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TITLE: Cooling to Help Injured Lungs (CHILL) Phase 2B Randomized Control Trial of Therapeutic Hypothermia in Patients with ARDS

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CONTRACTING ORGANIZATION: University of Maryland, Baltimore, MD

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14. ABSTRACT

The objective of this project is to conduct a 14-site Phase IIb randomized controlled clinical trial to address the following specific aims: (1) analyze the potential lung protective effect of 48h treatment with mild therapeutic hypothermia (TH; core temperature 34°-35°C for 48h) and neuromuscular blockade (NMB) in 340 patients with ARDS and P/F ≤ 200 compared with controls receiving standard temperature management; (2) evaluate the effects of TH and NMB on systemic inflammation and extrapulmonary organ dysfunction; (3) analyze safety of TH and NMB in patients with ARDS. In the past year we opened 14 clinical and replaced two of these sites for poor performance. We screened 2325 patients and enrolled 38. We took multiple measures to improve enrollment, including replacing two poorly performing sites and evaluating additional sites for replacement, having multiple group and one-on-one meetings with personnel from lagging sites, made multiple changes in the study protocol to facilitate enrollment, added affiliated hospitals and additional units to existing sites, provided screening tools to facilitate screening and enrollment, and given invited talks at clinical sites to increase the profile of the CHILL trial.

15. SUBJECT TERMS
ARDS, hypothermia, neuromuscular blockade

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1. INTRODUCTION:

The objective of this project is to conduct a 14-site Phase IIb randomized controlled clinical trial to address the following specific aims: (1) analyze the potential lung protective effect of 48h treatment with mild therapeutic hypothermia (TH; core temperature 34°-35°C for 48h) and neuromuscular blockade (NMB) in 340 patients with ARDS and P/F < 200 compared with controls receiving standard temperature management; (2) evaluate the effects of TH and NMB on systemic inflammation and extrapulmonary organ dysfunction; (3) analyze safety of TH and NMB in patients with ARDS.

2. KEYWORDS:

ARDS, hypothermia, neuromuscular blockade, lung injury

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Complete pre-enrollment regulatory tasks (months 0-5): Completed.
2. Preparation for Data Management/Randomization, Clinical Monitoring, and Medical Monitoring (months 1-4): Completed.
3. Preparation of clinical sites for enrollment (months 1-8): Completed
4. Enrollment:
- **a. 25% of planned enrollment (month 15)**: As of the time of this report, we are at 11.2% of planned enrollment. We have taken multiple steps to increase enrollment including replacing two poorly performing sites and evaluating additional sites for replacement, having multiple group and one-on-one meetings with personnel from lagging sites, made multiple changes in the study protocol to facilitate enrollment, added affiliated hospitals and additional units to existing sites, provided screening tools to facilitate screening and enrollment, and given invited talks at clinical sites to increase the profile of the CHILL trial.
- **b. 50% of planned enrollment (month 24)**
- **c. 75% of planned enrollment (month 33)**
- **d. 100% of planned enrollment (month 42)**

5. Post-enrollment data analysis and publications (month 48)

What was accomplished under these goals?

Pre-enrollment tasks were completed and enrollment started over a 6 month period between July, 2021 and December, 2021. Two sites were replaced for poor performance in early 2022. Protocol changes were made to meet enrollment challenges. Affiliated hospitals were added to four of our sites to further address slow enrollment. Specific accomplishments for the past year include:
1. Initiated and continued weekly meetings of the CHILL Executive committee to weekly.
2. Initiated and continued monthly Steering Committee meetings (with site PI's).
3. Initiated and continued monthly Coordinator meetings.
4. Initiated and continued weekly meetings with CSPCC (Perry Point) data management and randomization service about data management.
5. Completed multiple updates of the study protocol (v. 1.73) and manual of operations (v. 1.45).
6. Developed tools for sites (placed on website) to facilitate screening and enrollment.
7. All sites approved by Advarra central IRB and DoD HRPO.
8. Continuing Review for CHILL master protocol and all sites submitted and approved by Advarra central IRB and DoD HRPO.
9. Christiana site closed for inability to initiate screening and replaced with University of Wisconsin (started screening May, 2022).
10. University of Chicago site closed for lack of enrollment and institutional practice that conflicted with CHILL enrollment and was replaced by Intermountain Health – Utah (started screening July, 2022).
11. DSMB meetings held November, 2021 and May, 2022.
12. Had multiple messaging with sites about obstacles to enrollment and potential solutions.
a. the challenge of delayed intubation in COVID-19 (and now generalized to ARDS) – we discussed the data showing increased mortality in patients in whom intubation was delayed and the HACOR tool to predict failure of NIV.
b. how to distinguish between patients with rapidly resolving lung injury vs. those whose oxygen requirement is improved because of continued high PEEP.
c. consistent interpretation of chest imaging
d. appropriate evaluation of pressor requirement exclusion criterion
e. stressed reversibility and time-dependence of some exclusions
f. I developed and distributed an Excel tool to help track patients prior to and through the early screening process.
13. Added affiliated hospitals to existing (UMMC Midtown campus, Baltimore/Washington Medical Center (BWMC), and University of Maryland St. Joes Medical Center for total of 54 ICU beds to the UMB site; Presbyterian Hospital for total of 12 ICU beds to the University of Pennsylvania site; and Methodist Hospital for a total of 12 IUC beds to the Thomas Jefferson site). Added the UMMC PICU to the UMB site for potential 18-21 yo patients and enrolled an 18 yo patient.
14. Continuing talks with sites that have failed to enroll and outlining criteria for site termination.

