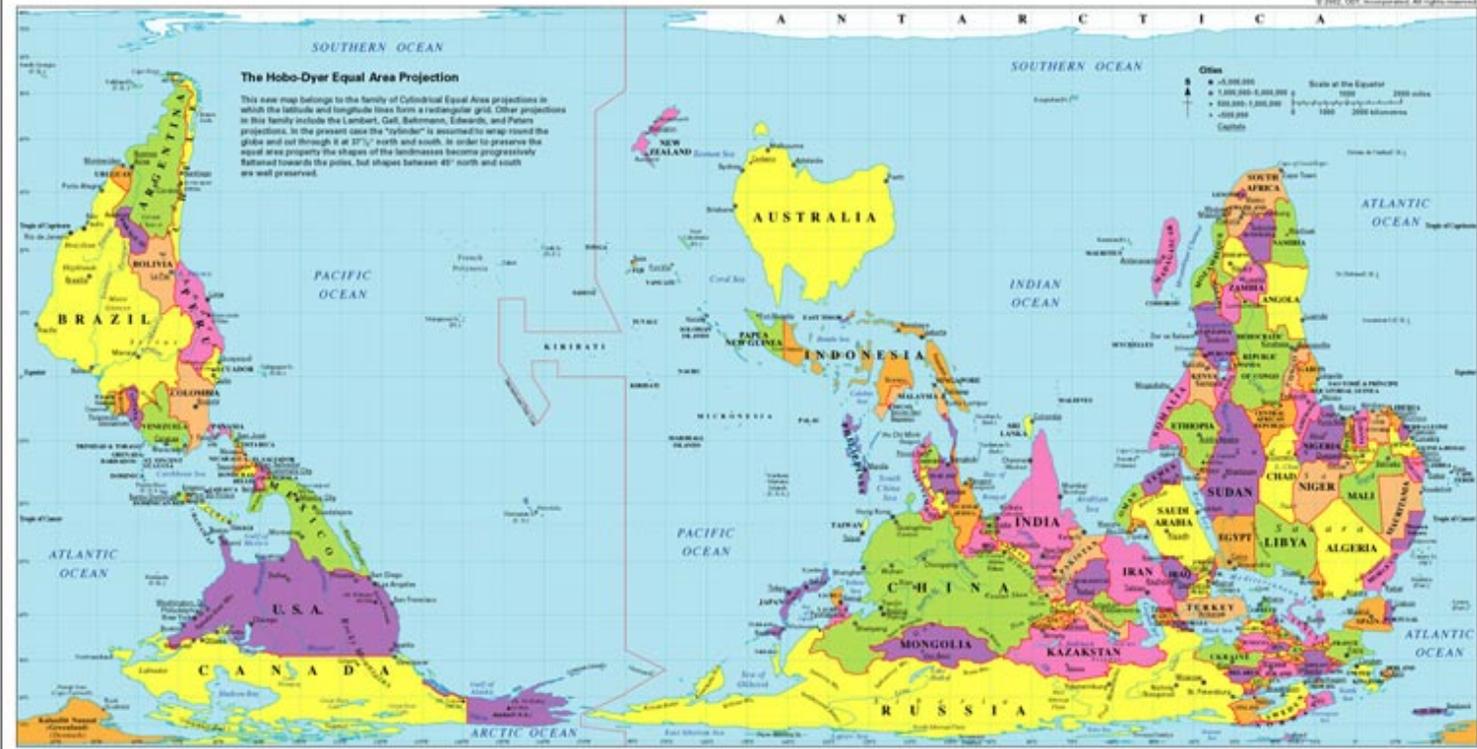


# The SAFE Study

(Saline v Albumin Fluid Evaluation)



Australian and New Zealand Intensive Care Society  
Clinical Trials Group,  
Australian Red Cross Blood Service

The George Institute for International Health, University of Sydney



## ***SAFE (Saline v Albumin Fluid Evaluation) Study Initiated in Australia and New Zealand***

- To compare the effects of two resuscitation fluids (4% human albumin or saline) on 28-day all-cause mortality in ICU patients requiring intravascular volume resuscitation
- Hypothesis: no difference in mortality at 28 days



## *Study Design and Sample Size*

- Multicenter, randomized, double-blind controlled trial
- To compare the effects of two resuscitation fluids (4% human albumin or saline) on 28-day all-cause mortality in ICU patients requiring intravascular volume resuscitation
- 7,000 patients, 16 ICUs in Australia and New Zealand
- 90% power to detect 3% difference in absolute mortality from an estimated baseline mortality of 15%

# ***SAFE Study: Participating Institutions***



1. **Alfred Hospital, Melbourne, Victoria** - Julie Charlton, James Cooper, Andrew Davies, Catherine Harry, Lisa Higgins, Katherine Moulden, Shirley Vallance.
2. **Auckland Hospital, Auckland (NZ)** - Janine Chadderton, Lynette Newby, Colin McArthur
3. **Austin & Repatriation Medical Centre, Melbourne, Victoria** - Samantha Bates, Rinaldo Bellomo, Donna Goldsmith, Alison Voss.
4. **Fremantle Hospital, Fremantle, Western Australia** - David Blythe, Annamaria Palermo.
5. **John Hunter Hospital, Newcastle, NSW** – Rosemary Carroll, Brett McFadyen, Peter Saul.
6. **Middlemore Hospital, Auckland (NZ)** - Jane Clarke, Juliet Powell, Anthony Williams, Judi Tai.
7. **Nepean Hospital, Penrith, NSW** – Louise Cole, Iveta Hynesova, Ian Seppelt, Leonie Weisbrodt.
8. **Princess Alexandra Hospital, Brisbane, Queensland** - Lisa Bradley, Christopher Joyce, Theresa Kelly, Anthony Limpus, Robyn Moore.
9. **Royal Adelaide Hospital, South Australia** - Marianne Chapman, Stephanie Creed, Sandra Kaplan, Justine Rivett.
10. **Royal Darwin Hospital, Northern Territory** - Dianne Stephens, Jane Thomas.
11. **Royal Hobart Hospital, Tasmania** - Anthony Bell, Kathy Marsden, Andrew Turner.
12. **Royal Melbourne Hospital, Victoria** - Catherine Boyce, John Cade, Belinda Howe, Jeffrey Presneill, Megan Robertson.
13. **Royal North Shore Hospital, Sydney, NSW** –Gordon Doig, Simon Finfer, Anne O’Connor, Julie Potter, Naresh Ramakrishnan.
14. **Royal Prince Alfred Hospital, Sydney, NSW** – Catherine Powell, Dorrilyn Rajbhandari, Clive Woolfe.
15. **St George Hospital, Sydney, NSW** - Kathryn Girling, Marie Hodgetts, Alina Jovanovska, John Myburgh.
16. **Western Hospital, Melbourne, Victoria** - Craig French, Lorraine Little.



