

# International Forum for Acute Care Trialists

# 10

THE FIRST 10 YEARS



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# A global collaboration of acute care clinical researchers

The International Forum for Acute Care Trialists (InFACT) was launched in 2008 as a network of investigator-led clinical research groups and academic institutions whose focus is the optimal care of critically ill children and adults. Our members include organizations from around the world, spanning a spectrum of research foci, structural formality, and experience.

## EXECUTIVE COMMITTEE

Dr. John Marshall, Chair  
Dr. Steve Webb, Vice Chair  
Dr. Derek Angus, Treasurer  
Dr. Kathy Rowan, Secretary

## WORKING GROUP LEADS

Prof. Bronagh Blackwood  
Dr. Bronwen Connolly  
Dr. Terri Hough  
Dr. Srinivas Murthy  
Dr. David Wallace  
Dr. Fernando Bozza

## PROGRAM MANAGER

Zahra Bhimani

## Member Groups

InFACT full members are established investigator-led clinical trials groups or academic research consortia who support the ideals of collaborative, collegial, and open research into the problems facing seriously ill patients. Emerging research consortia may join as affiliate members, while individual investigators who share these interests may join as non-voting members. Membership carries no financial or intellectual obligations beyond sharing the ideals of InFACT and being willing to work collaboratively to achieve these.

Acute Care for Africa Research and Training (ACART)	European Society of Intensive Care Medicine (ESCIM) Trials Group	Latin American Sepsis Institute (LASI)	Scottish Critical Care Trials Group (SCCTG)
Academisch Medisch Centrum (AMC) Amsterdam	George Institute for Global Health	Latin America Intensive Care Network (LIVEN)	Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC)
Asian Critical Care Clinical Trials Group (ACCCTG)	Global Research on Acute Conditions Team (GREAT) Network	National Institute for Health Research (NIHR)	Society of Critical Care Medicine Discovery Network
Australia and New Zealand Intensive Care Research Centre (ANZICS-RC)	Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GiVITI)	Neurocritical Care Research Network (NCRN)	South East Asian Research in Critical Care Health (SEARCH)
Australia and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG)	Hellenic Sepsis Group	North African Network for Intensive Care Medicine Research (NANICM Research)	TRIAL Group for Global Evaluation and Research in SEPSis (TRIGGERSep)
Brazilian Research in Intensive Care Network (BRICNet)	Intensive Care National Audit and Research Centre (ICNARC)	Prevention and Treatment of Acute Lung Injury (PETAL) Network	United Kingdom Critical Care Research Group (UKCCRG)
Canadian Critical Care Trials Group (CCCTG)	Irish Critical Care Trials Group (ICCTG)	Réseau Européen de Recherche en Ventilation Artificielle (REVA) Network	United Kingdom Intensive Care Society Clinical Trials Group
Center for Sepsis Control and Care (CSCC)	Kompetenz Network Sepsis (SEPNET)	Saudi Critical Care Clinical Trials Group	
China Critical Care Clinical Trials Group (CCCCTG)	Latin American Critical Care Trials Investigators Network (LACCTIN)	Scandinavian Critical Care Trials Group	
Clinical Research Investigation and Systems Modelling of Acute Illness (CRISMA Center)			

# Message from the Chair



**“There is no limit to what can be accomplished if it doesn't matter who gets the credit.”**

- Ralph Waldo Emerson

The Roman forum was a venue where public debate and conversation could occur; the concept implied dialog rather than governance. InFACT – the International Forum for Acute Care Trialists – is a forum, a platform to promote international collaboration in acute care research.

InFACT members include three dozen investigator-led research consortia from around the world. These groups have conducted many of the most impactful clinical trials in critical care. But the primary purpose of InFACT is not to conduct clinical research, but rather to enable clinical research by our member groups:

- To promote a model of high quality, investigator-initiated acute care research to patients, clinicians, policy-makers, and funders
- To build international collaboration in investigator-initiated acute care research
- To advance the science and conduct of acute care clinical research
- To build global clinical research capacity by mentoring emerging groups.

This booklet describes an evolving and imperfect vision of what global research collaboration might accomplish, and a tentative, though intensely held view that we can realize this promise. It is a selective, and abbreviated synopsis of ten years of collaboration.

We hope you find that the vision resonates.

A handwritten signature in black ink that reads "John Marshall".

