PREcision Care In Cardiac arrest – ICECAP ancillary

PIs: Karen Hirsch, MD

Jonathan Elmer, MD MS

Co-Is: Teresa May, DO

Romer Geocadin, MD

Zihuai He, PhD (Statistician)

Stephanie Kemp (Project Overlord)

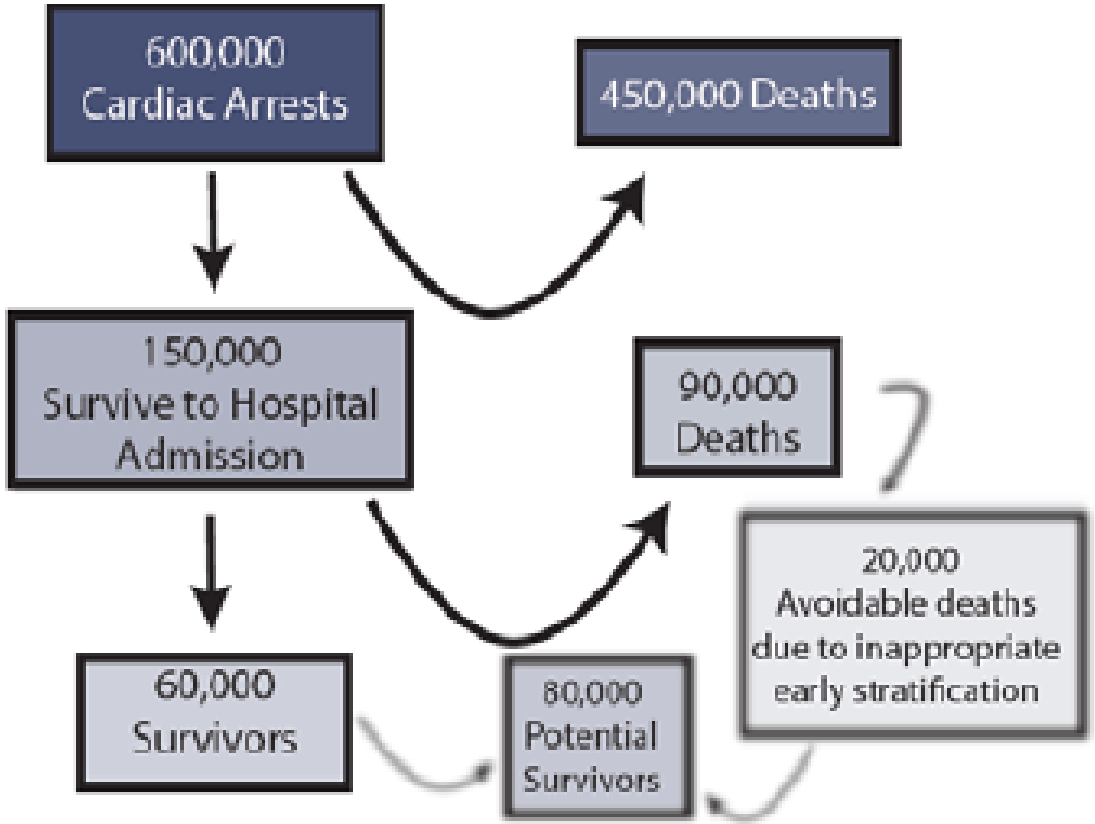
Elizabeth Osborn (Project Manager)

PRECICECAP Objectives

- Discover novel biomarker signatures that **predict treatment responsiveness** and **long-term recovery** in cardiac arrest patients

- We hypothesize: Not all post-arrest patients are identical!
  - Heterogeneity of treatment effect
  - **Multi-parametric, high-resolution, continuous or high-density data** will allow machine learning approaches to identify novel signatures that define patient subgroups