## *Pre-defined subgroups*

- Trauma
- Severe Sepsis
- Acute Respiratory Distress Syndrome



## *Main Inclusion Criteria*

- Needs intravascular fluid resuscitation in ICU
- Treating doctor has substantial uncertainty over best fluid to give
- Informed consent if competent, otherwise delayed consent



## *Main Exclusion Criteria*

- Age less than 18 years
- Burns
- Cardiac surgery
- Liver transplantation
- Allergy or religious objection to albumin
- Moribund



# Web-Based Study

## The SAFE Study

A multi-centre double blind randomised controlled trial of the effects on intravenous volume replacement with albumin compared to saline in critically ill patients

▶ [About the study](#)  
(PDF)

▶ [Contact Details](#)  
(PDF)



A joint initiative of:

Australian & New Zealand Intensive Care Society Clinical Trials Group  
Institute for International Health, University of Sydney  
Australian Red Cross Blood Service

Registered Users	
Username:	<input type="text"/>
Password:	<input type="password"/>
<input type="button" value="Login"/>	

Last updated: 21 April 2002



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# *Funding bodies*

- Auckland District Health Board, New Zealand
- Australian Commonwealth Department of Health and Aged Care
- Australian National Health and Medical Research Council
- CSL Limited, Melbourne (Australia)
- Health Department of Western Australia
- Health Research Council of New Zealand
- Middlemore Hospital, New Zealand
- New South Wales Health Department (Australia)
- Northern Territory Health Services (Australia)
- Queensland Health Services Department (Australia)
- Royal Hobart Hospital, Tasmania (Australia)
- South Australian Department of Human Services
- Victorian Department of Human Services (Australia)



## *Study Treatments:*

4% albumin  
(ALBUMEX<sup>®</sup>) or saline

Manufactured by CSL  
Limited, Melbourne,  
Australia.





# Study Design

- Blinding – formally tested prior to study



# Study Design

- Packaging



# Study Design

- Distribution



# Study Design

- Administration





## *Fluid administration*

- The treating clinicians decided the amount and rate of fluid administration according to each patient's clinical status and response to treatment.
- The allocated study treatment was used for all fluid resuscitation in the ICU until death or discharge or until 28 days following randomization.
- Administration of intravenous fluids outside the ICU was not controlled.
- All other aspects of patient care were performed at the discretion of treating clinicians.



## *Concomitant treatments*

- All other aspects of patient care were performed at the discretion of treating clinicians.



## *Outcome measures*

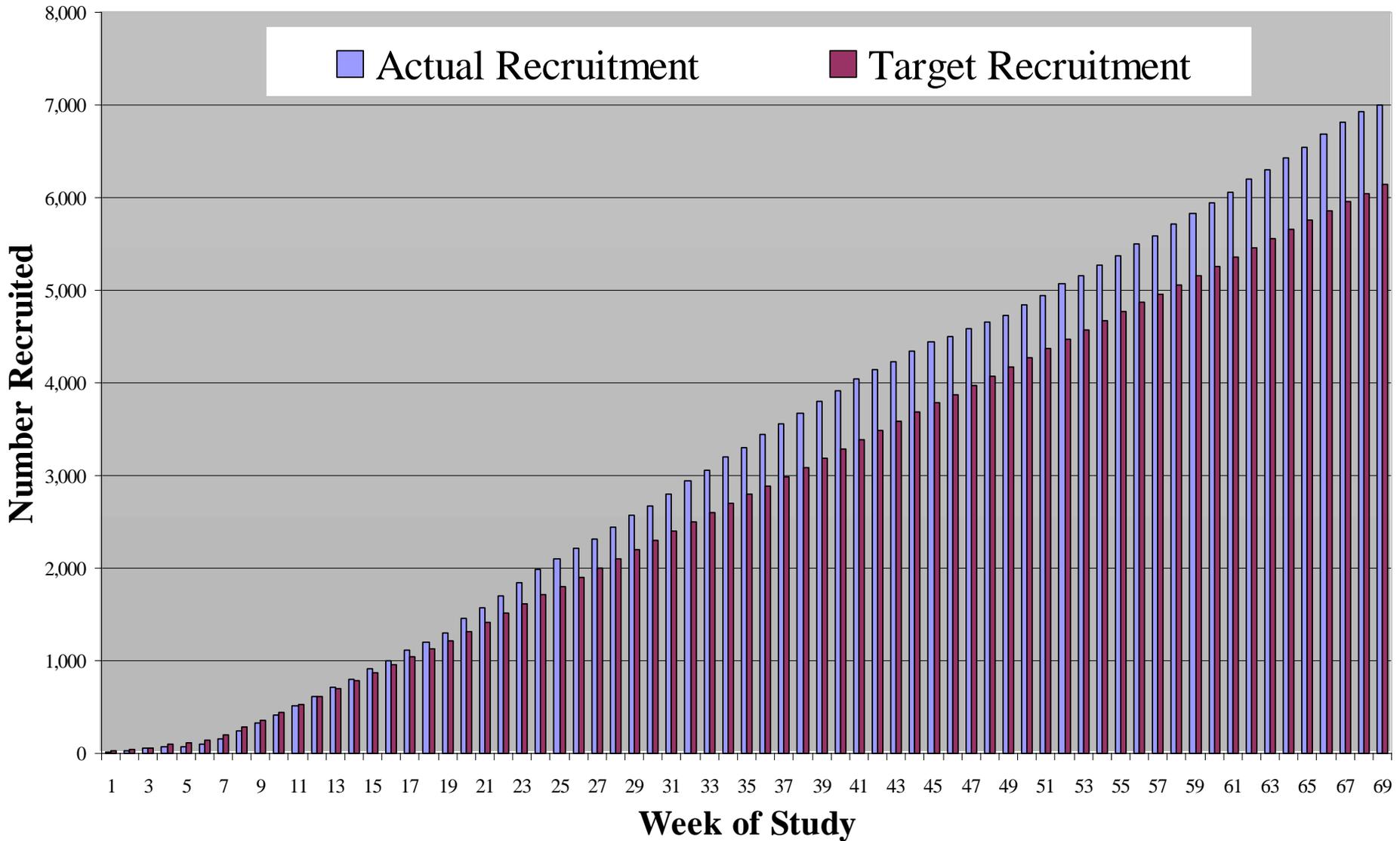
- Primary outcome: death from all causes at 28 days.
- Secondary outcomes:
  - survival during the first 28 days
  - proportion of patients with new organ failures
  - duration of mechanical ventilation
  - duration of renal replacement therapy
  - duration of ICU and hospital stay

