Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients

Investigator Meeting
Wednesday, May 4

P-ICECAP

NIH SIREN
Emergency
Trials
Network

Welcome

Dr. Frank Moler

Agenda

Time	Topic	Speaker
6:00 PM	Welcome and Review of Agenda	Dr. Frank Moler, MD
6:10 PM	Introductions	Dr. Alexis Topjian, MD
6:30 PM	Brief History and Overview	Dr. William Meurer, MD
7:15 PM	SIREN Overview	Drs. Robert Silbergleit, MD & Sharon Yeatts, PhD
7:25 PM	Q & A	All faculty
8:10 PM	Adjourn Day 1	

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Introductions

Dr. Alexis Topjian

History and Overview

Dr. William Meurer

Questions

Why be adaptive?

Why study hypothermia?

How will trial work?

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A randomized, response-adaptive, duration-finding, comparative effectiveness clinical trial with blinded outcome assessment.

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Part 1

INTRODUCTION TO ADAPTIVE CLINICAL TRIALS

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Why Clinical Trials Stink

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Why Clinical Trials Stink

ANALOGY*: Clinical Trial = Diagnostic Test

	Clinical Trial	Diagnostic Test
Looking For	Effective Treatment	Disease
1 – Type II Error (Beta)	"Power"	Sensitivity OR True Positive Rate
Type I Error (Alpha)	Significance Level	1- Specificity OR FALSE Positive Rate

*Note: My analogy does not stink

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Clinical Trials are Models with Tons of ~~Guesses~~ Assumptions

- Dose from animal models is close
- No heterogeneity of effect
- Subgroups respond equally
- Some subgroups excluded
- Effect size to create “reasonable” sample size
- “Noise” in outcomes can be understood and overcome
- Duration of treatment practical
- **LESSON: Make many compromises to reduce number of parameters to make model “solvable”**

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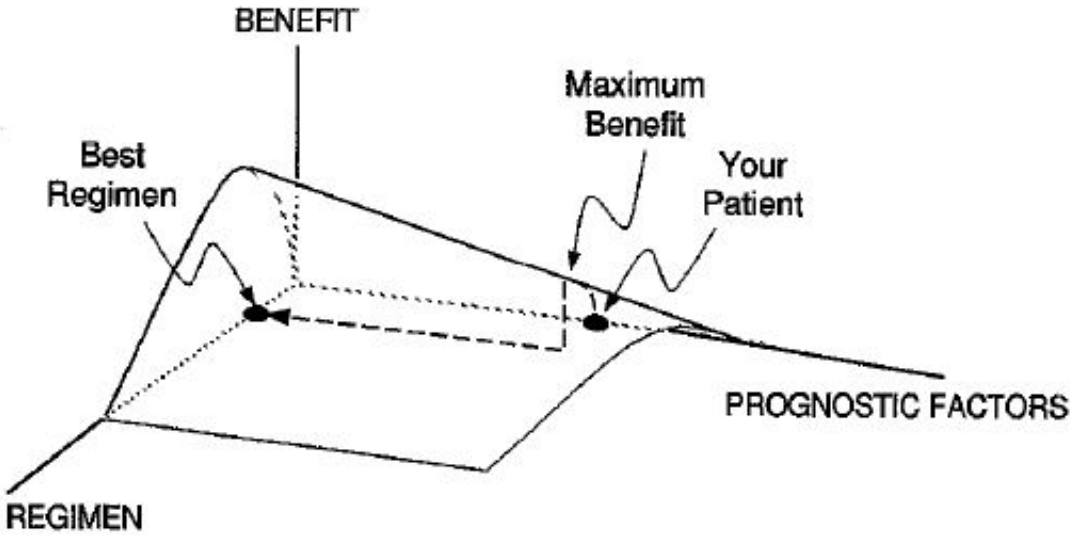
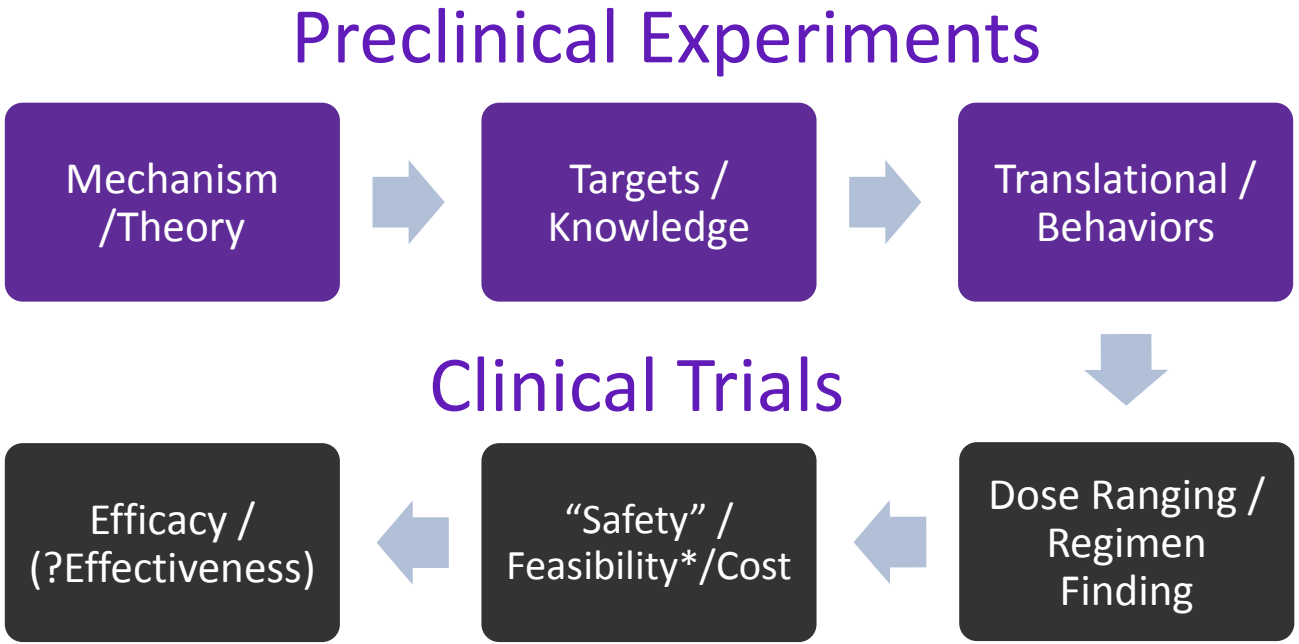
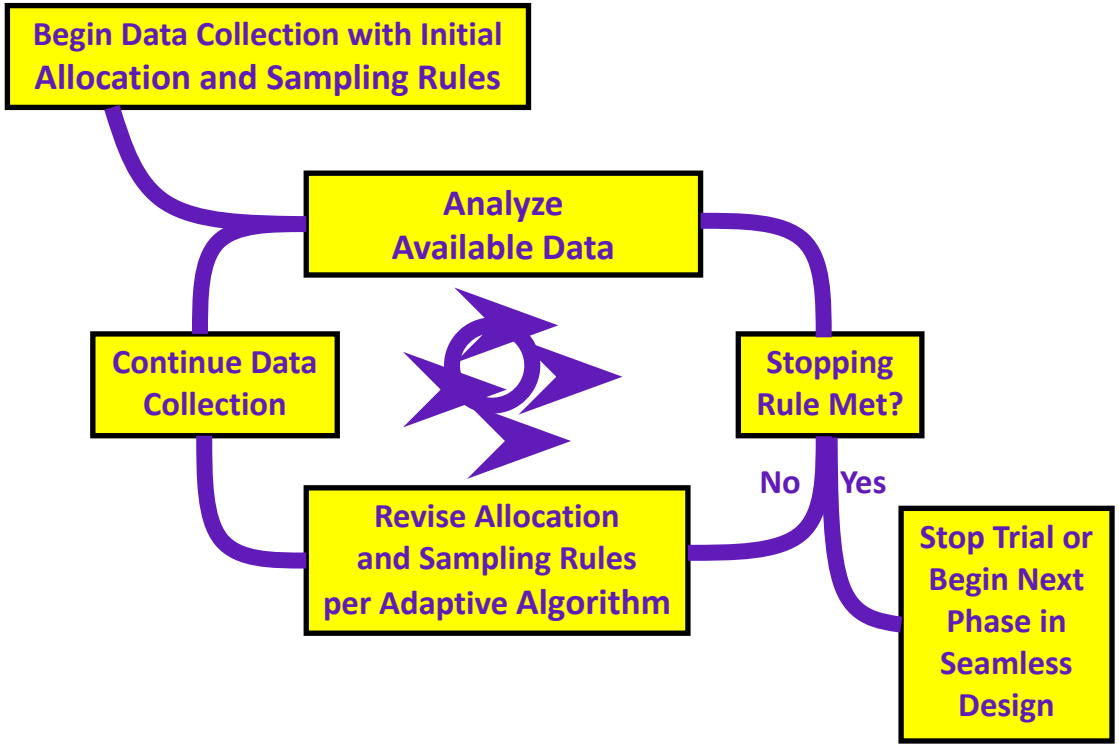
Therapeutic Response Surface



