OHSU SIREN NETWORK NEWS

Issue: July/August 2021

CALENDAR

7/28 12-1:30pm ET Steering Committee Meeting – Zoom Link

8/3 1-2pm ET Study Coordinator Meeting – Web Link

8/12 3-4pm ET Finance Committee Call – Web Link

8/25 12-1:30pm ET Steering Committee Meeting – Zoom Link

9/7 1-2pm ET Study Coordinator Meeting – Web Link

Journal club will resume in September

Contact us: Jenny Cook, Coordinator, 503.494.1230
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OHSU SIREN Website
Twitter: @OHSU_CPREM

Newsletter at a Glance

OHSU NETWORK SIREN RENEWAL GRANT

Team – We are still awaiting the funding announcement with the details needed for the renewal application. Once that announcement is issued, **we would like to schedule a call with all sites. We anticipate this will take place in early August, and we ask that each site have at least 1 team member from your SIREN leadership group present on the call.**

We are excited that all of our network partners are willing to resubmit with our hub application (barring any unforeseen barriers). Again, thank you for your partnership and strength. We continue to be the top performing network and have proven that our envisioned model from 2016 is not only viable, but highly successful. This is all thanks to the amazing teams you each have on site, and your willingness to be part of a unique collaborative of talented EM research units from across the country over the last 4 years.

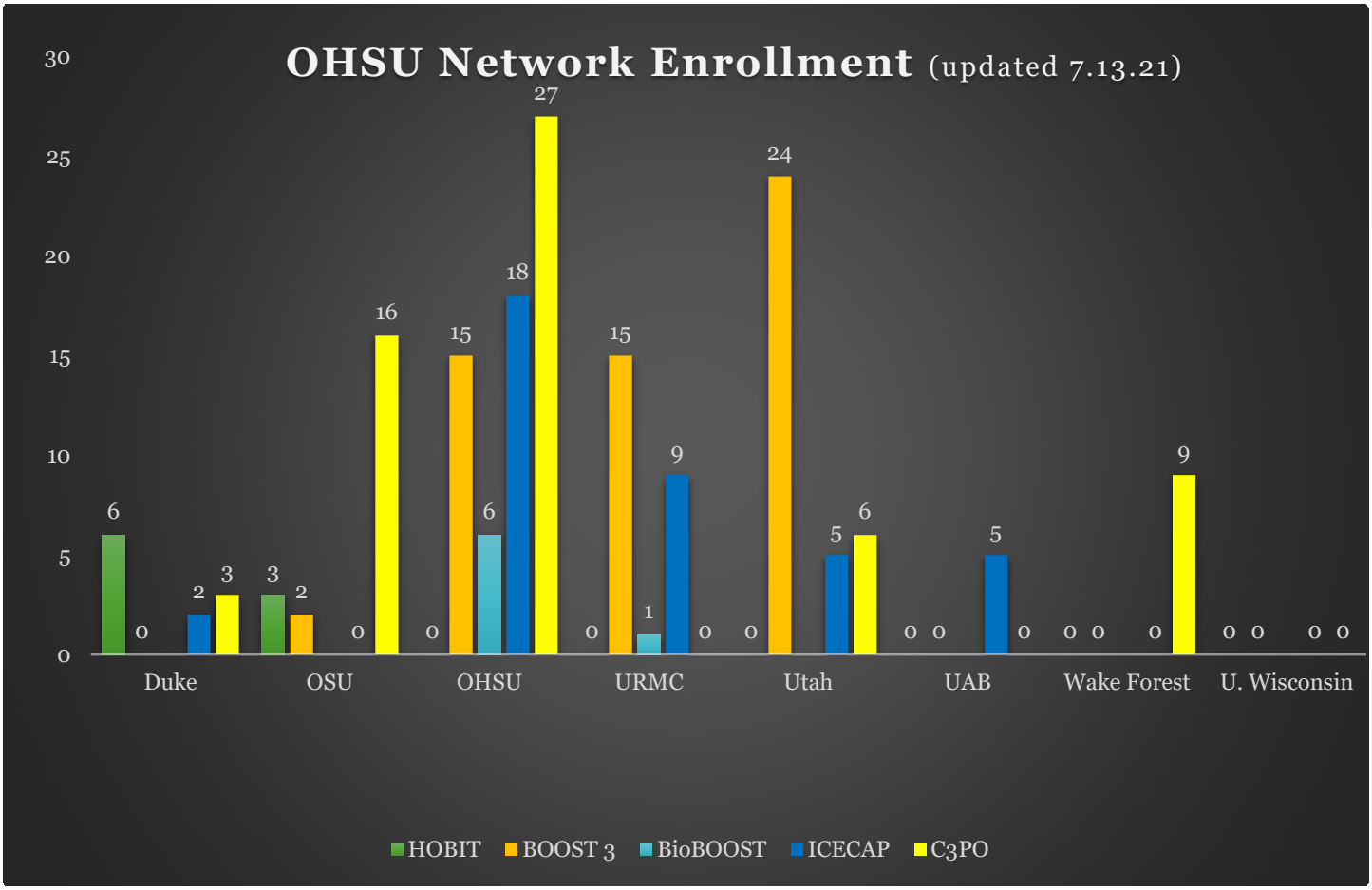
We expect to have 2 months to turn around this application, so our timeline will be tight for collecting all the necessary pieces. As the award hub, we are creating templates and draft documents that we can quickly update once we have the details requested in the FOA. We will send out the 'spoke packet' to you ASAP so that you can have the maximum amount of time to gather your site's information.

