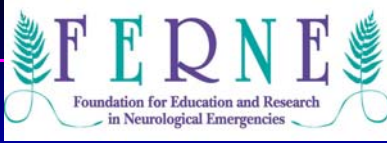


**FERNE / MEMC IV Brain Illness and Injury Course:
NETT: Neurological Emergencies Treatment Trials
William Barsan, MD, FACEP**




Welcome to the
NETT
Neurological Emergencies
Treatment Trials

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FERNE
Foundation for Education and Research
in Neurological Emergencies

**FERNE Brain Illness
and Injury Course**

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The Fourth
Mediterranean Brain and Injury Course (MEMC IV)
Sorrento, Italy
15-19 November 2007



**4th Mediterranean
Emergency Medicine
Congress
Sorrento, Italy
September 17, 2007**

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**Neurological Emergencies
Treatment Trials Network**




**Overview of
the new
network**

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Overview

1. The Problem - Neurological Emergencies
2. Developing a Solution
3. The Nuts and Bolts - NETT
4. Impact

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1. Neurological Emergencies


- Spectrum of pathology
- High burden of disease
- Importance of early treatment

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**FERNE / MEMC IV Brain Illness and Injury Course:
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Neurological Emergencies Spectrum of Pathology

- Neurotrauma: Brain & Spinal Cord Injury
- Stroke: Ischemic & Hemorrhagic
- Status Epilepticus
- CNS Infections: Meningitis & Encephalitis
- Anoxic Brain Injury
- Others: Bell's Palsy, Headache, etc.


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Neurological Emergencies High Burden of Disease

Acute Ischemic Stroke	Intracerebral hematoma
200 per 100,000 people	15 per 100,000 people
Mortality 17% at 30 days	Mortality 50% at 30 days
1 st Yr cost \$91,000 /patient	1 st Yr cost \$124,000 /patient

Kissela B et al. Stroke 2004;35(2):426-31.
Klijn CJ et al. Lancet Neurol 2003;2(11):698-701.
Taylor TN, Drugs 1997;54 Suppl 3:51-7
Williams GR et al. Stroke 1999;30(12):2523-8

Taylor TN, Drugs 1997;54 Suppl 3:51-7
Broderick JP, et al. J Neurosurg 1993;78(2):188-91
Oureshi AI et al. N Engl J Med 2001;344(19):1450-60


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Neurological Emergencies High Burden of Disease

Traumatic Brain Injury	Spinal Cord Injury
100 per 100,000 people	4 per 100,000 people
Mortality 29% at 30 days	Mortality 20% at 30 days
1 st Yr cost \$136,000 /patient	1 st Yr cost \$200,000 /patient

NIH Consensus Panel, JAMA 1999;282(10):974-83.
Brown AW, et al. NeuroRehabilitation 2004;10(1):27-43.
CDC Fact Sheet: Traumatic Brain Injury (NCIPC), 2005

Sekhon LH, et al. Spine 2001;26(24 Suppl):S2-12.


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Neurological Emergencies High Burden of Disease

Status Epilepticus	Subarachnoid Hemorrhage
40 per 100,000 people	6 per 100,000 people
Mortality 22% at 30 days	Mortality 50% at 30 days
1 st Yr cost \$40,000 /patient	1 st Yr cost \$228,000 /patient

Bassin S, et al. Crit Care 2002;6(2):137-42
Claassen J, et al. Neurology 2002;58(1):139-42
DeLorenzo RJ, et al. Neurology 1996;46(4):1029-35
Penberthy LT, et al. Seizure 2005;14(1):46-51
Wu YW, et al. Neurology 2002;58(7):1070-6

Taylor TN, Drugs 1997;54 Suppl 3:51-7
Broderick JP, et al. J Neurosurg 1993;78(2):188-91
Schievink WI, N Engl J Med 1997;336(1):28-40


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Importance of Early Treatment Lessons Learned

National Acute Spinal Cord Injury Study (NASCIS) Methylprednisolone

- I (1979-84) – enrolled up to 48 hours, negative
- II (1984-90) – enrolled up to 12 hours, negative....
....but positive in subset treated <8 hours
- III (1990-97) – enrolled up to 12 hours, negative

Bracken MB, et al. JAMA 1984;251:45-52, Bracken MB, et al. N Engl J Med 1990;322:1405-11
Bracken MB, et al. JAMA 1997;277:1597-604

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Importance of Early Treatment Lessons Learned


Thrombolytics in Acute Ischemic Stroke t-PA and streptokinase

ECASS (I-II) up to 6 hours, mean 4:24 negative

MAST (I+E) up to 6 hours, mean 4:36 negative

NINDS up to 3 hours, mean 1:59 positive

NINDS Stroke Study Group. N Engl J Med. 1995; 333:1581-7
MAST-E Study Group. N Engl J Med. 1996; 335:145-50, MAST-I Group. Lancet. 1995; 346:1509-14
Hacke W, et al. JAMA. 1995; 274:1017-25, Hacke W, et al. Lancet. 1996; 352:1249-51

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2. Developing a solution

- Boots on the ground
- Multi-disciplinary composition
- Emergence of a network
- Design for the future

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Boots on the ground Emergency Medicine driven

- Neurological emergencies are treated in the initial minutes and hours after arrival mainly by emergency physicians.
- The ED is a challenging and chaotic environment in which to conduct research.
- Emergency physicians represent the “boots on the ground”, those on the front line with the manpower and expertise to conduct research in the ED.