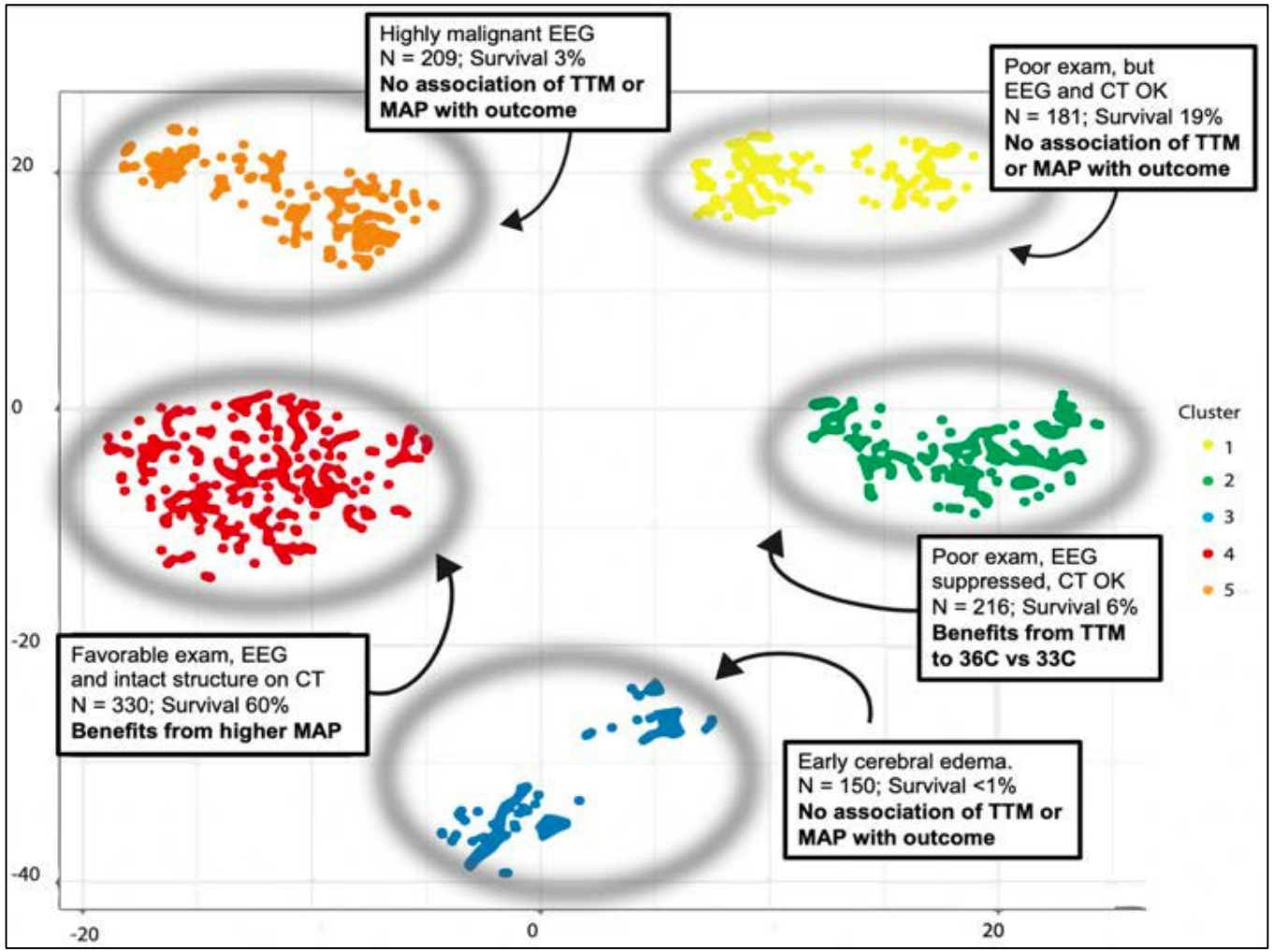
Inappropriate prognostication leads to excess death through **inappropriate care withdrawal**



