ADRENAL – the world’s largest trial in septic shock

Bala Venkatesh
Professor of Intensive Care
Wesley & Princess Alexandra Hospitals
The George Institute for Global Health
University of Queensland & NSW
17.30-18.00
ADRENAL: The World’s Largest Trial in Septic Shock
Prof Bala Venkatesh

12th October

13.44-14.06
The Steroid Story
Prof Jeremy Cohen
Disclosures

• Recipient of grants from NHMRC
• NHMRC-MRFF Practitioner Fellow
## ADRENAL key results – Primary outcome

<table>
<thead>
<tr>
<th></th>
<th>Hydrocortisone (N = 1832)</th>
<th>Placebo (N = 1826)</th>
<th>Odds Ratio</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D90 mortality</td>
<td>511 (27.9%)</td>
<td>526 (28.8%)</td>
<td>0.96</td>
<td>0.83</td>
<td>1.10</td>
<td>0.54</td>
</tr>
</tbody>
</table>

### Secondary outcomes

- **Hydrocortisone** – Shock reversal, IPPV, ICU discharge, blood transfusion

- **No difference** between the groups with respect to recurrence of shock, RRT, super-infections and 6 month mortality

### Adverse effects

A small but a slightly higher incidence of adverse effects in the hydrocortisone group, but these did not impact on patient-centred outcomes
Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

Long-Term Outcomes of the ADRENAL Trial

Balasubramanian Venkatesh, M.D.
Simon Finfer, M.D.
John Myburgh, M.D., Ph.D.

George Institute for Global Health
Sydney, NSW, Australia
bvenkatesh@georgeinstitute.org.au

Jeremy Cohen, M.D., Ph.D.
University of Queensland
Brisbane, QLD, Australia

Laurent Billot, M.Sc., M.Res.
George Institute for Global Health
Sydney, NSW, Australia

| Unadjusted | 571/1812  (31.5%) | 574/1803  (31.8%) | 0.99 | 0.86-1.13 | 0.83 |
Is ADRENAL the world’s largest septic shock trial?
Sample sizes of RCTS in septic shock

- 1970-2000: 583
- 2000-2010: 832
- 2010-2018: 1306
In doing a trial of this size........

• What did we gain?
• What are the challenges?
• What are the lessons learnt?
Comparative sample sizes of low dose steroids – RCTs - Septic shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane</td>
<td>2002</td>
<td>299 patients</td>
</tr>
<tr>
<td>CORTICUS</td>
<td>2008</td>
<td>499 patients</td>
</tr>
<tr>
<td>APROCCHSS</td>
<td>2018</td>
<td>1241 patients</td>
</tr>
<tr>
<td>ADRENAL</td>
<td>2018</td>
<td>3800 patients</td>
</tr>
</tbody>
</table>
What are the benefits of doing a large trial?
Are large randomised controlled trials in severe sepsis and septic shock statistically disadvantaged by repeated inadvertent underestimates of required sample size?