15. Completed the CHILL order sets for Epic at University of Maryland and distributed to CHILL sites.
16. Gave Grand Rounds at Intermountain, Rush, Jefferson, and BWMC.
17. Draft of protocol paper written and circulating with site PI's.
18. Screened 2325 patients and enrolled 38 patients.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

1. The CHILL website (CHILLtrial.org) has both private content for CHILL personnel and public content, including a forum to support CHILL-related discussions.
2. I distributed via a powerpoint to sites for local CHILL education and training.
3. I have updated the clinicaltrials.gov listing.
4. We distribute a monthly CHILL newsletter via email and through the CHILL website
5. A protocol paper describing the rationale, design, and planned analysis of the CHILL trial is ready for submission.
6. I gave remote site visits to all clinical sites.
7. I give talks across the University of Maryland site, including our affiliated hospitals and at the Rush, Jefferson, and Intermountain sites.

What do you plan to do during the next reporting period to accomplish the goals?

Pre-activation activities:

1. Monitor and consider replacing low performance sites for closure and replacement.

Enrollment:

1. Individual Zoom meetings with Drs. Hasday, Shanholtz, Terrin, Thelma Harrington, and PI and coordinators from individual underperforming sites and possible termination.
2. Assist Cleveland Clinic in adding additional affiliated hospitals – currently the obstacle is transporting research blood samples.
3. Identify additional affiliated hospitals to add to other CHILL sites
4. Finalize sample inventory system
5. Complete first batch of biomarker analysis if sufficient samples accrue.
6. Dr. Hasday will continue to give Grand Rounds/lectures to providers and ICU personnel at CHILL sites as requested by CHILL sites.
7. We are currently in the slow season for ARDS. The overall plan is to maximize the capacity for screening and enrollment across the CHILL clinical network before reaching the peak ARDS season (mid-autumn). We anticipate screening 2500 patients and enrolling at least 125 subjects this year (5% of screened patients) this year.

Regulatory:
1. Refine Adverse Event tracking and reporting protocols.
2. Prepare for next DSMB meeting in December (working on improving presentation of form completion and AE reporting).
3. Update CHILL trial entry in clincaltrials.gov.

Budgetary:
1. Complete last four outstanding contracts with clinical sites

Publication:
1. Submit protocol paper.

Miscellaneous:
1. Develop ideas for sub-studies with site PI's.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report.

What was the impact on other disciplines?
Nothing to report.

What was the impact on technology transfer?

1. Successful outcome of the CHILL trial demonstrating at least a four day increase in ventilator-free days in the TH + NMB arm would support a modification to the DoD Joint Trauma System (JTS) Clinical Practice Guidelines for ARDS Management to incorporate this treatment into the treatment protocol for ARDS.
2. Dissemination of the results at national meetings and in published papers will raise awareness of and interest in further studies of thermobiology and temperature management in the critically ill patients and enhance future basic and clinical studies.

What was the impact on society beyond science and technology?

Successful outcome of the CHILL trial would support a follow-up Phase III trial of TH + NMB in ARDS with a mortality endpoint to support wide adoption of this potentially life-saving treatment for ARDS.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

The overall objective and the specific aims have not changed. The following changes were made to address unanticipated problems that reduced enrollment.

1. Replaced Christiana and U. Chicago sites with Wisconsin and Intermountain Health.
2. Made the following changes in the protocol:
   (i) increasing the upper age from 65 to 72 years;
   (ii) (ii) increasing the ARDS window from 48 to 72 hours; (
   (iii) iii) increasing the neuromuscular blockade window from 12 to 48 hours;
   (iv) (iv) increasing the maximum number of COVID patients from 2 to 4 per site.
3. Added affiliated hospitals to UMB, Temple, University of Pennsylvania, and Thomas Jefferson U. sites.