Current prognostication is flawed

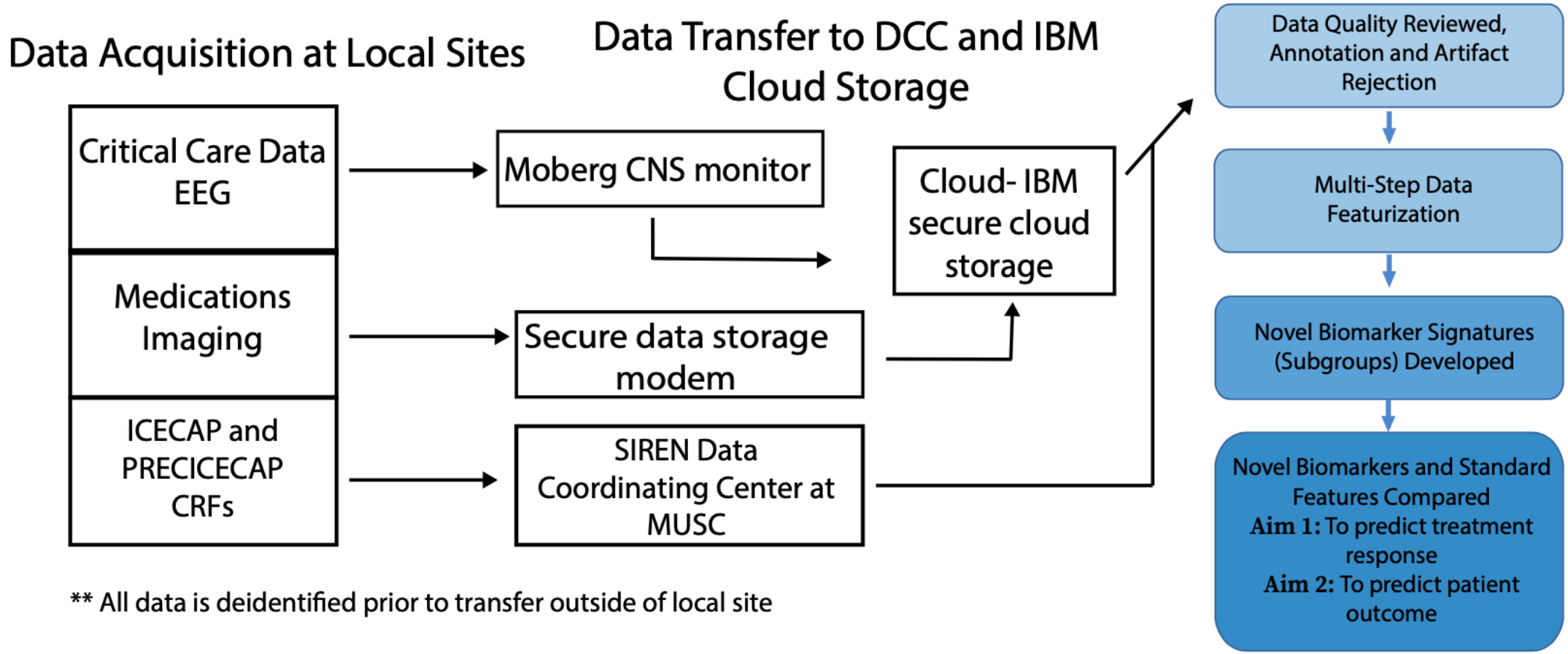
Past limitation	*Importance*	*How PRECICECAP addresses*
Limited population in derivation cohort	Small cohorts and single-center designs lead to uncertainty and limits generalizability	Multicenter approach will allow broad population inclusion and increased generalizability
Post-resuscitation care not standardized	Heterogeneity in clinical care leads to difficulty attributing effect of interventions	Clinical standardization protocol of ICECAP will define posts-resuscitation care
Lack of blinding	Care teams have access to diagnostic test being studied, leading to confounding	Neural network approach allows for unbiased approach to data analysis
Heterogeneous diagnostic testing and withdrawal of life-sustaining therapy	Sites differ in their approach to withdrawal of life-sustaining therapies	Clinical standardization protocol of ICECAP defines prognostication approach
Non-standardized outcomes	Definitions of good and poor outcome vary between studies, and outcome scales have significant limitations	Primary outcome of mRS is a recommended outcome and will be measured by trained assessors
Do not account for medications, hypothermia and organ dysfunction	Confounding due to medications, shock, organ failure and hypothermia	CRF from both ICECAP and PRECICECAP will allow for detailed assessment of these factors

