AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

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Economic evaluation of investigator-initiated clinical trials conducted by networks

Supplementary Appendix B: Individual trial level results

The Australian Clinical Trials Alliance, in association with Quantium Health Outcomes, has prepared this report on behalf of the Australian Commission on Safety and Quality in Health Care.

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Contents

Results for each trial are presented in a format similar to the figure below.

Supplementary Appendix B Figure 1. Format for trial level results

Outcome		**Difference in risk between control and treatment**	**Number of patients affected if implemented at 65%**	**Health service cost per person or day**	**Economic Impact on health service costs**	**QALY impact per person**	**Economic impact on QALYS**	**Total Economic Impact**
Primary	Outcome 1	+/-x%	A	V	A * V = C	Y	A * Y = D	C + D
Secondary	Outcome 2	+/-x%	B	X	B * X = E	Z	B * Z = F	E + F
Change in intervention costs **Total**		**INT**			**C + D**		**E + F**	**C + D + E + F** **+/- INT**

1 The ASTN – Trial level results

1.1 ARCH Trial (2014) – Clopidogrel plus Aspirin versus Warfarin in Patients with Stroke and Aortic Arch Plaques[1]

Context

- **Atherosclerosis refers to the thickening of an artery wall due to the invasion and accumulation of cellular material and the formation of fatty plaques.**
- The aortic arch is the portion of the aorta (the main artery of the body) that bends between the ascending and descending aorta.
- In patients with prior ischemic stroke; recurrent stroke or other vascular events are three to four times more likely to occur if the patient has an atherosclerotic plaque in the aortic arch, compared to patients with no aortic arch plaques.
- Therapy may reduce the risk of recurrent events. As blood clots are often found on the aortic arch plaque, it was suggested that antithrombotic therapy, to reduce the formation of blood clots, could reduce the risk of recurrent events in patients with aortic arch plaques.
- The ARCH trial assesses patient outcomes for two types of antithrombotic therapy: warfarin therapy and aspirin (75-150mg/d) plus clopidogrel (75mg/d).
- While the trial lacks statistical power due to its small sample size, it shows that both treatments were safe in patients with this sub-type of stroke.
- Overall the trial shows that in general, patients with stroke or transient ischemic attack with aortic arch atherosclerosis should be treated with aspirin plus clopidogrel, rather than warfarin, as warfarin therapy is more cumbersome and typically carries a higher bleeding liability.