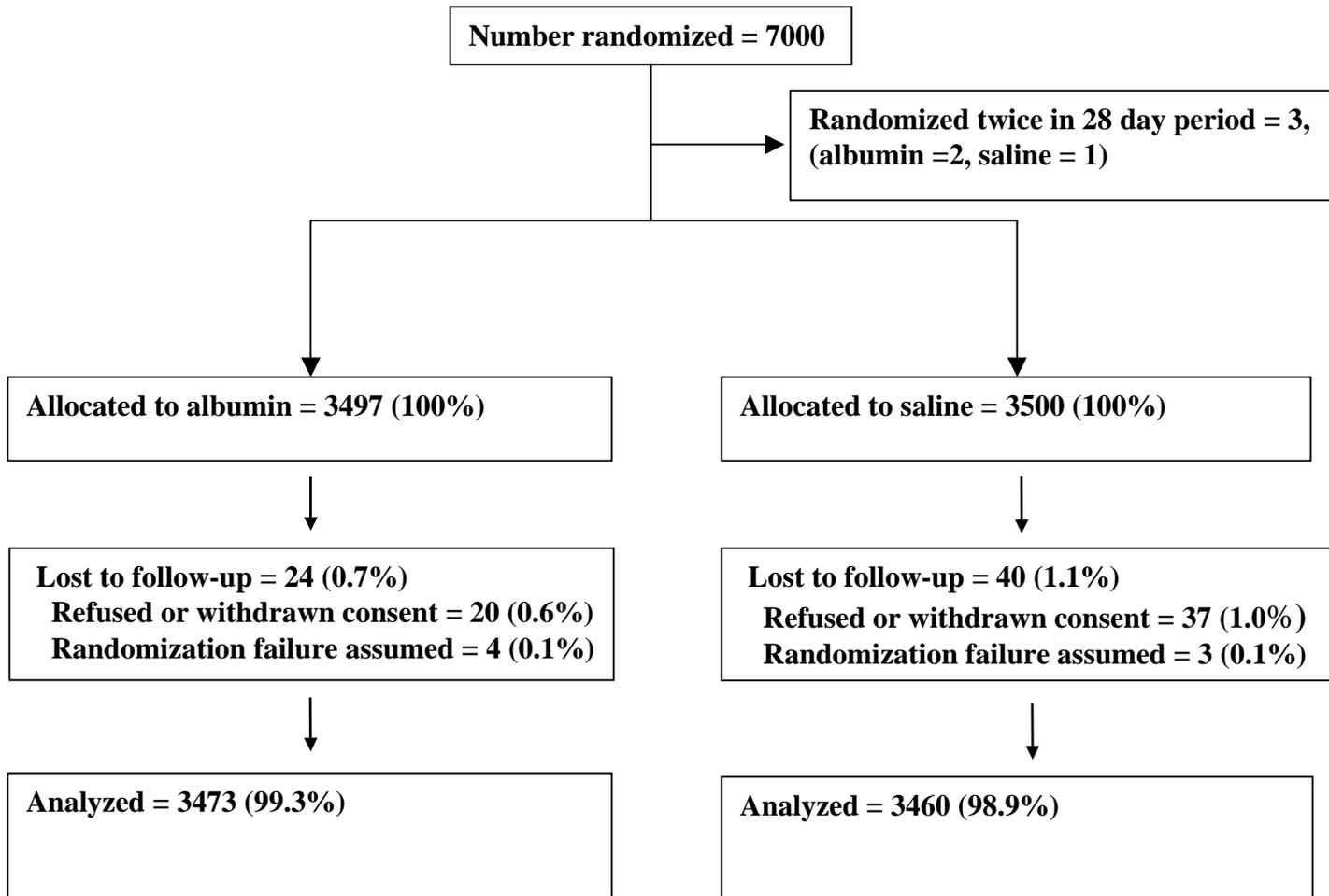


## *Interim analyses*

- Two pre-planned interim analyses
  - independent statistician
  - following recruitment of 2333 (33%) and 4666 (67%) patients
  - reviewed by the independent data monitoring committee (Chair – Prof. Sir Richard Peto)

# SAFE Study: Actual v Target Recruitment







<b><i>Baseline Characteristic</i></b>	<b>Albumin</b>	<b>Saline</b>
Age in years - mean $\pm$ SD	58.6 $\pm$ 19.1	58.5 $\pm$ 18.7
Female gender– N (%)	1424 (40.7)	1376 (39.3)
<b>Reason for admission to ICU – N (%)</b>		
Surgical	1,473 (42.9)	1,465 (42.7)
Medical	1,955 (57.1)	1,958 (57.3)
<b>Pre-defined sub-groups – N (%)</b>		
Trauma	597 (17.4)	590 (17.2)
Severe sepsis	603 (18.1)	615 (18.4)
ARDS	61 (1.8)	66 (1.9)
APACHE II score - mean $\pm$ SD	18.7 $\pm$ 7.9	19.0 $\pm$ 8.0



## ***Baseline Characteristic***

## **Albumin**

## **Saline**

### **Physiological variable - mean $\pm$ SD**

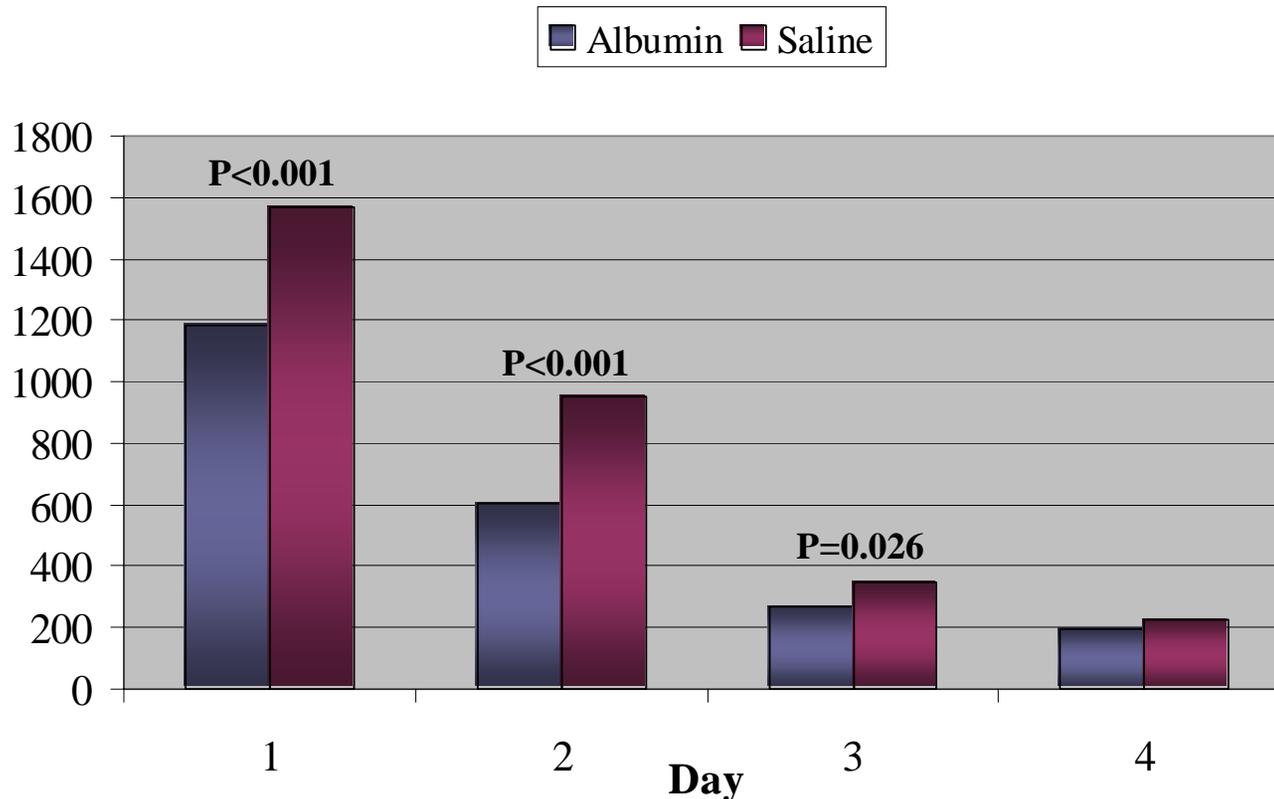
Heart rate (beats per minute)	91.4 $\pm$ 23.5	92.3 $\pm$ 23.5
Mean arterial pressure (mmHg)	77.8 $\pm$ 16.4	78.2 $\pm$ 16.3
Central venous pressure (mmHg)	9.0 $\pm$ 4.7	8.6 $\pm$ 4.6
Urine output (mL last hour)	89.7 $\pm$ 132.4	95.0 $\pm$ 161.4
Serum albumin (g/L)	27.4 $\pm$ 7.8	27.7 $\pm$ 7.9

### **Treatment at baseline**

Receiving mechanical ventilation – N (%)	2186 (63.8)	2217 (64.8)
Receiving renal replacement therapy – N (%)	45 (1.3)	41 (1.2)
Received albumin in prior 72 hours – N (%)	127 (3.7)	135 (3.9)