Distinct injury patterns predict **differential response to therapy**



Elmer, J et al: Resucitation 2020 Aug; 153-160

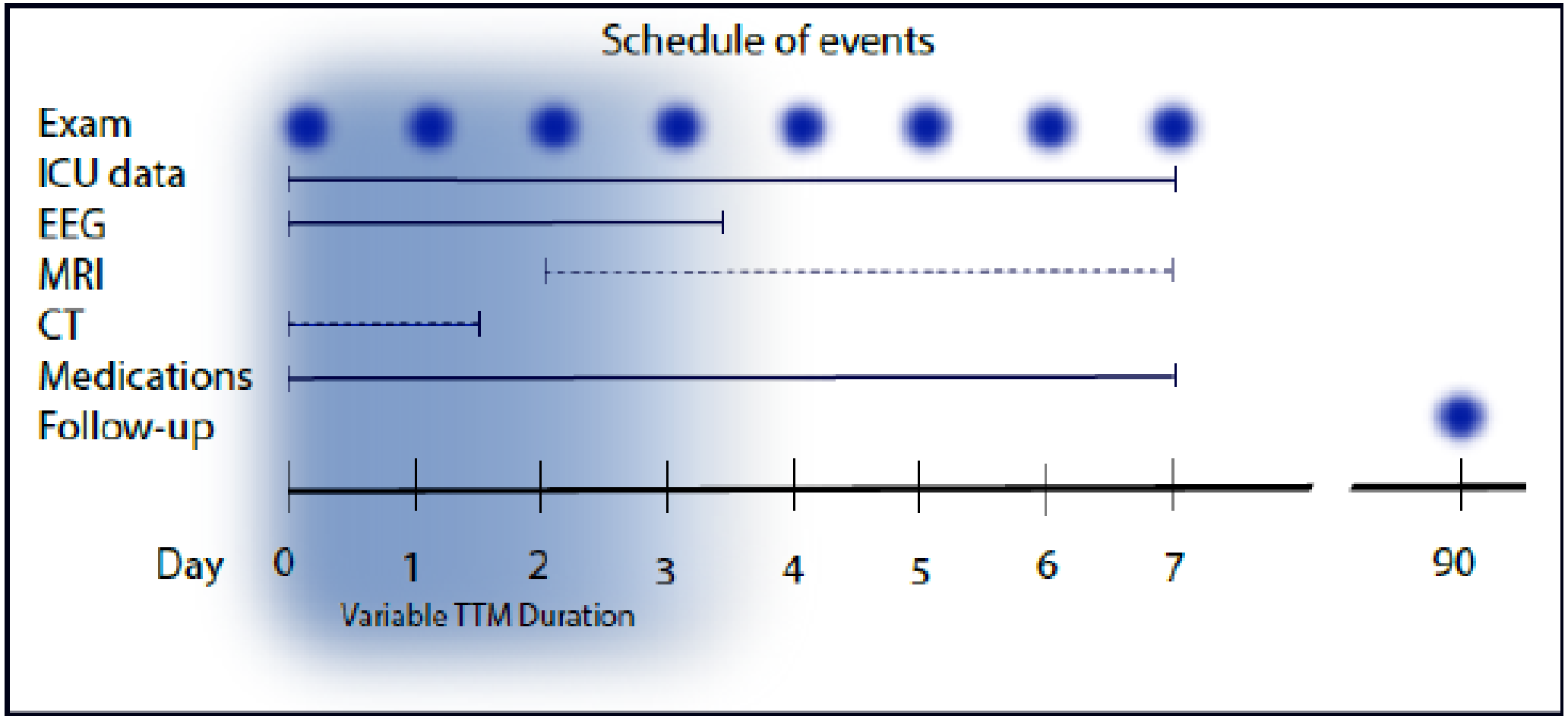
Approach


Data Acquisition at Local Sites
Data Transfer to DCC and IBM Cloud Storage
Critical Care Data EEG
Medications Imaging
ICECAP and PRECICECAP CRFs
Moberg CNS monitor
Secure data storage modem
SIREN Data Coordinating Center at MUSC
Cloud- IBM secure cloud storage
** All data is deidentified prior to transfer outside of local site
Data Quality Reviewed, Annotation and Artifact Rejection
Multi-Step Data Featurization
Novel Biomarker Signatures (Subgroups) Developed
Novel Biomarkers and Standard Features Compared
Aim 1: To predict treatment response
Aim 2: To predict patient outcome

