



# **History & Lessons Learned From Clinical Trials In TBI**

*FDA Public Workshop on Biomarkers for TBI  
Research*

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# Power of Community



## SPECIAL REPORT

A strategically aligned Food and Drug Administration:  
New ways to leverage research and deliver safe, effective, and  
secure devices for trauma care

*Allison Kumar and Suzanne Schwartz, MD, MBA, Silver Spring, Maryland*

*J Trauma Acute Care Surg 2015;79(4):S75-S77*

- **Strengthen clinical trial enterprise**
- **Balance of pre- & post-market data collection**
- **Provide excellent customer service**



# Overview





# History of Clinical Research



- **1930's Dr. Champ Lyons  
Harvard Medical School  
and MGH surgical training  
& attending with Edward  
D. "Pete" Churchill**

**Champ Lyons (1907-1965)**



# History in Clinical Research



- Microbiology interest and involvement in Cocoanut Grove fire (November 1942) led to use of penicillin in severely injured patients

**WEATHER**  
 Forecast:  
 7:45-8:15 AM  
 8:15-8:45 AM  
 8:45-9:15 AM

**The Boston Sunday Globe** EXTRA

THE BOSTON SUNDAY GLOBE—NOVEMBER 22, 1942—302 PAGES—PRICE 10 CENTS

# 400 DEAD IN HUB NIGHT CLUB FIRE

## Hundreds Hurt in Panic as the Cocoanut Grove Becomes Wild Inferno

By SAMUEL B. CUTLER

The worst disaster in Boston's history last night snuffed out the lives of 399 merrymaking men and women in the blazing inferno of the famous Cocoanut Grove nightclub amid scenes of utter panic and horror. Crushed, trampled and burned as nearly 1000 patrons, entertainers and employees fought desperately to gain the exits through sheets of flame, scores of victims were left lying on the floor helpless. Others reached the street enveloped in fire, only to die in agony in the street or in hospitals.

**Where Bodies Can Be Found**  
 (List of dead is compiled by...)

**State Police Told to Block Roads**  
 (List of injured...)

**Long List of Injured**

**List of Known Dead**  
 (List of names...)

**Frantic Parents Rush to Morgues in Vain Search**  
 (Text about parents...)

**COCOANUT GROVE FIRE TIMES**  
 (Timeline of the fire...)

**OTHOLE PRIEST, AT RIGHT, LIVES LAST MOMENTS OF CABINETS OUT BY FIREMAN**  
 (Caption for photo...)





# History of Clinical Research



- **1943 Army Surgeon General James Magee authorized experimentation in treatment of soldiers with this new drug called penicillin**
- **Lyons commissioned a Major and led a new unit for penicillin study and therapy at Buschnel General in Brigham City, Utah (Penicillin Therapy Section)**
- **Combined large burden of injury with supply of penicillin to advance knowledge of wound management**





# History of Clinical Research



## HISTORICAL FOREWORD

A formula for success in military medical research

Basil A. Pruitt, Jr., MD, Todd E. Rasmussen, MD, *and* Glen Gueller,  
*San Antonio, Texas*

*J Trauma & Acute Care Surg 2015;79(4)suppl1:S64-S69*

- **The studies performed under the direction of Lyons established PCN dosage schedules, indications and routes**
- ***Dec 18, 1943 JAMA***





# History of Clinical Research



- **Lyons was awarded Legion of Merit in 1944 by the War Department for successful treatment of wounded soldiers and advancement of the science of combat casualty care**





# Formula for Success in Clinical Research



**Clinically significant problem**

**+**

**Availability of patients of interest**

**+**

**Integration of clinical & laboratory scientists**

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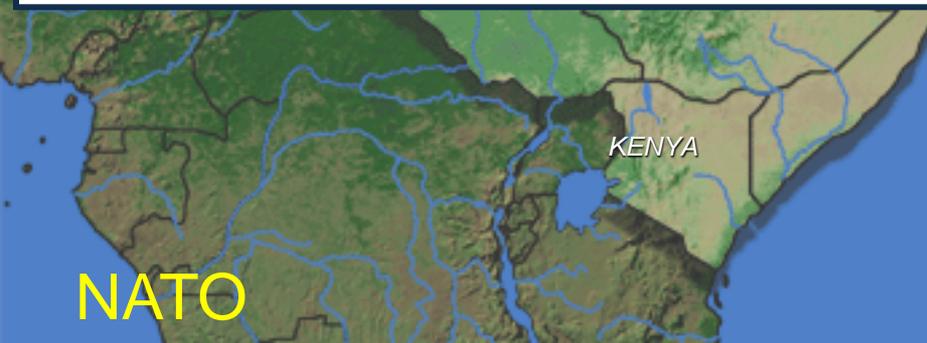
**Improved outcomes and decreased mortality**