Clin Pharmacol Ther 1997;61:275-91


Preclinical Experiments
Mechanism /Theory
Targets / Knowledge
Translational / Behaviors
Clinical Trials
Dose Ranging / Regimen Finding
"Safety" / Feasibility*/Cost
Efficacy / (?Effectiveness)

The Adaptive Process



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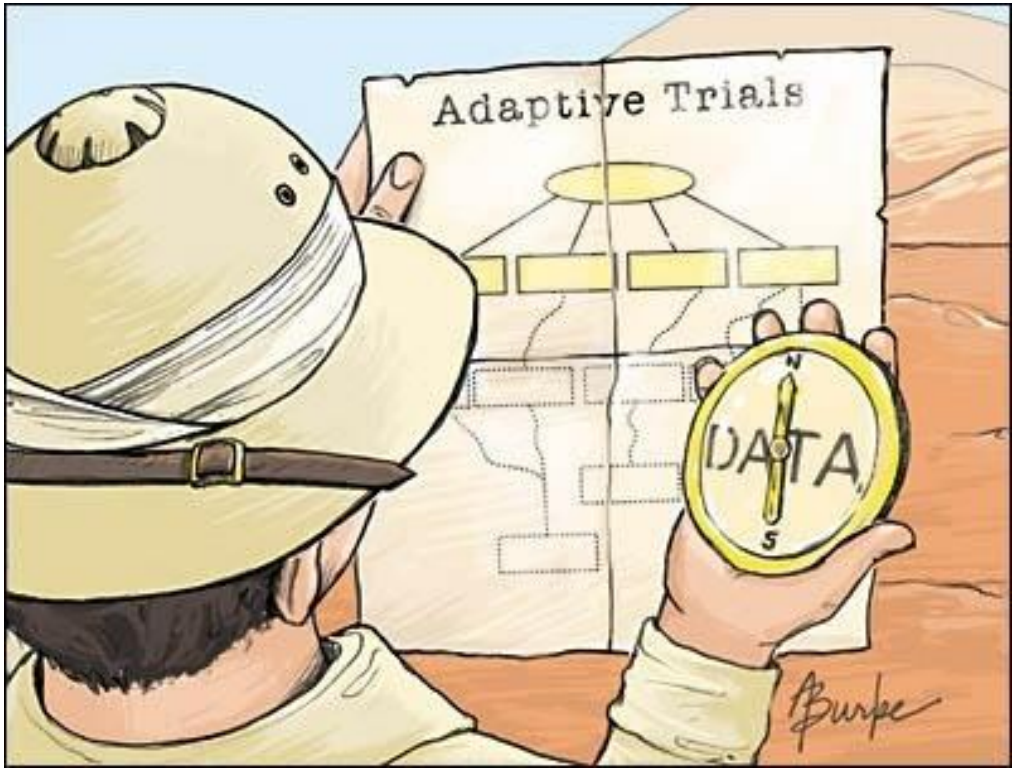
The Adaptive Process



JAMA
2006;296:1955-1957.

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GOAL:

Design a trial that leaves no (or few) regrets.

The clinical community and funders will know what to do next.

The “pre-mortem.”

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CAVEAT:

An adaptive or flexible design doesn't always make sense.

(We do not usually know as much before starting the trial as we will after we have data for most situations…)

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ADAPT-IT 2010-2012

- FDA / NIH Common Fund cooperative award that to develop adaptive clinical trial designs for confirmatory, large scale trials
- Process
  - Stakeholder Meeting to present the clinical problem
  - Preliminary design - Simulations and iterations
  - Stakeholder Meeting to review “final” design proposal
  - More simulations and validation
  - Development of protocol (IDE / clinical trial protocol)

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Thematic Adaptive Motivation for (adult) ICECAP

- Fixed design
- 1800 patients
- 12, 24, 48
- Anticipated regrets

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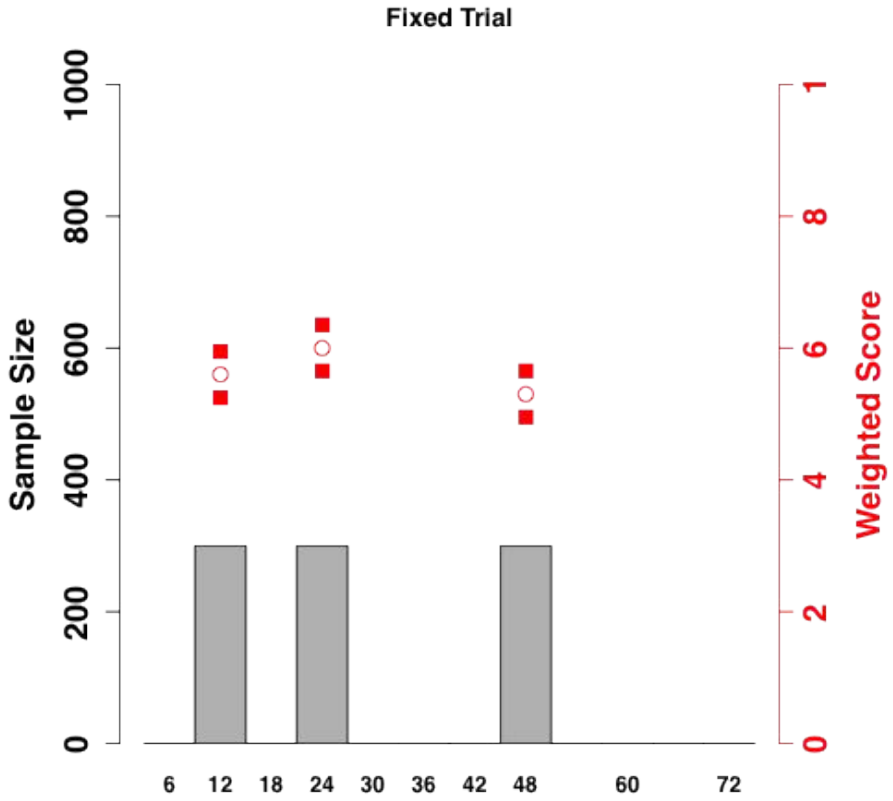
Example Outcome of Fixed



- Idealized Outcome?
- Answer All your questions?
- Do anything differently?

