



Transforming treatments, saving lives:

The SAFE, SAFE-TBI, CHEST & PLUS studies.

The
George
Institute
for Global Health



Better treatments
Better care
Healthier societies

Our research has saved many thousands of lives and hundreds of millions of dollars by changing the way the medical world views one of the most common intensive care treatments. Our studies have influenced intensive care treatment guidelines worldwide, prevented harmful yet common treatment choices, and demonstrated that cheaper treatments can be safer than more expensive ones. By tackling what was previously considered 'impossible' in intensive care research, our researchers initiated a culture of critical thinking in one of the most challenging and expensive areas of healthcare.

Life or death choices

In intensive care units (ICU), doctors are faced with making decisions quickly, and patients and their relatives are often scared and uncertain. Evidence-based interventions to reduce the amount of time people need to spend in ICU, not only provide better emotional outcomes for patients and their families, but also result in millions of dollars in healthcare and societal savings.

"There are a lot of tubes, machines and unfamiliar sounds in ICUs – it's dehumanising and confronting," says Professor John Myburgh AO, an ICU physician and Director of the Division of Critical Care at The George Institute for Global Health.

"We deal with the sickest and most vulnerable patients – those who need vital organ support to stay alive, such as those with traumatic brain injury, septic shock or following major surgery. The demand on ICU beds, resources and expertise has been highlighted and exacerbated during the COVID-19 pandemic," says John. Critical illness is much more than an admission to the ICU.

"Today, ICU patients have a better chance of survival compared to 20 years ago, but typically have longer term chronic health conditions and complications, like we are seeing with those that have survived moderate to severe COVID-19," he says. "Our job in ICUs is to make the best choices for our patients by relying on the best quality evidence."

"The demand on ICU beds, resources and expertise has been highlighted and exacerbated during the COVID-19 pandemic..."

Professor John Myburgh AO

Game-changing ICU research

In the early 1990s, up to one in six or seven people were dying in ICUs across Australia and New Zealand. John and other ICU physicians started running clinical trials to improve patient outcomes. The first major clinical trial that was conducted addressed the safety and efficacy of one of the most common treatments used in intensive care patients – intravenous fluid resuscitation.

"Just about every patient admitted to hospital via an emergency department to the ICU will receive intravenous fluids for resuscitation or as part of standard

ICUs at a glance

- Each year in Australia, 160,000 people are admitted to ICU, 7.7% of whom die*
- Intensive care is one of the most expensive aspects of healthcare globally
- In Australia**:
 - one day in ICU costs a minimum of \$4,104
 - a mechanical ventilator costs \$2,666 a day
 - renal replacement therapy costs \$268 a day
 - chronic dialysis costs \$79,918 a year

**2018 ANZICS Core Report*

***The Impact of Research in Critical Care, 2020, Health Technology Analysts Pty Ltd*



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treatment,” explains Professor Simon Finfer AO, an ICU physician and senior researcher at The George Institute. “However, the best choice of fluid has been a longstanding issue of debate.”

“Back then, ‘albumin’ was the most commonly used intravenous fluid in ICU in Australia,” says Simon. “When a study from the UK in 1997 suggested its use was associated with an increased rate of death, we decided that we had an ethical and scientific imperative to address this uncertainty by conducting a high-quality clinical trial.”

In 1999, Simon and John designed and conducted the [Saline vs. Albumin Fluid Evaluation Study](#) – the SAFE study – to determine whether the use of albumin as a resuscitation fluid had an increased rate of death when given to critically ill patients in the ICU compared to a cheaper fluid, ‘normal’ saline. The SAFE study would recruit 7,000 patients in Australia and New Zealand, heralding a new era in intensive care medicine research.

“The magnitude of the SAFE trial was not in the mindset back then - no-one had the experience or resources,” says Simon. “It was common to have 100 patients in an ICU trial – not thousands.”

“We applied the principles of large-scale medical trials used commonly in clinical trials for heart disease and stroke treatments to generate the best-quality evidence,” says Simon.