John Marshall MD, Chair, InFACT



# Mission, Vision and Values

## InFACT

The vision of InFACT is to improve the care of acutely ill patients around the world through the promotion of high quality clinical research into the causes, prevention, and optimal management of acute, life-threatening illness.

The mission of InFACT is to facilitate collaboration and cooperation between academic clinical research networks to:

- Advance an understanding of the global epidemiology, natural history, prevention, and optimal management of life-threatening acute illness
- Enable and expand high quality global collaborative investigator-led clinical research involving acutely ill patients
- Support local research education and mentorship activities through international exchanges and other co-operative educational activities related to the conduct of clinical research
- Develop and promote harmonized study metrics, outcome measures, and reporting for both academic and industry-initiated clinical research

- Facilitate the establishment of new national or regional investigator-led clinical trials groups in critical care
- Enhance research capacity and improve health outcomes in low and middle income countries
- Establish capacity for a rapid global research response to emerging pandemics and other disasters
- Enhance the profile of acute critical illness with the public, and with regulatory and granting agencies.

We value collegiality, mentorship, scientific rigour, intellectual generosity, and collaboration.



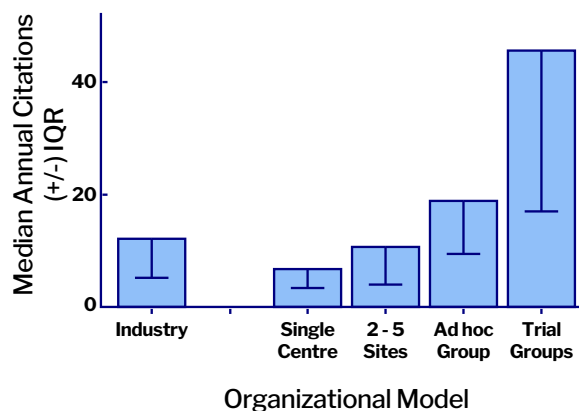


## The Impact of Investigator-led Critical Care Research

Investigator-led clinical trials, particularly those conducted by established clinical trials groups, are having an outsized impact on the knowledge base of critical care medicine. Industry-led trials make up only 15% of all trials listed on clinicaltrials.gov, and have led to only a handful of new medications – in particular, antibiotics and sedatives and analgesics<sup>1</sup>. In contrast, the most significant advances have come through an understanding of how to use standard therapies more effectively, in areas such as mechanical ventilation<sup>2</sup>, fluid administration<sup>3,4</sup>, transfusion<sup>5</sup>, and glycemic control<sup>6</sup>. The impact of these trials is both improved care and reduced costs to the health care system.

Seven of the top ten, and 12 of the top 20 landmark studies in critical care medicine are the work of investigator-led trials groups (<https://criticalcarereviews.com/index.php/majorstudies/landmark-studies/top-100-studies>). Judged as annual citation rates, trials conducted by these groups are cited more than twice as frequently as investigator-led trials conducted under other models, and almost four times as often as trials led by industry<sup>7</sup>. In 2018, investigator-led groups published 7 trials in the New England Journal of Medicine, 2 in the Lancet, and 6 in JAMA.

ICUs are a necessary element of the health care system throughout the world; they generate costs of up to 0.66% of GDP<sup>8</sup>, and provide multiple opportunities to rationalize the spending of limited health care dollars. Data from Australia, for example, show that improving ICU care through research results in savings of \$5.80 for every research dollar invested (<https://www.safetyandquality.gov.au/wp-content/uploads/2017/07/Economic-evaluation-of-investigator-initiated-clinical-trials-conducted-by-networks.pdf>). An economic analysis of the PROTECT study, a 3700 patient study of techniques for the prophylaxis of deep venous thrombosis<sup>9</sup>, showed that the use of low molecular weight heparin could result in cost savings of up to \$1 million a year for individual ICUs<sup>10</sup>.



# Investigator-led Acute Care Research: A History

The first investigator-led critical care trials group - the Canadian Critical Care Trials Group (CCCTG) - was formed in 1989<sup>11</sup>. Today the CCCTG has more than 300 members and 70 active research programs, and more than 300 peer-reviewed publications<sup>12-14</sup>.

Shortly thereafter, intensivists in Australia launched the Australia and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG). They have published the largest trials ever conducted in critical care on themes such as glycemic control<sup>6</sup>, fluid resuscitation<sup>15</sup>, and the management of head injury<sup>16</sup>. The Acute Respiratory Distress Syndrome Network (ARDSNet) group formed in the United States around the same time with funding from the NIH. ARDSNet has led landmark trials on the management of ARDS<sup>2,17</sup>, and recently become the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network.

