Management of a multi-national RCT
An Australian Experience

02/06/2020
Jikei ICU
Agenda

1. Introduction of ANZIC-RC, Monash SPHPM
2. 2-year journey of VITAMINS
3. Management of a multi-national RCT
The School’s predecessor, the Department of Social and Preventive Medicine was inaugurated in June 1968.

The department expanded.

becoming the School of Public Health and Preventive Medicine in 2008
Monash SPHPM

ASPREE Research
- ASPREE
- ASPREE sub-studies
- Biorepository
- Biological Neuropsychiatry and Dementia

Cancer Research
- Cancer Research
- CCRE Therapeutics
- Musculoskeletal Epidemiology
- Cabrini Epidemiology
- Infectious Diseases Epidemiology
- Women’s Health Research Program

Clinical Epidemiology
- Biostatistics
- Epidemiological Modelling
- Cochrane Australia
- Research Governance

Research Methodology
- Registry Science and Research
- Transfusion Research
- Prostate Cancer Registry
- Bariatric Surgery Registry
- Australian Breast Device Registry

Health Services
- Monash Centre for Occupational and Environmental Health
- Monash Centre for Epidemiology and Health Research
- ACHHRA
- Aviation Medicine
- Hazelwood Health Study

Occupational and Environmental Health Science
- Critical Care Research
- Intensive Care
- ANZCA Research
- Pre-hospital, Emergency and Trauma Research

Critical Care Research
- Postgraduate Courses
- Undergraduate Courses
- Medical Education Research and Quality
- Gambling and Social Determinants

Teaching and Learning
- Jean Hailes Research
- Michael Kirby Centre
- Andrology Australia
- Monash Ageing Research Centre
- Genomics

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Monash Centre for Occupational and Environmental Health

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Metabolism Ageing genomics
ASPREE trial

A trial of aspirin for the primary prevention in the Healthy Elderly.
# Academics
Monash SPHPM

<table>
<thead>
<tr>
<th>Role</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E</strong> Professor (Research or T&amp;R)</td>
<td>49</td>
</tr>
<tr>
<td><strong>D</strong> Associate Professor (Research or T&amp;R)</td>
<td>26</td>
</tr>
<tr>
<td><strong>C</strong> Senior Research Fellow</td>
<td>32</td>
</tr>
<tr>
<td><strong>B</strong> Research Fellow</td>
<td>58</td>
</tr>
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<td><strong>A</strong> Research Assistant</td>
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<tr>
<td>Research Staff</td>
<td>~400</td>
</tr>
<tr>
<td>Other Professional Staff</td>
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<tr>
<td>Senior Lecturer</td>
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<tr>
<td>Lecturer</td>
<td>15</td>
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<td>Assistant Lecturers</td>
<td></td>
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<tr>
<td>Teaching Associates</td>
<td>~ 100</td>
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<tr>
<td>Other Professional Staff</td>
<td>~ 100</td>
</tr>
</tbody>
</table>
Research (SPHPM) in 2017

RESEARCH FUNDING 2017

- Category 1: 54%
- Category 2: 23%
- Category 3: 23%
Total: AU$38,785,792 = ¥ 32 億

PUBLICATIONS 2017

- Books and book chapters, 18
- Journal articles, 1079
ANZIC-RC
Australian and New Zealand Intensive Care Research Centre

• Established in 2006
• Funded by the National Health and Medical Research Council and Monash Uni.
• To conduct high impact, large-scale, investigator-initiated clinical trials designed to determine best and most cost-effective practice in Intensive Care Medicine.
• To develop integrated clinical research programs that provide the training ground for future clinical trialists in the field of ICM.
• To encourage and support clinician researchers in research theory, study design, study conduct, data analysis and scientific writing.
NHMRC funding
ANZIC-RC administered grants

Year 2019 $8,504,500 = ¥6.5億
Publications by Year

Not cumulative
ANZIC-RC Staff
2019

Academic
7 Professors, 2 A/Professors, 3 Senior Research Fellows, 6 Research Fellows

Research Staff
Research Manager, Business Manager, Administration Manager, Senior Project Manager, 14 Project Managers, 3 Project officers, Research and Admin Officer
From publications

2017

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators


Meta-analysis published in the Journal!!