Study Procedures

- All subjects enrolled in ICECAP are eligible for PRCICECAP (**single consent**)
- **Able to connect** patient to Moberg CNS Monitor within 6 hours of ICECAP enrollment (sooner is better)
- Time of **enrollment**: Moberg connected to bedside monitor and collecting data
- **No study interventions**! Observational study of data collected as part of routine clinical care
- **Data transmitted** after patient death/discharge to the cloud

Study Procedures



Support for Participating Sites

- Research Moberg CNS Monitor
- Site start-up – $1,000 after released to enroll
- Per patient reimbursement - $2,000
- Scientific and technical support available 24/7

Our asks

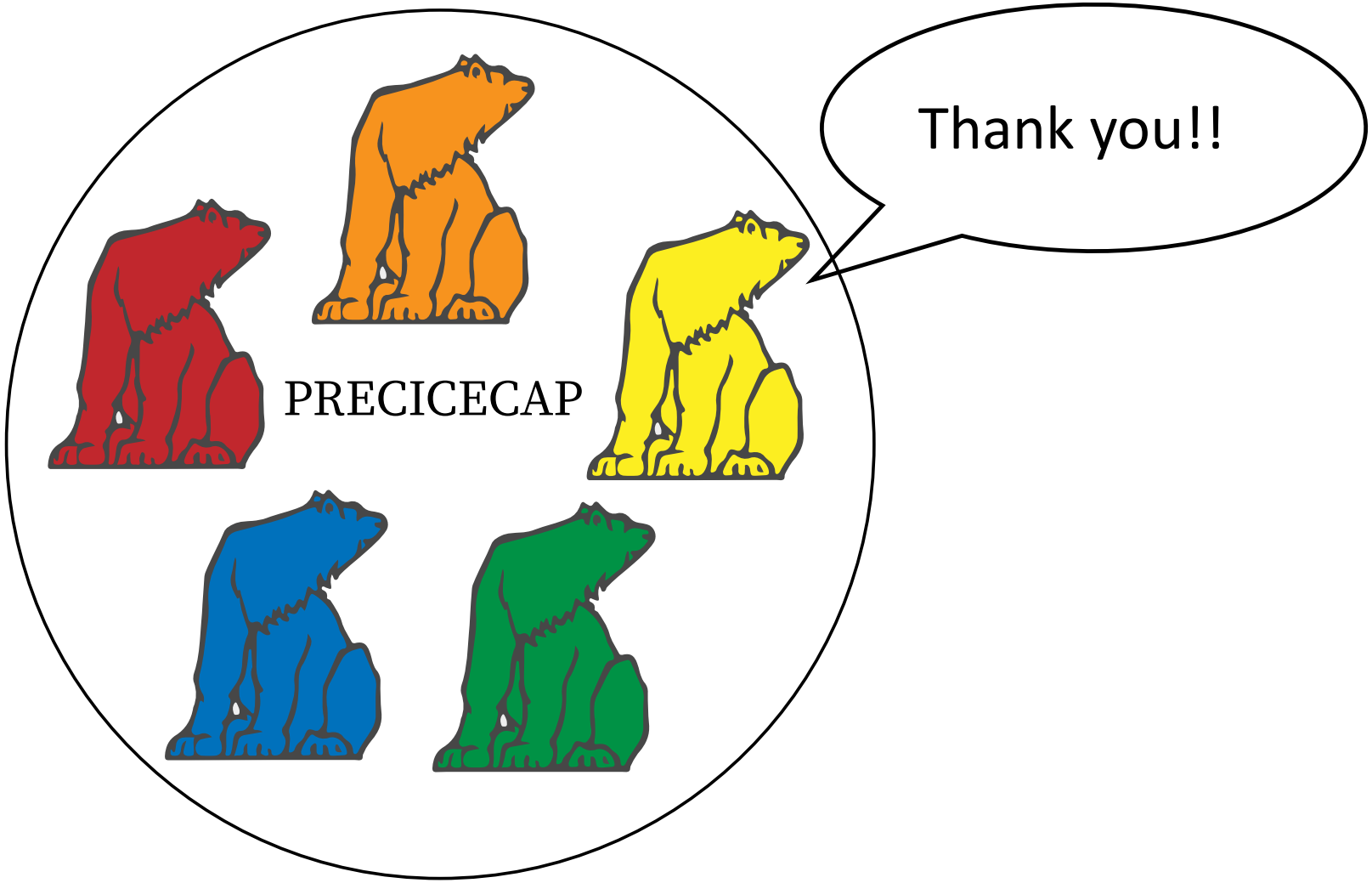
- At least 9 enrollments annually
- Daily structured neurologic exam
- Cardiopulmonary monitoring using invasive arterial pressure monitor (recorded to Moberg CNS monitor) x 5 days
- Admission brain CT imaging
- cEEG* recorded from ICU arrival until at least 12h after rewarming
- Brain MRI* on day 3-5 after cardiac arrest