Through this ground-breaking clinical trial, SAFE and a follow-up study in patients with traumatic brain injury

Types of fluids

Intravenous fluid resuscitation replaces fluids to restore normal body functions and prevent organ failure. It is used in around 35% of ICU patients. There are two main types of fluids - cheaper ‘crystalloids’, such as ‘normal’ saline, and the more costly ‘colloids’, such as albumin.

“The magnitude of the SAFE trial was not in the mindset back then - no-one had the experience or resources”

Professor Simon Finfer AO

(SAFE-TBI) showed that albumin did not provide better outcomes for critically ill patients compared to saline, and in fact was associated with an increased rate of death in patients with traumatic brain injury.

“SAFE gave clinicians a clear choice – the routine use of albumin was hard to justify,” says Simon.

SAFE and SAFE-TBI informed international guidelines, stopping the use of albumin in brain injury patients, and in most circumstances, in other critically ill patients. In Australia, up to 1,209 lives would be saved each year if the recommendations from SAFE-TBI were implemented in 100% of the eligible population, according to a 2020 report by Health Technology Analysts. In addition, if the findings of SAFE and SAFE-TBI were fully implemented, approximately \$125.6 million would be saved annually in ICU, other healthcare and societal costs.

In a published commentary about SAFE, world-leading critical care expert, Professor Deborah Cook, says: “(SAFE) addressed one of the most fundamental and contentious issues in critical care... The SAFE study is not only a landmark trial; it is also a milestone for the discipline of critical care.”

In a world first, SAFE showed it was possible to conduct the highest standard of clinical trial in intensive care medicine, laying the foundation for two decades of guideline-changing ICU studies by researchers at The George Institute.

Challenging common practice

Around the time that SAFE was published, an albumin alternative and a synthetic ‘colloid’, hydroxyethyl starch (HES), had become the most common fluid used in ICUs globally, particularly in patients undergoing major surgery and those with severe sepsis.

Its use had evolved in areas of the world where albumin was not widely used due to availability and cost. In 2009, the use of HES as a resuscitation fluid had not been licensed in Australia due to small-scale studies that raised concerns about its safety and efficacy, particularly an increased risk of acute kidney injury.

“Given this uncertainty and following our experience with the SAFE study, we decided to repeat the research design and conduct a clinical trial to test the safety and efficacy of HES in critically ill patients by determining whether HES was associated with an increased risk of death or kidney failure compared to saline,” explains John.

The landmark Crystalloid vs Hydroxyethyl Starch Study – the CHEST study – was subsequently conducted, involving 7,000 patients across more than 25 ICUs in Australia and New Zealand.

“The results from CHEST added substantive weight to a body of evidence from high-quality randomised controlled trials that not only did HES increase deaths and kidney failure, it did not provide any clinical benefit to critically ill patients,” says John. “The cumulative evidence is now clear that patients with sepsis are at increased risk of death and kidney failure.”

As a result of this emerging body of evidence, for which CHEST provided the majority of data, medical regulatory authorities worldwide suspended or restricted the licencing of HES in critically ill patients, particularly those with sepsis. Further evidence has subsequently emerged reporting that HES has no clinical benefit in patients undergoing fluid resuscitation for trauma or major surgery. As a consequence the use of HES in clinical practice has markedly declined.

In 2018, in an open letter to the World Health Organization published in *The Lancet*, global experts including John and Simon, used CHEST to caution against an increase in the use of HES in low- and middle-income countries, especially for vulnerable patients such as women with obstetric bleeding. The Surviving Sepsis Campaign guidelines, used widely in low- and middle-income countries, recommended against the use of HES as a choice of fluid for severe sepsis and septic shock patients.

“The George Institute was front and centre with CHEST – it was one of the highlights of my 40-year ICU career,” reflects John. “It’s really gratifying when we finish a trial that answers tough questions and it becomes a catalyst for life-saving changes in clinical practice globally.”

Thousands of patients globally are alive today because they were not given HES in ICUs. In Australia, if the findings from CHEST were fully implemented, up to \$109.5 million in ICU, healthcare and societal costs would be saved each year; and up to 12,924 days in ICU, 2,365 days of renal replacement therapy, and 6,252 days of mechanical ventilation avoided annually.