Actual or anticipated problems or delays and actions or plans to resolve them

• The anticipated problems are due to the current surge in COVID-19 and its impact on travel and visitors. We have developed a plan with NCR for all site initiation visits to be remote and are planning for at least the first semiannual clinical monitoring visit for each site to be remote as well. NCR is working on receiving credentials to remotely access the electronic medical record at each site for the clinical monitoring visits. We have developed a plan for remote site instruction, including a video of blood sample processing. We address the impact of COVID-19 and how sites are dealing with the challenges at our monthly Steering Committee meetings (stie PI's and CHILL leadership) and the monthly coordinators meetings.
• Heterogeneity in site performance: We are encouraging discussions among site PIs and coordinators at the Steering Committee meetings and the Coordinator meetings, respectively with CHILL leadership attending both. The discussion are meant to share problems/obstacles and solutions for individual sites and study-wide. We have added a forum function to host on-line discussions to the CHILL website. Drs. Hasday, Terrin, and Shanholtz have held meetings with poorly performing sites to help boost performance and clarify expectations. Dr. Hasday sends out weekly email updates on screening/enrollment to all sites. The Christiana site closed for inability to initiate screening and replaced with University of Wisconsin (started screening May, 2022). The University of Chicago site closed for lack of enrollment and institutional practice that conflicted with CHILL enrollment and was replaced by Intermountain Health – Utah (started screening July, 2022).
• Changes in management of COVID-19 patients favoring delayed intubation, which reduces the number of eligible patients and leads to worse outcomes in patients who are eventually intubated. We discussed at Steering Committee the new data showing that patients with COVID intubated after delay had worse outcomes than those intubated earlier in their course and how tools are available to predict those who will need to be intubated (e.g. HACOR scale) and encouraged the site PI's to share these data with their colleagues.

Changes that had a significant impact on expenditures

There was an increase in central IRB costs due to protocol changes and replacement of two sites.
There is a savings in travel expenses because of the shift to remote meetings and site visits due to COVID-19.
Due to slower than expected enrollment, the number of enrolled patients and the capitated costs were moved to years 3 and 4 and are budget neurtraol

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

  Journal publications. Nothing to report except for protocol paper which we will submit for publication this month.

  Books or other non-periodical, one-time publications. Nothing to report

  Other publications, conference papers and presentations. Nothing to report.

- **Website(s) or other Internet site(s)**

  https://www.clinicaltrials.gov

- **Technologies or techniques**

  Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jeffrey Hasday, MD
Project Role: PI
Research Identifier: 0000-0001-5011-5621
Nearest person month worked: 5
Contribution to the project: (1) wrote and updated the study protocol and manual of operations; (2) chaired weekly CHILL executive committee (CEC) meetings, including agenda and notes; (3) chairing monthly Steering Committee meetings; (4) attending biweekly meetings with NCR Clinical monitors; (5) attending monthly Coordinator Committee meetings; (6) worked with sites to complete Advarra approval and continuing review; (7) met with NCR and CSPCC to finalize plans for eDC, clinical monitoring, and AE reporting; (8) completed multiple rounds of edits of eDC forms and testing of eDC (9) supervised assembly of research materials including study binders and sample collection supplies, (10) updated clinicaltrials.gov record; (11) developed Epic order sets for CHILL at University of Maryland and guidelines for order sets to be developed at CHILL sites; (12) prepared draft of CHILL protocol paper; (13) developed a powerpoint presentation for Site Initiation Visits and for sites to use for inservice training; (14) prepared instruction video for sample processing and storage; (15) attend remote SIV training sessions for sites; (16) completed eDC and MOCA training; recruited replacement sites.

Name: Carl Shanholtz, MD
Project Role: Co-investigator and Director of the CHILL Clinical Coordinating Center.
Research Identifier: 0000-0003-3938-178X
Nearest person months worked: 3
Contribution to the project: (1) attended weekly CEC meetings; (2) attended monthly Steering Committee meetings; (3) attended Coordinator Committee meetings; (4) attended biweekly meetings with NCR; (5) helped design training for NCR personnel; (6) completed multiple rounds of eDC testing; (9) reviewed updated versions of protocol and Manual of Operations; (10) has been in contact with sites about finalizing IRB approval; (11) conducted inservice training for the participating medicine units at University of Maryland; (12) attended remote SIV training sessions for sites; (13) developed CHILL Epic order sets for UMB; (14) co-authored draft of CHILL protocol paper; and (15) Completed MOCA and eDC training.

