration.

B.3.1.2 Gas Calibration

Select 'Gas Calibration' from the software home screen.

Enter room temperature (Celcius), barometric pressure (mmHg), and room humidity (%) from the Davis Vantage Vue on Sara Biddle's desk.

Click ‘OK’.

When prompted, find the sample gas (gas container on the bottom left of the cart) and rotate the black handle on top of the gas container counter-clockwise until you cannot turn it anymore. Do not turn the black knob that is taped in place.



Click ‘OK’ and wait for the next prompt on the screen.

Rotate the black handle on top of the gas container clockwise as far as you can to the “OFF” position.



Click ‘OK’ to see calibration results.

DO NOT SAVE results if the percentage is greater than 1%. This means that this calibration differs from the last calibration by more than we want. If you save the results, since it is a percentage change from the last calibration, the

next calibration will have to decrease by greater than 1%.

Example: First calibration attempt results in a percentage of 1.5%. In order to be within 1% of the attempt prior to the first attempt, the second calibration attempt will need to result in a percentage of -0.5%.

To save us from doing this math in between calibration attempts, just do not save attempts greater than 1% difference.

If results are greater than 1%, try the following steps:

- open the lab door
- turn on the fans to blow air around the room
- wait at least 10 minutes and attempt calibration again

When the gas calibration results in less than 1% change from the previous calibration, save results and exit to the home screen.

If you have tried all of the steps above and the gas calibration still results in greater than 1% change from the previous calibration and you are out of time, save the gas calibration results. After the participant leaves, you can try to redo the gas calibration to get back under the 1% change from the previous calibration. There are several reasons that the calibration will still result in a difference greater than 1%, such as the weather, issues with the air conditioning, and more. The only things we can do to prevent issues with the calibration is limit the number of people in the lab. Have extra people stand out in the hallway or try to schedule fewer people to come in to the lab.

B.3.2 Mask Sizing

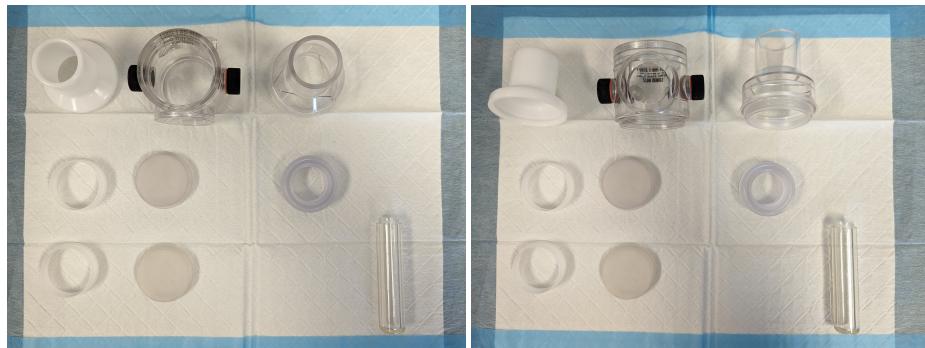
- Find the mask size guide in the caddy that sits on the wheeled cart that sits next to the ultrasound.
- Hold the mask size guide up to the face of the patient. Hold the top of the guide at the bridge of the nose.
- Look at the bottom of the guide and see where the chin sits. Choose the appropriate size. If the chin rests between two sizes, try the smaller size first.

B.3.3 Mask Assembly

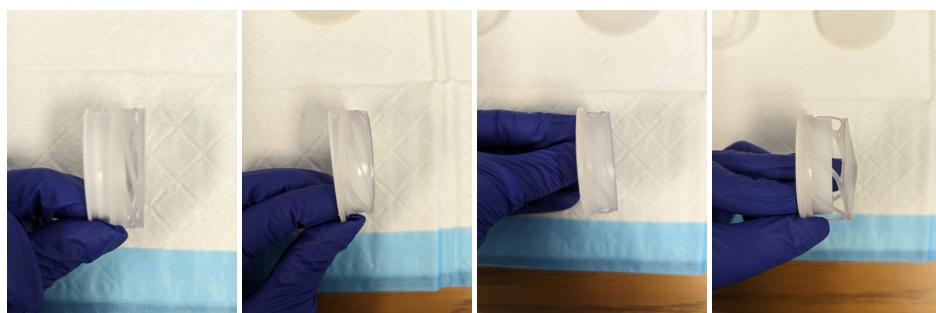
Pink buckets and mask parts are sterile and should NOT be touched without gloves. There are several boxes of latex gloves in different sizes in the lab. Pick whichever size fits you before touching ANY parts.

- Grab a pink bucket and ensure the following components are in the bucket:
 - Clear plastic with two black circles
 - Clear plastic with triangle
 - White plastic that narrows
 - Semi-transparent circle made of hard plastic

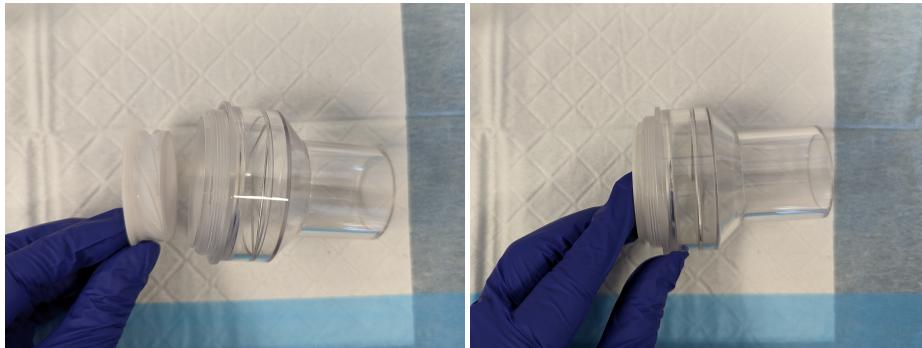
- Two hard plastic white circles
- Two silicone caps



- Take a silicone cap and place on a hard plastic white circle
 - The silicone cap and the hard plastic white circle should face the same direction (the outer rims should be on the same side)
 - Carefully pull the outer rim of the silicone cap over the lip of the hard white plastic circle. Be careful not to tear the silicone, handle these pieces very gently!
 - Rotate the hard white plastic circle to make sure that the outer rim of the silicone cap is pulled over the lip all the way around.
 - You should be able to gently push through the middle of the hard white plastic circle and stretch the top of the silicone cap out from the edge of the hard white plastic circle while the outer rim of the silicone cap stays in place over the lip of the hard white plastic circle.



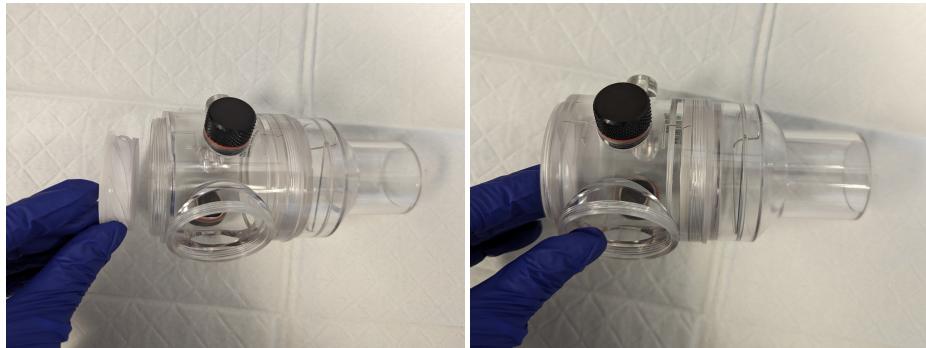
- Repeat with the other silicone cap and hard plastic white circle. There should be two pairs of silicone cap and hard plastic white circle.
- Take one of the pairs of silicone cap and hard plastic white circle and the clear tapered hard plastic piece.
- Place the silicone cap into the larger end of the clear tapered piece. The outer rim of the silicone cap should sit flush with the rim of the clear tapered piece. The silicone should face the inside of the clear tapered piece.