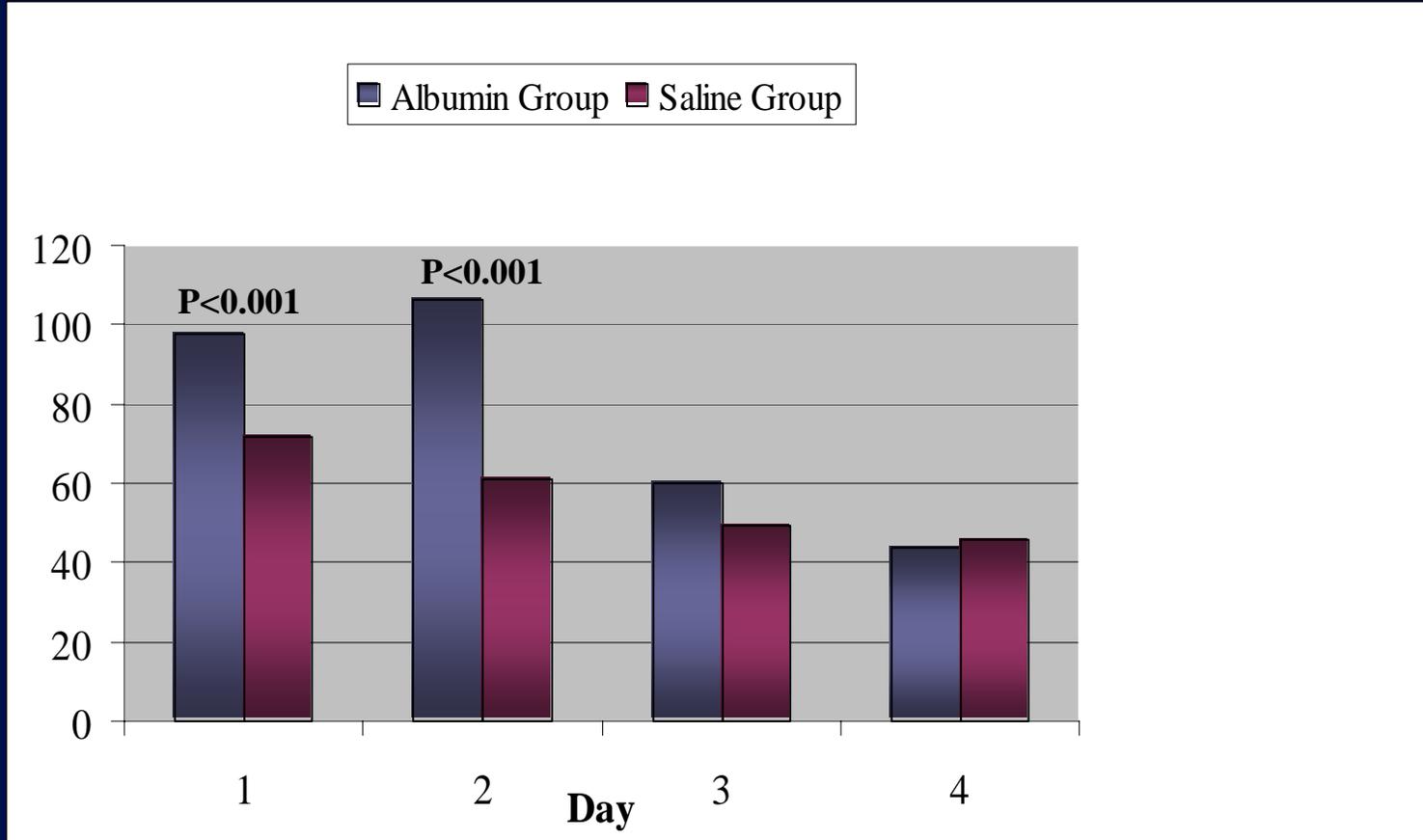
## Mean volume of study fluid administered (mL per patient per day)



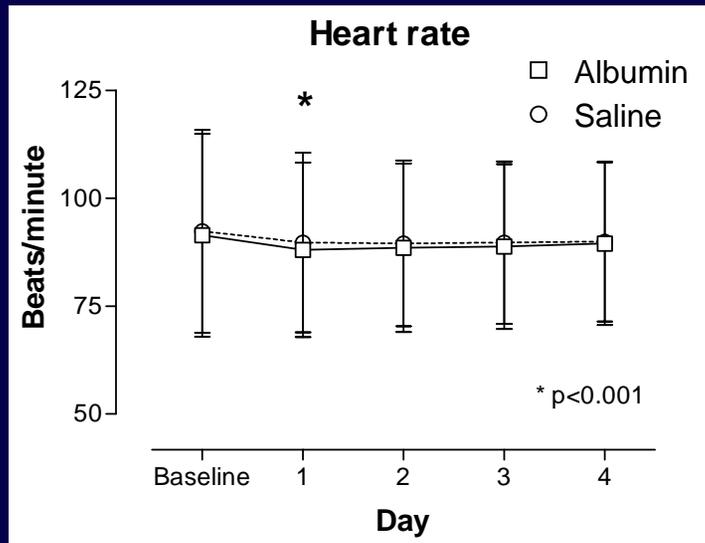
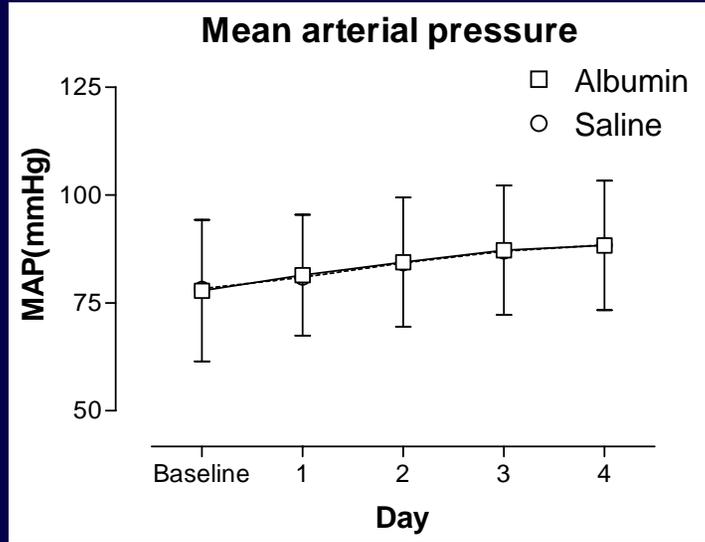
Ratio of albumin to saline for first four days = 1:1.4  
(Mean difference per randomized patient for first four days 749 mL)

