International Collaboration for Clinical Trials in the 21st Century

John Marshall MD
Critical Care Canada Forum
Toronto, Canada
November 1, 2016

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Increasing Numbers of Published RCTs

- Crit Care Med 44:663, 2016
Increasing Impact of Published RCTs

- Crit Care Med 44:663, 2016
The nature of ICU-based clinical research is changing
TREATMENT OF GRAM-NEGATIVE BACTEREMIA AND SEPTIC SHOCK WITH HA-1A HUMAN MONOCLONAL ANTIBODY AGAINST ENDOTOXIN

A Randomized, Double-Blind, Placebo-Controlled Trial

Elizabeth J. Ziegler, M.D., Charles J. Fisher, Jr., M.D., Charles L. Sprung, M.D., Richard C. Straube, M.D., Jerald C. Sadoff, M.D., Garrett E. Foulke, M.D.,

March 8, 2001

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

Gordon R. Bernard, M.D., Jean-Louis Vincent, M.D., Ph.D., Pierre-Francois Laterre, M.D., Steven P. Larosa, M.D., Jean-Francois Dhainaut, M.D., Ph.D., Angel Lopez-Rodriguez, M.D., Jay S. Steinger, M.D., Gary E. Garber, M.D., Jeffrey D. Helterbrand, Ph.D., E. Wesley Ely, M.D., M.P.H., and Charles J. Fisher, Jr., M.D., for the RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOLBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.S.C., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHELTZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.
A COMPARISON OF SUCRALFATE AND RANITIDINE TO PREVENT UPPER GASTROINTESTINAL BLEEDING

DEBORAH COOK, M.D., GORDON GUYATT, M.D., JOHN MARSHALL, M.D., DAVID LEASA, M.D., HUGH FULLER, M.B., RICHARD HALL, M.D., SHARON PETERS, M.D., FRANK RUTLEDGE, M.D., LAUREN GRIFFITH, M.SC., ALAN McLellan, M.D., GORDON WOOD, M.D., AND ANN KIRBY, M.D., FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

The Acute Respiratory Distress Syndrome Network*

The New England Journal of Medicine

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HEBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLACHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE FAGLIARELLO, M.D., MARTIN TWEEDALE, M.D., PH.D., IRWIN SCHWENZER, M.D., ELIZABETH YETISH, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*
The Trials Group Model
One-Year Outcomes in Caregivers of Critically Ill Patients


- September 1989
- 250 + members
- 240 publications; 17 in *NEJM*
ANZICS

- Founded 1994
- 10 papers in NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D.,
Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D.,
Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D.,
Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D.,
and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators
and the Australian and New Zealand Intensive Care Society Clinical Trials Group*
• NIH-funded

• 6 papers in New England Journal of Medicine
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Oaffen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ullrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D., Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D., Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D., Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D., Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D., Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D., Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D., Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D., Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sc., Thea P. Møller, M.D., Per Winkel, M.D., D.M.Sc., and Jorn Wetterslev, M.D., Ph.D., for the 6S Trial Group and the Scandinavian Critical Care Trials Group
Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O’Kane, Ph.D., Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D., Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D., Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators, for the Irish Critical Care Trials Group*

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*
Emerging Groups

Latin American Critical Care Trials Investigators Network (LACCTIN)

Asian Critical Care Clinical Trials Group

Acute Care for Africa Research and Training (ACART)
The Trials Group Model

- Clinician investigator-driven research agenda
- Self-funded
- Independent of university, professional society
- Minimal or no engagement with industry
- Emphasis on collegiality, mentorship, fun
- Successful, impactful
Influence of Organizational Model on Study Impact