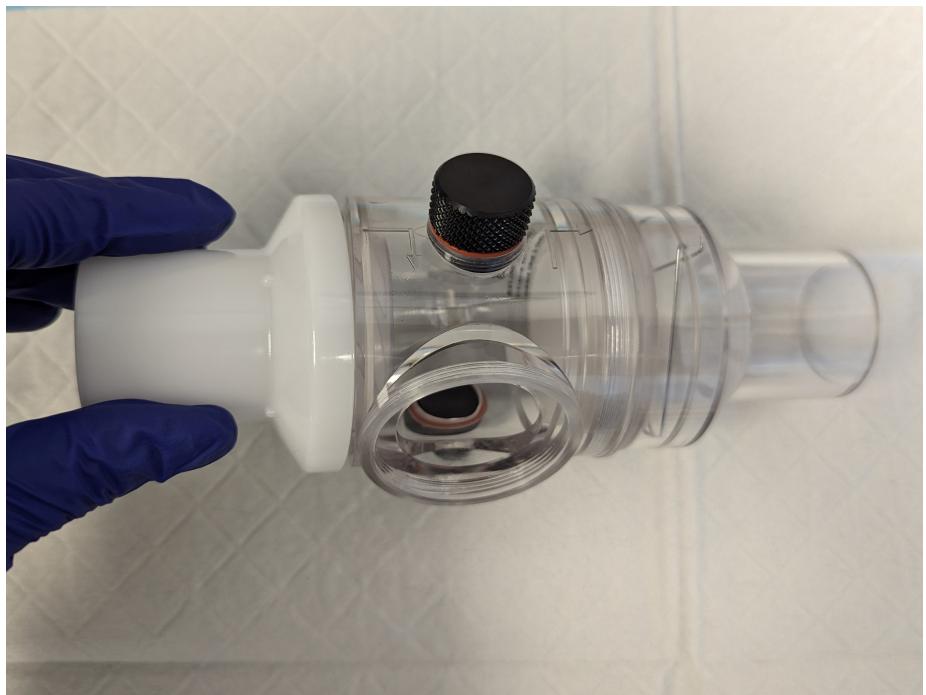
- Take the middle piece of the mask (the clear cylindrical piece with three openings and two black cylinders on it) and rotate it around until you can see the arrows etched into it.
 - The arrows etched into the piece show the direction of air flow through the pieces. The air comes “in” from one opening, into and out of the mask where someone is breathing in and out of one opening, and “out” of one opening into the tubing and finally into the gas analyzer. The silicone pieces allow air to flow in only one direction so that all air the person breathes out is sent into the gas analyzer.
- Find the arrow pointing “out” of the cylinder and rotate it so that the arrow pointing “out” points to your right.
- Take the clear tapered piece with the silicone vent inside it and screw it onto the opening facing the right



- Take the second silicone vent and place it in the left opening of the middle piece. This opening should be directly opposite the opening facing to the right of the middle piece, that now has the clear tapered piece screwed on.
- The silicone vent should have the outer rim flush with the outer rim of the opening, and the silicone should face into the middle piece.



- Take the white tapered plastic piece and screw on to the opening over the silicone vent.



- Take the semi-transparent hard plastic circle and screw onto the remaining opening of the middle piece.



- Select the blue rubber mask of the appropriate size.
 - The size is etched on the “chin” of the mask.
 - See B.3.2 for choosing the correct size.



- Orient the blue mask as if you were going to wear it on your face. The “nose” should be upward with the “chin” downward and the hard clear plastic pieces should face outward. You should only see blue rubber.
- Orient the assembled pieces so that the air flows in the appropriate direction.
 - The “out” arrow direction with the clear tapered end should point towards the station with the gas analyzer, i.e. if the gas analyzer will be on the left then the clear tapered end should point to the left, and if the gas analyzer will be on the right then the clear tapered end should point to the right. In the HPL, the stationary exercise bike will always have the gas analyzer on the left, therefore have the clear tapered end point to the left.

- The third opening with the semi-transparent circular piece should face the “mouth” of the blue rubber mask.



- Stretch the opening of the blue rubber mask over the semi-transparent circle opening of the assembled pieces.
 - This is difficult and you will have to manhandle the blue rubber mask a bit. It does not stretch super well.
 - Look through the mask and make sure that there is a good seal around the opening. If there is not a good seal, the blue rubber will not make a perfect circle around the opening.



B.3.4 Heart Rate Monitor

All men leave the room (except family the patient may or may not have brought with them to the lab). Spray water on the part of the monitor that will be in contact with the skin. Have the patient hold the center ‘button’ on the strap to their sternum. Clip the ends of the strap together. Tighten the strap to be snug around the patient’s chest. Push the strap up under the patient’s bra strap and make sure the monitor is in contact with the skin all the way across the chest.

Use the watch to check that the monitor is sending a good signal. Press the middle button to the left of the watch face and wait to see the watch display a heart rate. If the heart rate does not display or shows a number that seems off, try to adjust the monitor to get a better connection. Try to push the monitor up higher on the sternum. This can be difficult on some patients depending on breast tissue, so do your best. Check the signal again.

If the watch is having issues connecting with the heart rate monitor, you can check from the Parvo software. *add steps here*

B.4 Data Collection

Select ‘Metabolic Testing’.

Enter the following as BOTH the first and last name:

“NIRS_patientidnumber_protocoltypeprotocolnumber_protocoldate”

For example, patient ID 003 participating in the second on/off kinetics on 11/12/2023 would look like: “NIRS_003_FP2_11_15_2023”

Enter the participant’s height, weight, and age.

Select the testing protocol: NIRS Lactate Threshold or NIRS Full Protocol.

Enter appropriate testing wattage.

Click ‘OK’ and wait for the software to start the test.

When testing is complete, click ‘end test’.

Save results and print a copy of the report.

Check that the report will be printed with 10-second averages. Click ‘config’ in the bottom left and ensure that the data averaging selected is 10 seconds. Click ‘OK’ and print. The report will be printed on the printer on the bottom shelf of the cart.

B.5 After Data Collection

B.5.1 Data Export

The ParvoMedics software only exports metabolic cart data as Excel files. Select the data collection instance you wish to export and save it as an Excel file on the cart. Use a USB drive to transfer the Excel file from the Parvo cart to another computer. Since the Parvo cart is not connected to the internet and never gets Windows or any other software updates, the Excel format is a legacy format. You will have to manually open the Excel file and save it as a modern Excel format.

B.5.2 Cleaning Equipment

Put on a pair of gloves.

Everything that has touched the patient's skin will need to be cleaned. Place everything that needs to be cleaned into a pink bucket. This includes the mask, the mask straps, the clear tubing, the spit catcher, and the heart rate monitor strap.

Take apart the mask into its individual pieces. Take the button off the heart rate monitor strap and wipe the button down with an alcohol wipe.