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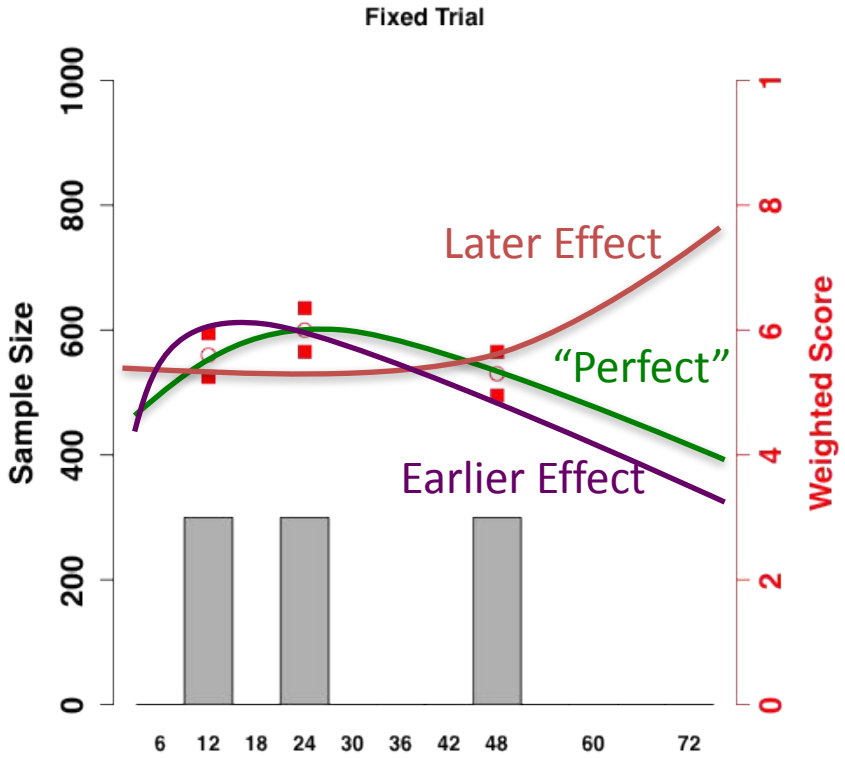
Example Outcome of Fixed (versus “truth”)



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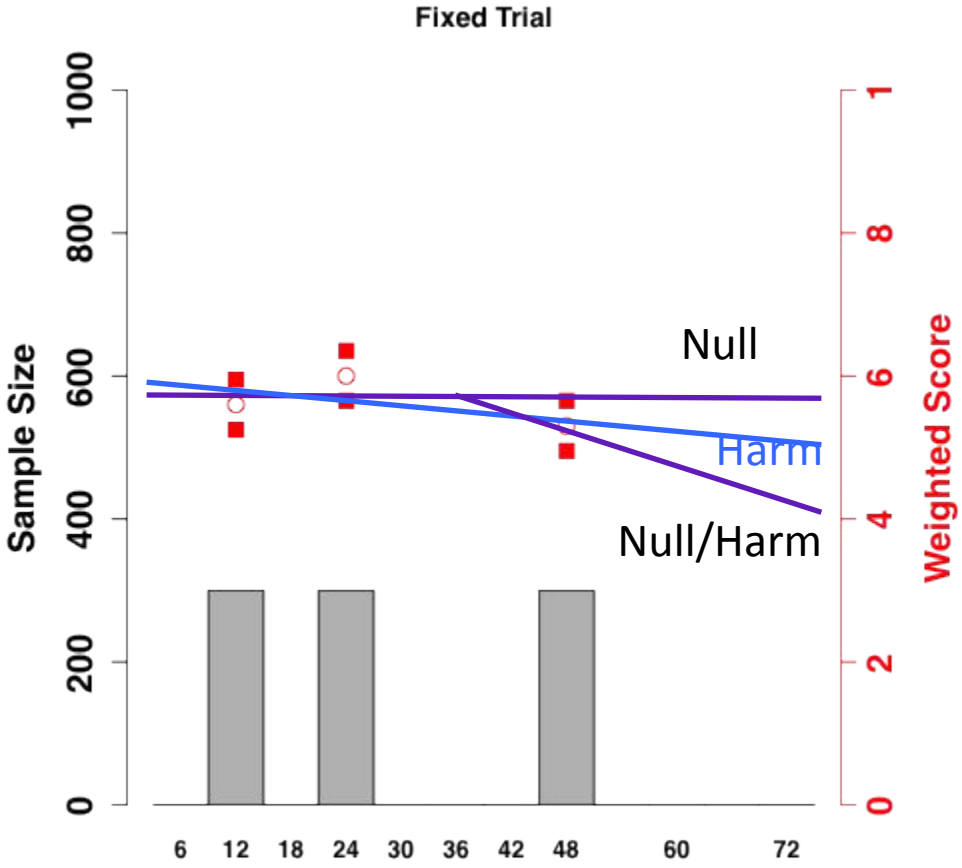
Example Outcome of Fixed (versus "truth")



- FDA Approval?
- Medical Controversy?
- Different rhythm types?
- 2 more Studies?

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Part 2

PRECLINICAL / PRIOR CLINICAL EVIDENCE

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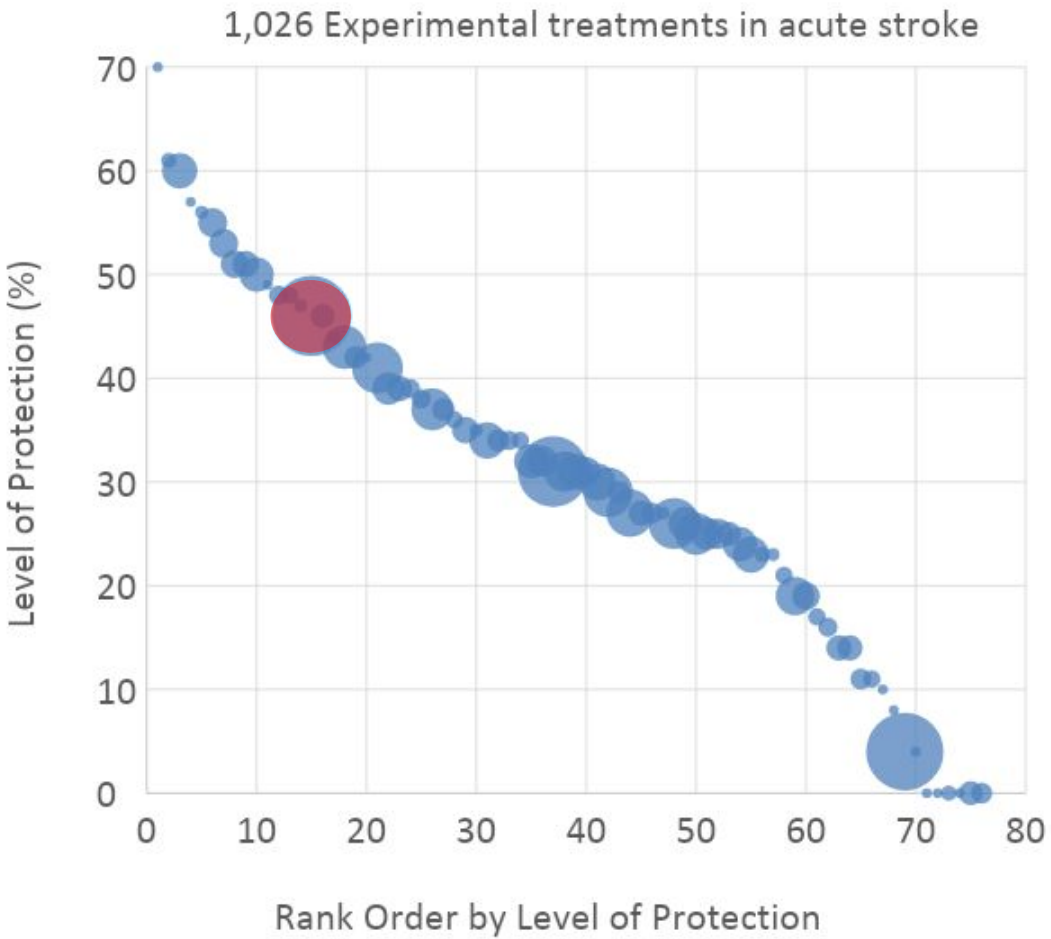
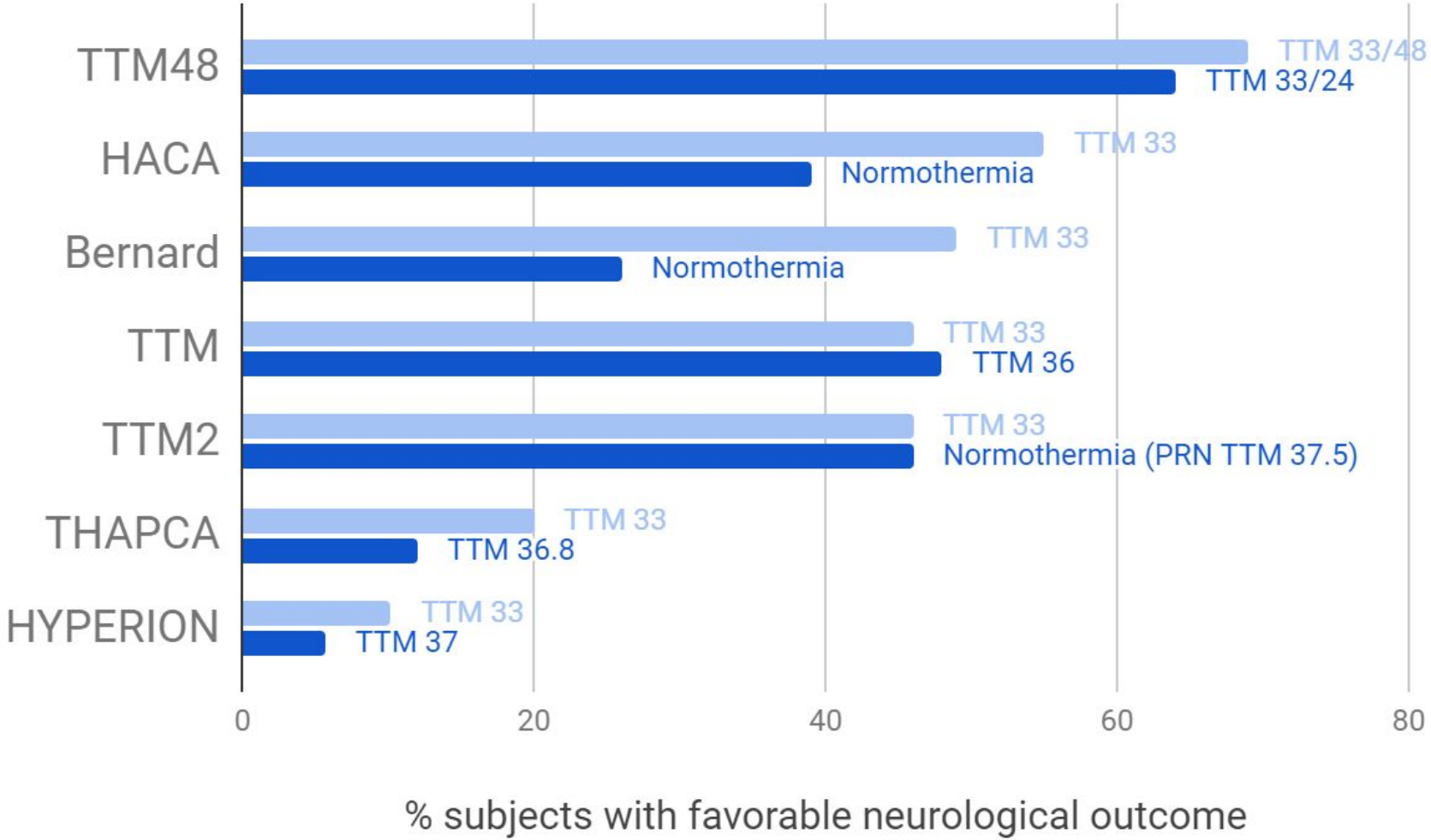
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