Joshua L C Wong,1,2 Alexina J Mason,3 Anthony C Gordon,1 Stephen J Brett1

Effect sizes in ongoing randomized controlled critical care trials

Elliott E. Ridgeon1, Rinaldo Bellomo2,3, Scott K. Aberegg4, Rob Mac Sweeney5, Rachel S. Varughese1, Giovanni Landoni6,7 and Paul J. Young8
<table>
<thead>
<tr>
<th>Trial name</th>
<th>Effect size (%)</th>
<th>Sample size</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Confirmatory Phase II/III Study Assessing Efficacy, Immunogenicity and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety of IC43 Recombinant <em>Pseudomonas</em> Vaccine in Intensive Care Patients</td>
<td>5 (2–6, 0–23))</td>
<td>3186</td>
<td>800</td>
</tr>
<tr>
<td>ADjunctive coRticosteroid trEatment iN criticaLLy iiLPatients with Septic</td>
<td>5 (3–10, 0–33)</td>
<td>3556</td>
<td>3800</td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Spontaneous Breathing in ARDS</td>
<td>5 (2–10, 0–35)</td>
<td>2748</td>
<td>700</td>
</tr>
<tr>
<td>Non-sedation versus Sedation with a Daily Wake-up Trial in Critically Ill</td>
<td>5 (3–15, 0–39)</td>
<td>2904</td>
<td>700</td>
</tr>
<tr>
<td>Patients Receiving Mechanical Ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress Ulcer Prophylaxis in the Intensive Care Unit</td>
<td>3 (1–5, 0–25)</td>
<td>8388</td>
<td>3350</td>
</tr>
<tr>
<td>The Augmented versus Routine Approach to Giving Energy Trial</td>
<td>3 (1–5, 0–25)</td>
<td>6266</td>
<td>4000</td>
</tr>
<tr>
<td>The SuDDICU Cluster RCT of Antibiotic Prophylaxis in Critical Illness</td>
<td>5 (3–9, 0–24)</td>
<td>Not calculated</td>
<td>24,000</td>
</tr>
<tr>
<td>Ticagrelor in Severe CAP</td>
<td>3 (1–5, 0–33)</td>
<td>7522</td>
<td>568</td>
</tr>
<tr>
<td>Tranexamic acid for the treatment of gastrointestinal haemorrhage: an</td>
<td>3 (2–5, 0–10)</td>
<td>3624</td>
<td>8000</td>
</tr>
<tr>
<td>international randomised, double-blind, placebo-controlled trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranexamic acid for the treatment of significant traumatic brain injury:</td>
<td>4 (2–5, 0–10)</td>
<td>3868</td>
<td>10,000</td>
</tr>
<tr>
<td>an international, randomised, double-blind, placebo-controlled trial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1) Confidence in the robustness of the primary and secondary outcomes

*The message is very clear* that there is no 90 day mortality difference - overall and in 6 sensible a priori subgroups (sex, illness severity, med-surg, vasopressor dose, shock duration and pulmonary infectious source vs other).

*Further, signals from prior research which may have been viewed skeptically in the past were confirmed by some results of ADRENAL* (e.g., shorter duration of vasopressor dependency).

*Signals from prior research or concerns about steroids were refuted by some results of ADRENAL* (e.g., worry about recurrence of shock, or short-term secondary bacteremia or fungemia).

Other findings of ADRENAL are relatively new and relevant to precious resource consumption (e.g., less red blood cell transfusion – conservatively interpreted). *Yet another finding is health services-relevant outcome* (e.g., 2 day earlier ICU discharge).
2) Minimises risk of a Type 1 error

<table>
<thead>
<tr>
<th>Patients randomised before 01JUL2014</th>
<th>123/483 (25.5%)</th>
<th>152/481 (31.6%)</th>
<th>0.73 (0.55 - 0.97)</th>
<th>0.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised before 01JUL2015</td>
<td>248/919 (27.0%)</td>
<td>266/920 (28.9%)</td>
<td>0.91 (0.74 - 1.11)</td>
<td>0.34</td>
</tr>
<tr>
<td>Patients randomised before 01JUL2016</td>
<td>405/1460 (27.7%)</td>
<td>425/1456 (29.2%)</td>
<td>0.93 (0.79 - 1.09)</td>
<td>0.36</td>
</tr>
<tr>
<td>All randomised patients at end of study</td>
<td>511/1832 (27.9%)</td>
<td>526/1826 (28.8%)</td>
<td>0.95 (0.82 - 1.10)</td>
<td>0.50</td>
</tr>
</tbody>
</table>
3) Affords generalizability