[1] Amarenco et al. (2014). Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. Stroke 45:1248-1257. Correspondence with senior trial investigators from the ASTN. George & Albers (2014). Aortic Arch Atheroma: A plaque of a different color or more of the same? Stroke 45:1239-40.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
The trial shows that treatment with clopidogrel and aspirin is advantageous, however, this difference is not statistically significant, due to a lack of power.[2]	Adults with non-disabling ischemic stroke, transient ischemic attack (TIA) or peripheral embolism = 30,491 [3,4] Proportion with an atherosclerotic plaque in the thoracic aorta = 14%[6] N= 4,116	Composite outcome: ischemic stroke, myocardial infarction, peripheral embolism, vascular death, or haemorrhagic stroke.	Ischemic stroke or TIA; myocardial infarction; vascular death; total death; death plus major haemorrhage.	The results suggest that patients with stroke or TIA with aortic arch atherosclerosis should be treated with aspirin and clopidogrel rather than warfarin. ARCH provides the impetus for further hypothesis formation and additional trials.[5]	The trial has influenced practice by showing that both treatment options are appropriate. Ongoing costs of care are equal between groups. Composite outcome cost is based on the relative frequency of each of its component elements. Stroke survivors expected to have moderate impairment (Rankin scale 2) at baseline.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Composite outcome	-33%	-100	- $37,130	-$4m	-$0.3m	-$26m	-$29m
Change in intervention costs		-$2m						
Totals					-$4m		-$26m	-$32m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[2] Correspondence with senior trial investigators from the ASTN.
[3] Access Economics (2013). The economic impact of stroke in Australia.
[4] AIHW (2013). Stroke and its management in Australia: an update. Cardiovascular disease series no. 37. Cat. no. CVD 61. Canberra: AIHW. Note, this could be an underestimate as many are unclassified.
[5] Amarenco et al. (2014). Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. Stroke 45:1248-1257.
[6] The French Study of Aortic Plaques in Stroke Group (1996). Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. N Engl J Med 334:1216-21.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Composite outcome	Service cost: -$37,130 QALY: -$256,296	The analysis is based on the relative frequency of each of the component elements (stroke, intracerebral haemorrhage, pulmonary embolism, vascular death or myocardial infarction). Survivors of stroke (i.e. the cohort of patients that this study applies to) have moderate impairment at baseline, equivalent to an average Rankin Scale score of 2. Confirmed through interview. Hospital and ongoing rehabilitation costs are broadly similar for ischemic and haemorrhagic stroke. Confirmed with Gloede et al. (2014). Service costs for stroke and intracerebral haemorrhage are based on the average cost by Tan Tanny et al. (2013). Casemix costs for myocardial infarction (AR-DRG codes F10A and F10B), pulmonary embolism (AR-DRG codes E61A and E61B) and vascular death (AR-DRG codes B70D for stroke and other cerebrovascular disorders, transferred <5 days) includes any overheads and clinician time. QALY savings are based on disability weights and life expectancies for the individual outcomes. Stroke disability weight is based on the average of mild, moderate and severe long-term consequences of stroke (0.237) by WHO. Disability impairment from myocardial infarction based on WHO. Disability weight for pulmonary embolism (0.023) from Access Economics report. Disability weight for intracerebral haemorrhage (0.329) from Hong and Saver. Patients who have a secondary event (e.g. stroke, intracerebral haemorrhage, pulmonary embolism) would survive an additional 3.5 years only, based on length of follow-up in the trial, patient age and baseline characteristics, and Harald Hannerz et al. (2001). Impairments from these events endure over this time. Patients who die of vascular causes would have otherwise survived for an additional 3.5 years. Impairment from myocardial infarction is acute, with no lasting symptoms (based on Moran et al. 2014).	Tan Tanny et al. (2013). Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke. Experience from Australian Stroke Centre. Stroke 44:2269:2274. Gloede et al. (2014). Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. Stroke 45:3389-3394. IHPA National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease. Stroke 32:1739-1744. Moran et al. (2014). The Global burden of ischemic heart disease in 1990 and 2010: The Global burden of disease 2010 study. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011. Access Economics (2008). The burden of venous thromboembolism in Australia. Hong & Saver (2009). Quantifying the value of stroke disability outcomes: WHO Global Burden of disease project disability weights for each level of the modified Rankin Scale. Stroke 40(12): 3828-3833.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Intervention costs	Service cost: -$911	Majority of intervention costs borne out of hospital. Average cost of intervention based on incremental cost difference between treatment with warfarin or aspirin and clopidogrel. Cost of aspirin and clopidogrel based on PBS listing. Cost of warfarin therapy based on drug cost (PBS), INR testing (MBS), and GP follow up (MBS) as estimated by Boehringer Ingelheim submission to Review (2012). Follow up testing as recommended in Qld 2012 guidelines.	http://www.pbs.gov.au/medicine/item/9296G http://www.pbs.gov.au/medicine/item/2209G-2211J-2843P-2844Q Commonwealth Government (2012). Submission by Boehringer Ingelheim into Review of Anticoagulation Therapies in Atrial Fibrillation. https://www.health.qld.gov.au/qhcss/mapsu/documents/warfarin-guidelines.pdf

1.2 EXTEND-IA Trial (2015) – Endovascular therapy for ischemic stroke[7]

Context

- **Ischemic stroke results from a blocked artery causing reduced blood flow to regions of the brain. Treatments to restore blood flow can reduce disability for stroke survivors.**
- Intravenous thrombolysis to dissolve blood clots has been used since the late 1990s. However, studies have shown that intravenous thrombolysis is unable to break down the larger clots that cause the most devastating strokes.
- Endovascular clot retrieval is an intra-arterial treatment that removes large clots in eligible patients after ischemic stroke to restore blood flow to the brain. Three neutral trials for endovascular stroke therapy were published in 2013, putting the highly specialised treatment at risk of disappearing.
- EXTEND-IA shows that endovascular therapy increases early neurologic improvement at three days, and improves functional outcomes at 30 days, with more patients achieving functional independence.
- EXTEND-IA is one of five positive trials that have led to changed US, European and Canadian stroke guidelines. Australian guidelines are currently being revised.
- Since the results of the trial were released, trial sites immediately implemented the intervention. The Victorian State Department of Health and Human Services has launched a state-wide protocol that has two 24-hour, seven-day designated thrombectomy centres (Royal Melbourne Hospital and Monash Medical Centre).[7] The rate of thrombectomy is projected to quadruple this year with many patients from rural areas now accessing the therapy.