By the turn of the century, similar groups were emerging in Scandinavia, France, the United Kingdom, and Germany. More recently investigator-led clinical trials groups have been established in Brazil, Latin America, Asia, Southeast Asia, China, sub-Saharan Africa, North Africa, and the Middle East. The model has become global.

Initial discussions about the creation of an international collaborative network were held in Buenos Aires in 2005. Two dozen participants from around the world reviewed the status of critical care research in their country, and agreed on the value of further dialog.

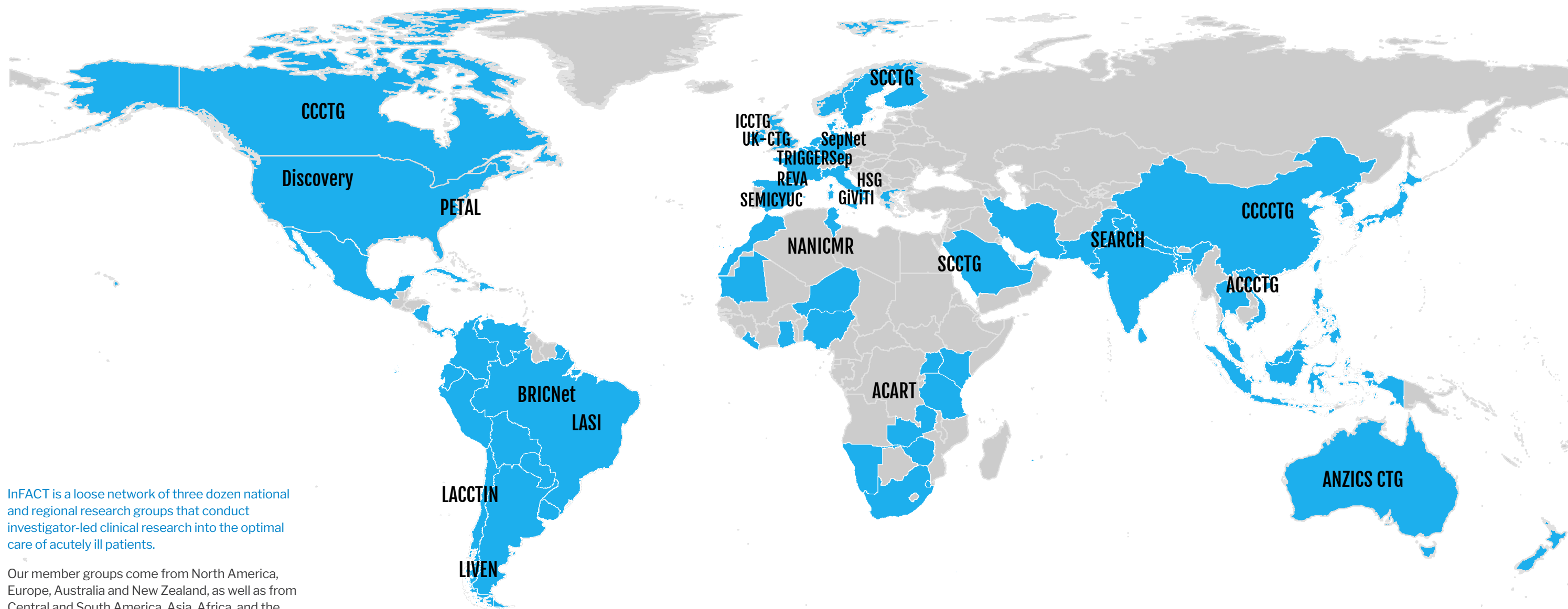
We met again in Granada Spain in 2008 in conjunction with the annual congress of the International Sepsis Forum. Representatives of those present - both dedicated investigator-led trials groups and academic consortia - agreed to form the International Forum for Acute Care Trialists (InFACT) as a platform to promote global collaboration in acute care clinical research.

In 2009, InFACT members joined forces in an international research response to the emerging H1N1 influenza pandemic<sup>18,19</sup>. Member groups coordinated studies on the epidemiology of severe influenza. We launched three trials of adjuvant therapies, and organized an international colloquium on developing a rapid research response to future pandemics.



The Canadian Critical Care Trials Group (CCCTG) meets in Quebec City for the 2013 Spring Meeting.