On the blue cart in the corner behind the door, there is a white bucket with a lid. Take this cart with the pink bucket. When you walk through the hallways of the hospital, you can NOT wear gloves. Take off your gloves and put a clean pair in a pocket to bring with you just in case. Take the cart with the pink bucket of dirty equipment and walk to the service room. In the service room, take the pieces of the mask, disassembled, and the mask strap and the heart rate monitor strap and place them all in the blue liquid in the white bucket. Ensure the blue liquid covers all the pieces. Start a timer for 12 minutes. Leave everything soaking for 12 minutes. Make sure to put the lid on the bucket while it soaks, as the blue liquid is light sensitive.

While everything is soaking, pump soap and water into the clear tubing. Swish the soapy water around the tubing, making sure to get every part of the tubing. Do this over the sink or you will spill water out of the ends of the tubing. Rinse the tubing out and get out all of the soapy water. Use soap and water to clean out the bottom of the pink bucket. It had dirty equipment in it and it needs to be cleaned before you put clean equipment back in it.

At the end of the 12 minutes, pull all the parts out of the blue liquid and rinse them off in the sink. Put them in the pink bucket. Close the bucket of blue liquid. Walk the blue cart back to the lab. Take all the equipment and set it out to dry behind the door.

Appendix C

Surveys

C.1 Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) is a 9 item survey designed to assess fatigue severity in cancer patients [Mendoza et al., 1999]. Each item is measured on a 0-10 numeric scale. The final score is the mean of the 9 measure items and can range from 0-10. A score can be calculated if at least 5 items out of 9 are answered by taking the mean of the completed items.

C.2 Godin Leisure-Time Exercise Questionnaire

Godin and Shephard made the **Leisure Time Exercise Questionnaire** (LTEQ) in 1985 [Godin and Shepherd, 1985]. The LTEQ was originally a two item survey: “Item 1 consists of 3 parts, in which participants note how often per week they do strenuous, moderate, and mild exercise. Item 2 asks participants to note how often they engage in an activity long enough to work up a sweat.” This was used to group people into several different categories of activity levels.

In 2011, Godin published the **Godin-Shephard Leisure Time Physical Activity Questionnaire** (GLTPAQ) [Godin, 2011]. This removed the second item and was used to group respondents into 2 categories, “insufficiently active” and “active” based on the ACSM guidelines for weekly moderate and strenuous physical activity levels.

The form that we use says **Godin-Leisure Time Exercise Questionnaire** across the top of the form, by the Oncology Nursing Society. At the bottom left, it says ‘adapted from: Godin, G. (2011). The Godin-Shephard leisure-time physical activity questionnaire. Health & Fitness Journal of Canada, 4(1), 18-22.’ I don’t know why that’s the title they chose to put on the top of the form,

it's made things more confusing than it needs to be. I have so far been unable to find the original paper that uses this form.

C.3 Mini-Mental State Examination

The Mini-Mental State Examination is a cognitive screening tool. We use it to screen for cognitive impairment before patients can participate in this study. Patients must score greater than 27 to continue with the study.

C.4 Physical Activity History

The Physical Activity History is intended to capture the physical activity history of the respondent using the FITVVP principles.

There are two physical activity history forms: Intake and Follow Up.

The Physical Activity History: Intake form asks the patient to describe their normal physical activities. It consists of 5 items. Item 1 asks if the respondent participates in moderate to vigorous physical activity. If the respondent answers yes, there are spaces to describe the physical activity below. Item 2 asks the respondent if this describes their physical activity from the past 5 years. If not, the respondent can describe how their physical activity habits have changed over the past 5 years. Item 3 asks if the respondent participates in interval training. If the respondent answers yes, there are spaces to describe the training. Items 4 and 5 ask about participation in recreational sports and whether the respondent has had any injuries that would contradict participation in exercise.

The Physical Activity History: FollowUp asks the respondent to describe their physical activities since the last time they answered the Physical Activity History survey. This form does not ask about physical history prior to the most recent visit visit.

C.5 PROMIS Global Health v1.1

We use the PROMIS Global Health v1.1 form. This is a discontinued PROMIS measure. Follow the scoring guidelines to convert the v1.1 questions and answers into v1.2. The scoring guidelines have been uploaded into the RedCap file repository and the RedCap instrument follows those guidelines.

Appendix D

Instruments

D.1 Ultrasound

D.1.1 Usage

Turn on the ultrasound by pressing the power button in the top left of the keyboard.

Locate the vastus lateralis. Find the ASIS (anterior superior iliac spine) by asking the participant to place their hands on their hips and feeling for the bony protrusion at the front of the hip. Measure from the top of the kneecap to the ASIS. Locate the vastus lateralis by moving superior to the kneecap one-third of the distance from the kneecap to the ASIS.

Use the ultrasound gel to cover the wand.

Place the wand over the pre-determined location of the vastus lateralis. Move around the wand until you find the location of the thinnest section of adipose tissue. Ensure that this is still over the vastus lateralis by marking the location with a marker, then removing the wand and asking the patient to extend their leg and flex their quadriceps muscles. If the dot is not on top of the vastus lateralis when the patient extends their leg, try again. If the dot is over the vastus lateralis, place the wand back over the dot.

Freeze the screen.

Press the ‘caliper’ button to use calipers on the frozen screen.

Move one end of the caliper to the top of the screen. Move the other end of the caliper to the area of the screen that looks like the boundary between the muscle belly and the edge of the adipose tissue. This will be a silvery line across the screen. Try to make the caliper measurement as vertical as possible, as a diagonal measurement will be larger than a straight one.

Record the measurement given by the caliper.