Ann Neurol 2006;59:467–477

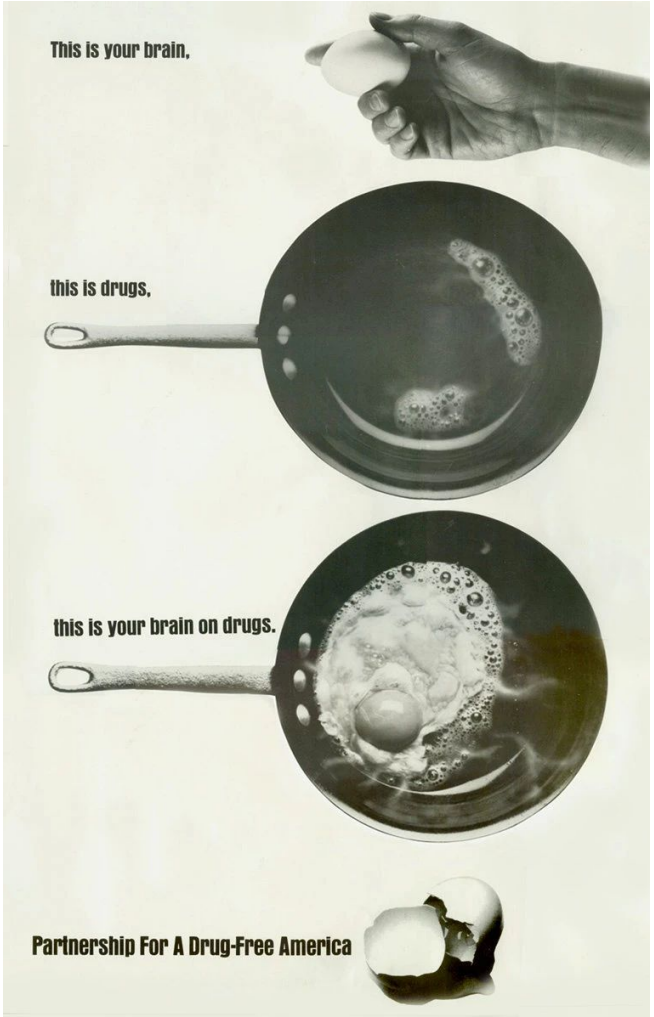


	Experimental Contrasts (n)	
Focal Ischemia Models	94	favors treatment
	28	neutral
	0	favors control
Global Ischemia Models	77	favors treatment
	28	neutral
	0	favors control
Culture Models	13	favors treatment
	3	neutral
	1	favors control


TTM48
TTM 33/48
TTM 33/24
HACA
TTM 33
Normothermia
Bernard
TTM 33
Normothermia
TTM
TTM 33
TTM 36
TTM2
TTM 33
Normothermia (PRN TTM 37.5)
THAPCA
TTM 33
TTM 36.8
HYPERION
TTM 33
TTM 37
0
20
40
60
80
% subjects with favorable neurological outcome

The brain is sensitive to temperature

Drugs = HYPERTHERMIA



History / Timeline

- 2003 THAPCA pre trial cohort study R21
- 2006 THAPCA R34
- 2009 THAPCA OH and THAPCA IH Trials U01
- 2011 ADAPT-IT - ICECAP planning
- 2013 THAPCA Last Outcomes Collected
- 2015 THAPCA OH - Publication
- 2016 ADULT ICECAP IDE
- 2020 ADULT ICECAP First Patient In
- 2021 P-ICECAP IDE (initial)
- 2021 P-ICECAP Award
- 2022 (Now)

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THAPCA-OH - Design

- Prospective RCT
- Out of hospital cardiac arrest
- GCS motor 4 OR less
- 48 hours of TTM to 33°C versus enforced 36.8 °C / 120 hours of TTM total in both
- Primary outcome: Survival with a good neurobehavioral outcome at 12 months of follow-up

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THAPCA-OH

Table 2. Primary and Secondary Outcomes.*

Outcome	Hypothermia Group	Normothermia Group	Risk Difference	Relative Likelihood (95% CI)	P Value
	no./total no. (%)		*percentage points (95% CI)*		
Primary outcome					
Alive with VABS-II score ≥70 at 1 yr	27/138 (20)	15/122 (12)	7.3 (−1.5 to 16.1)	1.54 (0.86 to 2.76)	0.14†
Detailed supportive analysis					0.14‡
Death	87/138 (63)	88/122 (72)			
Disability					
Profound§	16/138 (12)	11/122 (9)			
Moderate-to-severe¶	8/138 (6)	8/122 (7)			
Good functional status‖	27/138 (20)	15/122 (12)			

20%

12%

Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest in Children. N Engl J Med 2015;372:1898-809.