  - *MRI sequences, EEG montages, and devices left to local clinical practice

Site Selection

Site	Open for enrollment?	Enrollments to date
UPMC (Pittsburgh)	Yes	25
Harborview MC (UW)	Yes	9
UC San Diego MC (UCSD)	Yes	7
University of Michigan (Wayne)	Yes	6
Maine Medical Center (Tufts)	Yes	2
UC Davis	Yes	2
Hennepin County MC (Minnesota)	Yes	1
San Francisco General (UCSF)	Yes	1
Grady Memorial Hospital (Emory)	Yes	1
University of Alabama (UAB)	Yes	0
NYP Columbia MC	Yes	0
Stanford University	No	
Johns Hopkins	No	
Virginia Commonwealth (VCU)	No	
NYC Health Hospitals (Kings County)	No	
Boston University (BU)	No	
Yale	No	

Questions/Discussion



Karen: khirsch@stanford.edu
Jonathan: elmerjp@upmc.edu

Supplemental Information

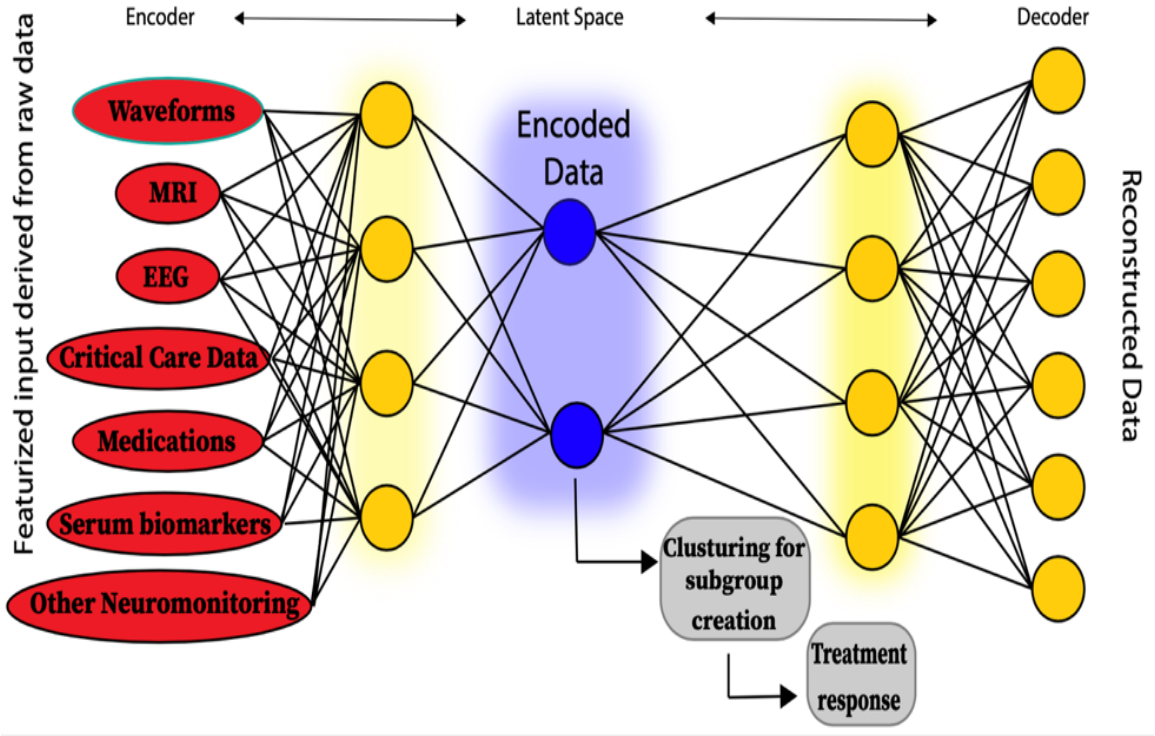
Aims