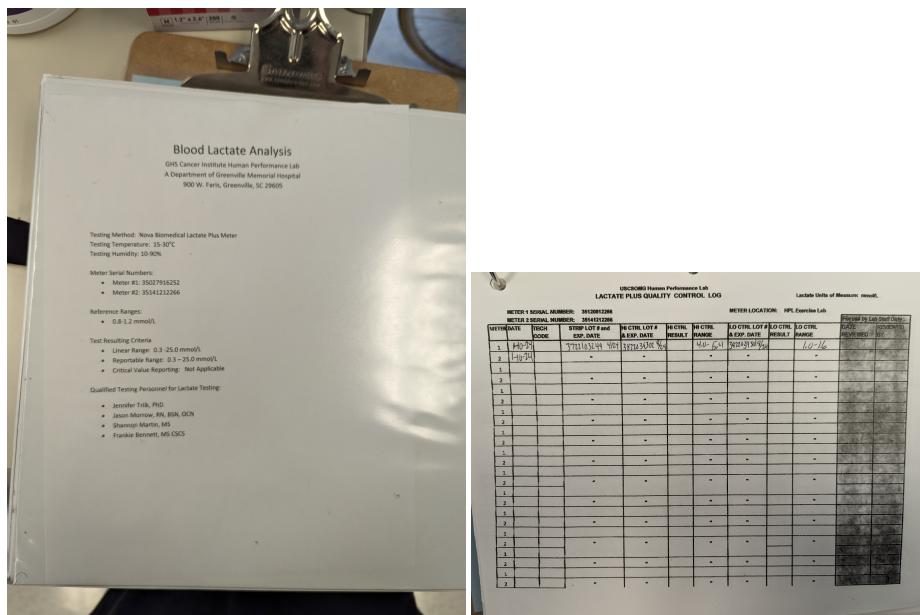
D.2 Lactate Meter

D.2.1 Usage

D.2.1.1 Quality Control Testing

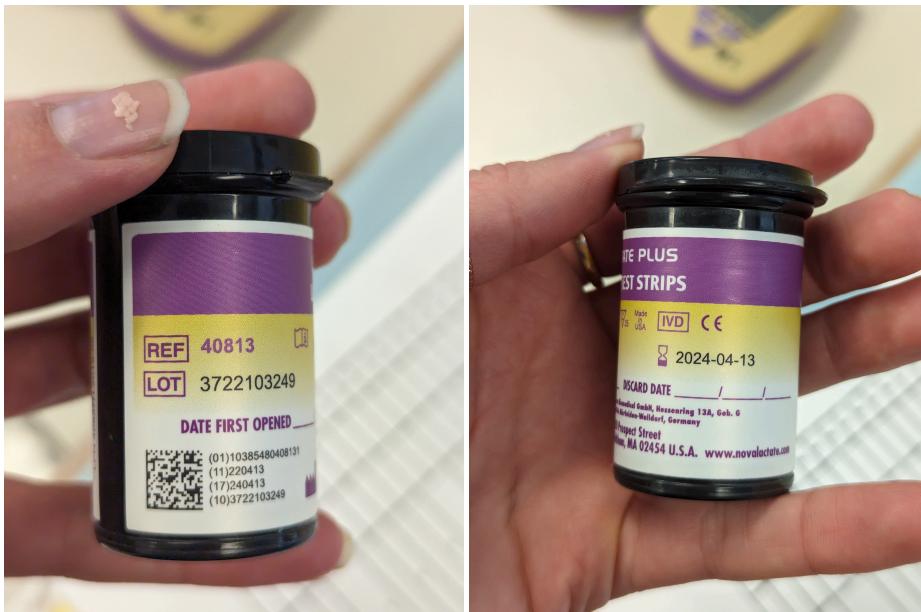
Before using the lactate meters, you must conduct a quality control test.

Get out the ‘Blood Lactate Meter’ binder from Frankie Bennet’s desk. Open the binder to the quality control log.

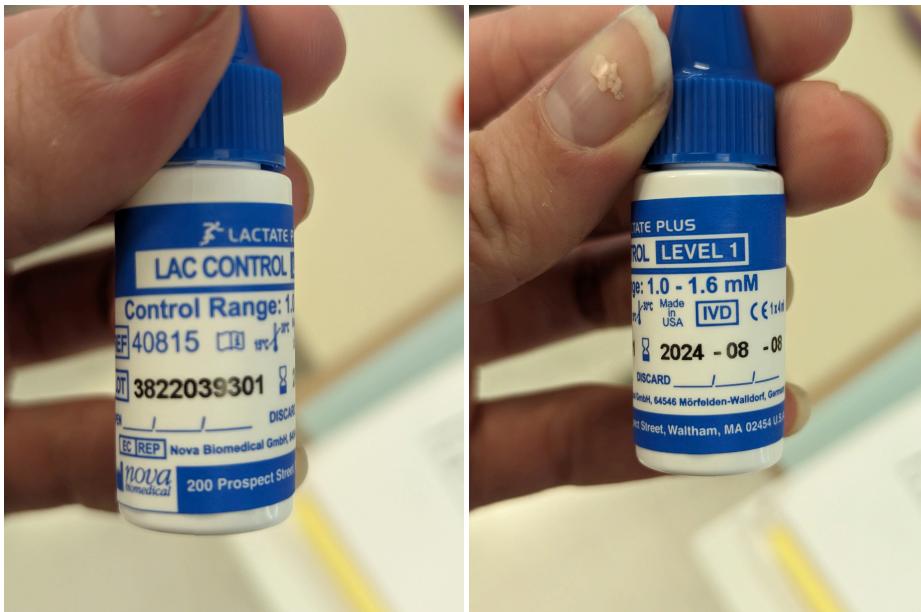


Record the date.

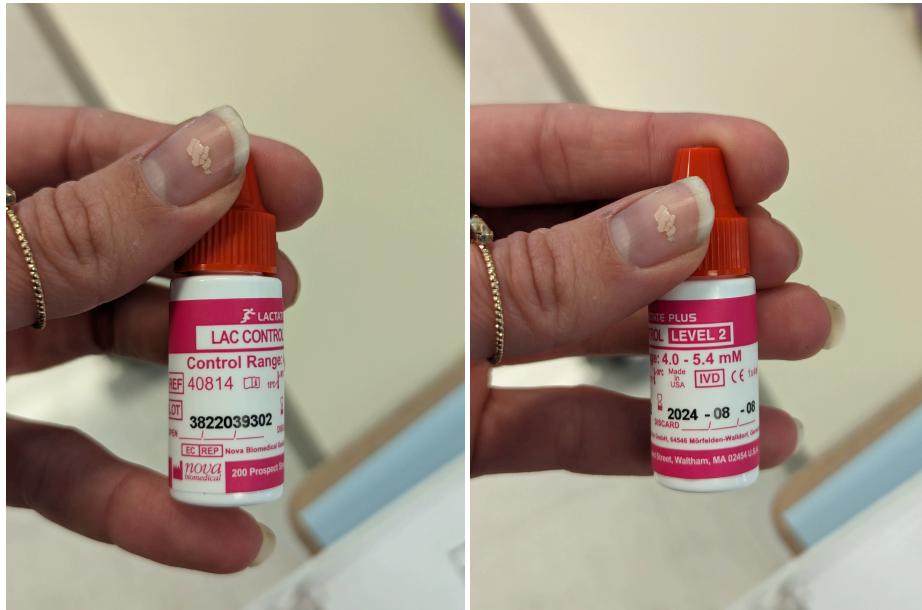
Look on the bottle of lactate strips and find the lot number. Record the lot number in the appropriate space.



Look on the low control bottle (blue dropper). Record the expected range for this bottle. Record the lot number and expiration date.



Look on the high control bottle (red dropper). Record the expected range for this bottle. Record the lot number and expiration date.



Turn on the lactate meter by pressing the center triangle-shaped button. Use the button to click through the screens until you reach the control screen, which has a star in the upper left corner and says 'CRL-1'.

Put a lactate strip in the lactate meter. The white end should stick out from the meter and the metal end should go in the meter.



Use the red control dropper to place a drop on the lactate strip. Wait for the lactate meter to give results (about 15 seconds). Record the results in the binder. Discard the used lactate strip in the trash and do another test with the red control with a new lactate strip.

If you get an error, you probably did not use enough liquid. Make sure the drops are of a size to completely soak the tip of the lactate strip.

Repeat with the blue control dropper.



Make sure results are recorded correctly in the log.

USC SOMG Human Performance Lab LACTATE PLUS QUALITY CONTROL LOG										Lactate Units of Measure: mmol/L		
METER	DATE	TECH CODE	STRIP LOT # and EXP. DATE	HI CTRL LOT # & EXP. DATE	HI CTRL RESULT	HI CTRL RANGE	LO CTRL LOT # & EXP. DATE	LO CTRL RESULT	LO CTRL RANGE	REVIEWED by Lab Staff	DATE REVIEWED	REV'D BY
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Appendix E

Exercise Testing

There are two types of exercise tests.

The lactate threshold test is conducted to determine what power output (wattage) is associated with a rise in lactate production. For the general population, lactate threshold is considered to be 4.0 mMol/L.