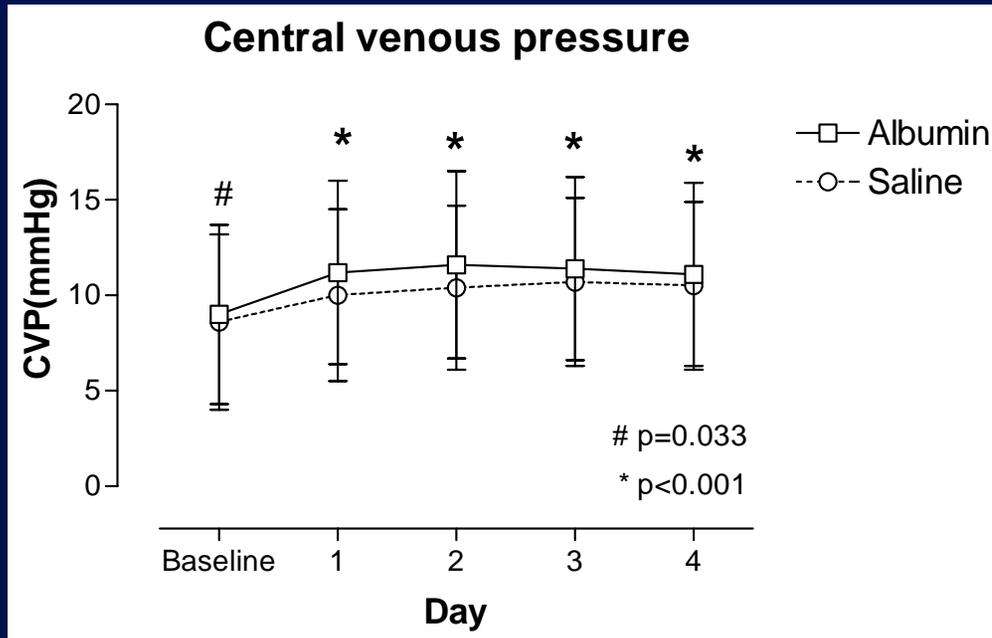


# *Mean Volume of Packed Red Blood Cells Administered (mL per patient per day)*

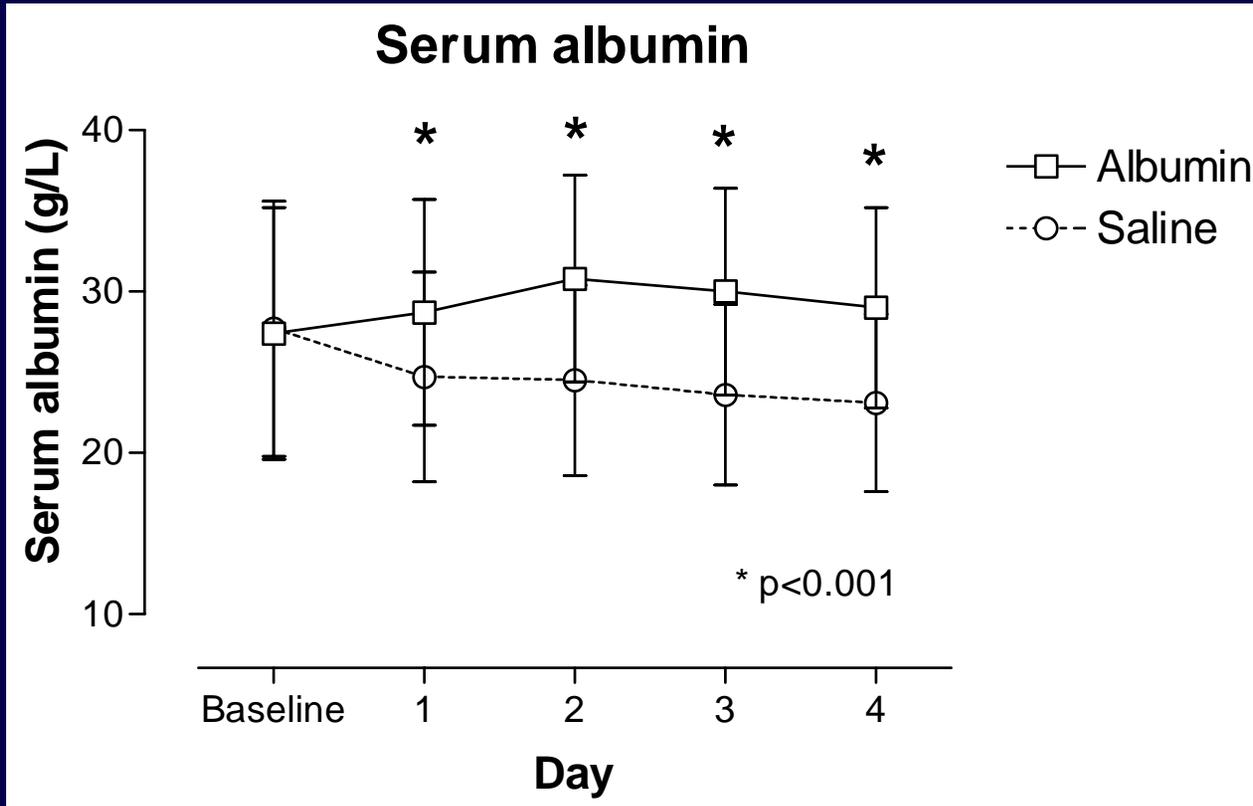


Mean difference per randomized patient first four days = 71.0 mL





Day	ALBUMIN	SALINE	DIFFERENCE
1	11.2	10.0	1.2
2	11.6	10.4	1.2
3	11.4	10.7	0.77
4	11.1	10.5	0.60



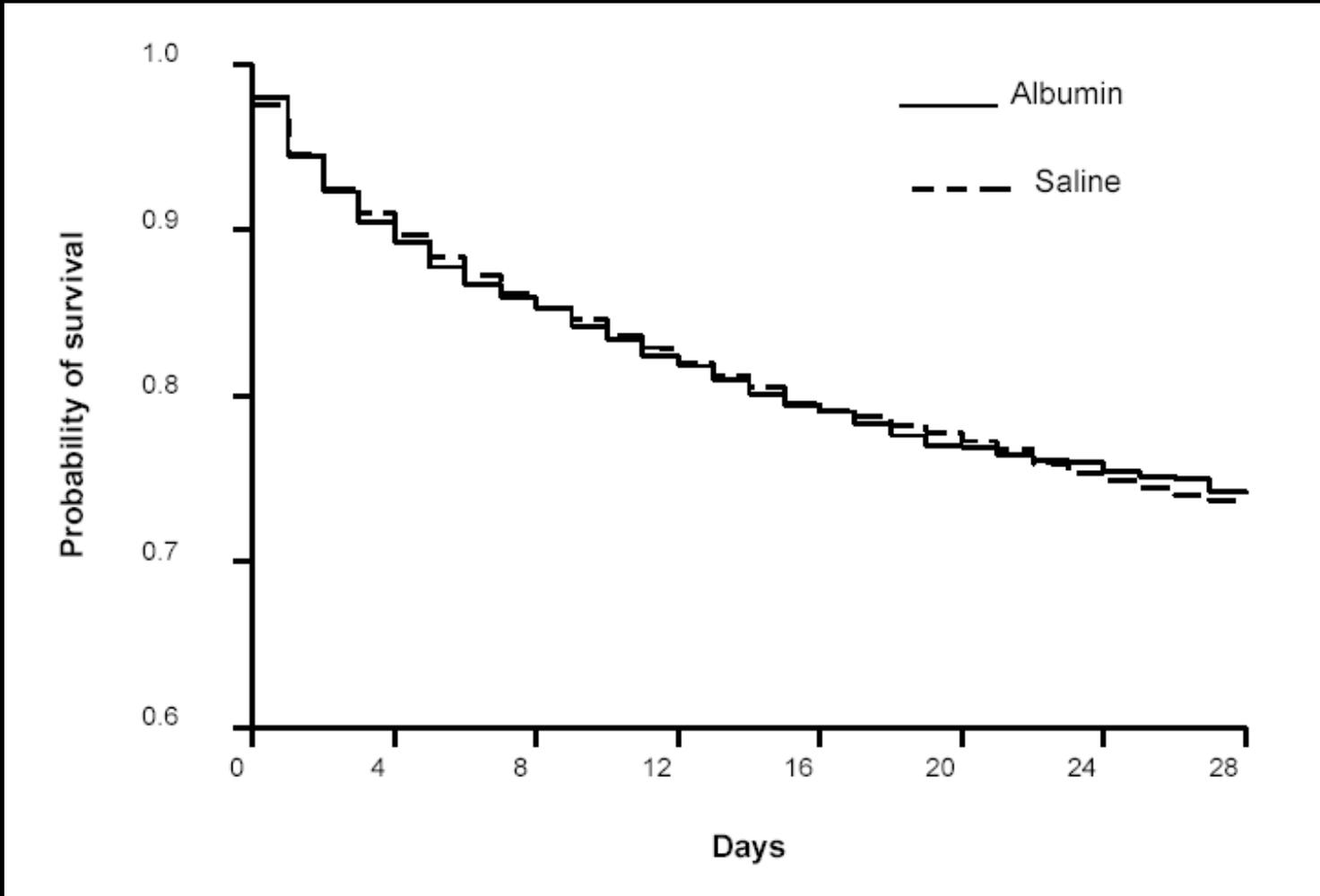


## *Primary Outcome - all patients*

- Albumin – 726 deaths in 3473 patients (20.9%)
- Saline – 729 deaths in 3460 patients (21.1%)
  