Original Article

Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults


Energy-Dense versus Routine Enteral Nutrition in the Critically Ill

The TARGET Investigators, for the ANZICS Clinical Trials Group®
Early Sedation with Dexmedetomidine in Critically Ill Patients


Conservative Oxygen Therapy during Mechanical Ventilation in the ICU

The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group®

ABSTRACT
Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial

Tomoko Fujii, MD, PhD; Nora Luethi, MD; Paul J. Young, MBChB, PhD; Daniel R. Frei, BSc, MBChB; Glenn M. Eastwood, PhD; Craig J. French, MB, BS; Adam M. Deane, MB, BS, PhD; Yahya Shehabi, MB, BS, PhD; Ludmilla A. Hajjar, MD, PhD; Gisele Oliveira, MD; Andrew A. Udy, MBChB, PhD; Neil Orford, MB, BS, PhD; Samantha J. Edney; BSN, PGDipNS; Anna L. Hunt, BN, PGDipHSM, PGDipClinRes; Harriet L. Judd, BSN, PGDipHC; Laurent Bitker, MD; Luca Cioccarri, MD; Thummaporn Naorungroj, MD; Fumitaka Yanase, MD; Samantha Bates, BN, PGDipCritCare; Forbes McGain, MB, BS, PhD; Elizabeth P. Hudson, MD; Wisam Al-Bassam, MBChB; Dhiraj Bhatta Dwivedi, BScNsg, MBA; Chloe Peppin, BN, PGDipCritCare; Phoebe McCracken, MPH; Judith Orosz, MD; Michael Bailey, PhD; Rinaldo Bellomo, MD, PhD; for the VITAMINS Trial Investigators

Published January 17, 2020

Available at jama.com

2020
The VitamIn C, HydrocorTisone and ThiAMINe in Patients with Septic Shock Trial
Vitamin C levels in Critical Illness

• Vitamin C levels fall in critical illness due to reduced intake increased oxidative consumption

• Septic shock patients have significantly depleted vitamin C levels compared with non-septic patients

• Humans and guinea pigs cannot synthesize vitamin C in their body

Carr Crit Care 2017
Vitamin C Cocktail therapy

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock
A Retrospective Before-After Study

Paul E. Marik, MD, FCCP; Vikramjit Khandapora, MD; Raquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravasis, PhD, FCCP

Single centre before-after study

Patients with severe sepsis or septic shock

Before (47 patients)
• 60 % of patients received hydrocortisone

After (47 patients)
• All patients received Vitamin C 6g/day + Hydrocortisone 200mg/day + Thiamine 400 mg/day

Mortality
40.4 %
8.5 %

Vasopressor doses
VITAMINS trial

The VitamIn C, HydrocorTisone and ThiAMINe in Patients with Septic Shock Trial

An international open-label randomised controlled trial

Aim

To determine whether the combination of vitamin C, hydrocortisone, and thiamine, compared with hydrocortisone alone, improves the duration of time alive and free of vasopressor administration in patients with septic shock
VITAMINS trial sites

10 study sites in 3 countries

- Austin Hospital
- Alfred Hospital
- the Royal Melbourne Hospital
- Geelong University Hospital
- Footscray Hospital
- Sunshine Hospital
- Monash Medical Centre
- Dandenong Hospital

- Wellington Regional Hospital
- Cancer Institute of the State of Sao Paulo
The VITAMINS team
Patients with septic shock

**Intervention group**
- Vitamin C 1.5g IV q6h
- Hydrocortisone 50mg IV q6h
- Thiamine 200mg IV q12h

**Control group**
- Hydrocortisone 50mg IV q6h

Treatment continued until (whichever occurs first)
- Cessation of vasopressor administration
- Discharge from the ICU
- 10 days of treatment
Outcomes