The On/Off Kinetics test is conducted to measure the patient's mitochondrial oxidative capacity. The transition from work to rest allows the NIRS device to capture the magnitude and rate of oxygen recovery after exercise. The power output of the exercise is 110% of the power output at lactate threshold. We use this power output in order to ensure that the exercise is difficult enough to produce a change in oxygen levels during exercise. ## Administering Exercise Testing {#AdministerExerciseTest}

We split up the work of administering the exercise test into three jobs:

- **RPE**

- For lactate threshold testing, the person doing RPE is the person taking the lactate measurements.
- For On/Off Kinetics testing, the person in charge of RPE tends to be the person who is in contact with the patient the most.
- With thirty seconds left in every stage of testing (both lactate threshold testing and on/off kinetics testing), they will hold up the clipboard with the RPE scale and say the following: “*What is the first number that comes to mind?*”. **Say those exact words.** The patient will then say or point to the number that corresponds to how they are feeling.
- This person is also in charge of watching the patient on the bike and checking in to see how they feel. If the exercise becomes too difficult or the patient does not feel well, they are in charge of communicating with the rest of the team to end the test early and get the patient off

the bike.

- **NIRS**

- Watch the NIRS computer as it is collecting data. Take note of any times when the signal from the NIRS is corrupted or when the patient is moving around during a rest. Record the time on the NIRS computer and note what was going on, i.e. if the DAQ for Tx3 was red or if the patient was moving.
- During the on/off kinetics test, this person also helps the patient put their foot on the box. The NIRS device is always placed on the right leg, so the left leg of the patient goes on the box. The left leg needs to go on the box during a rest section to help the patient stay perfectly still. If both feet are left in the stirrups of the bike, the patient will tend to rock their feet back and forth to stay balanced on the bike. This causes movement in the NIRS data that we do not want. We choose to put the left leg on the box rather than the right leg because if the right leg is placed on the box like that, then the patient will be tensing their right quadriceps muscles. This would mean that we are not getting a true rest measurement of the vastus lateralis. Therefore, we put the left foot on a box and allow the right leg to dangle at complete rest in the stirrups of the bike. With fifteen seconds left in a work section before a rest, kneel down by the box and get ready. The Parvo person will give you a countdown to the end of the stage and when it hits 0 and the patient stops pedaling, pull their left foot out of the stirrup and place their heel on the box. Remind the patient to stay completely still. During a rest period, they are more likely to want to talk to fill the silence and if you make them laugh too hard, the NIRS data will be effected. Try to keep them still and focused on the resting. This is especially true for the last rest section, as they are done with the exercise which is the “hard part”.

- **PARVO**

- Check during the initial rest on the bike that the Parvo is collecting valid data. At rest, VO₂ should be between 3-5. If VO₂ is lower than 3, check that the mask is forming a good seal around the patient’s face. If the seal is good and the VO₂ is still below 3, ask the patient to sit up straight and take normal breaths. Some people hunch over on the bike which decreases the volume of air that they breath in and out. Some people hold their breath a little bit when you put the mask on because it can feel a little claustrophobic. Remind them that the mask is not limiting their breathing, it is just measuring what they are breathing. Tell them that the system we use is the same one they use at NASA and the Olympic Training Centers. This tends to help people feel better.
- The Parvo shows the RPM of the bike. If the RPM drops below 60, encourage the patient to get the RPM back up above 60. If the RPM are higher than 110, remind the patient that they do not need to

work that hard and try to drop the RPM below 90.

- For each stage, record the VO₂, Heart Rate (bpm), and RPE. For a lactate threshold test, record the lactate measurements when the person taking the lactates yells them out. The VO₂ and Heart Rate will be on the Parvo screen. There is a real time heart rate number and a fifteen second average number. The real time number is smaller and will be blinking in time with the heart rate. The fifteen second average number will be in one of the blue boxes in the top left. The fifteen second average numbers refresh every fifteen seconds. If the stage is three minutes long, you will wait until two minutes and forty five seconds of the stage have passed and the final refresh has happened for that stage to record the VO₂ and heart rate.
- For each stage, tell the patient when a stage is starting, when they are halfway done with the stage, when there is 30 seconds left in a stage, and give a countdown to the next stage. This would result in the following statements during one stage: “The stage has begun. You are halfway done with this stage. Thirty seconds left in this stage. Ten. Nine. Eight. Seven. Six. Five. Four. Three. Two. One.” If this is a lactate threshold test, you can make a comment about how this next stage should be slightly more difficult or how they should feel a change in the wattage. If this is an on/off kinetics test, they can tell the patient what the next stage will be, i.e. work or rest. During a work stage, this could sound something like: “Two minutes of exercise starting now. You’re halfway to a rest. Thirty seconds left until rest.” All of these statements also help the other staff to do their jobs. The thirty second mark tells the RPE person to get an RPE measurement and the countdown allows the NIRS person to get ready to do the box. There are two places to look for the time on the Parvo. There is a total elapsed time and there is a time left in this stage. The time left in the stage is the easiest to look at for keeping track of timing.

E.1 Lactate Threshold Exercise Test

E.1.1 Specifications

The lactate threshold test is completed on a cycle ergometer.

Ventilatory measurements are collected breath by breath via metabolic cart. Lactate is measured via finger prick.

Prior to beginning exercise testing, measure resting blood lactate. This should be less than 2.0 mmol/L in order to begin testing. Normal resting blood lactate lies between 0.8-1.2 mmol/L, however stress or nervousness prior to an exercise test can increase resting blood lactate levels. If lactate levels are slightly elevated but still lower than 2.0 mmol/L, then lactate may drop back down as the body

uses lactate during warm up stages.

The exercise test is conducted as follows:

Begin with a two minute rest. The subject sits on the stationary bike without pedaling for two minutes. Each subsequent stage is three minutes in duration. The wattage increases by a consistent amount between each stage. During the last 30 seconds of each stage, blood lactate is measured via finger prick. Each lactate measurement is taken in pairs for duplicability.

Lactate will increase as exercise difficulty increases. When the subject's blood lactate exceeds 4.0 mmol/L, have the subject finish the next stage and then end the test. If the subject feels they cannot complete the next stage, end the test immediately. A blood lactate of 4.0 mmol/L should roughly correspond to a moderately difficult exercise intensity but should not be a maximal effort.

E.1.2 Selecting Wattage Jumps

Discuss the subject's physical activity levels. If the subject doesn't participate in much cardiorespiratory fitness activities, then start at a very low wattage (10 Watts) and make modest jumps (15 Watts). If the subject participates in long distance running, cycling, or swimming, then the subject may start at a higher wattage than less fit subjects and/or make larger jumps.

When selecting wattage jumps, remember that lactate should increase exponentially as wattage increases linearly. Also, when conducting testing, there is no second chance to get the testing correct. It is better to use a very low starting wattage with modest increases as the initial settings, because if the subject is fitter than expected and their blood lactate levels remain stagnant, the wattage jumps can be increased during testing. Blood lactate will not go down in the time it takes to conduct the testing, and if the difficulty increases too quickly then the blood lactate levels will increase so quickly that it will be difficult to analyze the lactate curve.

E.2 On/Off Kinetics Exercise Test

E.2.1 Specifications

The on/off kinetics test is completed on a cycle ergometer.