# What Is InFACT?



InFACT is a loose network of three dozen national and regional research groups that conduct investigator-led clinical research into the optimal care of acutely ill patients.

Our member groups come from North America, Europe, Australia and New Zealand, as well as from Central and South America, Asia, Africa, and the Middle East. We have called InFACT a forum, rather than a federation, to signal our commitment to a collegial and inclusive model of global research collaboration, and our desire to place collaborative success in implementing visionary programs ahead of parochial considerations of ownership and credit.

InFACT is actively engaged in building partnerships with organizations whose interests and activities parallel ours, including professional societies, other research consortia, and policy makers such as the WHO. We are currently based in Toronto Canada, at the Li Ka Shing Knowledge Institute of St. Michael's Hospital.

InFACT activities are overseen by an Executive Committee consisting of a Chair (John Marshall, CCCTG), Vice-Chair (Steve Webb, ANZICS-CTG), Secretary (Kathy Rowan ICNARC), and Treasurer (Derek Angus, CRISMA Center). Its overall direction is guided by a council, consisting of one representative from each member group, and its activities are conducted through working groups.

Over the next year, InFACT will be undertaking a strategic planning process to establish priorities for the next five years, to enhance value to our member groups, to build collaboration and capacity, and to ensure transparency and democratic leadership.

Join us in Melbourne, in partnership with the Australia and New Zealand Intensive Care Society, the

Australian College of Critical Care Nurses, and the World Federation of Societies of Intensive and Critical Care Medicine.



**October 13 – 18, 2019**  
**Melbourne Convention & Exhibition Centre**



# Antimicrobial Resistance



LEADS



Fernando Bozza (Rio de Janeiro, Brazil; BRICNet)



Ignacio Martin-Loeches (Dublin, Ireland; Irish Critical Care Trials Group)

On any given day, more than half of all ICU patients are assessed to be infected, and more than 70% are receiving systemic antibiotics<sup>22</sup>. International collaboration provides a unique opportunity to understand the epidemiology of ICU-acquired infection and antimicrobial resistance.

The Antimicrobial Resistance in Intensive Care (AMRIC) program, funded by the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), seeks to develop a globally representative ICU-based network for surveillance of AMR. We will use geographic variability in rates, bacteriology, and resistance profiles of nosocomial infection to identify modifiable risk factors. Initial funding supported studies to understand capacity for surveillance work on AMR in low and middle income countries. More recently, a JPIAMR-funded grant to Srinivas Murthy will support the development of a virtual surveillance network.

The ICU Microbiome project tests the hypothesis that patterns of ICU-acquired infection will reflect the local ICU microbiome, as sampled from water sources, inanimate surfaces, and ventilation systems in the ICU. Ignacio Martin-Loeches has received JPIAMR funding to study changes in the lung microbiome and its disruption in critical illness; additional studies that address the ICU water supply as a reservoir of resistant organisms are under review.

InFACT studies in antimicrobial resistance focus on an important international threat to acutely ill patients. They also provide a unique opportunity to build research capacity in emerging groups in low and middle income countries outside the EU/North America/Australia axis.

# Outcome Measures



## LEADS



**Bronagh Blackwood**  
(Irish CCTG)



**Bronwen Connolly** (UK ICS  
CTG)

Clinical research is only as impactful as the endpoints used to measure its consequences. The InFACT Outcome Measures Working Group has focused on three areas:

- Creation of a taxonomy and framework for outcome measures for acute care research
- Development of core outcome measure sets for specific areas of acute care research
- Characterization of the strengths, limitations and performance characteristics of commonly used outcome measures

Activities of the working group have included the development of an international Delphi panel to support the development of core outcome measures sets for studies of mechanical ventilation<sup>20</sup> and long term outcomes<sup>21</sup> from intensive care (<https://www.improvelto.com/>); the launch of core outcome set initiatives using the methodologic framework developed by the COMET (Core Outcome Measures in Effectiveness Trials) initiative (<http://www.comet-initiative.org/>) for sepsis, subarachnoid hemorrhage, delirium, and cardiac arrest; and a systematic review of the performance characteristics of mortality as an outcome measure in critical care clinical trials.



**Terri Hough** (PETAL)

# Pandemic Preparedness



Held in Toronto, Canada at the Li Ka Shing Knowledge Institute (LKSki) in June 2011, the InFACT/ISARIC/LKSki Colloquium on Pandemic Research Preparedness sought to build international capacity for pandemic research.