Primary Outcome: Time alive and free of vasopressors at day 7 (168 hours) after randomisation

Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>28-day mechanical ventilation-free days</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>28-day RRT-free days</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>Change in SOFA score at day 3</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>28-day ICU free days</td>
</tr>
<tr>
<td>28-day cumulative vasopressor-free days</td>
<td>Hospital length of stay</td>
</tr>
</tbody>
</table>
Sample Size

Difference in vasopressor-free hours of 25 hours - Clinically minimally important (> 1 day) 90% power

Initial sample size calculation
- 126 patients
  - Estimated SD = 42 hours (=168/4)

Adjusted using the actual data after the first 60 patients were enrolled.
- Pooled SD = 51.6 hours

Accounting for non-parametric distribution
- Inflated by 15%

Accounting for consent withdrawal
- Inflated by 5%

Sample size
- 216 patients
Study Protocol & SAP

Vitamin C, Hydrocortisone and Thiamine in Patients with Septic Shock (VITAMINS) trial: study protocol and statistical analysis plan

Tomoko Fujii, Andrew A Udy, Acam M Deane, Nora Luethi, Michael Bailey, Glenn M Eastwood, Daniel Frei, Craig French, Neil Orford, Yahya Shehabi, Paul J Young and Rinaldo Bellomo, on behalf of the VITAMINS trial investigators

- Published before study recruitment was completed
- Trial Registration ClinicalTrials.gov, NCT03333278
- Analysed according to the randomisation group
- Missing data were not imputed

Crit Care Resusc 2019 (June)
## Milestone dates

14 months to recruit 216 patients, 1 month to manuscript submission!!

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first enrolment</td>
<td>May 8(^{th}), 2018</td>
</tr>
<tr>
<td>The last enrolment</td>
<td>July 9(^{th}), 2019</td>
</tr>
<tr>
<td>Last day-90 follow up</td>
<td>October 6(^{th}), 2019</td>
</tr>
<tr>
<td>Database lock</td>
<td>October 25(^{th}), 2019</td>
</tr>
<tr>
<td>Manuscript submission</td>
<td>November 8(^{th}), 2019</td>
</tr>
<tr>
<td>Presentation &amp; Publication</td>
<td>January 17(^{th}), 2020</td>
</tr>
</tbody>
</table>
Patients screened N = 786

Excluded N = 570

Randomised N = 216

Randomised to screened patient ratio 1 : 3.6

TOP 3 reasons for exclusion

• Patients with a diagnosis of septic shock for >24 hours

• Death was deemed to be imminent or inevitable

• Clinician expected to prescribe systemic glucocorticoids for an indication other than septic shock
Randomised $N = 216$

Intervention Group $N = 109$
- Consent withdrawn $N = 2$
- Primary Analysis $N = 107$
  - Lost to f/u $N = 2$
  - Day 90 Analysis $N = 105$

Control Group $N = 107$
- Consent withdrawn $N = 2$
- Primary Analysis $N = 104$
  - Consent withdrawn or Lost to f/u $N = 2$
  - Day 90 Analysis $N = 102$
## Baseline Characteristics