Ventilatory measurements are collected breath by breath via metabolic cart (ParvoMedics OneTrue 2400, B). Muscle oxygenation measurements are collected via SR-NIRS (Artinis Medical Systems PortaMon, A)

The exercise test consists of three square-wave transitions from exercise at 110% of wattage at lactate threshold to rest. Each stage of the test is two minutes long.

Time	Intensity
0-2	Baseline Rest
2-4	Warm Up (0 Watts)
4-6	Exercise Transition
6-8	Rest 1
8-10	Exercise Transition
10-12	Rest 2
12-14	Exercise Transition
14-16	Rest 3

Appendix F

RedCap

F.1 Access

Frankie Bennett, Sara Biddle, Jennifer Trilk and Randolph Hutchison have full access to the RedCap. They can edit the RedCap structure, view and download data with identifying information, access and edit the calendar, etc.

Medical students and Furman students have limited access to the RedCap. They can enter data using instruments but cannot use the data import tool. They can view and download de-identified data sets. They can access and edit the calendar.

Frankie Bennett or Sara Biddle must give RedCap access to new users. Students should be given access using their Prisma Health username, which is generally their initials, the last 2 digits of the year they got the credentials, and a letter. For example, Sara Biddle's is `sgb21f`.

F.2 Structure

F.2.1 Surveys

One instrument is enabled as a survey: `New Patient`. The research coordinators Katie Banenas and Sydney Hackwell, along with the Research Nurse Navigators have the link to this survey. When they consent a patient, they can fill out the survey with the required information. After they have saved the survey or submitted it, Frankie Bennett and Sara Biddle will automatically receive an email that the survey has been filled out. Whoever filled out the survey will see an exit page that says "Thank you for your response. This patient is ID#NNN" with the record ID assigned to this patient in RedCap.

The survey has links to the recruitment videos, a downloadable PDF of the

pamphlet, and downloadable PDFs of the English and Spanish consent forms.

The research coordinators can upload scans of signed consents and medical clearance notes. Mostly they choose to bring the signed consent to the HPL in person.

F.2.2 Project Bookmarks

In the left panel under the header Project Bookmarks, there are links to several web pages.

On-Off Kinetics Analysis App takes you to the Shiny application to conduct monoexponential regression of On/Off kinetics NIRS datasets.

Recruitment Video takes you to the recruitment video.

Study Information takes you here, to this web page.

F.2.3 Record Status Dashboard

The Record Status Dashboard is the widest view of current data collection on the study.

The **Default** view shows all patients who have signed a consent form for the study.

The **Enrolled Patients** view shows all patients who participated in at least one On/Off Kinetics visit.

F.2.4 Calendar

We use the RedCap calendar to track upcoming patient appointments.

Appointment information must be manually taken from EPIC and put in the calendar. The RedCap calendar can only take a date and start time. It cannot create a block of time, for example an hour long appointment. Any duration information must be put in the event notes.

Medical students have access to the calendar to schedule appointments for the patients they are in contact with. When they have scheduled the appointment after communicating with the patient regarding time and date preferences, they can add new events to the calendar.

F.2.4.1 New Calendar Events

At the top of the square for the correct date, click the **+New** button. This will open a new window, with the header **Add New Calendar Event**.

In the **Time** input, select the time. Use 24 hour format or the sliders that pop up when you click into the input box. If you are unsure of a time or the event is an all day event, do not put a time. If the date is scheduled but a time is

not yet scheduled, type ‘Time TBD’ in the notes. This helps with remembering which events are yet to be completely scheduled.

In the notes box, give the event a name. The first word or two will be visible on a Month view of the calendar. If the event is specific to a participant, do not put the participant ID number in the notes. Use the drop down below to associate the event with a Record ID.

If this event is specific to a participant, use the drop down by **Record ID** to select the appropriate record ID for the participant. If not, do not select a record ID.

When event information is completely filled in, click **Add Event to Calendar** at the bottom of the window.

Check that the event is in the calendar with the correct date, time, and ID number.

F.2.4.2 Infusions

When a patient begins their treatment, put all tentative Day 1 of cycle dates into the calendar. Events can be deleted later if they are rescheduled. You do not need to put events in the calendar for other days of the cycle, since that would load the calendar with events that are not necessary for our scheduling purposes.

Label the event as follows: **Infusion Cycle N Day 1**.

Depending on the cycle length (two weeks, three weeks, one month), put one final event in the calendar that is the appropriate length after Day 1 of the final cycle. In the notes for this event, type something like “Post Final Cycle. Schedule last on/off kinetics around this date.” This will help us remember to schedule the final visits for patients.

F.2.5 File Repository

The RedCap File Respository can be found in the left panel in the **Applications** section.

RedCap has no size limit on the amount of data that can be stored in the File Repository, unlike Google or Microsoft.

Updated survey and data collection sheets are in the folder **Surveys and Data Collection Sheets**.

In the **Onboarding** folder, there are copies of forms that new medical and undergraduate students must fill out to get IRB approval.

In the **IRB** folder, there are copies of all forms that must be approved through IRB. This includes the consent form (English and Spanish versions), IRB protocol, and brochure.

The **OXYSOFT** folder contains all NIRS data files. The folder has two subdirectories. In the **Oxy4 Files** subdirectory, all raw .oxy4 files are uploaded. In the **Exported Text Files** subdirectory are all files exported from Oxysoft. The files are named according to the following conventions: For Lactate Threshold tests, **NIRS_idnumber_LT_MM_DD_YYYY**, with idnumber being a 3 digit number corresponding to the Record ID in RedCap with leading zeroes to fill extra digit space, “LT” for Lactate Threshold, and the date in “MM_DD_YYYY” format.

For On/Off Kinetics tests, **NIRS_idnumber_FP_MM_DD_YYYY_CYCLEN**, with idnumber being a 3 digit number corresponding to the Record ID in RedCap with leading zeroes to fill extra digit space, “FP” for On/Off Kinetics (which were originally called Full Protocol tests), the date in “MM_DD_YYYY” format, and “N” being the current infusion cycle. The On/Off Kinetics test that takes place before the first infusion is named “CYCLE0”, the On/Off Kinetics test that takes place before the second infusion and after the first infusion is named “CYCLE1”, and so on.

The **PARVO** folder contains all VO2 data files.

Appendix G

Electronic Medical Record

G.1 Access

Prisma Health uses EPIC as their electronic medical record service. You can only access EPIC with permission from Prisma Health. The medical students may technically have access to EPIC but they have not had much training on how to use it and actually accessing it can be cumbersome and difficult for them. It is much easier for a Research Coordinator to do any work in EPIC.

Use the Production Environment of EPIC, if possible. In the Production Environment, you can create and run reports that you cannot in the Read Only Environment.

Log in with your Prisma Health log in information and select the department CANCER-FARIS ONCOLOGY [100224000].

G.2 Views and Customization

G.3 Research Study

The study code is 1853511 and the ID is PHU ITOR: NIRS. Dr. Larry Gluck is the principal investigator. Sara Biddle, Katie Bananas, Sydney Hackwell, Frankie Bennet, and Jim Rosenmeyer have research coordinator access to the study information.

Email Jan Keuber to give someone access to the Research Study Build. Send her their Prisma Health username, full name, and reason you want to give them access.

The research study build allows you to associate patients with the research study with different statuses.

G.3.1 Study Statuses

Dr. Martin has indicated that study statuses will be changing in the future to streamline the number of possible statuses. There are more possible statuses in Epic than will be discussed below, as not all statuses are applicable to this study. Follow up with Dr. Martin as needed about future changes to available study statuses.

