HYPERBARIC OXYGEN BRAIN INJURY TREATMENT TRIAL: A MULTICENTER PHASE II ADAPTIVE CLINICAL TRIAL

Virtual Investigator Meeting

Friday, May 2 2025

10:00 am - 12 pm ET

2:00 pm – 4:00 pm ET

HO$_2$BIT

SIREN

Agenda

Friday, May 2, 2025 10:00am - 12:00pm ET and 2:00pm - 4:00pm ET			
Start	**End**	**Item**	**Presenter**
2:00pm	2:05pm	Welcome	Gaylan Rockswold
2:05pm	2:15pm	NIH Partners Feedback from Council Meeting	Gretchen Scott Alva Recinos
2:15pm	2:30pm	Lessons learned from Highest Enrolling Site (HCMC)	Abbey Staugaitis Chris Logue
2:30pm	2:50pm	Enrollment projections and open discussion on strategies to overcome enrollment challenges and enrollment pledges	Bill Barsan
2:50pm	3:00pm	Management of elevated ICP in HOBIT	Gaylan Rockswold
3:00pm	3:20pm	Recent MOP updates and other reminders	Natalie Fisher Sarah Rockswold
3:20pm	3:30pm	GOSE Story (St. Mary's)	Alyha Benitez Tracy Rodriguez
3:30pm	3:40pm	BioHOBIT	Fred Korley
3:40pm	3:50pm	Qualitative study of the feasibility of HBO implementation as a treatment for severe TBI if the trial is successful	Fred Korley
3:50pm	4:00pm	Matters Arising and Adjourn	Gaylan Rockswold

HO$_2$BIT

SIREN

Welcome

Gaylan Rockswold, MD

- We appreciate your time and attention
- The HOBIT trial is at a critical juncture
- We have a renewal grant funded, but adequate enrollment is crucial
- We will hear more about this from our colleagues from NINDS
- Their support and advocacy for HOBIT were essential in obtaining this funding

HO$_2$BIT

SIREN

NIH Partner Feedback

Gretchen Scott, Clinical Research Project Manger, NINDS

HO$_2$BIT

SIREN

Lessons Learned (HCMC)