- By its sheer size
  - Multiple sites
  - Multiple geographic regions
  - Multiple health care systems
4) Post hoc-sensitivity analysis – applying Sepsis-3 criteria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hydrocortisone (N = 969)</th>
<th>Placebo (N = 968)</th>
<th>Odds Ratio</th>
<th>Lower CI 95%</th>
<th>Upper CI 95%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=1937)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality D90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>312/963 (32.4%)</td>
<td>337/958 (35.2%)</td>
<td>0.88</td>
<td>0.73</td>
<td>1.07</td>
<td>0.20</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td>0.86</td>
<td>0.70</td>
<td>1.06</td>
<td>0.19</td>
</tr>
<tr>
<td>Mortality D28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>259/969 (26.7%)</td>
<td>300/968 (31.0%)</td>
<td>0.81</td>
<td>0.67</td>
<td>0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td>0.80</td>
<td>0.64</td>
<td>0.99</td>
<td>0.06</td>
</tr>
</tbody>
</table>
### 5) Understand Shock reversal (About 2700 patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time to reversal of shock</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;=2 days</td>
</tr>
<tr>
<td>Days alive-free of ICU</td>
<td>82 (8.35)</td>
</tr>
<tr>
<td>Days alive-free of Hospital</td>
<td>61 (24)</td>
</tr>
<tr>
<td>Days alive-free of RRT</td>
<td>88 (12)</td>
</tr>
<tr>
<td>Days alive-free of IPPV</td>
<td>85(8)</td>
</tr>
<tr>
<td>Recurrence of shock</td>
<td>10.2%</td>
</tr>
<tr>
<td>Any RRT received</td>
<td>13.2%</td>
</tr>
<tr>
<td>New bacteraemia/fungemia</td>
<td>10.3%</td>
</tr>
</tbody>
</table>

NHMRC grant under review
6) Understand Septic shock associated AKI

- 31% of patients went on to require RRT during the course of the study (This means that about 1200 patients required RRT in the setting of septic shock)

This cohort provides an opportunity to understand
- clinical factors predicting need for RRT
- correlation between types of sepsis and need for RRT
- outcomes of patients requiring RRT
- proportion of patients recovering from AKI
- proportion of patients requiring long term dialysis

This cohort were enrolled from 5 different health care systems. There is an opportunity to study dialysis practices, membrane and filter usage in different parts of the world.

NHMRC grant under development
7) Understand biological mechanisms: Genomics

- ADRENAL GEPPS – Largest genomic resource
- 580 patients
- GWAS
- Methylation
- RNA Seq

NHMRC funded- led by David Evans UQ
8) Understand biological mechanisms: Corticosteroid & Vit C pathophysiology

• 580 patients
• Measured plasma free and total cortisol and aldosterone
• Vitamin C
9) Robust data on long term outcomes

• QOL and HEA
• Gender disaggregation

NHMRC & ICF funded - led by Kelly Thompson
What were the challenges in doing ADRENAL?
The story behind adrenal

- Developing the proposal
- Attempts to secure funding
- Obstacles
- Importance of collaboration
- Importance of persistence
Why is ADRENAL different?

- CTG studies – SAFE/ CHEST/NICE-Sugar
- Enrolment criteria were stringent—required sepsis + VP dependent shock + IPPV
- Blinded parenteral placebo – powder
- Need for GMP licensed manufacturing of placebo
Attempts to fund ADRENAL related research

1 Background and Research Plan 2005 - unsuccessful 401617

AIMS
The basic hypothesis driving this project is that:

The use of corticosteroids in patients with sepsis and septic shock continues to remain controversial. Central to this debate is the issue of whether there is adrenal insufficiency in

Dear Associate Professor Venkatesh 2006 - unsuccessful

Project Grant Application: 455950
Scientific Title: A prospective multi-centre blinded phase II study of relative adrenal insufficiency in adult patients with septic shock

I am writing to advise that your application for NHMRC Project Grant funding to commence in 2007 has been rated in category 3. NHMRC funding will not extend into this category. Each