<table>
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<tr>
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<th>Intervention (n = 107)</th>
<th>Control (n = 104)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.9 (15.9)</td>
<td>61.6 (13.9)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>68 (63.6)</td>
<td>65 (62.5)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>39 (36.4)</td>
<td>39 (37.5)</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>81.0 (66.0 to 95.0)</td>
<td>83.0 (67.5 to 102.0)</td>
</tr>
<tr>
<td>ICU admission source, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>49 (45.8)</td>
<td>49 (47.1)</td>
</tr>
<tr>
<td>Operating room - emergency surgery</td>
<td>20 (18.7)</td>
<td>14 (13.5)</td>
</tr>
<tr>
<td>Hospital ward</td>
<td>17 (15.9)</td>
<td>20 (19.2)</td>
</tr>
<tr>
<td>Transfer from another hospital</td>
<td>13 (12.1)</td>
<td>10 (9.6)</td>
</tr>
<tr>
<td>Operating room - elective surgery</td>
<td>4 (3.7)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Transfer from another ICU</td>
<td>4 (3.7)</td>
<td>4 (3.8)</td>
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<tr>
<td>Hydrocortisone for septic shock before randomisation, No. (%)</td>
<td>45 (42.1)</td>
<td>39 (37.5)</td>
</tr>
<tr>
<td>Intervention at randomisation, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>66 (61.7)</td>
<td>65 (62.5)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>99 (92.5)</td>
<td>97 (93.3)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>22 (20.6)</td>
<td>22 (21.2)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>13 (12.1)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>8 (7.5)</td>
<td>10 (9.6)</td>
</tr>
<tr>
<td>Inotropes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>6 (5.6)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>12 (11.2)</td>
<td>12 (11.5)</td>
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<td><strong>Physiological variables</strong></td>
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<td></td>
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<tr>
<td>White cell count, mean (SD), x10³/µl</td>
<td>17.5 (11.3)</td>
<td>15.3 (10.4)</td>
</tr>
<tr>
<td>Platelet count, median (IQR), x10³/µl</td>
<td>162 (104 to 239)</td>
<td>173 (107 to 251)</td>
</tr>
<tr>
<td>Lactate, median (IQR), mmol/l</td>
<td>4.2 (2.8 to 5.9)</td>
<td>3.3 (2.6 to 4.9)</td>
</tr>
<tr>
<td>Serum creatinine, median (IQR), mg/dl</td>
<td>1.73 (1.16 to 2.64)</td>
<td>1.78 (1.07 to 2.90)</td>
</tr>
<tr>
<td>Acute kidney injury, No. (%)</td>
<td>74 (69.2)</td>
<td>75 (72.1)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Stage 2</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Stage 3</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>APACHE III score, mean (SD)</td>
<td>77.4 (29.7)</td>
<td>83.3 (28.8)</td>
</tr>
<tr>
<td>SOFA score, mean (SD)</td>
<td>8.6 (2.7)</td>
<td>8.4 (2.7)</td>
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<td><strong>Primary site of infection, No. (%)</strong></td>
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</tr>
<tr>
<td>Pulmonary</td>
<td>31 (29.0)</td>
<td>33 (31.7)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>31 (29.0)</td>
<td>31 (29.8)</td>
</tr>
<tr>
<td>Urinary</td>
<td>18 (16.8)</td>
<td>14 (13.5)</td>
</tr>
<tr>
<td>Skin or soft tissue</td>
<td>14 (13.1)</td>
<td>15 (14.4)</td>
</tr>
<tr>
<td>Blood</td>
<td>9 ( 8.4)</td>
<td>2 ( 1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>4 ( 3.7)</td>
<td>9 ( 8.7)</td>
</tr>
<tr>
<td><strong>Hospital-acquired infection, No. (%)</strong></td>
<td>18 (16.8)</td>
<td>13 (12.5)</td>
</tr>
<tr>
<td><strong>Time from ICU admission to randomisation, median (IQR), h</strong></td>
<td>13.7 (7.1 to 19.3)</td>
<td>11.4 (5.5 to 17.8)</td>
</tr>
</tbody>
</table>
### Study Treatment

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<th>Intervention (n = 107)</th>
<th>Control (n = 104)</th>
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</thead>
<tbody>
<tr>
<td>At least one dose administered, No. (%)</td>
<td>106 (99.1)</td>
<td>102 (98.1)</td>
</tr>
<tr>
<td>Treatment duration, mean (SD), d</td>
<td>3.4 (2.1)</td>
<td>3.4 (2.2)</td>
</tr>
<tr>
<td>Time from the eligibility to the first dose of vitamin C, median (IQR), h</td>
<td>12.1 (5.7 to 19.0)</td>
<td>–</td>
</tr>
<tr>
<td>Time from the eligibility to the first dose of hydrocortisone, median (IQR), h</td>
<td>–</td>
<td>8.9 (4.0 to 15.0)</td>
</tr>
</tbody>
</table>
## Primary Outcome