The 2009 H1N1 influenza pandemic posed a new challenge: how to mobilize a research response to a rapidly emerging and incompletely understood international threat, and how to communicate data emerging from any studies to decision-makers who were charged with leading a clinical response. This challenge framed InFACT's initial forays into international research collaboration<sup>18</sup>.

With funding from the Canadian Institutes of Health Research and the Public Health Agency of Canada to host an international meeting in Toronto in 2011, and working in collaboration with the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), we began to design a strategy to create the research infrastructure for future pandemics in the inter-pandemic period, built on the model of the platform trial. A platform trial uses Bayesian methods, and evaluates multiple interventions for a single disease both simultaneously and sequentially.



The resulting trial – the Randomized Embedded Multinational Adaptive Platform (REMAP) trial – studies severe community-acquired pneumonia as the dominant phenotype of an emerging infectious disease. REMAP-CAP is now funded in the EU, Australia, New Zealand, and Canada.



Another InFACT-ISARIC initiative is the Short Period Incidence Study of Severe Acute Respiratory Infection – SPRINT-SARI – an annual short period incidence study designed to understand the global epidemiology of severe acute respiratory infections. SPRINT-SARI is led by Srinivas Murthy and Steve Webb.

# Mapping Critical Care

## LEADS



David Wallace  
(CRISMA Center)



Srinivas Murthy (CCCTG)

Led by David Wallace and Srinivas Murthy, the InFACT Critical Care Mapping Group seeks to create the infrastructure to support large epidemiologic studies.

In addition to proving a platform for the AMRIC initiative, a global and representative network of ICUs provides capacity for public health and health care planning. The ICU is the venue where the sickest patients are treated, and so emerging infectious disease outbreaks such as SARS, H1N1 influenza, and MERS-CoV first appeared in the ICU, and their course can be tracked by monitoring ICU admissions. An InFACT-led pilot study evaluated regional variability in the capacity to provide acute care services<sup>23</sup>, while another initiative has provided the first global estimates of the prevalence and mortality of sepsis<sup>24</sup>.

ACCESS-MAPS (<http://www.accessmaps.org/>) is an online platform created by David Wallace as an inventory of global capacity for acute care. It will provide a platform for the AMRIC program, and a resource for future studies of the global prevalence of disease.



Intensive Care Med (2014) 49:342–352  
DOI 10.1186/s13054-014-093-7

ORIGINAL ARTICLE

Shamly Austin  
Srinivas Murthy  
Haasab Waseeh  
Neill K. J. Adhikari<sup>1</sup>  
Veena Karir  
Kathryn Rowan  
Shervin T. Jacob  
Jorge Salath  
Fernando A. Borza  
Bin Du  
Yuezhong An  
Bruce Lee  
Felicia Wu  
Yen-Lan Nguyen  
Chris Oppong  
Ramesh Venkataraman  
Vimalraj Veluputhum  
Carmelo Decias  
Derek C. Angus  
On behalf of the International Forum  
of Acute Care Trialists

**Access to urban acute care services in high- vs. middle-income countries: an analysis of seven cities**

Yet another initiative has begun to explore methods to reliably estimate the denominator in large epidemiologic studies, using approaches championed by the Global Burden of Disease Project and the World Bank.

## ORIGINAL ARTICLE

### Assessment of Global Incidence and Mortality of Hospital-treated Sepsis Current Estimates and Limitations

Carolin Fleischmann<sup>1,2</sup>, André Scherag<sup>3</sup>, Neill K. J. Adhikari<sup>4</sup>, Christiane S. Hartog<sup>1,2</sup>, Thomas Tsaganos  
Peter Schlattmann<sup>5</sup>, Derek C. Angus<sup>7</sup>, and Konrad Reinhart<sup>1,2\*</sup>, on behalf of the International Forum of  
Trialists

<sup>1</sup>Department for Anesthesiology and Intensive Care Medicine, <sup>2</sup>Integrated Research and Treatment Center, Center for Intensive Care and Care, <sup>3</sup>Clinical Epidemiology, Integrated Research and Treatment Center, Center for Sepsis Control and Care, and <sup>4</sup>Medical Statistics, Computer Sciences and Documentation, Jena University Hospital, Jena, Germany; <sup>5</sup>Department of Medicine, Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Ontario, Canada; <sup>6</sup>4th Department of Medicine, University of Athens, Medical School, Athens, Greece; and <sup>7</sup>Critical Care Medicine Division, Department of Intensive Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