[7] Campbell et al. (2015). Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 372:1009-18.
https://www2.health.vic.gov.au/about/publications/policiesandguidelines/endovascular-clot-retrieval-for-acute-stroke-statewide-service-protocol Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
The treatment is associated with faster and more complete reperfusion, and a reduction of infarct growth - thus better functional and neurological outcome at 3 months. There is no change in mortality or other factors.	No. of ischemic strokes treated with alteplase = 3,153 [8,9,10] Proportion of eligible patients = 51% [13] N= 1,613	Median reperfusion (process measure for early neurological improvement).	Safety (death), infarct growth, home time versus hospital time, Rankin scale score.	After 3 neutral trials, the field of endovascular stroke therapy was at risk of disappearing. EXTEND-IA is one of 5 positive trials for endovascular therapy which have led to changed US, European and Canadian stroke guidelines, with Australian guidelines in revision currently.[11]	Modelled for functional outcomes, home time and difference in treatment costs only. No immediate QALY benefit is associated with early home discharge. Life expectancy is based on Harald Hannerz et al. (2001).[12]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Reperfusion & early neurologic outcome	Captured in other outcomes.	-	-	-	-	-	-
Secondary	Functional outcomes at 3 months (Rankin scale score)	Based on $ difference for treatment and QALY between treatment and control groups.	-1,048	-$4,978	-$5m	-$140,227	-$147m	-$152m
	Median home time (days)	+58[14]	-1,048	-$829	-$50m	-	-	-$50m
Change in intervention costs		+ $16m						
Totals					- $56m		-$147m	-$187m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[8] Access Economics (2013). The economic impact of stroke in Australia.
[9] AIHW (2013). Stroke and its management in Australia: an update. Cardiovascular disease series no. 37. Cat. no. CVD 61. Canberra: AIHW. Note, this could be an underestimate as many are unclassified.
[10] Campbell et al. (2015). Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 372:1009-18. Note, this is assumed to be representative.
[11] Correspondence with senior trial investigators.
[12] Harald Hannerz et al. (2001). Life expectancies among survivors of acute cerebrovascular disease. Stroke 32:1739-1744.
[13] Campbell et al. (2015). Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 372:1009-18.
[14] Counterfactual to home time is rehabilitation. Increased number of days at home means fewer days spent in rehabilitation, and a saving in service costs.

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Functional outcomes at 3 months (Rankin scale score)	Service cost: -$4,978 QALY: -$140,227	Treatment costs for stroke are based on cost breakdown by functional outcome in Tan Tanny (2013). Life expectancies for these patients range from an additional 0 to 8.1 years, based on average age of patients in the study. Additional reference is taken from Harald Hannerz et al. (2001). Cross-checked with Slot et al. (2008) and Hong et al. (2010). Each Rankin Scale score was assigned to a different WHO disability weight, where a Rankin Scale score of 0 is equivalent to a full, healthy life, with no disability, and a Rankin Scale score of 6 is equivalent to death, and a disability weight of 1.	Tan Tanny et al. (2013). Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke. Stroke. 44:2269-2274. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease. Slot et al. (2008). Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. Hong et al. (2010). Years of Optimum Health Lost Due to Complications after Acute Ischemic Stroke: Disability-Adjusted Life Years Analysis. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Median home time (days)	Service cost: -$829	Home time is costed as a reduction in rehabilitation time (rather than stay in acute care). Confirmed through interview. Based on codes 4AA1-7 in Australian National Subacute and Non-acute Patient Classification (AN-SNAP) v4.[15] Range is $829-900. The lower end is more appropriate for patients >68 years (patients of this study). No home-based care is expected. No immediate impact on QALYs, though it is expected there will be increased QALYs preserved on tertiary outcomes (due to patient's ability to be at home, be independent etc.). Tertiary outcomes are, however, not costed here.	Centre for Health Service Development, Australian National Subacute and Non-acute Patient Classification (AN-SNAP) v4.
Intervention costs	Service cost: +$15,086	Average cost of intervention based on Health Policy Advisory Committee on Technology 2015. Confirmed through interview.	Unpublished economic analysis of EXTEND-IA, examined the effects on resource utilisation, length of stay and cost of care, reported in Health Policy Advisory Committee on Technology (2015). Technology brief endovascular clot retrieval with thrombolysis for ischaemic stroke. https://www.health.qld.gov.au/healthpact/docs/briefs/wp226-mech-thrombectomy.pdf