There are three groups of study statuses.

1. Pre-Consent: *Identified, Interested, Waiting for Consent*
2. Active: *Consented- In Screening, Active, Follow Up*
3. Inactive: *Ineligible, Declined, Completed, Disqualified, Withdrawn*

When the association is one of the *Active* statuses, a yellow **Research Participant** tag is displayed with the patient's information. This lets other physicians see that the patient is participating in a research study.

Use the study statuses as follows:

Ineligible: Patient with breast or primary gynecological cancer who does not meet one or more of the eligibility criteria based on a chart screen. Do not use this status for all patients who are not ineligible, such as a patient with lung cancer, as that would create unnecessary associations that will slow down any reporting. Use when patient will likely have more appointments in the department to prevent double screening in the future. Identified: Patient may be eligible and will need to be followed up with. Use the comments section to make notes about when to follow up, such as upcoming appointments. Patients who have not been assigned a treatment plan are frequently assigned this status to monitor their chart for further appointments and treatment planning. Interested: Patient was approached about the study and has not given a definitive answer about participation, neither to decline or sign a consent form. Declined: Patient was approached about the study and declined to sign a consent form. Withdrawn: Patient signed a consent form and subsequently decided to stop participation in the study. Active: Patient is receiving active treatment and will be coming in to the HPL for visits.

For further information about Research Studies in Epic, log in to the Epic UserWeb go to the Training Home. Look for the 2023 training companion to **RSH100 Research Fundamentals**.

G.3.2 Creating a New Association

1. Open the patient's chart in a chart review.
2. Open the **Research Studies** tab in the top.
3. There should be a box with **Add study** and a plus sign in the top left. Click into it or on the plus sign.
4. Research studies you have access to will pop up. Click the appropriate study row.

5. Status is required to save the association. Choose the appropriate status as defined in G.3.1.

G.4 Oncology Schedule {#EPIC-Oncology Schedule}

In the top left of the screen, there is a tab for the schedule. The icon is a calendar.

Open the schedule.

Under **My Schedule**, you can create schedules that are applicable to you. Depending on what department you are logged in under, you will see the schedule for that department underneath the **My Schedule** tab.

Appendix H

IRB

H.1 IRBNet

Prisma Health uses IRBNet to manage the IRB status of research projects.

Students who wish to participate in this research study must have an IRBNet account. In their IRBNet profile, they must have a certificate of the CITI Training for **Biomedical/Clinical Course GCP Social and Behavior Research Best Practices for Clinical Research** and an Investigator Assurance Form uploaded.

For new students to be able to interact with patients and administer testing, we have to submit an IRB amendment with their names in it. We cannot submit an IRB amendment until they have an IRBNet account with those files uploaded and submitted. Without the IRB amendment, students can only shadow or observe. An amendment can take a few days to be approved so all of the following steps must be completed as soon as possible.

H.1.1 Create an IRBNet Account

1. Go to <https://www.irbnet.org>.
2. Click **New User Registration** in the top right corner under the Log In.
3. Fill out your first and last name and choose a username and password.
 - Always use your proper name with standard capitalization.
 - Passwords must be at least 8 characters.
 - 4. Accept the terms and conditions.
4. Search for your organization.
 - Medical students search for the University of South Carolina.
 - Furman students search for Furman University.
5. Select your organization and click **Continue**.

6. Input your contact information using the email associated with your organization.
7. Click **Register** to continue.
 - If you mistyped your email, click the **edit** button next to the email field
8. Click **Continue**. An activation email will be sent to you.
9. Open the email from IRBNet and click on the activation link.

H.1.1.1 CITI Training

Some students may have already completed the necessary CITI training. If that is the case, ensure you have the certificate for the completed courses and skip the next steps.

1. Log into the CITI website at <https://www.citiprogram.org> – sign in using a USER ID and password (one you already have or if needed – created one).
2. Affiliate yourself with your organization – medical students will choose the University of South Carolina and Furman students will choose Furman University. You will answer a few questions. (Question 1; (A) 2; (Not at this time); 3; (No) 4; (GCP – Social and Behavioral Research Best Practices for Clinical Research); 5;(Not Require) 6;(Not at this time) 7;(Not at this time) 8; (Select None) After answering these questions, you will arrive at a screen where you will choose which module to take, and you will choose the Biomedical/Clinical Course or GCP Social and Behavior Research Best Practices for Clinical Research. What will happen next is that any courses you previously have taken, through CITI, should populate if they are the same as what we require. Any courses that need to be completed will show up as a live link. You will only need to take those courses and not retake what you have already done.

H.1.1.2 Upload files into IRBNet

1. Log into IRBNet.
2. Under **Manage your User Profile**, under **Training & Credentials**, click **Add New Record**.
3. In the **Document Type** field, select **My CITI Training**.
4. Under **Effective Date**, put the date on the certificate.
5. In the **File:** field, click **Browse** and select the file for your CITI Training certificate.
6. Click **Attach**.
7. Under **Manage your User Profile**, under **Training & Credentials**, click **Add New Record**.
8. In the **Document Type** field, select “.
9. Under **Effective Date**, put the date you signed the Investigator Assurance Form.

10. In the **File** field, click **Browse** and select the file for your *signed* investigator assueance form.
11. Click **Attach**.
12. Both files should be listed under **Training & Credentials**.
13. Under **Training & Credentials** click **submit**.
14. When it prompts you to select a committee to submit to, select **Prisma IRB Subcommittee C**.

H.2 Protocol

H.2.1 Participants

Participants recruited for this study will be breast cancer or gynecological cancer patients (N=40) who agree to participate in an exercise study examining the effects of chemotherapy on muscle mitochondrial oxidative capacity, a measure of skeletal muscle health. A written informed consent will be obtained from the participants before data collection. This study has been submitted for review by the Institutional Review Board at the Prisma Office of Research Compliance and Administration (ORCA). We pledge to abide by all applicable institutional and governmental regulations regarding the ethical use of human volunteers for the duration of this research.

This study focuses on breast cancer or gynecological cancer patients who will undergo a standard of care chemotherapy treatment as directed by their oncologist. Other eligibility requirements for this study are as follows:

- Patients diagnosed with breast cancer or gynecological cancer without distance metastasis
- Ages > 20 years old
- Able to perform exercise on a stationary cycle ergometer at moderate intensities for a maximum of 15 minutes
- Hemoglobin values greater than 10 at baseline
- ALT and AST values less than 2.5X the upper limit of normal by institutional standards
- Godin-Shepard Leisuretime Physical Activity Questionnaire (GLTEQ) score of 14 or greater will be included. A score of less than 14 is considered insufficiency active/sedentary.

The exclusion criteria include patients with:

- Clinically advanced cardiovascular disease
- Clinically advanced pulmonary disease
- Disease requiring continuous oxygen supplementation
- Greater than 2 centimeters or more of subcutaneous adipose tissue on the anterior thigh
- Inability to walk or stand
- Movement disorders

- Spinal cord injuries
- Autoimmune disorders
- Pregnant or breastfeeding
- Mini-Mental State Examination (MMSE)

Participants for this study will be recruited through informative pamphlets at the Center for Integrative Oncology Survivorship, Prisma Health System's Cancer Institute at Greenville Memorial Hospital and affiliated physician offices.