<table>
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<tr>
<th>Model</th>
<th>N</th>
<th>Median Citations/Year</th>
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<tr>
<td>Single site</td>
<td>116</td>
<td>6.8</td>
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<tr>
<td>2-5 sites</td>
<td>59</td>
<td>11.0</td>
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<tr>
<td>Ad hoc group</td>
<td>89</td>
<td>25.1 &lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Trials group</td>
<td>44</td>
<td>44.1 &lt;sup&gt;a,c&lt;/sup&gt;</td>
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<tr>
<td>Industry</td>
<td>85</td>
<td>12.3 &lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> p<0.001 vs single site,  
<sup>b</sup> p<0.01 vs single site,  
<sup>c</sup> p<0.01 vs industry  

InFACT exists to promote international collaboration between academic research networks that study the care of the acutely ill patient, and to enhance the profile, science, and impact of investigator-led acute care research.
<table>
<thead>
<tr>
<th>Organization</th>
<th>Collaboration</th>
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<tr>
<td>ACART</td>
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<td>GIVITI</td>
<td>TRIGERSEP</td>
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<td>Hellenic Sepsis Group</td>
<td>USCIITG</td>
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InFACT: a global critical care research response to H1N1

The H1N1 pandemic presents acute care researchers with an extraordinary challenge and an unprecedented opportunity. By early October, 2009, there had been more than 340 000 reported cases of H1N1 infection in 191 countries, with more than 4100 deaths. WHO initially projected that up to 2 billion people could become infected with the virus over the next 2 years. Although vaccination programmes and other factors should reduce this number, plausible estimates of the number of infected individuals who might benefit from admission to intensive care range from 200 000 to 10 million. Influenza killed at least 50 million people during the 1918 pandemic. Today, with antibiotics and antiviral agents, mechanical ventilation, and the supportive measures available in intensive care, most of those deaths could have been prevented.

The mortality for H1N1-infected patients admitted to intensive care ranges from 10 to 40% over the first month, and survivors spend a median of 2 weeks in the intensive care unit. To reduce this toll requires a better understanding of the epidemiology and clinical and treatment of severe H1N1 disease. In parallel, we will develop a biobank to facilitate studies of genetic susceptibility and clinical biology.

We are starting a programme of collaborative, investigator-led randomised trials of treatment strategies that target both the virus and the host response. Our initial three studies will evaluate inexpensive interventions that are available in both the developed and the developing world: corticosteroids and statins. They use adaptive designs to ensure that results can be quickly incorporated into practice, and that ineffective treatments are dropped. As measures of efficacy, they will measure survival of individual patients and the rapidity with which patients can be liberated from limited intensive-care resources.

We seek to reduce the consequences of severe H1N1 infection in the developed world, where available research infrastructure is most robust, and in the developing world, where the human toll is likely to be the greatest. To this end, we will catalogue international critical care capacity, and promote, mentor, and support clinical research activities in resource-poor areas.
Why Should We Collaborate?

- Increase study power
- Increase generalizability of results
- Understand geographic variability
- Accelerate knowledge generation
- Build global research culture
Funding of Trials in clinicaltrials.gov

- Cancer: 56353
- Arthritis: 5758
- Diabetes: 14359
- Heart disease: 23817
- Intensive/Critical Care: 4292

Percentage of Trials with Industry Funding
Models of Collaboration

Informal

- Lead group
- Ad hoc participation by members of other groups
Models of Collaboration

Harmonized

- Multiple independent lead groups
- Harmonized protocols
- Agreement to pool data
Models of Collaboration

Integrated

- Two or more groups
- Single protocol
- Shared ownership and responsibility
Models of Collaboration

Platform Trial

• Two or more groups
• Single protocol; single research focus
• Multiple questions led by different groups
• Adaptive design

REMAP-CAP
Challenges of Collaboration

- Funding
- Ethical oversight
- Language
- Meetings
- Ownership
- Authorship, credit
- Regulatory requirements
- Contracts
The Promise of Collaboration

• Large, adequately powered trials

• Global understanding of best practice

• Integration of research and quality improvement

• New models of research and funding

• Better patient care
Thank You!