- Relative risk                      0.99,    (0.91 - 1.09)
  
- $P = 0.87$



# Kaplan-Meier estimates for probability of survival; P=0.96





## *Secondary outcomes – all patients*

- Days of mechanical ventilation
  - Albumin  $4.5 \pm 6.1$
  - Saline  $4.3 \pm 5.7$        $P = 0.74$
- Days renal replacement therapy
  - Albumin  $0.48 \pm 2.28$
  - Saline  $0.39 \pm 2.0$        $P = 0.41$

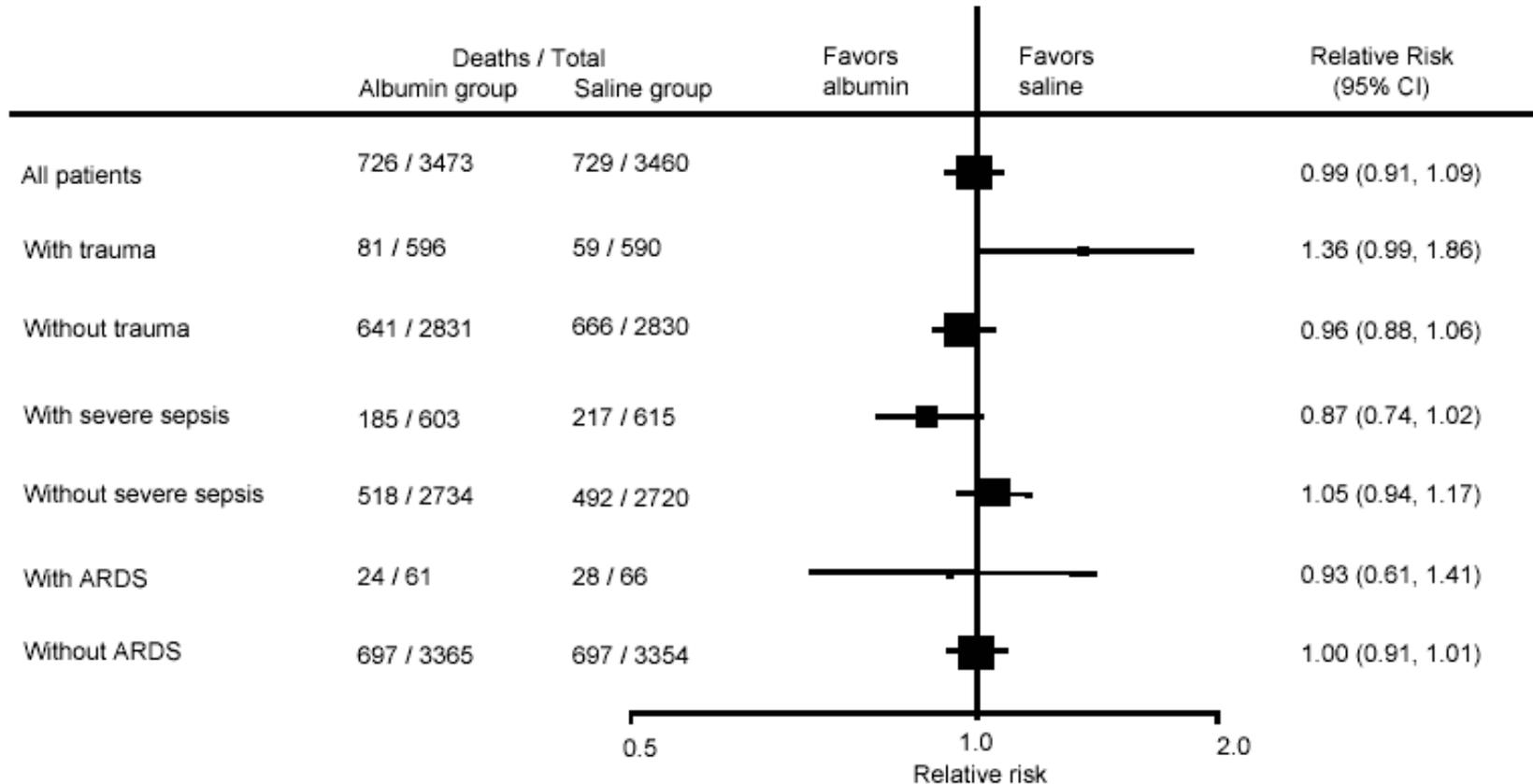


## *Secondary outcomes – all patients*

	Albumin	Saline
0 new organ failures	<b>1,397 (52.7%)</b>	<b>1,424 (53.3%)</b>
1 new organ failures	<b>795 (30.0%)</b>	<b>796 (29.8%)</b>
2 new organ failures	<b>369 (13.9%)</b>	<b>361 (13.5%)</b>
3 new organ failures	<b>68 (2.6%)</b>	<b>75 (2.8%)</b>
4 new organ failures	<b>18 (0.7%)</b>	<b>17 (0.6%)</b>
5 new organ failures	<b>2 (0.1%)</b>	<b>0 (0.0%)</b>
		<b>P = 0.85</b>