## LEADS



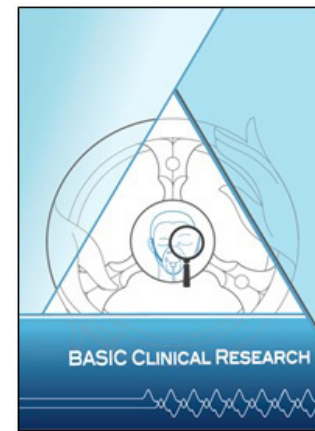
Charles Gomersall  
(ACCCTG)



Shay McGuinness  
(ANZICS-CTG)



Rachael Parke  
(ANZICS-CTG)



A priority for InFACT is to build research capacity outside of North America, Australasia and Europe, and to enable groups in Central and South America, Africa, and Asia to assume leadership roles in framing an international research agenda for the best care of critically ill patients.



The first Basic Research Course was held in November 2016 at the Aga Khan University, Karachi, Pakistan

Building on the success of the BASIC (Basic Assessment and Support in Intensive Care) Collaboration, developed and led by Charles Gomersall, chair of the Asian Critical Care Clinical Trials Group, InFACT has developed a course in BASIC Clinical Research, an intensive two-day program, supported by a manual on basic research principles. The course is co-directed by Shay McGuinness and Rachael Parke (ANZICS-CTG), and was written by Rob Fowler and Neill Adhikari (Canadian Critical Care Trials Group), Anthony Delaney and Ed Litton (ANZICS-CTG) and Charles Gomersall. The course has now been given in Karachi, Sydney, Hong Kong, Singapore, Riyadh and Addis Ababa including the first BASIC Clinical Research Instructor course in Riyadh (October 2018). A course for research coordinators (BASIC Research Coordination) is under development with the first course planned for late 2019.

InFACT is developing a fellowship program to support the education and mentorship of trainees and junior investigators from areas where critical care research is under-developed.



Dr Charles Gomersall teaching participants of the first Basic Research Course held at the Aga Khan University, Karachi, Pakistan.

# Stratification and Staging

Heterogeneity is an intrinsic element of diseases such as cancer or heart disease. Advances in these disciplines has come through a better understanding of natural history and the development of better taxonomic classifications that identify sub-populations of patients who are more likely to respond to particular treatment strategies.

InFACT has been promoting a collaboration amongst trialists and investigators with an interest in large scale “omics” technologies and those with expertise in the aggregation and interpretation of large data sets to rethink how we classify acutely ill patients to better match biologic derangements to available treatments.

This is an ambitious project whose time frame is measured in decades. Our early goals are to:

- Develop a common taxonomy to describe the process
- Standardize sample collection, data annotation, and sharing agreements
- Optimize and harmonize data platforms
- Conduct secondary analyses of completed clinical trials to look for signals of differential treatment responsiveness
- Encourage trialists to collect samples to use the RCT as a platform for study

Benjamin Tang from Australia has drafted an initial overview of the project. Through recent discussions in Toronto, Bangkok, and Paris, we are working to develop an organizational structure and initial research program.



The Staging and Stratification Working Group gathers for program planning in Bangkok, Thailand, September 2018.

# Building Research Collaboration

A core role for InFACT is building collaboration amongst member groups to accelerate research, enhance study rigour, and increase the generalizability of its findings.

InFACT supported an individual patient data meta-analysis of three trials of goal-directed resuscitation in sepsis. It is supporting international collaboration in a number of ongoing trials, including:

- **SuDDICU** A multinational evaluation of selective digestive tract decontamination
- **REVISE** A re-evaluation of the need for stress ulcer prophylaxis
- **HALO** A study of the potential benefit of heparin in sepsis
- **STARRT-AKI** A study of the timing of onset of renal replacement therapy
- **BLING** A study of continuous vs. intermittent beta lactam infusion
- **REMAP-CAP** A platform trial of interventions for community-acquired pneumonia

International collaboration brings new opportunities and new challenges, including academic credit – a particular consideration for young investigators, and addressed in an InFACT-authored commentary <sup>25</sup>.

We are working with international collaborative research networks in stroke (the Global Alliance of Investigator Networks in Stroke – GAINS) and emerging infections (the International Severe Acute Respiratory and Emerging Infections Consortium – ISARIC) to articulate the opportunities, challenges, and needs of increased international collaboration.