1 Background and Research Plan 2007 - unsuccessful 511164

Introduction

Steroid therapy has not been shown to consistently provide benefit in severe sepsis and may even be associated with adverse effects. The driver for steroid therapy is based on the
<table>
<thead>
<tr>
<th>Application Id</th>
<th>Chief Investigator A</th>
<th>Application Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>569722</td>
<td>Prof Balasubramanian (Bala) Venkatesh</td>
<td>2008</td>
<td>Activity of 11-beta hydroxysteroid dehydrogenase in septic shock: Relationship to organ failure and mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Application Id</th>
<th>Chief Investigator A</th>
<th>Application Year</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>631538</td>
<td>Prof Bala Venkatesh</td>
<td>2009</td>
<td>Development of a reliable marker of tissue steroid responsiveness in septic shock</td>
</tr>
</tbody>
</table>

"Illegitimi non carborundum"
In reply please quote: NHMRC Project Grant Application 1004108

Prof Bala Venkatesh  
Department of Intensive Care  
Ipswich road  
Woolloongabba QLD 4102

Dear Prof Venkatesh

Project Grant Application: 1004108  
Scientific Title: A randomised controlled trial of the effect of hydrocortisone on mortality in critically ill patients with septic shock

I am pleased to advise that the Minister for Mental Health and Ageing, the Hon Mark Butler MP, has approved funding for your National Health & Medical Research Council (NHMRC) Project Grant to commence in 2011.
Time lines

- Grant Announcement: Nov 10
- Management Committee: Nov 10
- Grant commencement: Jan 11
- Protocol development: In progress
- Ethics submission: Apr 11
- EOI and site selection: Apr-July 11
- Enrollment date: Aug-Sep 11

Study expected to run over 4 years
Obstacles

- Acquisition of placebo
- Regulatory approvals
- Internationalisation
- Unforeseen obstacles
- Inconsistency in interpretation of the rules
- Collateral damage from other trials
Challenge 1: Acquisition of placebo – to match a parenteral drug in powder form
Treatments

Hydrocortisone came in vials containing 100 mg of hydrocortisone hemisuccinate powder and ampoules containing 2 mL of glucose solution solvent, which was administered intravenously every 6 hours as a 50-mg bolus (Roussel-Uclaf, Romainville, France). One tablet containing 50 μg of 9-α-fludrocortisone was administered daily through a nasogastric tube with 10 to 40 mL of water over 30 seconds (Pharmacie Centrale des Hôpitaux, Paris, France). Placebos were indiscernible from active treatments. Treatment duration was 7 days.

STUDY DRUGS

Hydrocortisone (Rotexmedica) was prepared in vials containing 100 mg of hydrocortisone hemisuccinate powder with ampules containing 2 ml of sterile water diluent; the vials were then coded and masked centrally (Klocke Verpackungs Service). Vials containing placebo were identical to those containing hydrocortisone. The study drugs were administered as a 50-mg intravenous bolus every 6 hours for 5 days, then tapered to 50 mg intravenously every 12 hours for days 6 to 8, 50 mg every 24 hours for days 9 to 11, and then stopped. A total of 29 doses were given. Evidence-based guidelines for the treatment of patients were encouraged.24
Acquisition of placebo

- Added 1.5 years to the study – GMP licensed supplier
- Blew the budget by $400,000
- Pfizer
- Companies which supplied the French and CORTICUS
- Companies in India and China
- Blinding device
- First negotiation commenced Oct 2011
- Drug finally delivered Feb 2013
Establish pharmaco-compatibility

• Infusion line - Mixing with other drugs

The compatibility of a low concentration of hydrocortisone sodium succinate with selected drugs during a simulated Y-site administration

Andrew J Semark, Karthik Venkatesh, Brett C McWhinney, Carel Pretorius, Jason A Roberts, Jeremy Cohen and Bala Venkatesh

Critical Care and Resuscitation • Volume 15 Number 1 • March 2013
The hydrocortisone sodium succinate sterile powder (Pfizer Australia Ltd, West Ryde, Australia) was supplied in a plain glass vial, equivalent to 100mg of hydrocortisone. The powder is a white odourless, hygroscopic amorphous solid which is highly water soluble.