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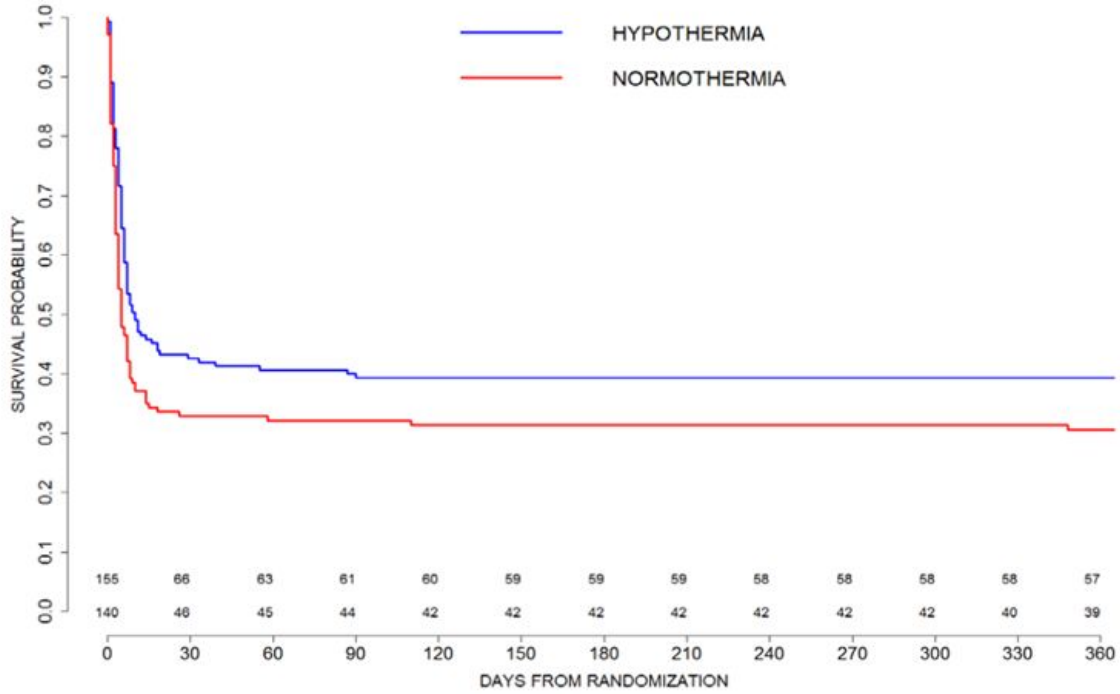
Figure S1 from THAPCA-OH: Probability of survival to one year following cardiac arrest, according to assigned treatment



The two lines represent Kaplan-Meier survival rates from 0 to 365 days after cardiac arrest for patients in each study arm (p=0.04 for a log-rank test, stratified by age category, comparing survival distributions between treatment arms).

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Part 3

P-ICECAP OVERVIEW

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Specific Aim 1: Can the efficacy of hypothermia be confirmed by evaluating duration response?

- To determine in pediatric comatose survivors of OHCA, whether the duration response curve as assessed by the VABS-3* mortality composite score is initially increasing, thus demonstrating efficacy of hypothermia versus normothermia (i.e. zero duration of cooling). Secondary endpoints include the Pediatric Cerebral Performance Category Score, Pediatric Resuscitation after Cardiac Arrest score, and survival at 12 months.

*Vineland Adaptive Behavioral Scale 3 - a standardized measure of neurobehavioral functioning

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Specific Aim 2: Can the optimal duration of cooling be identified?

- To determine in pediatric comatose survivors of OHCA, the shortest duration of cooling that provides the maximum treatment effect as determined by a higher VABS-3 Mortality Composite Score.

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Specific Aim 3: Does duration have a differential effect on safety and quality of life?

- To characterize the effect of duration of hypothermia on overall safety and adverse events, and parent reported quality of life.

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P-ICECAP Comparison to Adult ICECAP

Aspect	P-ICECAP	Adult ICECAP
Durations (hours)	0-96 (10)	6-72 (10)
Eligibility Timing	Within 6 hours of ROSC - must start device before randomization must set device to 33°C within 15 minutes	Must be below 34°C within 4 hours of arrest
Sample Size	900	1800 (with different models / randomization vectors for shockable versus non-shockable)
Outcome Timing	3 and 12 months	1 and 3 months
Sites	40 (with more needing FDA approval)	Up to 75

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P-ICECAP Comparison to THAPCA

Aspect	P-ICECAP	THAPCA
Duration of cooling (hours)	0 to 96 (10 durations) at 33°C	48 at 33°C or 36.8°C
Eligibility GCS Motor	5 or lower (more inclusive)	4 or lower (less inclusive)
Sample Size	900	295 randomized (260 eligible for primary outcome)
Outcome Timing	3 and 12 months	3 and 12 months
Outcome	VAB3 mortality composite (continuous)	VABS2 >= 70 and alive = good (binary)

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Inclusion

- Age 2 days to <18 years with corrected gestational age of at least 38 weeks
- coma or encephalopathy after return of spontaneous circulation (ROSC) following out-of-hospital cardiac arrest;
- requiring mechanical ventilation;
- **definitive temperature control device started;**
- informed consent from legally authorized representative (LAR) **including randomization within 6 hours of ROSC;**
- intent to maintain life support for 120 hours

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Exclusion (Major)

- **Glasgow Coma Motor Score (GCMS) of 6,**
- **severe hemodynamic instability;**
- pre-existing condition confounding outcome determination
- pre-existing terminal illness;
- planned early withdrawal of life support before 120 hours;
- pre-existing contraindication to cooling*;
- **CPR duration > 60 minutes;**
- Prisoner;
- KNOWN pregnancy

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Intervention

- Duration 0-96 hours
- Measured from definitive cooling initiation and being set to 33° C (or normothermia if assigned to no additional cooling)
- Any definitive surface, servo controlled cooling device*
- Clinical standardization

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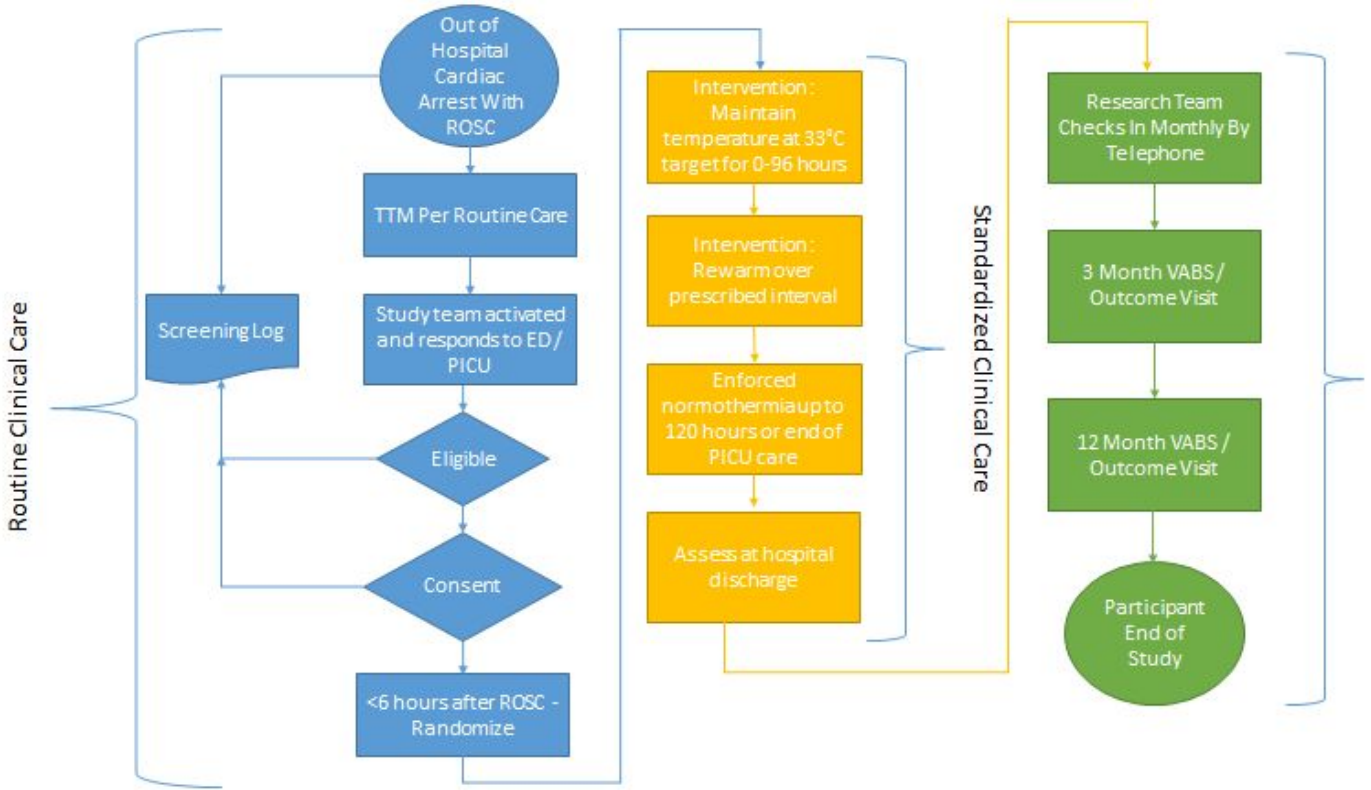
Enrollment and Patient Flow



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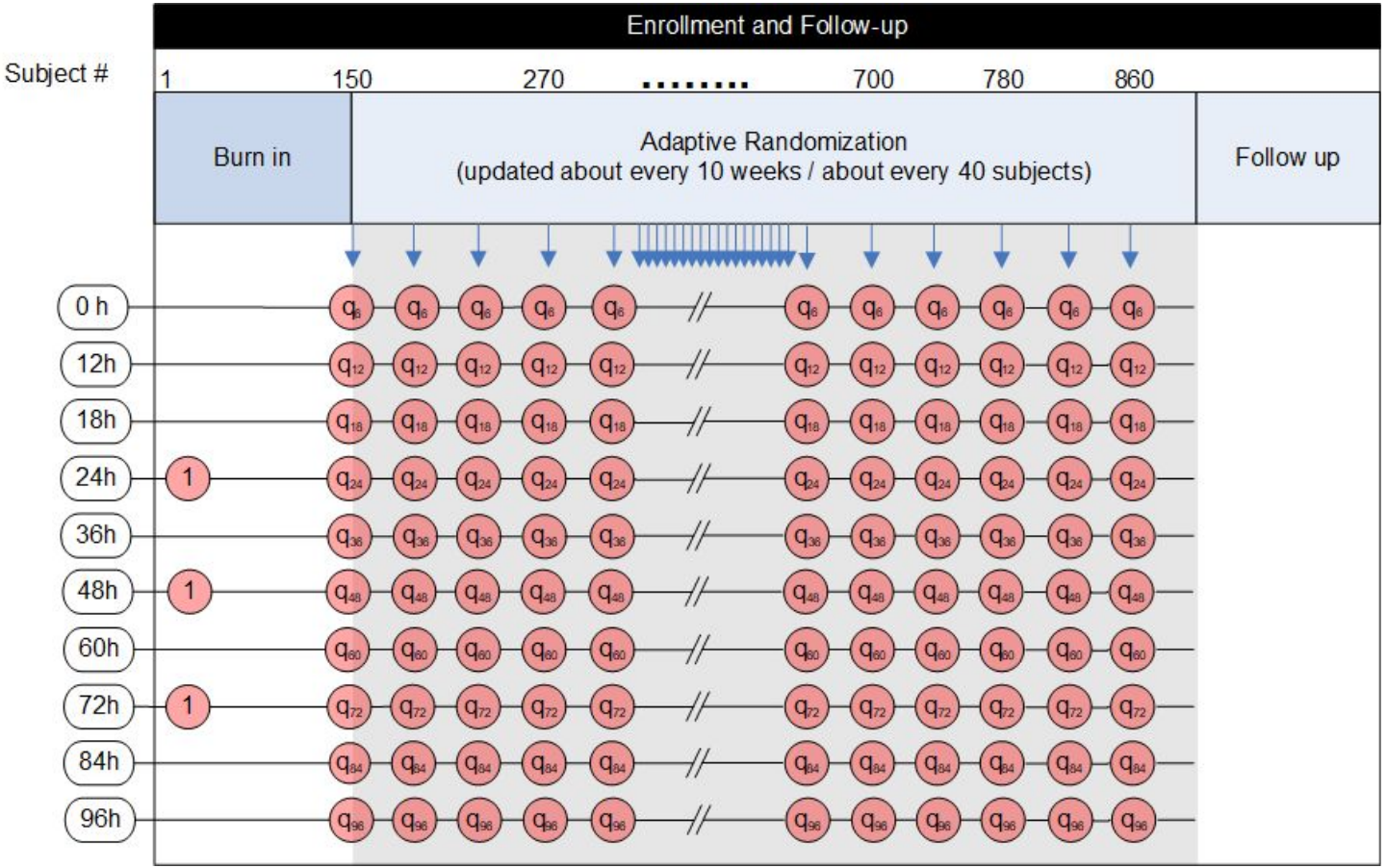
Enrollment and Follow-up
Subject #
1
150
270
700
780
860
Burn in
Adaptive Randomization
(updated about every 10 weeks / about every 40 subjects)
Follow up
0 h
12h
18h
24h
36h
48h
60h
72h
84h
96h
1

Why be adaptive

-To get closer to the “truth”

-To put kids where they will do best

-To avoid cooling kids too much (or too little)

-First 150 kids - equal allocation 24,48,72 (reduce noise)

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Primary Outcome: VABS-3 - Mortality Composite Score

- Vineland Adaptive Behavior Scale - Third Edition
- Standardized caregiver report measure of neurobehavioral function appropriate from birth through adulthood

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Primary Outcome:
VABS-3 Mortality Composite Score

- Measured VABS-3 composite scores range from 20-140 (mean=100, SD=15).
- Patients who die before 12 month outcome assessment will be assigned zero
- Used continuously to simultaneously account for mortality and neurological status

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Other Outcomes

- PCPC (Pediatric Cerebral Performance Category)
- PedsQL (Pediatric Quality of Life Inventory TM)
- Family Burden
- Structured Neuro Exam
- Mortality at 12 months

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Safety Outcomes
(anticipated)

- **Infection** (pneumonia, UTI, BSI, culture positive bacterial sepsis and other culture positive infections)
- **Life-threatening cardiac arrhythmias** requiring intervention (cardiac arrest, ventricular fibrillation, ventricular tachycardia, atrial arrhythmias with hemodynamic compromise)
- **Coagulopathy** Increased bleeding requiring blood product replacement
- **Neurological worsening** (i.e. cerebral edema and herniation, intractable status epilepticus, cerebral hemorrhage, cerebral infarction)

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QUESTIONS?

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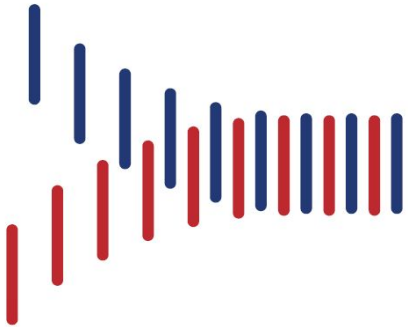
SIREN Overview

Drs. Robert Silbergleit & Sharon Yeatts



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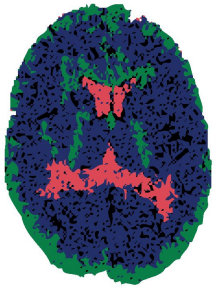
Network Overview
P-ICECAP Investigators Meeting