HO$_2$BIT

SIREN

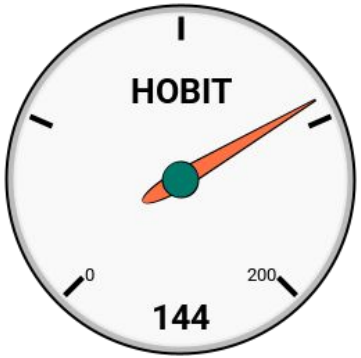
Enrollment Updates & Projections

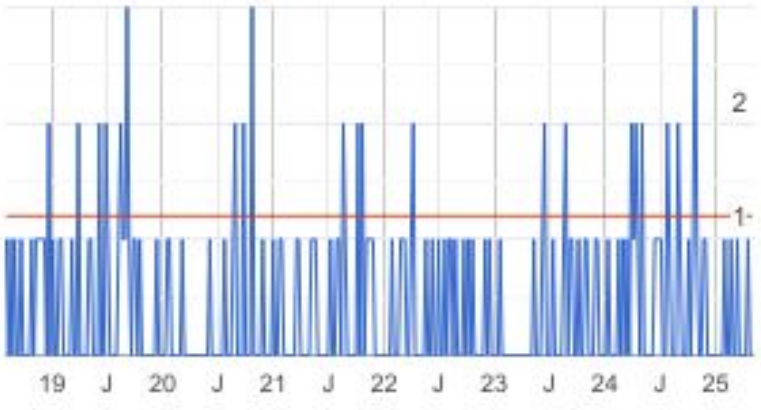
Bill Barsan

HO$_2$BIT

SIREN

Accrual - tracking



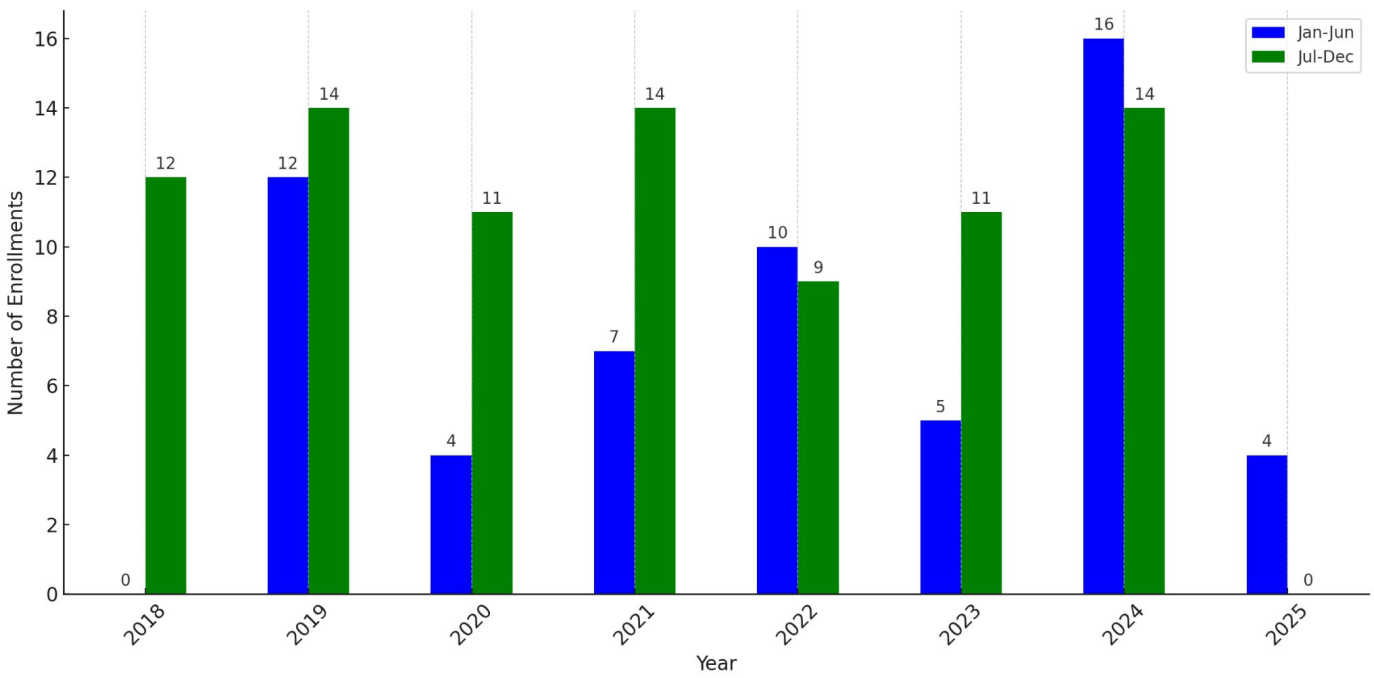


You can always see up to the minute accrual data by clicking the "enrollment dashboard" tile on the siren.network website

HO$_2$BIT

SIREN

Enrollment in 6-month blocks



HO$_2$BIT

SIREN

Inactive

HO$_2$BIT

SIREN

Enrollment Projections

Decision Interim	Current Prediction	95% Prediction Interval
N=116 (1st)	Completed April 3, 2024	--
N=136 (2nd)	Completed October 22, 2024	--
N=156 (3rd)	September 30, 2025	July 15, 2025 to January 23, 2026
N=176 (4th)	June 22, 2026	February 5, 2026 to December 20, 2026
N=200 (Maximum)	May 7, 2027	October 25, 2026 to January 5, 2028

HO$_2$BIT

SIREN

Open discussion on strategies to overcome enrollment challenges

Bill Barsan

HO$_2$BIT

SIREN

Enrollment Pledges

Site	Contribution to get to 156 by Sept 30th
Detroit Receiving	1
Duke	1
Hennepin County	4
St. Mary's	2
UCSD	2
U of Iowa	3
U of Kentucky	2
U of Maryland	2

HO$_2$BIT

SIREN

Management of Elevated ICP in HOBIT

Gaylan Rockswold, MD

HO$_2$BIT

SIREN

- Intracranial hypertension is the major treatable cause of deterioration and death from severe TBI
- If ICP cannot be controlled, HBO will not be effective

Introduction

- Osmotic therapy is a cornerstone of nonsurgical management of ICP. Its effectiveness depends on
  - integrity of the blood brain barrier (BBB)
  - osmotic gradient created
  - reflection coefficient of the agent

HO$_2$BIT

SIREN

ICP Effects

- HTS has the advantage of creating large osmotic gradients without the diuretic properties of mannitol. Thus, volume/electrolyte depletion and hypotension are avoided

HO$_2$BIT

SIREN

ICP Effects

- HTS has a perfect reflection coefficient of 1.0 because of its high polarity and exclusion from the BBB. Mannitol has a reflection coefficient of 0.9

Hemodynamic Effects

- Primary goals of TBI management include avoidance of hypotension and hypoxia
- Significant hypotension doubles mortality rate

HO$_2$BIT

SIREN

Hemodynamic Effects

- HTS maintains mean arterial pressure (MAP) by plasma volume expansion
- High infusion volumes are avoided in contrast to isotonic solutions

HO$_2$BIT

SIREN

Hemodynamic Effects

- Improvement in MAP and reduction in ICP result in increased cerebral perfusion pressure (CPP) and improved cerebral oxygen delivery

HO$_2$BIT

SIREN

How HTS is used at HCMC

- Continuous infusions of 3% HTS at 30 cc/hr
- All severe TBI patients (GCS ≤ 8)
- Moderate intubated TBI patients with central line (GCS 9-13)

HO$_2$BIT

SIREN

Serum Na and osmolarities are monitored every 6 hours

- Goal
  - Serum Na: 140-150
  - Serum osmolarity: 300-320

ICP is monitored

- Goal
  - ≤ 15-20 mmHg
  - HTS infusion increased to serum Na levels 150-160; occasionally up to 170 to control ICP; serum osmolarities to 360

HO$_2$BIT

SIREN

Bolus injections of 30 cc of 23.4% HTS

- Severe TBI patients with ICP > 20 mmHg for > 20 minutes
- At present, mannitol used only very occasionally in ICU

Tapering HTS important as opposed to abrupt discontinuation

- 3% → 2% HTS. No central line or ICU required for 2%
- Occasionally use NaCl tabs 1 gm (17 mEq NaCl) to continue taper and maintain Na ≥ 140

HO$_2$BIT

SIREN

Advantage of HTS Over Mannitol

- Mannitol has caused acute renal failure; much less of a problem with HTS. Cannot exceed serum osmolarity of 320 with mannitol.
- HTS has less “rebound” due to higher reflection coefficient

HO$_2$BIT

SIREN

Advantage of HTS Over Mannitol

- Continuous infusions of HTS seem to stabilize ICP
- Prior to use of HTS, occasional patient with contusion, etc., would clinically deteriorate secondary to hyponatremia late in course

Reference

Rockswold GL, et al: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurg 65:1035-1042, 2009

HO$_2$BIT

SIREN

Decompressive Hemicraniectomy: Two reasons for failure to relieve intracranial pressure

1. Performed too late. Best done when medical treatment begins to fail and before clinical deterioration occurs.
2. Hemicraniectomy is incomplete.
    - Must go close to midline and include the temporal fossa as well as from frontal to occipital poles
    - Dura must be left widely open with dural graft
    - Leaving the bone flap done for a SDH out is not adequate decompression

HO$_2$BIT

SIREN

MOP Updates and Other Reminders

Natalie Fisher & Sarah Rockswold, MD

HO$_2$BIT

SIREN

MOP Updates and Other Reminders

Study Intervention

MOP Section 3.4 | Page 17

For all study arms that include HBO2 plus NBH, the 3-hour **NBH treatment should not be given** if the HBO2 treatment is missed.

HO$_2$BIT

SIREN

MOP Updates and Other Reminders

Intracranial Pressure

MOP Section 3.7.1 | Page 23

Patients with irreversible coagulopathy should be excluded from enrollment in the trial. If there are questions, do not hesitate to call the HOBIT PI Hotline.

HO$_2$BIT

SIREN

MOP Updates and Other Reminders

Management of the Severe TBI Subject in the HBO2 Chamber

MOP Section 3.10.5 | Page 46

Pre-HBO_2 ABG Requirements

- Obtain a pre-HBO_2 ABG:
  - After subject is placed on the hyperbaric ventilator
  - While on baseline FiO_2 (not 100% oxygen)
- Record ABG values on the “Chamber and Subject Log”
- Hold HBO_2 treatment if PF ratio < 200, unless approved by a Hotline call to the HOBIT clinical PIs

Dive Log Version 9

HOBIT Trial – Chamber and Subject Log (Rev. 9) Date: _____

Institution: _____ Subject ID: _____ HOBIT Study Arm: _____

Treatment No. _____ of 10 Circle Type of Chamber: Multiplace / Monoplace

NOTE: Information in this **GRAY BOX** is with the subject **ON THE HYPERBARIC VENTILATOR** and **ON BASELINE FiO2.**

HBO Vent Settings: Vt _____ Vent Set RR _____ Additional Spont. RR _____ Total MV _____

PEEP: _____ PIP: _____ Baseline FiO2: _____ (ABG sample while still on ICU FiO2 not on 100% Oxygen)

ABG: PH _____ PCO2 _____ PO2 _____ PF ratio _____ **NOTE:** If these ABG values require changes to the hyperbaric ventilator, please record those vent changes and the repeat ABG values on the "Comments" line below.

SYMBOLS: **Brain O2** (Oxygen level of brain tissue in mmHg) **MAP** (Mean arterial pressure) **ICP** (Intracranial Pressure)

HO$_2$BIT

SIREN

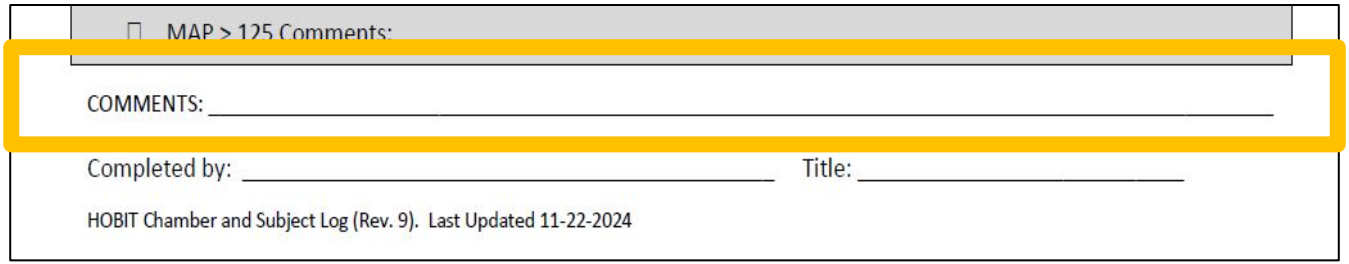
MOP Updates and Other Reminders

Management of the Severe TBI Subject in the HBO2 Chamber

MOP Section 3.10.5 | Page 46

If Ventilator Settings Are Changed

- Take a repeat ABG
- Document repeat values in the “Comments” section of the log
- May switch to 100% FiO_2 and begin treatment only after verifying:
  - Acceptable $PaCO_2$ & Acceptable PF ratio
- Consider an additional ABG after returning to ICU ventilator



HO$_2$BIT

MOP Updates and Other Reminders

Management of the Severe TBI Subject in the HBO2 Chamber

MOP Section 3.10.5 | Page 46

NBH Only Arm

- Obtain ABG pre-NBH treatment on baseline FiO2 (not 100% oxygen)
- Hold NBH treatment if:
  - PF ratio is < 200, unless approved via Hotline call to the HOBIT clinical PI.
- Proceed with treatment only after confirming proper ventilation and PF ratios.

HO$_2$BIT

SIREN

MOP Updates and Other Reminders

Baseline CT Scans

HO$_2$BIT

SIREN

MOP Updates and Other Reminders: SAEs

- Updated combined CPP/ICP/MAP SAE template in the MOP
- Enrolling sites have been using it regularly

HO$_2$BIT

SIREN

MOP Updates and Other Reminders: SAEs

- Please remember to put where the episode occurred, i.e. ICU, during transport, during treatment
- Email and/or call me if any questions

HO$_2$BIT

SIREN

MOP Updates and Other Reminders: Outcomes

- Both the participant and their caregiver must be interviewed (separately) unless the participant is vegetative or unable to communicate

MOP Updates and Other Reminders: Outcomes

- If the primary outcome has not been done 2 weeks prior to the window closing, a meeting will be scheduled with the site's entire team and the central outcome monitors

MOP Updates and Other Reminders: Outcomes

- Obtaining the primary outcome is crucial
- St. Mary's success story

HO$_2$BIT

SIREN

ST. MARY'S MEDICAL CENTER
PRINCIPLE INVESTIGATOR: ROBERT BORREGO
STUDY COORDINATOR: ALYHA BENITEZ
RESEARCH MANAGER: TRACY RODRIGUEZ

Agenda

- Subject follow up
- Day 30, Day 90, Day 180
- Tips & Takeaways

Patient consented Now what?

EFIC

- Stay connected with Trauma Resuscitation and ICU nurses for family contact.
- Communicating with Law enforcement.
- Check the case managers and nurse's notes for family contact information or numbers.

Family Present

- Family Contact information

  *Get as many contacts numbers as possible

  * Language spoken at home (You may need a language line)

  * Explain how important follow up calls are

  * When contacting families assure them that you are not calling for anything other than patients well-being.

PATIENT DISCHARGED

- The patient was discharged out of the country in October 2024.

90-day assessment arrived; patient's family was not answering phone calls.

Contact information that was given the family denied involvement.

How do we contact out of the country??

Take aways

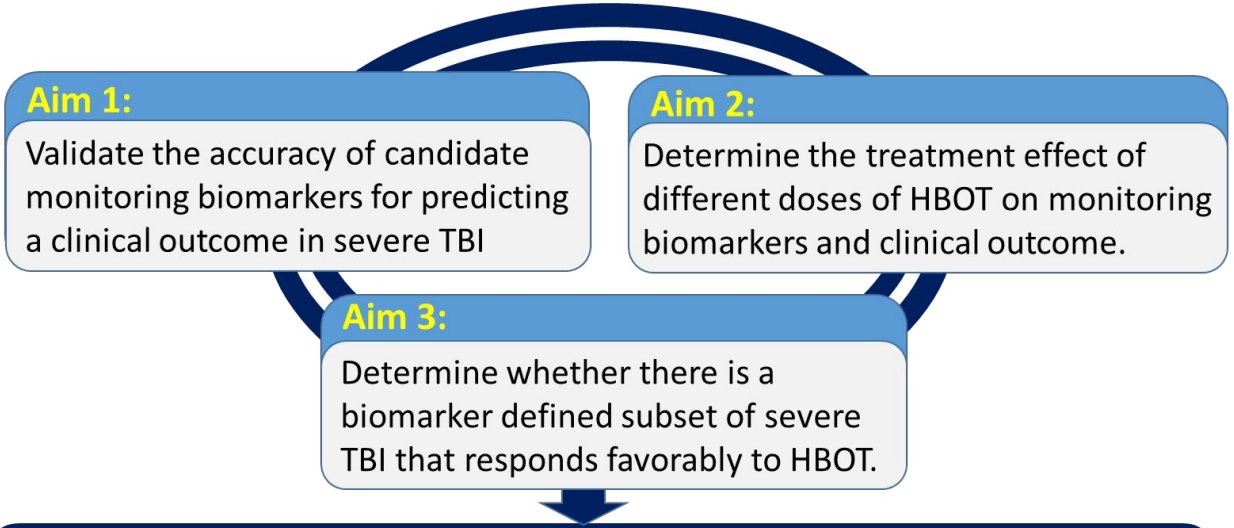
- Communication is key, especially during discharge.
- Persistence
- Teamwork
- Coordinate time with GOSE accessor and family.
- Utilizing different tools (I.e. WhatsApp)

- Finally able to complete 180 in April of 2025

Questions?

THANK YOU- FROM THE ST. MARY'S TEAM.

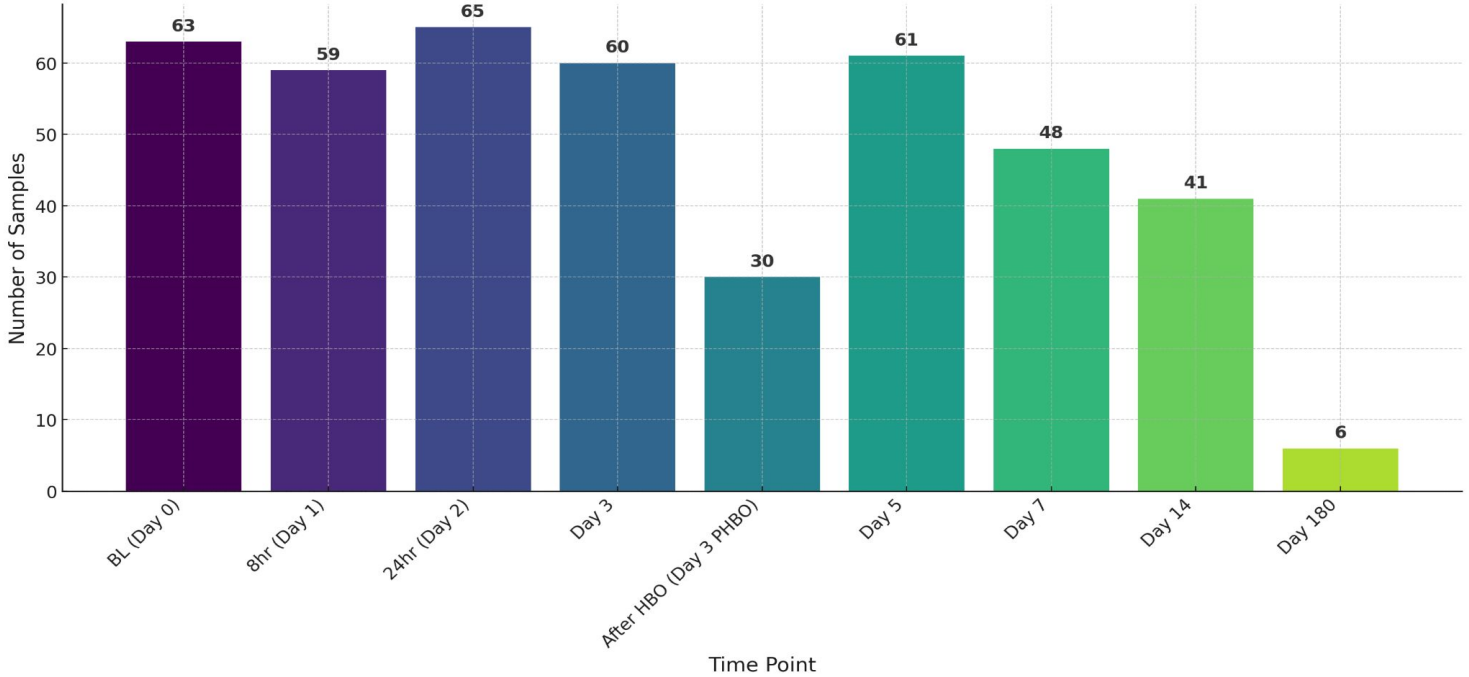
BioHOBIT - Study Overview



HO$_2$BIT

SIREN

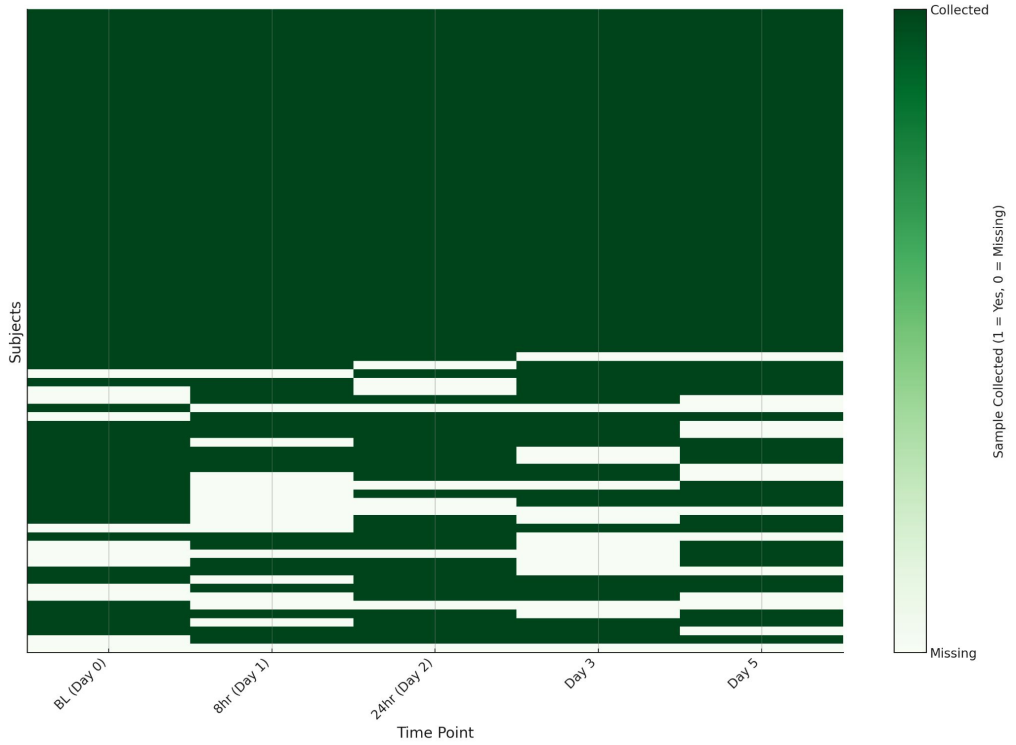
BioHOBIT - Samples as of 2/21/2025



HO$_2$BIT

SIREN

Patterns of missingness in samples Days 1-5



HO$_2$BIT

SIREN

NULISAseq™ Inflammation Panel 250

Most complete coverage of cytokines and chemokines on the market

~250
biomarkers from 25µL

Attomolar sensitivity
(10 fg/mL)

~12 logs
dynamic range without dilution

Highly reproducible
CV <10%

TARGETS

CYTOKINES	IL17A|IL17F	LIF	CCL16	CXCL16	IL17RA	TEK	FGF19	CD40LG	GZMA	PDCD1LG2
CNTF	IL17B	LTA	CCL17	CXCL2	IL17RB	TLR3	FGF2	CD46	GZMB	PTX3
CSF1	IL17C	LTA|LTB	CCL19	CXCL3	IL18BP	TNFRSF11A	FGF21	CD70	HLA-DRA	S100A12
CSF2	IL17F	OSM	CCL2	CXCL5	IL18R1	TNFRSF11B	FGF23	CD80	ICAM1	S100A9
CSF3	IL18	SPP1	CCL20	CXCL6	IL1R1	TNFRSF13B	GDF15	CD83	ICOSLG	SCG2
CTF1	IL19	THPO	CCL21	CXCL8	IL1R2	TNFRSF13C	GDF2	CD93	IL1RN	SDC1
CX3CL1	IL1B	TNF	CCL22	CXCL9	IL1RL1	TNFRSF14	HGF	CHI3L1	IRAK4	SELE
FLT3LG	IL2	TNFSF10	CCL23	TAFA5	IL2RA	TNFRSF17	NGF	CLEC4A	KITLG	SELP
IFNA1; IFNA13	IL20	TNFSF11	CCL24	**RECEPTORS**	IL2RB	TNFRSF18	NTF3	CST7	KNG1	THBS2
IFNA2	IL22	TNFSF12	CCL25	AGER	IL3RA	TNFRSF1A	PDGFA	CTLA4	LAMP3	TIMP1
IFNB1	IL23A|IL12B	TNFSF13	CCL26	CD3E	IL4R	TNFRSF1B	PDGFB	FURIN	LCN2	TIMP2
IFNG	IL24	TNFSF14	CCL27	CD4	IL5RA	TNFRSF21	PGF	**OTHER**	LGALS9	VCAM1
IFNL1	IL27|EBI3	TNFSF15	CCL28	CD40	IL6R	TNFRSF4	TGFB1	AGRP	MICA	VSNL1
IFNL2;IFNL3	IL32	TNFSF18	CCL3	CSF1R	IL6ST	TNFRSF8	TGFB3	BST2	MICB	VSTM1
IFNW1	IL33	TNFSF4	CCL4	CSF2RB	IL7R	TNFRSF9	VEGFA	C1QA	MIF	WNT16
IKBKG	IL34	TNFSF8	CCL5	CSF3R	KDR	TREM1	VEGFC	CALCA	MMP1	WNT7A
IL10	IL36A	TNFSF9	CCL7	CXADR	KLRK1	TREM2	VEGFD	CEACAM5	MMP12	
IL11	IL36B	TSLP	CCL8	FLT1	LAG3	**GROWTH FACTORS**	**REGULATION**	CRP	MMP3	
IL12A|IL12B	IL36G	**CHEMOKINES**	CXCL1	FLT4	LILRB2	ANGPT1	ANXA1	CTSS	MMP8	
IL12B	IL4	CCL1	CXCL10	HAVCR1	MERTK	ANGPT2	CD200	EPO	MMP9	
IL13	IL5	CCL11	CXCL11	IL10RB	NCR1	AREG	CD200R1	FASLG	MPO	
IL15	IL6	CCL13	CXCL12	IL12RB1	OSMR	BDNF	CD27	FTH1	MUC16	
IL-16	IL7	CCL14	CXCL13	IL13RA2	SIRPA	BMP7	CD274	GFAP	NAMPT	
IL-17A	IL9	CCL15	CXCL14	IL15RA	SLAMF1	EGF	CD276	GRN	PDCD1	

NULISAseq™ CNS Disease Panel 120

Comprehensive analysis across major hallmarks of CNS Disease

AMYLOID & TAU PATHOLOGIES		
Abeta38 (aβ38)	BACE1	PSEN1
Abeta40 (aβ40)	BASP1	pTau181
Abeta42 (aβ42)	CD63	pTau217
ACHE	CST3	pTau231
APOE	IGFBP7	SFRP1
APOE (APOE4)	KLK6	tTau(totalTau)

SYNUCLEIN & SYNAPTIC		
AGRN	IL6R (IL6Rα)	SNCB (β-Syn)
ARSA	MDH1	SOD1
BDNF	NGF	TDP43
DDC	Oligo-SNCA (Oligo-α-Syn)	pTDP43-409
FABP3	PARK7	UCHL1
FOLR1	pSNCA-129	VGF
HTT	SNCA (α-Syn)	VSNL1 (VILIP-1)

VASCULAR & METABOLISM	
FLT1 (VEGF R1)	PGK1
HBA1; HBA2	POSTN
KDR (VEGF R2)	PTN
MME	SAA1
PDGFRB	VEGF-A
PGF(PLGF)	VEGF-D

NEURODEGENERATION	
ANXA5	NPTX2
CALB2	NPTXR
CNTN2	NPY
ENO2	NRGN
FGF2 (FGF basic)	PDLIM5
GDI1	REST
GDNF	SMOC1
GOT1	SNAP25
MSLN	SQSTM1
NEFH	UBB
NFL	YWHAG
NPTX1	YWHAZ

INFLAMMATION			
CCL2 (MCP1)	CSF2 (GM-CSF)	IL4	PRDX6
CCL3 (MIP1a/CCL3)	CX3CL1 (Fractalkine)	IL5	RUVBL2
CCL4 (Mip1b/CCL4)	CXCL1 (GROa)	IL6	S100A12
CCL11 (Eotaxin)	CXCL8 (IL8)	IL7	S100B
CCL13 (MCP4)	CXCL10 (IP-10)	IL9	SFTPD
CCL17 (TARC/CCL17)	FCN2	IL10	SLIT2
CCL22 (MDC)	GDF15	IL12A|IL12B (IL-12p70)	TAFA5
CCL26 (Eotaxin-3)	GFAP	IL13	TEK (Tie-2/TEK)
CD40LG (CD40L/TNFSF5)	ICAM1	IL15	TIMP3
CHI3L1 (YKL40)	IFNG (IFN-gamma)	IL16	TNF (TNF-a)
CHIT1	IGF1R	IL17A	TREM1 (sTREM1)
CRH	IL1B(IL-1 beta)	IL18	TREM2
CRP	IL2	IL33	VCAM1(CD106)

Designed with input from pharmaceutical and academic KOLs

Enabled by NULISA's combination of ultra-sensitivi and high-plex using 25 µL

Covers key biomarkers of hallmarks of neurodegenerative diseases

High Detectability:
~98% in plasma
~88% in CSF

Qualitative Study

Identify

a) at the hospital level
b) at the provider level

key barriers and facilitators to widespread adoption of HBO as a therapeutic intervention for severe TBI, if a phase III study demonstrates efficacy

HO$_2$BIT

SIREN

Matters Arising, Adjourn

Gaylan Rockswold

HO$_2$BIT

SIREN