As we prepare for renewal, there are a few things your teams can do:

1. Keep your CRF's current – direct data entry into WebDCU is best practice when practical. We realized that sometimes it's just simpler to write it down on paper and then transpose work into the electronic database, but until the data is in WebDCU, it's invisible to the study.
2. Keep your regulatory documents current. There are a number of missing or expired regulatory documents in the system right now. Please submit as many of these as soon as possible.

3. Know where to find your hospital statistics. It is likely we will ask for ED volume #'s, a breakdown of case types (for example TBI's/year). We will send you a list of requested statistics soon after the FOA is released, so knowing where to look or who to ask will help get these turned around quickly.

Our goal is for all sites to have WebDCU as current as possible by 8/1. We anticipate pulling statistics in early August, but will give you 1 weeks' notice to wrap up any pending data/documents prior to our pull.



NETWORK NEWS & UPDATES

- Congrats to Utah, the #1 enrolling site nationwide in BOOST3!
- Collectively, we have enrolled 41 more subjects than any other SIREN network Hub. Kudos to all!

ICECAP NEWS & UPDATES

- Enrollment: 241 (Goal: 1800)
- **OHSU Network Enrollment: 39**
- New cooling duration arms opened in June. Here are a few reminders and notes from trial PI Dr. Meurer: *"As you all know from the protocol and training, after 200 participants the study algorithm may or may not start to open additional shorter, longer, or intervening durations of cooling. We have now passed this point, so you may see allocation to other durations. We are all blinded to which durations are currently being assigned and in what ratios, and these will change about every 50 enrollments. Sites should not try to infer anything from the small portion of assignments that they randomly see. Sites should remember that for all durations of cooling of 24 hours or greater, rewarming still occurs over 24 hours. For durations of cooling 18 hours or less, rewarming occurs over the same number of hours as the duration of cooling. Refer to the protocol for any further detail"*

- TTM2 Trial – below is the information each ICECAP site should have received from the ICECAP trial PI's with talking points on the TTM2 trial results. Please review (page 5), and if you did not receive these, please let Jenny know!

BOOST 3 NEWS & UPDATES

- BOOST 3 enrollments: 196 (Target enrollment 1094)
- **OHSU Network Enrollment: 56**
- Bio-BOOST enrollments: 9; **OHSU Network: 7. Impressive!**
- Electro-BOOST intent to collaborate agreements were sent out. If your site is intending to pariticpate and did not receive an e-mail, please let us know.

HOBIT NEWS & UPDATES

- Enrollment: 61 (Goal:200)
- **OHSU Network enrollment: 9**
- New head CT scan uploading feature is coming to WebDCU – watch your e-mail for updates soon!

C3PO NEWS & UPDATES

- Primary paper has been submitted to NEJM and reviewed. Revisions have been resubmitted and a decision on acceptance is expected soon.
- Have an idea for a secondary research paper? Submit your C3PO ideas here: Please note that additional data related to inflammatory markers as well as other tests will be available soon. https://siren.network/clinical-trials/c3po/research_ideas
- **Not funded:** Unfortunately, we received word in June, **R2D2** was not funded, so at this time we do not expect to be contacting C3PO subjects about PASC in COVID-19. Special thanks to Bory Kea from our team for leading the R2D2 effort.