“PLUS will tell us definitively which is the best choice of fluid for critically ill patients – it will have a transformative impact on intensive care medicine”

Sharon Micallef

“The return on investment on our clinical trials is phenomenal, in particular when I think back to where we started and how this research has also influenced practice in many countries,” says John.

Ending the debate

SAFE and CHEST were the two largest clinical trials ever conducted in intensive care medicine until the [Plasma-Lyte 148@ versUs Saline \(PLUS\) study](#) was launched in 2017 by researchers at The George Institute. The study will recruit more than 5,000 patients across 50 sites to determine whether saline or the increasingly popular “buffered” or “balanced” salt solutions produce the best outcomes for ICU patients.

“We will combine the data from PLUS with data from a parallel study in Brazil to analyse results from 16,000 patients – one of the largest number of patients ever included in ICU research.,” says Sharon Micallef, Senior Project Manager at The George Institute.

Preliminary findings suggest an alternative saline fluid could reduce deaths in ICUs by 12.5% and lower the risk of acute kidney injury.

“PLUS will tell us definitively which is the best choice of fluid for critically ill patients – it will have a transformative impact on intensive care medicine,” says Sharon.

Before the SAFE and CHEST trials, it was generally thought that the type of fluid used in ICUs did not affect patient outcomes. Our researchers changed the way the medical world thinks about intravenous fluids and demonstrated that the choice of fluid should be treated with the same care and attention as the prescription of a drug.

In addition to averting thousands of deaths and saving hundreds of millions of dollars in Australia, these ground-breaking trials paved the way for ICUs across the country to conduct high-quality research, positioning Australia as a world leader in ICU research, and highlighting the significant health and economic benefits of high-quality clinical trials.





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Projects: SAFE, SAFE-TBI, CHEST, PLUS

Research leads: Professor John Myburgh AO,
Professor Simon Finfer AO

Project cycle: 1999–2020

Partners and supporters:

SAFE: Collaborators - The Australian and New Zealand Intensive Care Society (ANZCIS) Clinical Trials Group
Supporters: National Health and Medical Research Council, Australia (NHMRC), CSL Limited

CHEST: Collaborators - ANZICS Clinical Trials Group, The University of Sydney. Supporters: NHMRC; NSW Ministry of Health (Australia), Fresenius Kabi

PLUS: Collaborators: ANZICS Clinical Trials Group, The Medical Research Institute of New Zealand (MRINZ)
Supporters: NHMRC, Baxter Healthcare, Health Research Council of New Zealand

About The George Institute for Global Health:

The George Institute for Global Health is focused on generating robust evidence to create better treatments, better care and healthier societies. This means not only generating evidence to determine what works, and doesn't work, but also which health service or treatment is value for money and where the cost of healthcare can be reduced. Paramount to our work is finding new ways to fund healthcare so health systems can become more sustainable, as well as operate more equitably.

About The PRISM Initiative:

Through interviews with investigators and research partners, project staff and peers in the research community, The Project & Research Impact Story Mapping (PRISM) Initiative examines key research milestones of The George Institute and explores the impact of its projects on health sectors and systems, government policies, communities and more. Join us as we explore key research achievements of the past 20 years, examine how conventional thinking was challenged, who benefitted and what led the research to be transformed into practice.

Our research impact

Each year that SAFE, SAFE-TBI and CHEST recommendations are implemented in Australia, up to*:

- 1,465 lives saved
- \$235.1 million in ICU and other healthcare and societal costs saved
- 27,179 days in ICUs prevented
- 12,363 days of mechanical ventilation avoided
- 2,418 days of renal replacement therapy prevented

*The Impact of Research in Critical Care, 2020, Health Technology Analysts Pty Ltd

According to a report by the Australian Commission on Safety and Quality in Health Care and the Australian Clinical Trials Alliance, SAFE, SAFE-TBI and CHEST are among a group of Australian clinical trials that together can save almost \$2 billion in savings a year in Australia, highlighting that for each \$1 invested in an Australian clinician-driven clinical trial, \$5.80 in returns are generated.