## CORRESPONDENCE

**Who Says There Is No “I” in Team? Achieving Individual Success in Collaborative Clinical Research in Critical Care**

## The Next Decade

Global collaboration is complicated and slow to build, but ultimately powerful.

Our vision is to transform clinical research in acute care through large scale global collaboration, recognizing that the unanswered questions about the optimal fluid management of a septic patient in Belfast do not fundamentally differ from those regarding the management of a multiply traumatized patient in Kathmandu, and that when they do, there is a wealth of knowledge to be gained from a full understanding of those differences that are shaped not only by disease, but also by geography, politics, and economics. Our goals over the next decade are to:

- Promote and empower collaboration across national barriers, so that the results of clinical research are maximally relevant to acutely ill patients around the world
- Build the collaborative infrastructure – case report forms, outcome measures, data collection processes, contracts, ethics and logistics etc. – that will allow this to happen

- Mentor and develop expertise in emerging groups, so that information generated, and the questions asked are broadly representative
- Establish a funding model that can ensure the long term stability of the InFACT collaboration
- Create the collaborative structures and leadership models that will lead this vision forward into the future

Over the next year, we will be developing these aspirations into a strategic plan to guide InFACT over the next decade. We have a unique opportunity to change the narrative for clinical research that addresses the most challenging questions within the contemporary health care system.

# References:

1. Marshall JC. Global Collaboration in Acute Care Clinical Research: Opportunities, Challenges, and Needs. *Crit Care Med* 2017; 45(2): 311-20.
2. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342(18): 1301-8.
3. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367(20): 1901-11.
4. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med* 2016; 42(11): 1695-705.
5. Hebert PC, Wells G, Blajchman MA, et al. A multicentre randomized controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340: 409-17.
6. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360(13): 1283-97.
7. Marshall JC, Kwong W, Kommaraju K, Burns KE. Determinants of Citation Impact in Large Clinical Trials in Critical Care: The Role of Investigator-led Clinical Trials Groups. *Crit Care Med* 2016; 44(4): 663-70.
8. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit Care Med* 2010; 38(1): 65-71.
9. Cook D, Meade M, Guyatt G, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011; 364(14): 1305-14.
10. Fowler RA, Mittmann N, Geerts W, et al. Cost-effectiveness of dalteparin vs unfractionated heparin for the prevention of venous thromboembolism in critically ill patients. *JAMA* 2014; 312(20): 2135-45.
11. Cook DJ, Todd TRJ. The Canadian Critical Care Trials Group: A collaborative, educational organisation for the advancement of adult ICU research. *Intens Care World* 1997; 14(2): 68-70.
12. Lacroix J, Hebert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. *N Engl J Med* 2015; 372(15): 1410-8.
13. Ferguson ND, Cook DJ, Guyatt GH, et al. High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. *N Engl J Med* 2013; 368(9): 795-805.
14. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013; 368(16): 1489-97.
15. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350(22): 2247-56.
16. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; 364(16): 1493-502.
17. National Heart L, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354(24): 2564-75.
18. Collaborators I. InFACT: A global critical care research response to H1N1. *Lancet* 2010; 375(9708): 11-3.
19. Cook D, Burns K, Finfer S, et al. Clinical research ethics for critically ill patients: a pandemic proposal. *Crit Care Med* 2010; 38(4 Suppl): e138-e42.
20. Blackwood B, Ringrow S, Clarke M, et al. Core Outcomes in Ventilation Trials (COVenT): protocol for a core outcome set using a Delphi survey with a nested randomised trial and observational cohort study. *Trials* 2015; 16: 368.
21. Needham DM, Sepulveda KA, Dinglas VD, et al. Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study. *Am J Respir Crit Care Med* 2017; 196(9): 1122-30.
22. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; 302(21): 2323-9.
23. Austin S, Murthy S, Wunsch H, et al. Access to urban acute care services in high- vs. middle-income countries: an analysis of seven cities. *Intensive Care Med* 2014; 40(3): 342-52.
24. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med* 2016; 193(3): 259-72.
25. Bartz RR, Gantner D, Gordon AC, et al. Who Says There Is No "I" in Team? Achieving Individual Success in Collaborative Clinical Research in Critical Care. *Am J Respir Crit Care Med* 2016; 194(7): 911-2.



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LAYOUT DESIGN: GROUP JKC

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