SPOTLIGHT ON FORMS

Each month Dr. Silbergleit has been doing a mini training on a CRF. We are working with the DCC to see if these mini tutorials can be posted to the study websites for reference as questions come up on how to fill out these forms. Stay tuned!

NIH SYMPOSIUM ON BIOETHICS AND BIOMEDICAL RESEARCH

On July 20, 2021 (next Tuesday) from 1:00-4:00 PM ET, the NIH Office of Science Policy (OSP) will convene a symposium entitled "A Match Made in Science: Integrating Bioethics and Biomedical Research" to highlight the integral role that bioethics plays in advancing science and to discuss strategies for fostering collaboration between bioethicists and biomedical researchers.

Dr. Collins will provide introductory remarks and the two panels will focus on 1) concrete examples of how successful integration of bioethics into biomedical research can strengthen study designs, mitigate future hurdles, and inspire future research inquiries, and 2) best practices and potential challenges in establishing successful collaborations, including identifying mechanisms for partnership and strategies for aligning incentives. Click the link above for more information!

A LITTLE LIGHT READING FOR SUMMER

Did you miss June's Journal Club? Check out some great articles that were discussed.

https://pubmed.ncbi.nlm.nih.gov/25979922/

https://pubmed.ncbi.nlm.nih.gov/32222766/

https://pubmed.ncbi.nlm.nih.gov/32702084/

https://pubmed.ncbi.nlm.nih.gov/33111140/

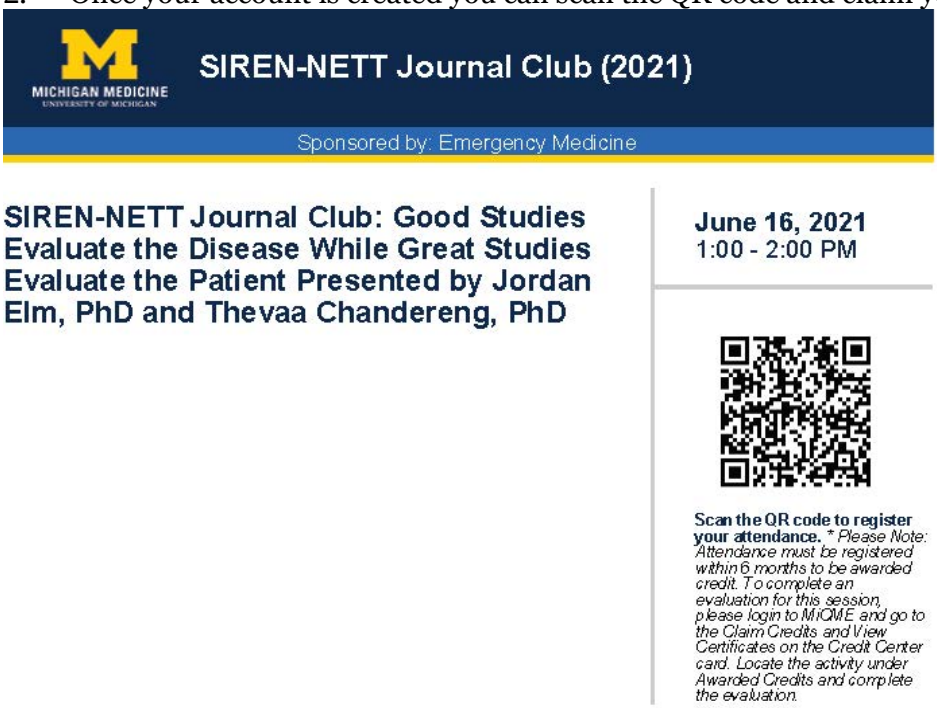
There was also a special Journal Club in July – missed it? Catch the recording here:
https://siren.network/node/3031

If you attended June's Journal Club and would like CME Credit, please find the instructions below for internal UM participants and external UM participants.

In order to claim CME credit you need an MiCME account. If you have an account you can scan the attached QR code with your smart phone and claim your attendance. Let me know if you have issues with this and I can add your attendance manually.

If you don't have an account please follow the instructions below to create one. Once you have an account you can claim your attendance for this journal club and future ones.
Create an MiCME Account:

1. Click here to create an account.
2. Once your account is created you can scan the QR code and claim your attendance.



Certificates and transcripts can be viewed in your MiCME Account.