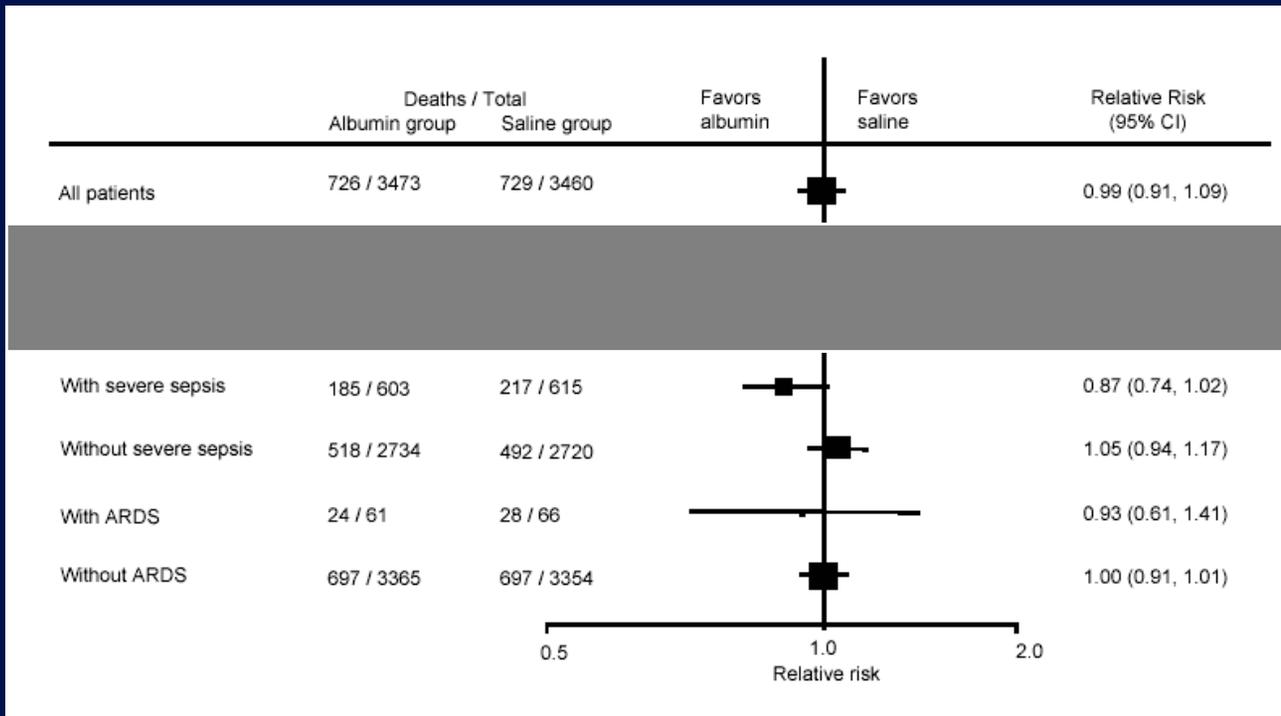


## *Relative risk of death for all patients and subgroups.*





## Comparison of Treatment Effects With trauma vs. without trauma



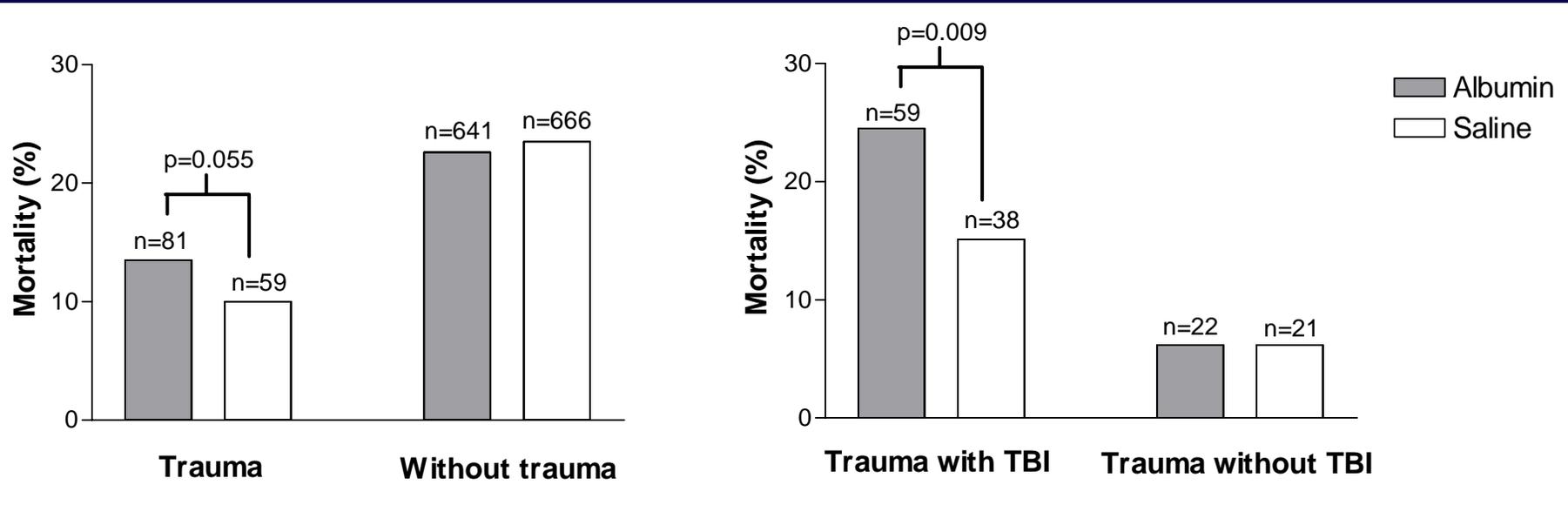
Relative risk of death for patients assigned albumin versus saline:

With trauma 1.36, without trauma 0.96

P=0.04 (Test for common relative risk)

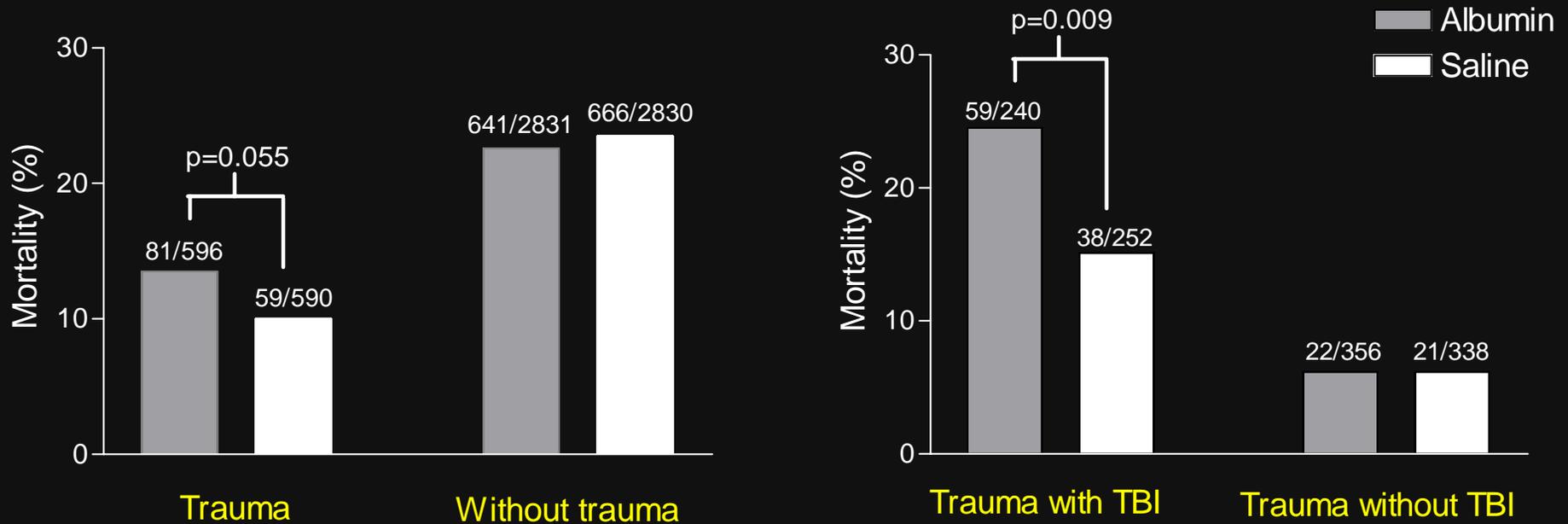


# *Mortality in patients with trauma, with and without brain injury.*





# Trauma with and without brain injury (TBI)





# SAFE TBI: Aim

- To better define baseline balance of factors known to influence outcome in patients with TBI
- To quantify outcomes in terms relevant to TBI