- **Sound familiar?**

# Today's Legacy of Long Wars in Iraq & Afghanistan (2001 – 2014)



- **Once in a generation burden of injury from in Iraq & Afghanistan has provided occasion for improvements in management of injured service personnel including recognition of the prevalence & impact of TBI...**



NATO

Wounded: 52,311

Deaths: 6,850

*[defense.gov/news/casualty](https://www.defense.gov/news/casualty)*



# Historical Perspective - What Have We Learned?



- Value of a *Joint Defense Centers of Excellence (DCoEs)* –Joint Trauma System Defense and DCoE for Psychological Health & TBI including Defense & Veterans Brain Injury Center
- Value of dedicated, requirements driven, planned and programmed (i.e. top down) research equity in trauma & injury related topics (CCCRP)
- Value of *Military Medical Academy (USUHS)* as academic foundation & proprietor of career medical leadership “America’s Medical School”



# Lessons in Contemporary Clinical Research



- **Out of 72 multicenter RCTs**
  - Only 10 reported positive impact on mortality
  - 7 reported a detrimental effect
  - 55 showed no effect
- **What field of clinical study is this referring to?**

Multicenter, randomized, controlled trials evaluating mortality in intensive care: Doomed to fail?

Gustavo A. Ospina-Tascón, MD; Gustavo Luiz Büchele, MD; Jean-Louis Vincent, MD, PhD

**(Crit Care Med 2008; 36:1311–1322)**



# Why RCTs have “Failed”



- **Ineffective interventions**
- **Wrong timing of interventions including dosing**
- **Lack of power or powered incorrectly**
- **Diverse severity of injury condition**
- **Less than appropriate endpoints**
- **Too heterogeneous of a study population**



# PROTECT III



## *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

DECEMBER 25, 2014

VOL. 371 NO. 26

### Very Early Administration of Progesterone for Acute Traumatic Brain Injury

David W. Wright, M.D., Sharon D. Yeatts, Ph.D., Robert Silbergleit, M.D., Yuko Y. Palesch, Ph.D., Vicki S. Hertzberg, Ph.D., Michael Frankel, M.D., Felicia C. Goldstein, Ph.D., Angela F. Caveney, Ph.D., Harriet Howlett-Smith, R.N., Erin M. Bengelink, M.A., Geoffrey T. Manley, M.D., Ph.D., Lisa H. Merck, M.D., M.P.H., L. Scott Janis, Ph.D., and William G. Barsan, M.D., for the NETT Investigators\*

- **Primary endpoint – Extended GOS @ 6 months**

#### CONCLUSIONS

This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI. (Funded by the National Institute



# SYNAPSE



## ORIGINAL ARTICLE

*N Engl J Med* 2014;371:2467-76

# A Clinical Trial of Progesterone for Severe Traumatic Brain Injury

Brett E. Skolnick, Ph.D., Andrew I. Maas, M.D., Ph.D., Raj K. Narayan, M.D., Roland Gerritsen van der Hoop, M.D., Ph.D., Thomas MacAllister, Ph.D., John D. Ward, M.D., Neta R. Nelson, M.P.H., and Nino Stocchetti, M.D.,  
for the SYNAPSE Trial Investigators\*

- **Primary endpoint – Extended GOS @ 6 months**

### CONCLUSIONS

Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI. These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials. (Funded by BHR Pharma; SYNAPSE ClinicalTrials.gov number,



# How to Overcome Pitfalls?



- **Better endpoints (i.e. *realistic vs. ideal goals*)**
- **Consider implementation of *theragnostics***
- **Identify the “sweet spot” study population**
- **Consider alternatives to RCT**

*Power of Community vs.  
Individual Effort/Ego*

- **Increase volume of studies**



# Biologically-Targeted Therapy



## Toward theragnostics

Frédéric Pene, MD; Emilie Courtine, PhD; Alain Cariou, MD; Jean-Paul Mira, MD, PhD

Theragnostics is a treatment strategy that combines therapeutics with diagnostics. It associates both a diagnostic test that identifies patients most likely to be helped or harmed by a new medication, and targeted drug therapy based on the test results. Bioinformatics, genomics, proteomics, and functional genomics are molecular biology tools essential for the progress of molecular theragnostics. These tools generate the genetic and protein information required for the development of diagnostic assays. Theragnostics includes a wide range of subjects, including personalized medicine, pharmacogenomics, and molecular imaging to develop efficient new targeted therapies with adequate benefit/risk to patients and a better molecular understanding of how to optimize drug selection. Furthermore, theragnostics aims to monitor the response to the treatment, to increase drug efficacy and safety. In addition, theragnostics could eliminate the unnecessary treatment

of patients for whom therapy is not appropriate, resulting in significant drug cost savings for the healthcare system. However, the introduction of theragnostic tests into routine health care requires both a demonstration of cost-effectiveness and the availability of appropriate accessible testing systems. This review reports validation studies in oncology and infectious diseases that have demonstrated the benefits of such approach in well-defined subpopulations of patients, moving the field from the drug development process toward clinical practice and routine application. Theragnostics may change the usual business model of pharmaceutical companies from the classic blockbuster model toward targeted therapies. (Crit Care Med 2009; 37[Suppl.]:S50–S58)