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Multi-disciplinary composition

Neurology, Neurosurgery, EMS, Neuro Critical Care, and Trauma

- Research encompassing a continuum of care that starts in the ambulance or in the emergency department and continues in the ICU, in the OR, on the stroke unit, or in the clinic.
- Network leadership, Hub PI's, and Trial PI's represent a range of specialties.

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Multi-disciplinary collaborations Workforce by Specialty in the US

- 12,000 adult neurologists*
- 1,500 pediatric neurologists
- 3,500 neurosurgeons
- 4,000 hospital emergency departments
- 22,000 emergency physicians

*30% in solo private practice

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Emergence of a Network

Oct	2003	First organizational NET*2 meeting
Mar	2004	NIH conference on ENTEN
2004-2005		NET*2 planning/pilot grant applications
Nov	2005	RFA for NETT Coordinating Center
Apr	2006	RFA for NETT Hubs and SDMC
Aug	2006	NETT Coordinating Center awarded

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Design for the future Large simple trial designs

- Streamlined protocols
- Collect only essential data (short case report forms)
- High enrollment – lower per-patient costs

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Design for the future Emphasis on intervention

- Focus on phase III intervention trials
- Patient-oriented readily-applicable results
- Diverse enrollment (patients & practice environments)

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Design for the future Consent issues

- Exception to informed consent for emergency research
- Optimize methods that respect human subjects
- Dedicate network resources to facilitate local efforts
- Help develop centralized IRB review

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3. Nuts and Bolts

- What – the mission and vision
- Who – the participants
- Why – the incentives
- How – the organizational structure
- When – the time line

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Mission

The mission of the Neurological Emergencies Treatment Trials (NETT) Network is to improve outcomes of patients with acute neurological problems through innovative research focused on the emergent phase of patient care.

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Vision

NETT will engage clinicians and providers at the front lines of emergency care to conduct large, simple multi-center clinical trials to answer research questions of clinical importance.

The NETT structure will be utilized to achieve economies of scale enabling cost effective, high quality research.

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NETT Coordinating and Hub Sites



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What is an appropriate NETT study?

- Conducted in the emergency care setting with the primary intervention in the prehospital or emergency phase of treatment
- Patient oriented primary outcomes
- “Simple” designs with clearly defined endpoints and gather only essential data to answer the scientific question.

What is an appropriate NETT study?

- Sample sizes amenable to eleven hubs (and their spokes if needed)
- Phase III interventional treatment or health services trials. Not pilot studies.
- Be designed such that the results are easily translated into clinical practice.

Study Selection Investigator Initiated Studies

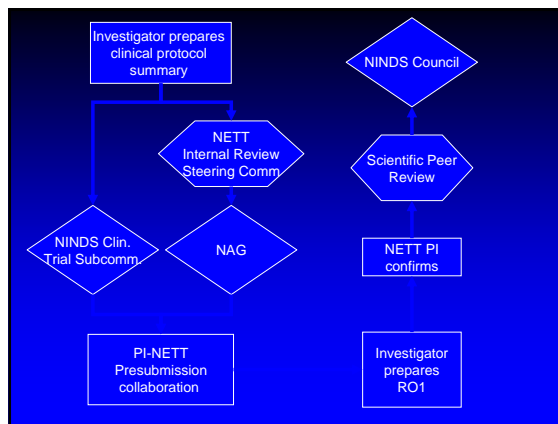
- Investigator Initiated Studies
 - Incentives and Limitations
 - Application Process
- Industry Sponsored Studies
 - Network / Investigator Design

Study Selection Investigator Initiated Studies

- Incentives
 - Investigator receives the trial award
 - Scientific control, credit, authorship preserved
 - Infrastructure already established
- Limitations
 - Fewer funds stay at investigators institution
 - Commitment to stay within the network

Study Selection Investigator Initiated Studies


- Process
 - NETT Trial Guidelines
 - Clinical Trials Subcommittee & NETT-AG
 - Administrative Consultation
 - Submission for Scientific Review



Study Selection


Industry Sponsored Studies

- Network / Investigator Design
 - Scientific Control
 - Shared Economies of Scale
 - No Direct Subsidy
 - NETT-AG solicits scientific review

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Timeline


- Several simultaneous trials
- Staggered planning / enrollment

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How much does it cost? Grant support of NETT


		FY 2006		FY 2007-10	
		Direct	Total	Direct	Total
CCC	U01	\$1M	\$1.5M	\$4M	\$6M
SDMC	U01	\$500K	\$750M	\$2M	\$3M
Hubs	U10	\$200K	\$300K	\$800K	\$1.2M
All 11		\$2.2M	\$3.3M	\$8.8M	\$13.2M
Total		\$3.5M	\$5.25M	\$14.8M	\$22.2M

\$18.3M Direct \$27.4 Total over 5 years

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4. Impact

- Opportunity to advance care of patients with neuro-emergencies
- Large NIH investment in emergency medicine clinical research
- Re-engineering the clinical research enterprise

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NETT studies in the pipeline

- RAMPART
 - Seizures
- ALIAS
 - Ischemic stroke
- ProTECT
 - TBI
- NBPS
 - Bell's Palsy

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nett.umich.edu

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