GLOSSARY OF FREQUENTLY USED ABBREVIATIONS

CCC = Central Coordinating Center (i.e. University of Michigan)
EFIC= Exception from informed consent
CC = Community Consultation
PD = Public Disclosure

cIRB = Central IRB (in this case Advarra)

TTM2 TRIAL TALKING POINTS

Dear ICECAP Investigator,
We wanted to let you know that the results of the TTM2 trial (Hypothermia versus Normothermia after Out-of-hospital Cardiac Arrest) are expected to be published in the next few days. We wanted to remind you that we considered the possible impact of TTM2 while designing ICECAP, and that we discussed it in our grant application and during the investigator kick off meeting. Peer review agreed with our assessment that ICECAP is the most important next step in this field regardless of what TTM2 shows. We just wanted to take a moment to remind you why.

- ***What are the differences between the TTM2 and ICECAP trials?***
- TTM2 compared a proactive strategy of TTM with cooling to 33°C for 28 hours plus 12 hours of rewarming, to a reactive strategy in which TTM is initiated the first time the patient's temperature goes over 37.8°C and then is left on for 49 hours. Investigators randomized within 3 hours of ROSC, did not cool until after randomization, and did not control time to target temperature. TTM2 compared two target temperatures, but for a fixed duration. TTM2 is a large trial, but like the original TTM trial, enrolled a selected subset of patients whose OHCA was presumed cardiac in origin with mostly shockable initial rhythms.
- ICECAP, by comparison, enrolls patients cooled to a fixed target of 33°C and compares many durations of cooling using a duration-response methodology. ICECAP seeks to answer both the questions of whether hypothermia can be protective, and what duration is most likely to be optimal in a broader population of survivors. ICECAP has much tighter control on time to target temperature. Patients enrolled in ICECAP are cooled more quickly and rewarmed more slowly.
- TTM2 and ICECAP both compare different aspects of "dose" of TTM, understanding that "dose" is a function of both depth of cooling and duration. TTM2 only compares two doses (insufficient to understand the dose-response relationship) and these may be relatively close to one another. Whereas ICECAP looks at a much wider range (up to 12 fold difference) in dose, in enough gradations to understand the shape of the curve. As such, TTM2 and ICECAP ask, and will answer, very different questions.
- ***What are the possible outcomes of TTM2? Why will the ICECAP trial remain important?***
- TTM2 may show that the outcomes after a reactive TTM strategy look the same, better, or worse than after a proactive cooling strategy. The continued importance of ICECAP in each of these, as provided here, has already been shared with both the FDA and the DSMB. Given the results of the original TTM trial, the first seems mostly likely. Similar looking outcomes would statistically mean only that neither group is better by the proposed 20% margin, but may get misinterpreted as showing equivalence, which the study is not designed to determine. It would certainly indicate that cooling was not as effective as previously hoped. Clinically, however, similar results would provide no reason for health care providers to choose one strategy over the other, especially since neither strategy is clearly easier, safer, or cheaper. Others will be concerned that cooling in TTM2 was too slow, or rewarming too fast, and that many patient types were not represented. Finding little difference in clinical outcomes would leave the community confused and divided. If this is what TTM2 observes, the demonstration of either a flat or positive duration response curve in ICECAP will provide a more convincing and clinically informative direction for care decisions. Alternatively, if TTM2 observes better outcomes with proactive cooling than with reactive TTM, there will still be a need for ICECAP so that we can learn whether such outcomes could be further improved by identifying optimal durations of cooling. Finally, TTM2 might observe significantly better outcomes with a reactive TTM strategy than with a proactive cooling strategy. This would seem the least likely, and the hardest to understand, given the results of the original TTM trial, the weight of other trial and observational data, and the lack of a biological understanding for how cooling might cause harm. Again, critics would express concern that TTM2 represented insufficient duration of cooling, too rapid rewarming or too slow cooling. Certainly, if the reactive TTM arm looks superior in TTM2, ICECAP would be very much needed to confirm or refute these unexpected observations. Without confirmation, such findings would again be more likely to divide the community, rather than provide clear guidance. We have great respect for our colleagues who undertook the TTM2 trial and for their work. While we are all eager to see the results of the TTM2 trial, and what may be learned from their data, we are confident that their findings, whatever they show, will

provide a richer context for why ICECAP is such an important opportunity to further understand the use of TTM in post-cardiac arrest management. We are grateful for your participation in the ICECAP trial. We believe that our collective efforts will yield results that will advance the care of cardiac arrest survivors.

Sincerely,

Will Meurer
Romer Geocadin
Sharon Yeatts
Ramesh Ramakrishnan
Robert Silbergleit