**Time alive and free of vasopressor up to day 7 median (IQR)**

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<th>Intervention (n = 107)</th>
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<tbody>
<tr>
<td>122.1 (76.3 to 145.4) hours</td>
<td>124.6 (82.1 to 147.0) hours</td>
</tr>
</tbody>
</table>

**Median of all-paired differences (95% CI)**

<table>
<thead>
<tr>
<th>Median of all-paired differences (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>−0.6 (−8.3 to 7.2) hours</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Sensitivity Analysis

Multivariable quantile regression adjusting for
• Stratification variable – Site
• Baseline imbalance ( \( P < 0.2 \) ) – APACHE III score, lactate levels, white cell counts and the usage of milrinone

**Difference of medians** −4.6 hours [95% CI, −15.7 to 6.5], \( P = 0.41 \)
## Secondary Outcomes - mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>Differences</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>28-day mortality</strong></td>
<td>24/106 (22.6)</td>
<td>21/103 (20.4)</td>
<td>2.3 (−8.9 to 13.4)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>90-day mortality</strong></td>
<td>30/105 (28.6)</td>
<td>25/102 (24.5)</td>
<td>4.1 (−8.0 to 16.1)</td>
<td>0.51</td>
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<tr>
<td><strong>ICU mortality</strong></td>
<td>21/107 (19.6)</td>
<td>19/104 (18.3)</td>
<td>1.4 (−9.2 to 11.9)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Hospital mortality</strong></td>
<td>25/107 (23.4)</td>
<td>21/103 (20.4)</td>
<td>3.0 (−8.2 to 14.1)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Survival Analysis

Hazard ratio 1.18 (95%CI, 0.69 to 2.01); P=0.54

Number at risk
- Intervention: 107
- Control: 104

Days from randomisation
- Intervention: 82, 77, 76, 75, 0
- Control: 83, 81, 79, 78, 0
## Secondary Outcomes – artificial organ support

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>Differences</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day cumulative vasopressor-free days</td>
<td>25.6 (17.8 to 26.8) N = 106</td>
<td>25.8 (19.6 to 26.8) N = 103</td>
<td>−0.2 (−1.7 to 1.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>28-day cumulative mechanical ventilation-free days</td>
<td>25.3 (5.2 to 28.0) N = 106</td>
<td>24.8 (9.5 to 28.0) N = 103</td>
<td>0.4 (−2.6 to 3.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>28-day RRT-free days</td>
<td>28.0 (23.5 to 28.0) N = 105</td>
<td>28.0 (21.0 to 28.0) N = 103</td>
<td>0.0 (−0.6 to 0.6)</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Vasopressor dose

Ratio of geometric means 0.93 (95%CI, 0.69 to 2.01, P = 0.54)
### Secondary Outcomes - organ dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>Differences</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Δ SOFA score at day 3</strong></td>
<td>–2 (–4 to 0), N = 82</td>
<td>–1 (–3 to 0), N = 75</td>
<td>–1.0 (–1.9 to –0.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute kidney injury, n/N (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>18/107 (16.8)</td>
<td>14/104 (13.5)</td>
<td>3.4 (–6.3 to 13.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Stage 2</td>
<td>18/107 (16.8)</td>
<td>22/104 (21.2)</td>
<td>–4.3 (–14.9 to 6.2)</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>39/107 (36.4)</td>
<td>39/104 (37.5)</td>
<td>–1.1 (–14.1 to 12.0)</td>
<td></td>
</tr>
</tbody>
</table>
## Secondary Outcomes - length of stay