**KEY WORDS:** theragnostics; personalized medicine; pharmacogenetics; biomarkers; predictive medicine; pharmacogenomics; oncology



# Biologically-Targeted Therapy

The EUPHRATES Clinical Trial - Windows Internet Explorer provided by USAISR - NOT FOR CLINICAL USE

http://www.spectraldx.com/euphrates-trial.html

File Edit View Favorites Tools Help

Suggested Sites ATAAPS - 13.1.4 BAMC In House Pager BAMC MRM CNN.com - Breaking New... Defense Enterprise E-mail ISR Intranet Patient Safety Report USAISR INTRANET USAISR-BAMC VPN

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## EUPHRATES Trial

**EUPHRATES:**  
**Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic Shock**

EUPHRATES is a randomized, double-blind controlled, clinical trial that compares standard of care versus standard of care and Toraymyxin, directed by Spectral's EAA™ Endotoxin Activity Assay. The target population is critically ill patients with septic shock and endotoxemia (as measured by the EAA™). The trial is expected to enroll approximately 650 patients at 50 sites throughout the U.S. and Canada, and will have a primary end point of 28 day mortality.

Spectral's EUPHRATES trial is the world's first theranostics trial conducted in the area of sepsis. Theranostics, a combination diagnostic and therapeutic, is a relatively new way of approaching patient

**ClinicalTrial.gov**  
Safety and Efficacy of Polymyxin B Hemoperfusion (PMX) for Septic Shock (EUPHRATES)...more »

**Trial FAQ**

**Sepsis Links**



# EUPHRATES – First Biomarker Based Clinical Study in Sepsis



Klein et al. *Trials* 2014, **15**:218  
<http://www.trialsjournal.com/content/15/1/218>



**STUDY PROTOCOL**

**Open Access**

The EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial

David J Klein<sup>1\*</sup>, Debra Foster<sup>2</sup>, Christa A Schorr<sup>3</sup>, Kazem Kazempour<sup>4</sup>, Paul M Walker<sup>2</sup> and R Phillip Dellinger<sup>3</sup>

- **First sepsis trial designed to use biomarker (EAA) as enrollment criteria for therapy against that marker**
- **Theragnostics approach offers opportunity to move beyond “syndrome-based” definition & inclusion**



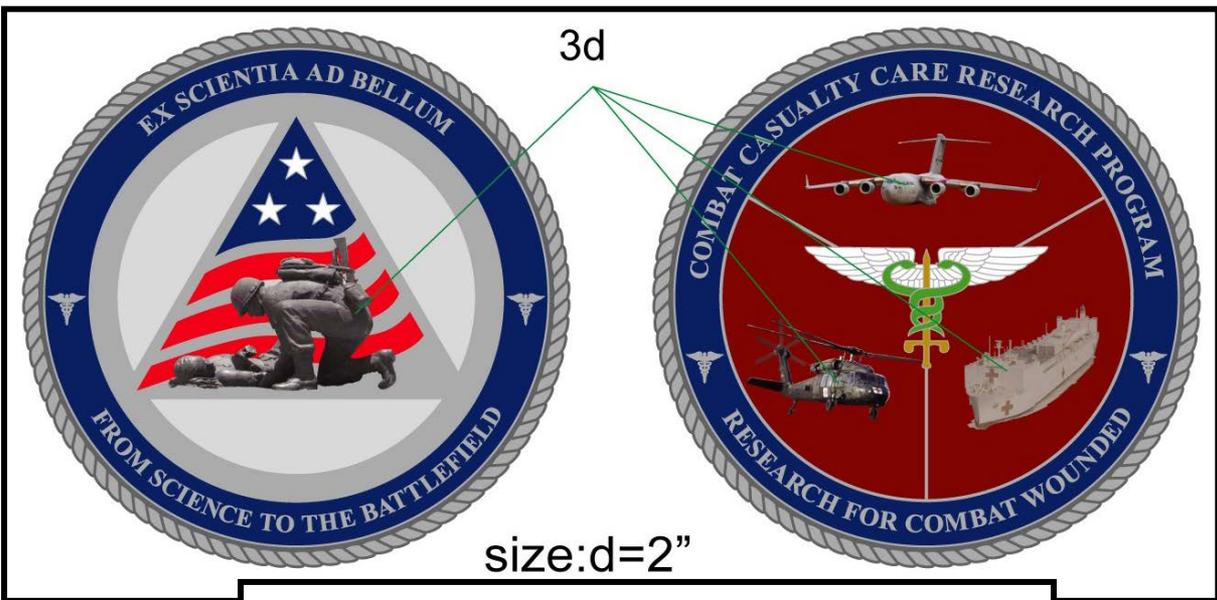
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<https://ccc.amedd.army.mil>