- **<u>Aim 1:</u> Use advanced analytical approaches to create novel biomarkers from multimodality high-resolution data and test these markers against established predictors to determine optimal duration of hypothermia after cardiac arrest.**

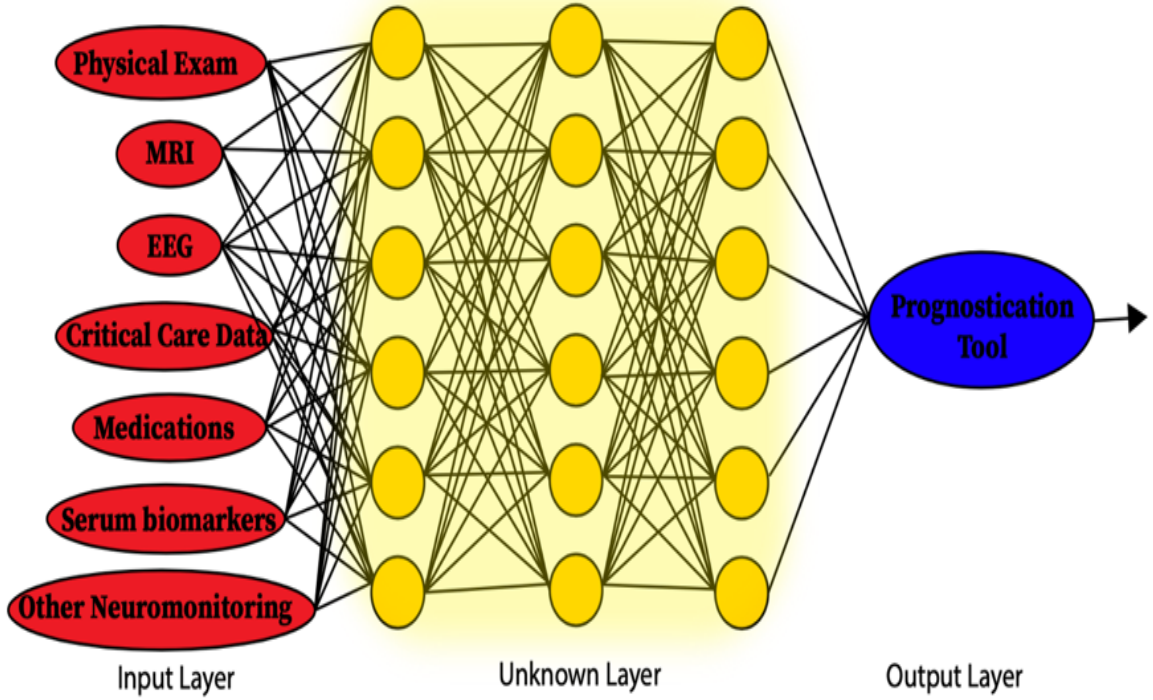
- **<u>Aim 2:</u> To evaluate the performance of novel and established biomarkers to predict 90-day function.**

Statistical Approach

Auto-encoder neural network to identify complex and informative relationship among heterogenous features



Deep learning neural networks to develop a tool to predict 90-day outcome using the composite features



Data Management

- MOBERG CNS monitor data uploaded to cloud after 5 days of recording.
- Within 4 weeks of enrollment, DICOM images should be uploaded
- Yearly upload of EMR medication, laboratory and vital sign data

Study startup

- IRB approval
- Training on Moberg (via zoom)
- Readiness call
- Moberg delivery
- Enrollment starts