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>Differences</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day ICU-free days</td>
<td>21.9</td>
<td>22.1 (3.9 to 25.8)</td>
<td>-0.2 (–4.1 to 3.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>12.3 (6.2 to 26.0)</td>
<td>12.3 (6.2 to 26.1)</td>
<td>0.0 (–4.9 to 4.9)</td>
<td>0.75</td>
</tr>
</tbody>
</table>
### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2 events in 2 patients)</td>
<td>(1 event in 1 patient)</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>1 event in 1 patient</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0</td>
<td>1 event in 1 patient</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 event in 1 patient</td>
<td>0</td>
</tr>
</tbody>
</table>

### Serious adverse events
None reported.

### Suspected unexpected serious adverse reactions
None reported.
Conclusion of the VITAMINS trial

In patients with septic shock, treatment with intravenous vitamin C, hydrocortisone, and thiamine, compared with intravenous hydrocortisone alone, did not significantly improve the duration of time alive and free of vasopressor administration over 7 days.

The finding suggests that treatment with intravenous vitamin C, hydrocortisone, and thiamine does not lead to a more rapid resolution of septic shock compared with intravenous hydrocortisone alone.
## Two-year journey of VITAMINS

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Date</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first enrolment</td>
<td>May 8(^{th}), 2018</td>
<td>Executing &amp; Controlling</td>
</tr>
<tr>
<td>The last enrolment</td>
<td>July 9(^{th}), 2019</td>
<td></td>
</tr>
<tr>
<td>Last day-90 follow up</td>
<td>October 6(^{th}), 2019</td>
<td></td>
</tr>
<tr>
<td>Database lock</td>
<td>October 25(^{th}), 2019</td>
<td></td>
</tr>
<tr>
<td>Manuscript submission</td>
<td>November 8(^{th}), 2019</td>
<td></td>
</tr>
<tr>
<td>Presentation &amp; Publication</td>
<td>January 17(^{th}), 2020</td>
<td>Closing</td>
</tr>
</tbody>
</table>
Management – Preparation

- Protocol
- Study materials:
  - CRF, Data dictionary, Study tools
- Database
GCP
Good Clinical Practice

and many abbreviations...

Registration to the authority – “submit CTN to TGA”
Contract with study sites – “contact OGC for CTRA”
Ethics application – “submit HREA via ERM”
Management – Executing and Controlling

• Start-up meeting/teleconference
• Weekly/bi-weekly progress report by email
• Monitoring – source data verification
• Time management
  sample size recalculation @ 60 pts
  • completion of data entry & calculation
  • protocol amendment
  • ethics approval for the amendment
  • BEFORE we reach the initial sample size of 126.
Recruitment Tracker

For fun

Celebrated the completion of recruitment
Management – Cost/Funding

• At the beginning of the trial… no funding
• Intensive Care Foundation research grant
• Alfred Research Trusts
• Austin Intensive Care Trust Fund
• Program to Support Institutional Development of Universal System (PROADI-SUS, Brazil)
Management - Closing
A little more to do after publication

Final report to the Ethics
Site closure
Per patient payment to sites
Project Management without a proper Project Manager

Management Committee
- Rinaldo Bellomo
- Adam Deane
- Glenn Eastwood
- Daniel Frei
- Craig French
- Tomoko Fujii (from JPN)

- Ludhmila Hajjar
- Nora Luethi (from CHE)
- Gisele Oliveira
- Neil Orford
- Yahya Shehabi
- Andrew Udy
- Paul Young

No funding to pay Project Manager at the beginning of the trial.
2 international senior research fellows managed the trial.
Challenges

In managing a highly-topical research project
• many ongoing similar trials
• trial design & results matter, but the 1st report will be highly spoken

For international research fellows
• language
• regulations
• relationships with local research coordinators and site investigators
ANZIC-RC Staff 2019

Academic
7 Professors, 2 A/Professors, 3 Senior Research Fellows, 6 Research Fellows

Research Staff
Research Manager, Business Manager, Administration Manager, Senior Project Manager, 14 Project Managers, 3 Project officers, Research and Admin Officer
Management of a multi-national RCT

Team effort