# SAFE TBI - Outcome data

## Vital status

6months and 12 months

## Functional status

24 month extended Glasgow Outcome Score

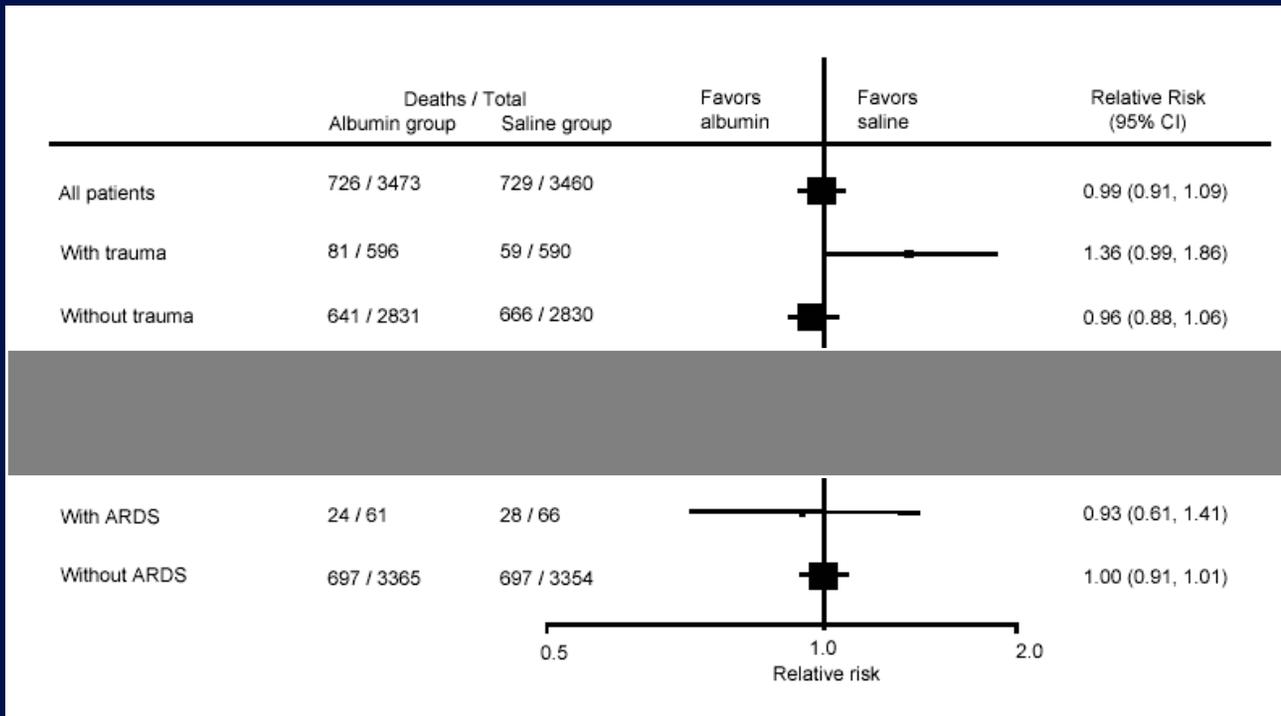
## Completion

Follow up – June 2005

Analysis – December 2005

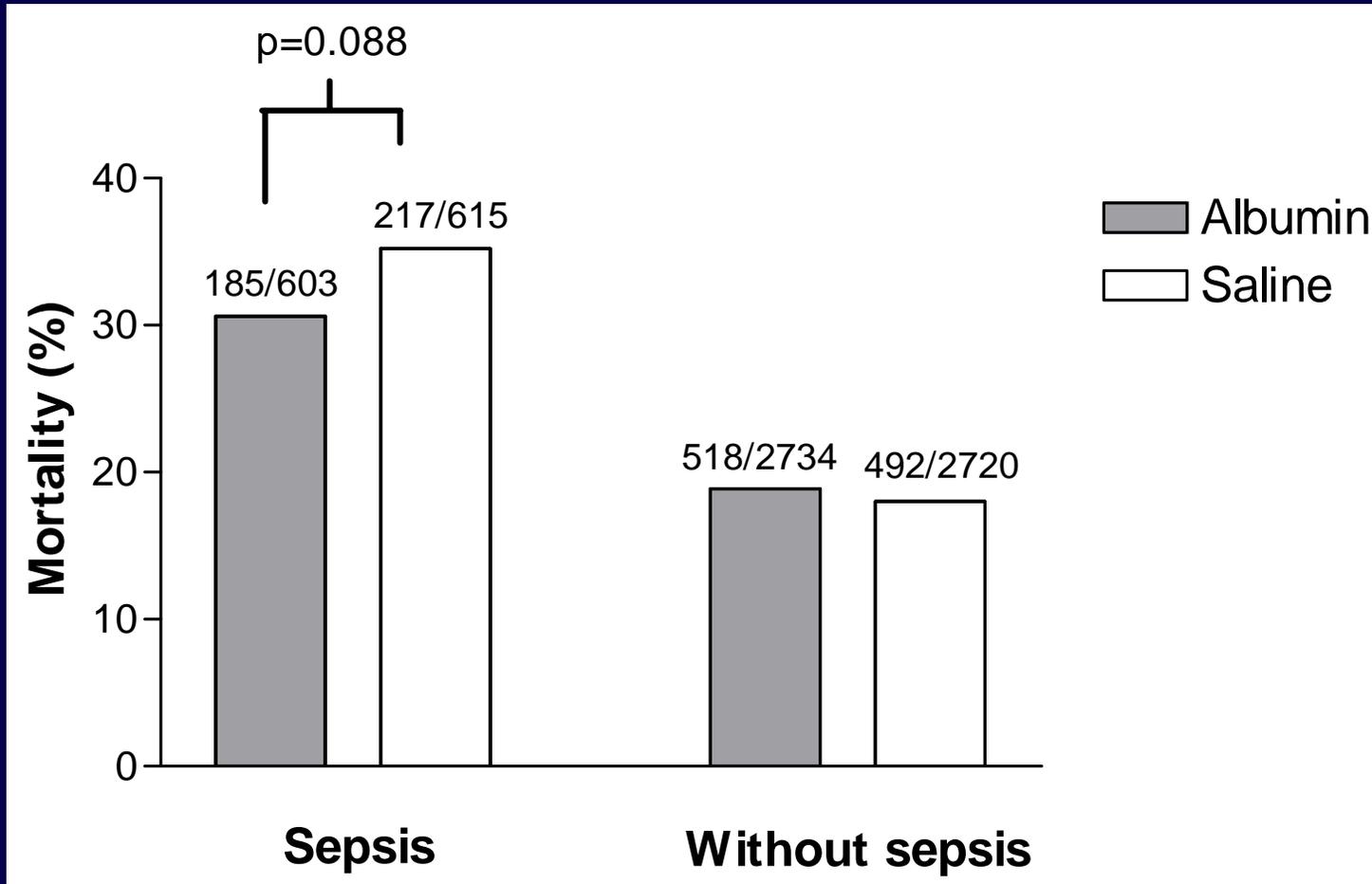


## Comparison of Treatment Effects With vs. without severe sepsis



Relative risk of death for patients assigned albumin versus saline:  
 With severe sepsis 0.87, without severe sepsis 1.05  
 P=0.06 (Test for common relative risk)

# *Mortality in patients with and without severe sepsis.*





# *Study Conclusions*

- In heterogeneous population of ICU patients, albumin and saline are clinically equivalent treatments.
- Use of either results in:
  - Similar mortality
  - Similar time to death in those who die
  - Similar use of mechanical ventilation and renal replacement therapy
  - Similar incidence of new organ failures
  - Similar ICU and hospital length of stay



## *Further analyses*

- By baseline albumin
- Sepsis cohort
- Trauma and TBI
- Patterns of organ dysfunction



**THANK YOU**