Name: Michael Terrin, MD
Project Role: Co-investigator and co-director of the CHILL Data Coordinating Center
Research Identifier: 0000-0002-6342-2900
Nearest person month worked: 4
Contribution to the project: (1) attended weekly CEC meetings; (2) attended monthly Steering Committee meetings; (3) attended monthly Coordinator meetings; (4) attended biweekly meetings with NCR; (5) attended weekly meetings with CSPCC to develop the eDC; (6) worked with Dr. Brown to finalize the randomization and data analysis plan; (7) reviewed final eDC source forms and developed cross-check data plan; (8) oversaw CHILL web site design and activation; (9) reviewed updated versions of the CHILL protocol and Manual of Operations; (10) attended remote SIV training sessions for sites; (11) worked with NCR to finalize clinical monitoring and adverse event reporting plans; (12) oversaw appointment of DSMB and planned DSMB meetings.

Name: Clayton Brown, PhD
Project Role: Co-investigator and co-director of the CHILL Data Coordinating Center
Research Identifier: 0000-0002-0748-4509
Nearest person month worked: 2
Contribution to the project: (1) attended weekly CEC meetings, (2) attended monthly Steering Committee meetings; (3) attended biweekly meetings with NCR; (4) finalized randomization plan; (5) finalized data analysis plan; and (6) attending weekly meetings with CSPCC.

Name: Thelma Harrington, RRT
Project Role: Lead Coordinator
Research Identifier: N/A
Nearest person month worked: 12
Contribution to the project: (1) attended weekly CEC meetings; (2) attended monthly Steering Committee meetings; (3) attended biweekly meetings with NCR; (4) Chaired monthly Coordinator Committee meeting; (5) helped to generate and finalize eDC source documents; (6) multiple rounds of eDC testing; (7) worked with Dr. Hasday and all sites about to facilitate their initial IRB and CR approval; (8) collected training certificates and licenses from all site; (8) helped Dr. Hasday update the CHILL protocol and Manual of Operations; (9) prepared and shipped of randomization kits; (10) keeping updated delegation logs; (10) developed CHILL Epic order sets for UMB; (11) answered questions from sites about screening and enrollment; (12) facilitated remote consent protocols for sites; (13) supervised enrollment of 22 patients at UMB.

Name: Beth Guizzardi (replaced Christina Riggs who moved to a different department at UMB
Project Role: Budget Manager
Research Identifier: N/A
Nearest person month worked: 4
Contribution to the project: (1) attended all CEC meetings; (2) processed renewals of contracts with CSPCC, NCR, Calibre (website), Advarra, and clinical sites; (3) processing all orders for CHILL supplies, freezer, label printer; (4) processed all invoices from clinical sites and vendors; (5) managed internal budgeting process.

Name: Andrea Lefever
Project Role: Clinical Research Specialist
Research Identifier: N/A
Nearest person month worked: 4
Contribution to the project: Contribution to the project: (1) hosted and attended all CEC meetings; (2) hosted and attended all Steering Committee meetings; (3) hosted and attended all Coordinators meetings; (4) scheduled and hosted all CSPCC and NCR meetings; (5) scheduled DSMB meetings; (6) CHILL website design, activation, and management of content; (7) CHILL newsletter design and management of content; (8) communication with site personnel; and (9) distribution of all meeting agenda and notes.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Clinical sites through subcontracts with UMB:
• Johns Hopkins University (Baltimore, MD)
• Thomas Jefferson University (Philadelphia, PA)
• University of Pennsylvania (Philadelphia, PA
• Temple University (Philadelphia, PA)
• Emory University (Atlanta, GA)
• Mayo Clinic (Rochester, MN)
• Cleveland Clinic (Cleveland, OH)
• University of Illinois at Chicago (Chicago, IL)
• Loyola University – Chicago (Chicago, IL)
• Rush University (Chicago, IL)
• University of Wisconsin (Madison, WI)
• Brooke Army Medical Center (Fort Sam, TX)
• Intermountain Healthcare (Salt Lake City, Utah)

US Department of Veterans Affairs Cooperative Studies Program Coordinating Center (CSPCC), Perry Point VAMC (Perry Point, MD): providing electronic database and randomization services through a subcontract.

Navitas Clinical Research (Rockville, MD): providing Clinical Monitoring service through a subcontract.

Calibre: provides website support for the CHILLtrial.org website.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: