HOBIT

Hyperbaric Oxygen Brain Injury Treatment Trial:

A Multicenter Phase II Adaptive Clinical Trial

Funded by the NINDS

Goals

- **Explain the rationale for the potential efficacy of HBO_2 in the treatment of severe TBI**
- **Review the preliminary data supporting the funding of the HOBIT trial**
- **Review the structure and current progress of the HOBIT trial**

Need for a Multicenter Randomized Clinical Trial

- **Outcome from severe TBI has been flatlined for several decades**
- **No specific treatment despite multiple randomized clinical trials**
- **Medical and economic costs of severe TBI are large**
- **HBO_2 has significant potential as a treatment**

Traumatic Brain Injury: Magnitude of Problem

- **3.65 million brain injuries per year**
- **2.2 million emergency department visits**
- **280,000 hospitalizations**
- **53,000 deaths**
- **Direct & indirect costs of $76.5 billion**

- **Source CDC**

TBI Statistics

- **Major issue is premature death and disability**

- **TBI is a disease of the young**
  - **84% of the 3.5 million TBIs are sustained by people age 64 or less**

Definition of Severe Traumatic Brain Injury

- **Glasgow Coma Scale (GCS) score 3-8**
- **Intracranial hypertension 40-50%**
- **Multiple injuries 50%**
- **Surgical mass lesion 40-50%**
- **Mortality 30-35%**
- **Favorable outcome 40-45%**
- **Represents only 10% of all TBI**

The Brain

- **2% of body weight**
- **15% of cardiac output**
- **20% of oxygen consumption**
- **25% of glucose consumption**
- **No oxygen storage**

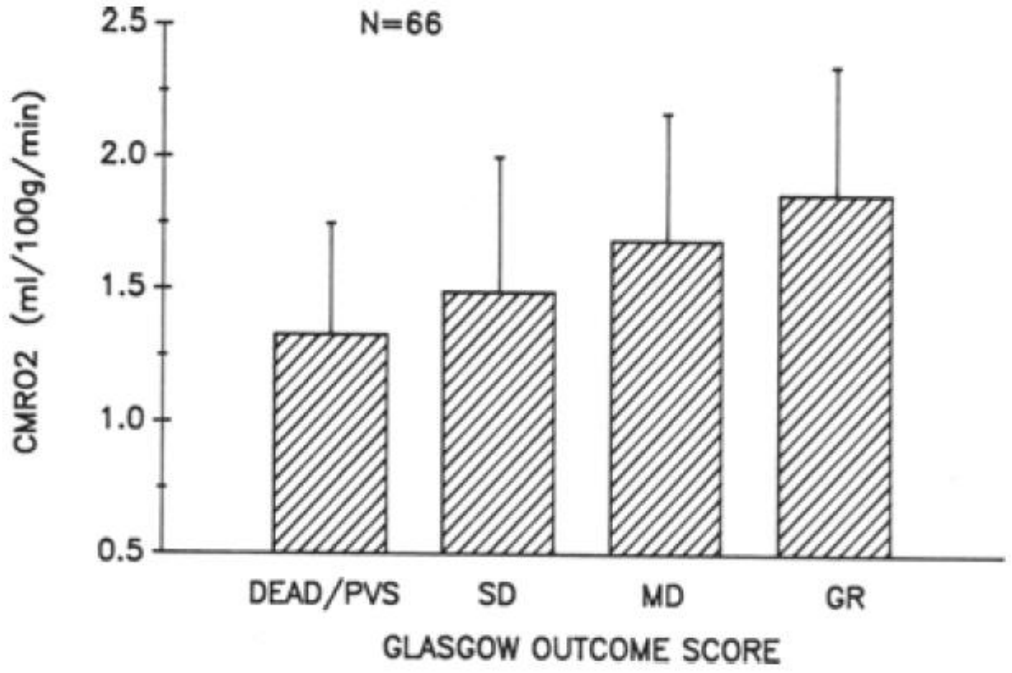
More than 90% of the oxygen consumed by the brain is used by the mitochondria to generate energy to maintain complicated synaptic functions (50%), ionic balance (25%), and protein synthesis (25%).

- **The immediate reaction of the brain to injury is to actually increase its metabolic demands in response to the stress**
- **At the same time, there is a decrease in oxygen delivery to the brain due to decreased blood flow and swelling in the brain, i.e., a flow/metabolic mismatch**

Potential Mechanisms for HBO_2 Efficacy

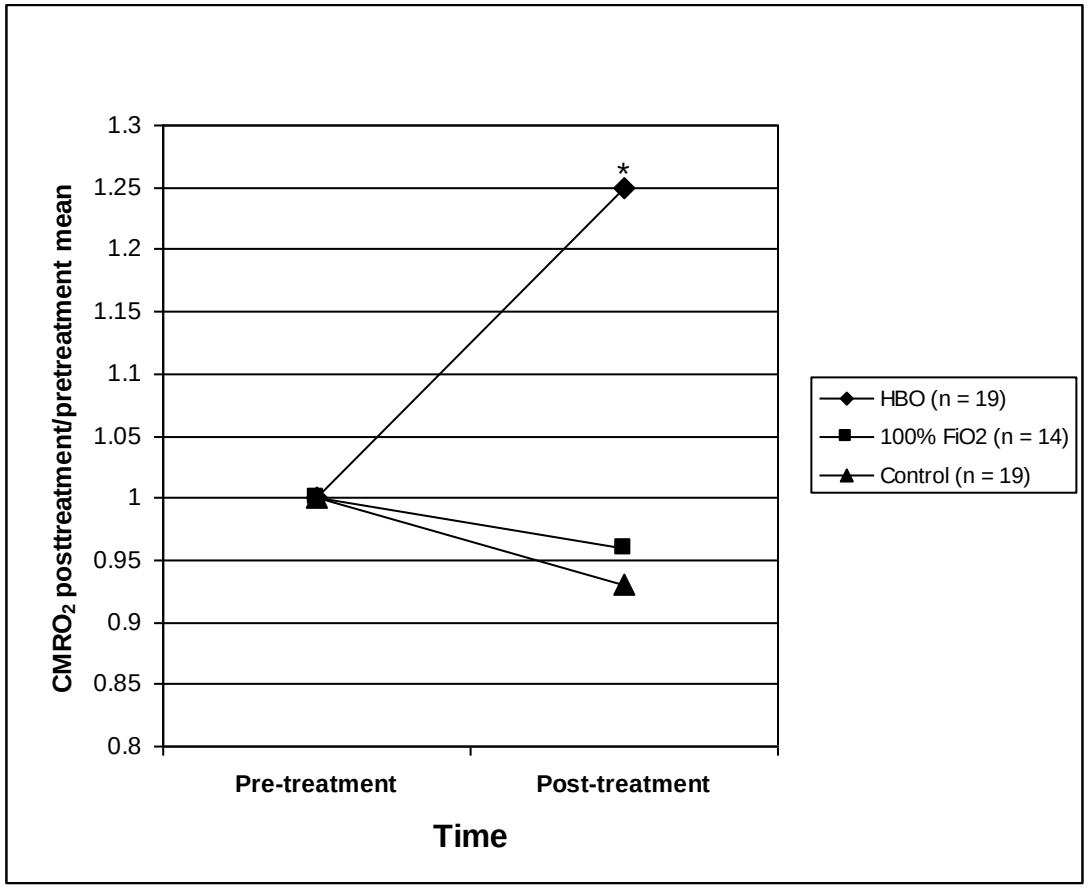
- **Since more than 90% of oxygen consumed by the brain is used by mitochondria, global oxygen consumption by the brain is a surrogate measurement of mitochondrial function, i.e., energy production**
- **Cerebral metabolic rate of oxygen = cerebral blood flow *x* arteriovenous difference of oxygen ($CMRO_2$ = CBF *x* $AVDO_2$)**

Low $CMRO_2$ is Associated with Poor Outcome



*Jaggi and Obrist, J Neurosurg 72:176-182, 1**990***

Cerebral Metabolic Rate of Oxygen



Rockswold, J Neurosurg 112:1080-1094, 2010

Potential Mechanisms for HBO_2 Efficacy

- **Pre-clinical findings**
  - **Depressed mitochondrial function following injury is restored**
  - **ATP production is improved**
  - **Ischemia-induced brain cell loss is attenuated**
  - **Neural apoptosis is reduced**
  - **Cognitive deficits are markedly attenuated**
  - **Intracranial hypertension is reduced**
- **These findings are based on investigations in 8 injury models, 4 different animal species, and at least 12 established laboratories and were published in multiple peer-reviewed scientific journals**

MULTIPLACE CHAMBER

Monoplace Chamber

Inclusion Criteria

- **Age 16-65 years**
- **Severe TBI defined as an iGCS of 3 to 8 in the absence of paralytic medication**
- **For patients with a GCS of 7 or 8 or motor score = 5, Marshall CT score > 1**
- **For patients with an alcohol level > 200 mg/dl, Marshall CT score > 1**
- **For patients not requiring a craniotomy/craniectomy or any other major surgical procedure, the first HBO_2 treatment can be initiated within 8 hours of admission**
- **For patients requiring a craniotomy/craniectomy or major surgical procedure, the first HBO_2 treatment can be initiated within 14 hours of admission**

Treatment Arms

	Arm	Dose (Oxygen Toxicity Units, $\nu_a * 100$)
1.	Control (1.0 ATA)	0
2.	1.5 ATA	260
3.	2 ATA	416
4.	NBH (100% FiO2 at 1.0 ATA)	540
5.	2.5 ATA	592
6.	1.5 ATA+NBH	620
7.	2 ATA+NBH	776
8.	2.5 ATA+NBH	952

Treatments given BID x 5 days
Compression/decompression at 2 feet/minute
At depth for 60 minutes

Adaptive Trials

- **A clinical trial design that allows prospectively planned modifications based on accumulating data.**
- **Responsive Adaptive Randomization (RAR). At set points of enrollment more patients are randomized to the more effective treatment arms.**
- **200 patients to be enrolled.**
- **First interim analysis for efficacy/futility at 116 patients.**

Objectives

- **Objective 1**
  - **Signal of efficacy: To determine, in subjects with severe TBI, whether there is a > 50% probability of hyperoxia treatment demonstrating improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial**

- **Objective 2**
  - **Dose selection: To select, in subjects with severe TBI, the combination of treatment parameters (pressure +/- intervening normobaric hyperoxia) that is most likely to demonstrate improvement in the rate of good neurological outcome versus control in a subsequent confirmatory trial**

Primary Endpoint

- **The treatment groups will be compared with respect to the proportion of subjects with favorable outcome at 6 months post randomization utilizing the injury severity adjusted GOS-E**

GOS-E

1	Dead	
2	Vegetative	Condition of unawareness with only reflex responses but with periods of spontaneous eye opening
3	Lower severe disability	Patient fully dependent for all activities of daily living. Requires assistance to be available constantly. Unable to be left alone at night
4	Upper severe disability	Can be left alone at home for up to eight hours but remains dependent. Unable to use public transport or shop by themselves
5	Lower moderate disability	Able to return to work in sheltered workshop or non competitive job. Rarely participates in social and leisure activities. Ongoing daily psychological problems (quick temper, anxiety, mood swings, depression)
6	Upper moderate disability	Able to return to work but at a reduced capacity. Participates in social and leisure activities less than half as often. Weekly psychological problems
7	Lower good recovery	Return to work. Participates in social and leisure activities a little less and has occasional psychological problems
8	Upper good recovery	Full recovery with no current problems relating to the injury

The advantages of the GOS-E are its simplicity, wide recognition, and the fact differences in disability are clinically meaningful

GOSE

- **Categories are subdivided into upper and lower stratifications for the outcomes of**
  - **“Severely disabled” (three, four), “Moderately disabled” (five, six) and “Good recovery” (seven, eight)**
- **“Death” is scored as one, and “persistent vegetative state” as two.**

GOSE Scoring

- **Favorable outcome in the HOBIT trial will be defined based on the sliding dichotomy methodology**
  - **Subjects whose initial GCS scores are 6-8 are considered to have a favorable outcome if their 6-month GOS-E score is upper good recovery to lower moderate disability**
  - **Subjects whose initial GCS scores are 3-5 are considered to have a favorable outcome if their 6-month GOS-E score is upper good recovery to upper severe disability**

HOBIT Clinical Outcome Assessment

- **HOBIT is a single blinded trial not double blinded**
- **Treatment is not blinded but outcome determination is blinded**
- **Rationale**
  - **Virtually impossible to blind HBO_2 treatment**
  - **Controls should not be subjected to the transport to and from the ICU to the HBO_2 unit twice a day for 10 treatments. This is a potential source of morbidity for HBO_2-treated patients**

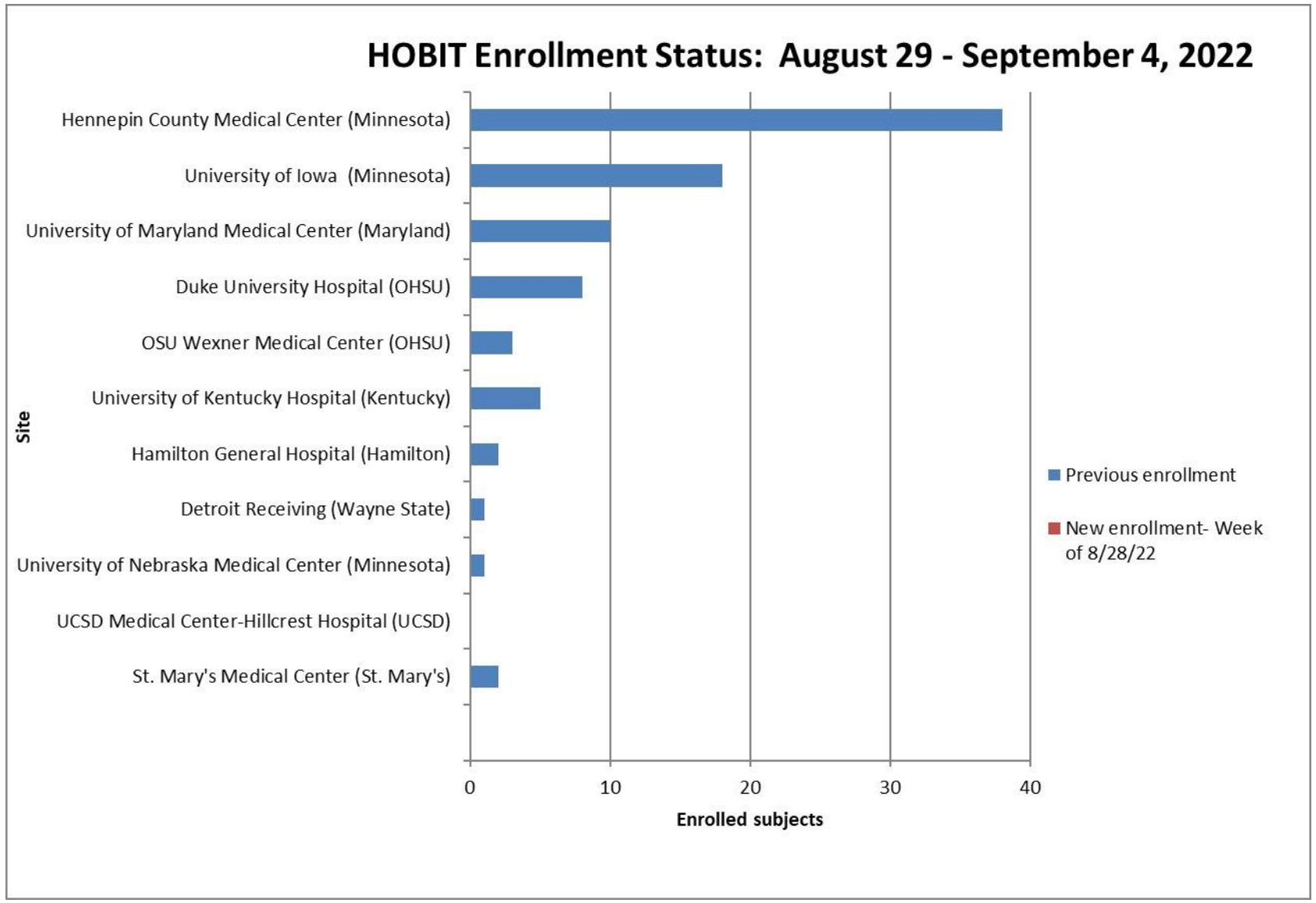
Secondary Endpoints

- **To analyze the level and duration of intracranial hypertension (>22 mmHg) in HBO_2-treated versus control group**
- **To analyze the therapeutic intensity level scores for controlling intracranial pressure in HBO_2-treated subjects compared to controls**
- **At sites utilizing $PbtO_2$ monitoring, analyze the level and duration of brain tissue hypoxia ($PbtO_2$ < 20 mmHg) in HBO_2-treated groups versus control)**
- **To compare the type and rate of serious adverse events between hyperoxia treatment arms and control**
- **Peak $PbtO_2$ levels during HBO_2 treatments will be correlated with outcome at 6 months**

Enrolling Site Requirements

- **Expertise in management of severe TBI**
- **Significant experience in critical care HBO_2 medicine, i.e., intubated, ventilated patients**
- **A team of neurosurgeons, intensivists, trauma surgeons and hyperbaric physicians working together**
- **Level I trauma center preferred**

***There is a lack of institutions doing critical care HBO_2 in the USA. A successful HOBIT trial may help improve that situation.**


HOBIT Enrollment Status: August 29 - September 4, 2022
Hennepin County Medical Center (Minnesota)
University of Iowa (Minnesota)
University of Maryland Medical Center (Maryland)
Duke University Hospital (OHSU)
OSU Wexner Medical Center (OHSU)
University of Kentucky Hospital (Kentucky)
Hamilton General Hospital (Hamilton)
Detroit Receiving (Wayne State)
University of Nebraska Medical Center (Minnesota)
UCSD Medical Center-Hillcrest Hospital (UCSD)
St. Mary's Medical Center (St. Mary's)
Site
0
10
20
30
40
Enrolled subjects
Previous enrollment
New enrollment- Week of 8/28/22

Problems Encountered in HOBIT

- **The major problem is a depressed enrollment rate due to several factors**
  - **The complexity of the treatment delivered to these severely injured patients**
  - **The 8-hour treatment window is very demanding**
  - **COVID has halted clinical research altogether at all sites for varying time periods and reduced available staff when the trial was restarted**
- **Recruiting qualified enrolling sites**

Progress so Far

- **88 patients enrolled**
- **Mean GCS = 6.2**
- **Craniotomy/decompressive craniectomy = 54%**
- **365 HBO_2 treatments delivered**
- **14 SAEs judged related to HBO_2 by the IMSM**
- **None unexpected**
- **Overall mortality = 23.7%**
- **Exception From Informed Consent (EFIC) has been instituted at 8 of our 9 enrolling sites**

HOBIT GOSE

Allison Carolan MS CCC-SLP

Consciousness

- Is the person able to obey simple commands or say words?
  - False negatives could be due to trach tube (can't voice without a speaking valve), apraxia (can't move limbs to follow commands), new paralysis due to brain injury. I voice these observations on the recording "I see you have a trach tube, and your arms are in casts."

    - Stick out your tongue
    - Smile

    →Some people may have broken jaw/ tight jaw wiring that limits tongue excursion but they will still generally "try" to move lips when cued to smile to demonstrate understanding. Do not smile at them when commanding them to smile.

    →If talking to the patient, keep it simple, keep statements direct and brief.

Independence in the home

- Clues in the hospital room:
  - If there is nurse in the room throughout your assessment, ask the nurse if they are a “1:1 sitter.” 1:1 sitters are employed when a patient cannot be left alone for 15 minutes or less.
  - Check the room for a video monitor machine. This is a clue that a patient is on a remote 1:1 sitter.

  If a patient is very low level, needs frequent help, focus on baseline information for remaining assessment with family.


Weigh
Zero Bed
0.0
OFF
Surface
Alarms
Turn R
Turn L
Bed Exit Sensitivity
Normal
Max. Inflate
Bed Exit
Alarm Silence
Volume

Independence in the home

For 90+ day assessments, if they are NOT living at home, try to assess what type of place they are at and why.

- Is it a skilled nursing facility or rehab unit? If so, determine if they are there because of the TBI, or if they are primarily there (versus at home) because of something like pelvic fractures or non-weight bearing status (ortho injuries). About 50% of the time, the patient lacks insight into the primary reasons why they are staying there so family is often best able to answer these questions. In most cases (aside from bilateral lower limbs out), if they are in a SNF or rehab setting, they can’t be left alone for 8 hours.

Independence in the home:

An example of poor insight (watch family members' expressions if in the room)

- Example: (phone)
- "What kind of place are you staying at currently?"
  "It's in (city). There are old people there and some people like me."
- Do you think you could you be left alone without help for 8 hours?
  - "I think so."

  Some sample follow up questions:
- Do you have supervision or lots of help during the day at your rehab facility like to go to the bathroom?
- What therapies do you have daily at the rehab facility? (OT/PT/SLP vs. just PT)
- Do you have any alarms on your bed or wheelchair to remind you to call for help?
  - *"Sometimes"*
- Do you know what medications you are taking and what time you take them?
  - *"They bring those for me."*
- Can you walk by yourself to the bathroom or use a commode independently?
  - *"I think I can, but I'm not supposed to, they don't want me to."*

If they can’t be left alone, move on to asking about baseline information.

- Corroborate everything (do this gently, or pull family member aside afterwards as this can be distressing).
- Confabulation and insight impairments are common especially in the early 1-3 months post TBI.

Examples:

- “I went outside alone last night, they let me go to the corner store.”
- “My boss is expecting me back at work tomorrow.”
- “They stole my cell phone!”

Ranchos Los Amigos

Level 1	**No Response** to ALL Stimulus	Total Assist
Level 2	**Response to Pain** through Gross bodily movement and vocalization=Inconsistent	Total Assist
Level 3	**Response to Discomfort** stimuli inconsistently when localized with commands	Total Assist
Level 4	**Confused Agitated inappropriate** *Short Attn Span	Max Assist
Level 5	**Confused Non-Agitated Inappropriate** *May Respond to Simple commands and habilitual tasks	Max Assist
Level 6	**Confused Appropriate Response** *Problem solving issues	Mod Assist-Max Assist
Level 7	**Automatic-Robotlike, Appropriate** *Better with habitual tasks *Unsafe and Impulsive *Decreased Social Awareness *Can carry an intelligent conversation with minimum confusion	Mod Assist
Level 8	**Purposeful Appropriate** response *Decreased tolerance to stress *Some reasoning skills *Retains new tasks learned with SBA	Min Assist-SBA
Level 9	**Purposeful Appropriate** Response *Attn span 2hrs *Good with familiar tasks from memory	SBA
Level 10	**Purposeful Appropriate** *Problems Solves *Anticipates	Modif Ind-Ind

Psychological Problems

"Coming out of coma" versus "Psychological problem"

Confusion most common at 30-Day:

"He was agitated and swearing and striking out at people and I was worried he would be stuck in the mental state he was in when he was injured, he was using drugs at the time he was hurt."

Agitation might be no-change.