Neurological Emergencies Treatment Trials

Evolution

ROC

SIREN

NIH National Heart, Lung, and Blood Institute

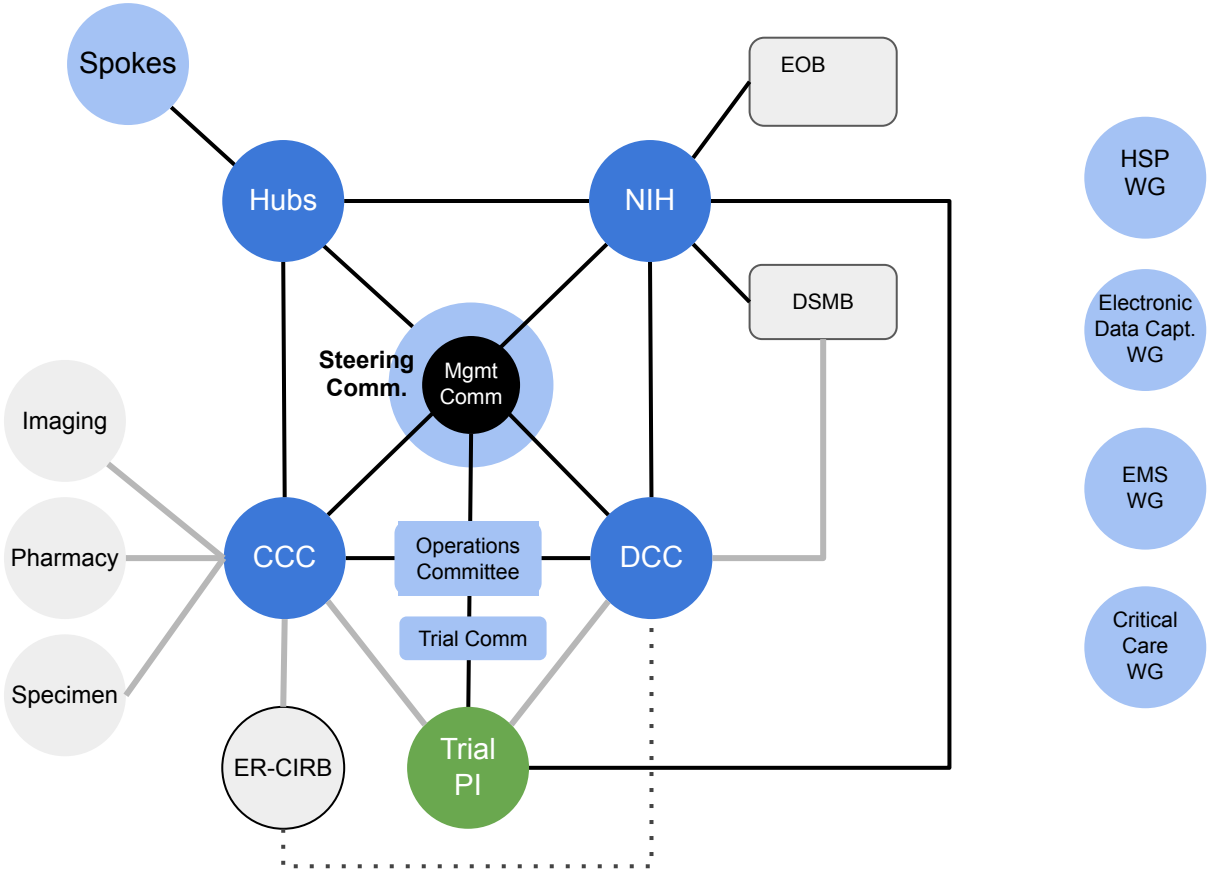
NIH National Institute of Neurological Disorders and Stroke

NIH National Center for Advancing Translational Sciences

Design principles and organizational values

- Focus on **early treatment**.
- Focus on **meaningful outcomes for patients**.
- Focus on **efficiency**.
- Focus on **collaboration**.
- Focus on **transforming the clinical trials enterprise**.

Organizational Structure



William Barsan
SIREN PI

Robert Silbergleit
SIREN Co-PI

Cliff Callaway
SIREN Co-PI

Valerie Stevenson
Finances

CCC Leadership

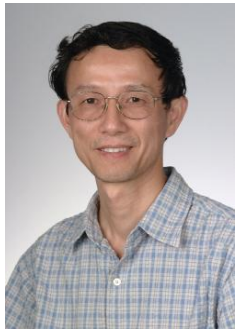
DCC Infrastructure Team

Valerie Durkalski-Mauldin
Co-PI

Sharon Yeatts
Co-PI

Catherine Dillon
Co-Investigator

Chris Arnaud
IT



Wenle Zhao
Co-Investigator

Vanessa Sullivan
Administrator

Sara Butler
Data Mgmt Core Leader

Lydia Foster
Biostatistics

Keith Pauls
IS Core Leader

Renee Martin
HOBIT DCC
PI

Caitlyn Ellerbe
HOBIT
Co-Investigator

Abby Teklehaimanot
Biostatistics
HOBIT, BOOST

Jonathan Beall
Biostatistics
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Grey Clevenger
Biostatistics
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Peyton Kline
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CCC
Hubs
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External
Investigators