The placebo (Radpharm Scientific Pty Ltd, Belconnen, Australia) was a matching vial containing 0.2mL sterile water for injection. Both hydrocortisone and placebo vials were completely covered in blinding label (Mater Pharmacy Services, Brisbane, Australia) and labelled with the allocated medication kit number.

Trial treatment was prepared aseptically by reconstituting a trial treatment vial with 2mL of sterile water. The vial was agitated for 20 seconds and then rested for 3 minutes. The reconstituted solution was withdrawn in a syringe and inspected visually for the presence of particulate matter and discoloration prior to administration.

The reconstituted solution was added to an intravenous infusion bag of either 100mL 0.9% sodium chloride or 100mL 5% dextrose. The solution was administered as a continuous infusion over 12 hours using a volumetric infusion pump. Either peripheral or central venous lines could be used. Once reconstituted and added to a bag of intravenous fluid, the trial treatment was stable for 24 hours.

The image below depicts a masked vial with attached label.

ADRENAL manuscript – Table S3b – Supplementary appendix
Challenge 2: International collaborations

• UK
• Denmark
• KSA
• India
• Ireland
• Hong Kong
• Canada
• Mayo Clinic
Running pharmaceutical trials in Europe

- MHRA – GMP licensed facility
- EMA
- Eudract
India

• Ethics approval
• Central government ruling about RCTs
• Compensation rules
• Need for video recording of consent
Ireland

- Ethics approved
- Waiting for MHRA approval
- Change of administrators in the hospital and loss of RC positions
- Indemnity cover in Ireland – unresolved for 6 months.
- No definite decision on final approvals by the hospital
Hong Kong

- Ethics approved
- Indemnity issues unresolvable
Canada & Mayo Clinic

• Canada – competing trials
• Mayo - Indemnity
Challenge 3: Once trial up and running ......, revocation of ethics approvals, varied interpretation of rules and suspension of trials
Dear Professor Venkatesh,

Re: Protocol No X11-0148 & HREC/11/RPAH/214 - “GI-CCT372273 : A randomised blinded placebo controlled trial of hydrocortisone in critically ill patients with septic shock (ESCAPE - Evaluation In Sepsis of Corticosteroid And Pimobendan)”

The Executive of the Ethics Review Committee, at its meeting of 30 June 2011, considered Ms D Rajbhandari’s correspondence of 28 June 2011. In accordance with the decision made by the Ethics Review Committee, at its meeting of 8 June 2011, ethical approval is granted.

The proposal meets the requirements of the National Statement on Ethical Conduct In Human Research.

Thank you for submitting the above research protocol to the Metro South Health Human Research Ethics Committee for ethical and scientific review, on behalf of the following Principal Investigators (see appendix). This protocol was first considered by the Human Research Ethics Committee (HREC) at the meeting held on 6 December 2011.

I am pleased to advise that the HREC has granted approval of this research protocol.
CAT Exemption

11 April 2012

Professor Balasubramanian Venkatesh
Intensive Care Unit
Princess Alexandra Hospital
Woollongabba QLD 4102

Dear Professor Venkatesh,

HREC Reference number: HREC/11/QPAH/619

On the 05 April 2012 the Chair of the Metro South Health Service District Human Research Ethics Committee noted and approved the following:-

- That the provisions of the Guardianship Act 2000 are not relevant for this study and that a QCAT submission is there not required.
Dear [Name]

Re: REC Reference 12/EE/0368, the ADRENAL study

Could I ask your assistance with the ethics application for this study? I would like to formally appeal a decision taken by the Cambridge Central committee who have withdrawn the ethics approval of the study in the last few weeks.