H.2.2 Experimental Design

We will use an observational, 2-way, treatment x time, within-subjects research design to compare skeletal muscle oxidative capacity of the vastus lateralis muscle, during stationary cycling, across breast cancer or gynecological cancer patients at baseline and across their chemotherapy regimen. Muscle mitochondrial oxidative capacity of the Vastus Lateralis muscle will be non-invasively evaluated using continuous wave, Near Infrared Resonance Spectroscopy (NIRS, PortaMon by Artinis Medical Systems BV in The Netherlands).

H.2.3 Study protocol

The NIRS participant testing will be performed in the University of South Carolina School of Medicine Greenville's Human Performance Laboratory located within Cancer Institute Faris Road facility. Testing will take approximately 30 minutes per session, with a maximum of 180 minutes of participation per patient. The independent variables in this study are drug regimen and number of chemotherapy treatments. The dependent variables in this study will be the change in oxygenation and deoxygenation status of the vastus lateralis as measured by the NIRS device, indicative of mitochondrial oxidative capacity, after a bout of cycling. Patients will be asked to avoid exercise and use of certain substances (tobacco, alcohol, caffeine, and contraindicated medications) 24 hours prior to testing.

The NIRS device consists of three LED transmitters that transmit light waves into muscle tissue and one high sensitivity PIN diode receiver, equipped with ambient light protection, which assesses light received from the transmitters. The three transmitters each emit light at two wavelengths. These wavelengths correspond to the absorption wavelengths of oxyhemoglobin (O_2Hb) and deoxyhemoglobin in the skeletal muscle tissue (approximately 760 nm and 850 nm). These wavelengths of light will be received from three separate transmitter distances (30mm, 35mm, and 40mm) at 10 Hz. The ΔO_2Hb and Δ tissue saturation index (TSI%) will be calculated as the change from the last 30-s average of the work interval to the last 30-s average of the recovery interval. Oxygen uptake (VO_2) will be obtained by using open-circuit spirometry (Parvo Medics, Inc, Salt Lake City, Utah). Cycling power will be determined via lactate threshold curves generated for each participant. Participants will be asked to perform exercise in shorts or equivalent. Participants will first sit at rest in a chair, as

the NIRS device is applied to the vastus lateralis. The device will have double sided adhesive tape to lightly secure its position to the skin. The device will be wrapped in a black cloth to fully secure its position, limit device mobility, and block ambient light in the laboratory. Participants will then stand and walk to the cycle with the NIRS secured to the participant's leg. Participants will sit on the bike for a 2-minute rest while wearing a fitted mask that comfortably measures the participant's rate and amount of oxygen uptake (VO₂) and other ventilatory measurements at rest and during exercise.

H.2.3.1 Visit 1

Researchers will determine the participant's lactate threshold curve and ventilatory threshold during a graded exercise test (Table 1). The lactate threshold is a measure of the rate at which capillary blood lactate measurements rise as an effect of increased exercise intensity. The blood lactate curve will be used to determine an individualized power wattage for subsequent exercise testing of "on-off kinetics" (see below description). Capillary blood lactate levels will be obtained by finger stick for point of care testing. Ventilatory threshold will be measured using indirect calorimetry via a metabolic cart that captures expired gasses (O₂ and CO₂) through a comfortable silicone mask worn by the participant.

A baseline blood lactate level will be obtained at rest, then the participant will be instructed to cycle for three minutes beginning at 10W. After the 3-minute stage is complete, the power output will increase by 15 watts. The participant will cycle for 3 minutes at each stage until their lactate threshold reaches 4.0 mmol/L. Once the blood lactate reaches 4.0 mmol/L, one final, three-minute stage will be performed. A final lactate reading will be obtained at the completion of this exercise stage. The power output that is equivalent to 1.1x the wattage at which their lactate threshold exceeded 4.0 mmol/L will be used as the exercise intensity ("on-kinetics") for subsequent visits accompanying chemotherapy treatments.

H.2.3.2 Subsequent Visits

Participants will return for each subsequent visit within a week before their next chemotherapy infusion as long as they are able to safely continue the exercise protocol (Table 2). The NIRS device will be secured to the participant's leg similar to the first visit and the participants will put on the mask to measure ventilation. Participants will begin pedaling for a warmup at 0 watts for 2 minutes. After the two-minute warm up period is completed, the power output will increase to the previously calculated wattage of 1.1x LT. The participant will cycle at a self-selected cadence at this power wattage for a duration of 2 minutes ("on-kinetics"). At the end of each on-kinetics stage, participants will be asked to rate their level of effort during exercise, Rate of Perceived Exertion (RPE). The participant will then stop pedaling and will remain in recovery, sitting on the bike for 2 minutes ("off-kinetics" stage). With 5 seconds

remaining in the “off-kinetics” stage, the participant will start pedaling at the same self-selected cadence for their next “on-kinetics” stage, followed by another 2-min “off-kinetics” period. This cycle of exercise followed by rest, known as on-off kinetics, will repeat for a total maximum of 3 times, or until the participant reaches volitional fatigue.

H.2.3.3 Collection of Surveys and Biometrics at Each Visit

We will be administering MoCA, BFI, Physical Activity Intake, PROMIS Global Health, and GLTPAQ surveys prior to participant engagement in cycling exercises. We will also be administering BFI, PROMIS Global Health, and Physical Activity Follow-up surveys after each individual study session to assess changes in cancer related fatigue associated with chemotherapy treatment that may develop throughout the study time period.

Patients will undergo routine, standard of care blood draws for a CBC and metabolic testing per their managing physician with an additional tube, during the same venipuncture, for a study covered aliquot for biomarkers related to mitochondrial health for correlative research.

For biomarker analysis, exosomes from patient serum (approximately 250 uL samples) will be isolated using an ExoQuick ULTRA EV Isolation System (System Biosciences). Exosomes will then be detected with Western blotting with exosome specific antibodies. Exosome samples will be sent for RNASeq analysis of RNA within the isolated exosomes at System Biosciences. Bioinformatics analysis of the RNAs identified from the RNASeq will then be used to determine if there are specific RNAs present in patient blood associated with changes in mitochondrial function. In addition, selected mRNAs associated with mitochondrial function will be assessed (expression levels determined) with RT-qPCR using aliquots of the isolated serum exosomes.

H.2.4 Statistical Analyses

ANOVA one way with tukey post-hoc analysis to detect differences between drug regimen groups at each time point (baseline, all subsequent chemotherapy treatments) for time constant response and change in mitochondrial function for mitochondrial oxidative capacity. One-way ANOVAs will be used to additionally detect differences between different timepoints from baseline to final chemotherapy treatment for each individual chemotherapy regimen.

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T. R. Mendoza, X. S. Wang, C. S. Cleland, M. Morrissey, B. A. Johnson, J. K. Wendt, and S. L. Huber. The rapid assessment of fatigue severity in cancer patients: use of the brief fatigue inventory. *Cancer*, 85(5):1186–1196, 1999. doi: 10.1002/(sici)1097-0142(19990301)85:5<1186::aid-cncr24>3.0.co;2-n.

Internal reliability of the BFI when measuring a single dimension- the severity of fatigue. Sample included 305 inpatient and outpatient adults with cancer and a comparison sample of 290 community-dwelling adults. Fatigue severity can be categorized as either 'severe' or 'non-severe' with a BFI score greater than or equal to 7 indicating severe fatigue and a BFI score less than 7 indicating non-severe fatigue levels.