Additional Team Members

Liz O' Donohue

Operations

Peyton Kline

Sara Butler

Keith Pauls

Grey Clevenger

Sharon Yeatts

Biostatistics

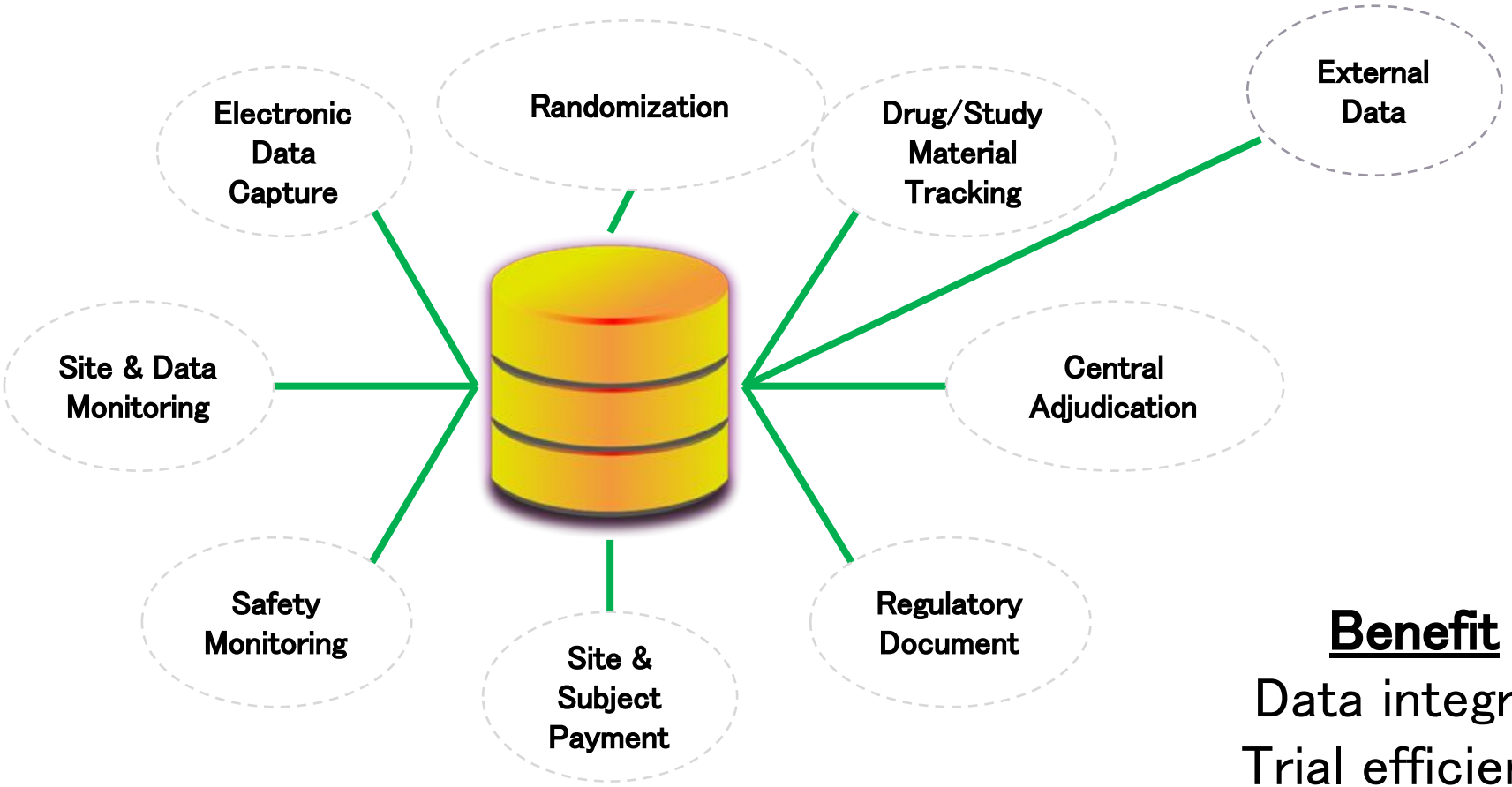
John VanBuren

Kent Page

Richard Holubkov

P-ICECAP Team Members

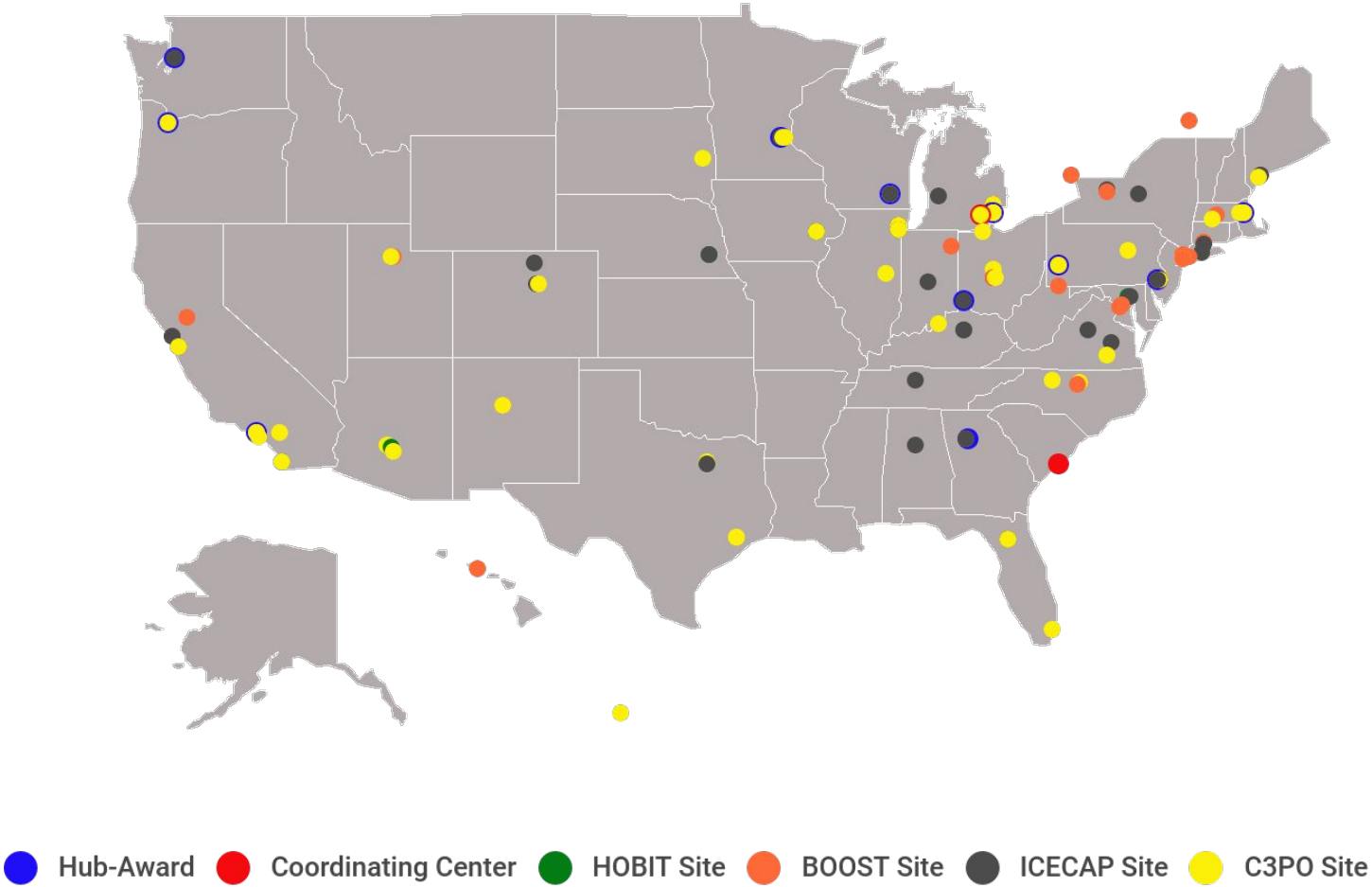
WebDCU™ – Integrated system built on innovative design



Benefit

Data integrity

Trial efficiency


Hub-Award
Coordinating Center
HOBIT Site
BOOST Site
ICECAP Site
C3PO Site

SIREN Clinical Trials

What else are we doing?

5

Number of SIREN clinical trials currently active

10

Number of SIREN trial or ancillary grants and supplements funded

17

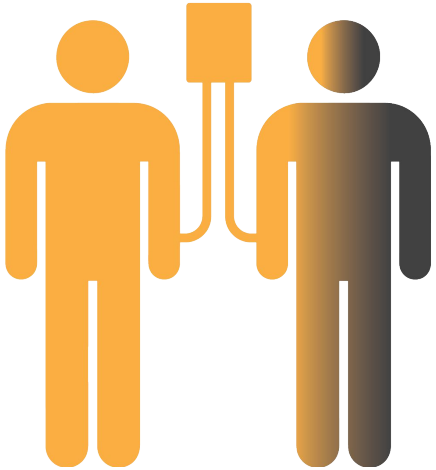
Trials and other grant applications in the SIREN development pipeline

1287

Participants enrolled as of 12 February 2022

9

Days from C3PO last participant visit to data base lock



C3PO

Clinical Trial of COVID-19 Convalescent Plasma in Outpatients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Convalescent Plasma for High-Risk Outpatients with Covid-19

F.K. Korley, V. Durkalski-Mauldin, S.D. Yeatts, K. Schulman, R.D. Davenport, L.J. Dumont, N. El Kassar, L.D. Foster, J.M. Hah, S. Jaiswal, A. Kaplan, E. Lowell, J.F. McDyer, J. Quinn, D.J. Triulzi, C. Van Huysen, V.L.W. Stevenson, K. Yadav, C.W. Jones, B. Kea, A. Burnett, J.C. Reynolds, C.F. Greineder, N.L. Haas, D.G. Beiser, R. Silbergleit, W. Barsan, and C.W. Callaway, for the SIREN-C3PO Investigators*

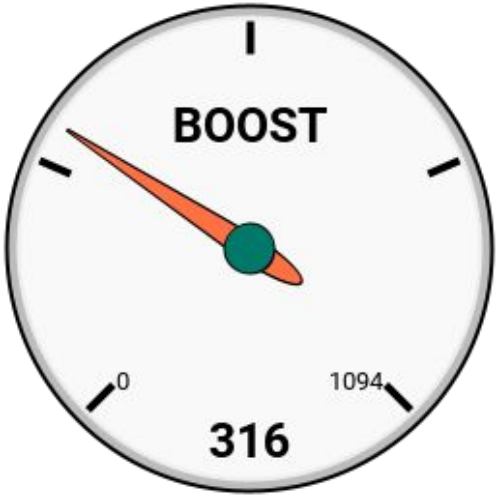
ABSTRACT

BACKGROUND

BOOST-3

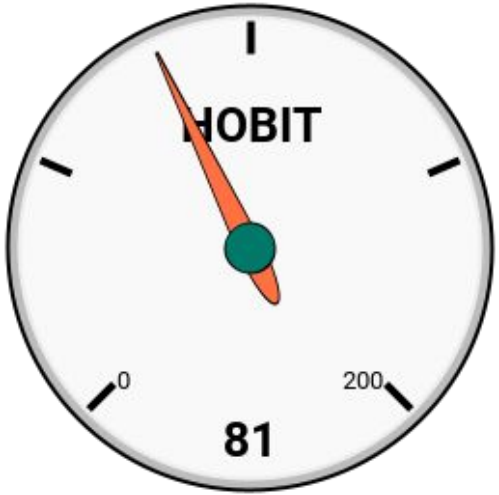
BIO-BOOST

E BOOST

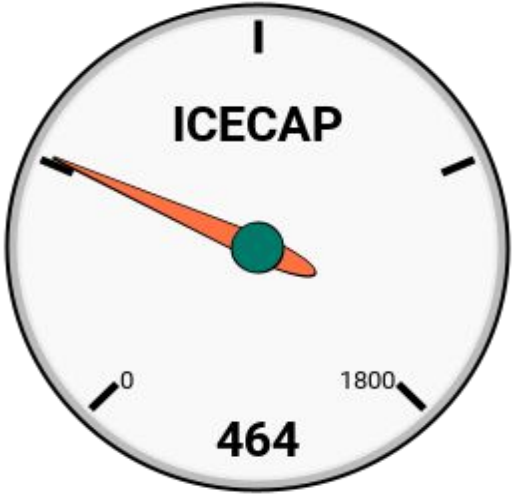


HO_2BIT

Bio HOBIT



ICECAP



P-ICECAP

Q&A

All Faculty

Thank you!