This is a multi-national multi-centred study looking into the use of low dose hydrocortisone in the treatment of patients with septic shock. To date approx. 1000 patients have been enrolled Worldwide. We gained ethical approval from the Cambridge Central committee in February 2013 but due to delays in obtaining the necessary MHRA approvals have not been able to start enrolling in the UK. In recent months we have now received the MHRA approval and have updated the study paperwork in line with personnel changes (contact names) over the time period and submitted them back to the ethics committee as amendments (as they suggested). On the basis of the delay and now the change in paperwork the ethical approval has now been reversed. Nothing has changed in the running of the study since the initial approval apart from the updated paperwork.

I would like to appeal this decision. There has been no change to the ethical basis of the study. In deed it has been assessed by multiple ethical committees worldwide who have all given it the green light and the study (outside of the UK) is still actively recruiting. The reversal of the decision in this case has been made due to starting delays (16 months from granting of the approvals) which is not out of line with the original decision that stated the study had to start within 24 months of the approval. The delays have all been necessary to comply with UK legislation to obtain regulatory agency approval.

Please could I ask you to:

1. Confirm receipt of this email and
2. Inform me of the necessary steps I would need to take to formally lodge this appeal.

Yours sincerely
Dear Dorrilyn

Thank you for your application of 25 August 2014 seeking approval to export goods for clinical trial use under s19(1)(b).

The following issues have been identified with the application:

1. A copy of a GMP licence/clearance/certificate for Mater Pharmacy Services has not been provided.
2. The certificate of GMP compliance for Radpharm Scientific is only valid until 8 June 2014.
3. The copy of the letter from HPRA of 8 August 2014 is not signed.

In order to proceed with your application, could you please provide documentation that addresses each of the above issues.

Kind Regards
NCAT ruling – 2015 & suspension of trial in NSW

- SPICE ruling – Jan 2015
- Definition of a clinical trial / deferred consent
- Suspension of trial for 7 months in NSW
- Legal costs
- Loss of RC jobs
- Morale
- Doubts in mind.
Hi [Name],

Further to previous email. We do not require QCAT approval for this study as it is not a new experimental drug but standard treatment. We also do not require PHA approval as patients are being consented or consented by a legal person on a patient’s behalf. These treatments are available as standard care.

I will arrange for sign off and advise you when this is done.

Kind regards
Challenge 4: Recruitment challenges
Moving average of % of monthly recruitment by C24 ICU's-ADRENAL

Courtesy: Mahesh Ramanan
5) Potential impact of other trials

- SSC-CORTICUS
- SUPICU-REVISE
- APROCCHSS ADRENAL

<table>
<thead>
<tr>
<th>APROCCHSS</th>
<th>ADRENAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last enrolment: June 2015</td>
<td>Apr 2017</td>
</tr>
<tr>
<td>Manuscript sub: Sep 2017</td>
<td>Nov 2017</td>
</tr>
<tr>
<td>Publication: Mar 2018</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>
6) Need for a top up application

• Admin costs

• Time lag to commencement
Keeping sites engaged & avoiding trial fatigue

- Emails
- Milestones
- Newsletter
- SMS

Dear Matt and Anand, hope your Easter Monday call is not too hectic. A gentle reminder about ADRENAL. We only have 20 to go!!
Personal time

- LSL
- LWOP
- Unpaid time
- Travel costs
- O/C - 24/7 for the entire duration of the trial
Estimation of budget: What did ADRENAL cost?

Total cost – 5 million

Initial NHMRC - 3.27 M
NZ-HRC - 700 K
Top up NHMRC - 300 K
NIHR - 177 K
GEPPS – provided buffer
Will a study like this fund a RC?

- The PAH enrolled about 260 patients. At $500 per patient, it totals $130000, which is 1.5 FTE of an RC over the 4 year period.
Valuable lessons

• Patience
• Persistence
• Engage
• Deal with frustrations
• Thick skin
• Work with people because people are working for you
• Colleagues
• A good team
Valuable lessons learnt for future trials

- Excellent knowledge within the CTG
- Parenteral placebo challenges
- GMP manufacture / TGA guidelines
- MHRA regulations
- Ability to build on international collaborations
- Feasibility of conducting large scale trials within ANZ
### Key study Dates

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study commencement</td>
<td>Mar 2013</td>
</tr>
<tr>
<td>Last enrolment</td>
<td>21 Apr 2017</td>
</tr>
<tr>
<td>Last D90 follow-up</td>
<td>21 Jul 2017</td>
</tr>
<tr>
<td>Database lock</td>
<td>3 Oct 2017</td>
</tr>
<tr>
<td>Initial results</td>
<td>6 Oct 2017</td>
</tr>
<tr>
<td>MC presentation</td>
<td>17 Oct 2017</td>
</tr>
<tr>
<td>Investigator presentation</td>
<td>19 Oct 2017</td>
</tr>
<tr>
<td>Manuscript submission</td>
<td>4 Nov 2017</td>
</tr>
<tr>
<td>Open presentation</td>
<td>19 Jan 2018</td>
</tr>
</tbody>
</table>
Comparative timelines

- Annane trial 3.5 years, n=299, 19 sites
- CORTICUS 3.5 years, n=499, 52 sites
- VASST 5 years, n=778, 27 sites
- APROCCHS 6.9 years, n=1241, 26 sites
- ADRENAL 4.3 years, n=3800, 69 sites
Australia
• Austin Hospital
• Bendigo Hospital
• Blacktown Hospital
• Calvary Mater Hospital Newcastle
• Footscray Hospital
• Fremantle Hospital / Fiona Stanley Hospital
• Geelong Hospital
• Gold Coast University Hospital
• Gosford Hospital
• Ipswich General Hospital
• John Hunter Hospital
• Liverpool Hospital
• Logan Hospital
• Lyell McEwin Hospital
• Mackay Hospital
• Mater Health Services (Private), Brisbane
• Mater Health Services (Public), Brisbane
• Monash Medical Centre
• Nambour General Hospital
• Nepean Hospital
• Northern Hospital
• Prince Charles Hospital
• Prince of Wales Hospital
• Princess Alexandra Hospital
• Redcliffe Hospital
• Royal Adelaide Hospital
• Royal Brisbane & Women's Hospital
• Royal Darwin Hospital
• Royal Hobart Hospital
• Royal Melbourne Hospital
• Royal North Shore Hospital
• Royal Perth Hospital
• Royal Prince Alfred Hospital
• St George Hospital
• St John of God Hospital Murdoch
• St Vincent’s Hospital (Melbourne)
• St Vincent’s Hospital (Sydney)
• Sunshine Hospital
• Tamworth Rural Hospital
• The Queen Elizabeth Hospital
• The Tweed Hospital
• The Wesley Hospital
• Toowoomba Hospital
• Wollongong Hospital
• Tauranga Hospital
• Waikato Hospital
• Wellington Hospital

United Kingdom, England
• Bristol Royal Infirmary
• Freeman Hospital - Newcastle upon Tyne
• King's College Hospital
• Lewisham Hospital
• Queen Alexandra Hospital - Portsmouth
• Queen Elizabeth Hospital - Birmingham
• Royal Surrey County Hospital
• St George’s Trust NHS
• St Peter’s Hospital - Surrey
• St Thomas’ Hospital
• University Hospital Southampton

United Kingdom, Wales
• Royal Gwent Hospital

Denmark
• Rigshospitalet

Kingdom of Saudi Arabia
• King Abdulaziz Medical City, Riyadh
• King Fahad Medical City
• King Khalid University Hospital, King Saud University

New Zealand
• Auckland City Hospital CVICU
• Auckland City Hospital DCCM
• Christchurch Hospital
• Middlemore Hospital
• North Shore Hospital
The superb team at the George Institute