[15] Same reference used by Dewey et al. (2001). Cost of Stroke in Australia from a Societal Perspective Results from the North East Melbourne Stroke Incidence Study. Updated to v4.

1.3 INTERACT2 Trial (2013) – Rapid blood-pressure lowering in patients[16]

Context

- **Acute intracerebral haemorrhage affects more than 1 million people worldwide each year. It is the least treatable form of stroke.**
- Blood pressure often becomes elevated after intracerebral haemorrhage, frequently reaching very high levels, and is a predictor of long-term outcome for the patient.
- Several studies suggested that early intensive lowering of blood pressure could be beneficial in patients with intracerebral haemorrhage.
- The INTERACT2 trial found that intensive lowering of blood pressure did not result in a significant reduction in the rate of death or severe disability, but did marginally improve functional outcomes and health-related quality of life.
- As a result of the trial, there is a general move towards more intensive blood pressure lowering in patients with intracerebral haemorrhage, influenced by the improved functional outcome. However, the degree of uptake around the world is variable. The European Stroke Organisation published recommendations for early intensive blood pressure lowering.
- There is wide cost variation in available intravenous blood pressure lowering agents globally, and variation in ease of use of agents. Both of these factors influence practice.
- More research is said to be required in relation to the timing, intensity, duration and approach to blood pressure lowering.

[16] Anderson et al. (2013). Rapid blood-pressure lowering in patients with acute intracerebral haemorrhage. N Engl J Med 368:2355-65. Anderson & Qureshi (2015). Implications of INTERACT2 and Other Clinical Trials. Blood pressure management in acute intracerebral haemorrhage. Stroke 46:291-295. Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Intensive lowering of blood pressure does not result in significant reduction in death or severe disability though it does marginally improve functional outcomes (ordinal Rankin score) and health related quality of life.	Adults with acute intracerebral haemorrhage = 6013[17] Proportion eligible =88%[21] N= 5,273	Death or major disability at 90 days (modified Rankin score 3-6).	Serious adverse events, ordinal analysis of Rankin score.[18]	There is a difference in mortality/ primary outcome in favour of the treatment group (intensive blood pressure lowering). While this is not statistically significant, it is thought that the overall improvement in outcomes in the treatment group favours a shift in treatment to this.[19]	Functional outcomes are measured through two of the trial's outcome measures. Only one is costed to avoid duplication. EQ-5D related outcomes and functional outcome persist for the duration of life expectancy. Life expectancies are based on Harald Hannerz et al. (2001).[20]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Death or major disability	Included in secondary outcomes.	-	-	-	-	-	-
Secondary	Functional outcomes at 3 months (Rankin scale score)	Based on $ difference for treatment and QALY between treatment and control groups.	-3,428	-$713	-$2m	-$13,906	-$48m	-$50m
Change in intervention costs		+$0.7m						
Totals					-$2m		-$48m	-$49m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[17] Gattellari et al. (2014). Declining rates of fatal and nonfatal intracerebral haemorrhage: Epidemiological trends in Australia. JAHA.
[18] The modified Rankin scale is a scale from zero to six, with six being the worst clinical outcome. Ordinal analysis interprets these ordered categories, by analysing how each patient changes from their baseline status. http://emcrit.org/emnerd/the-adventure-of-the-cardboard-box/
[19] Correspondence with senior trial investigators.
[20] Harald Hannerz et al. (2001). Life expectancies among survivors of acute cerebrovascular disease. Stroke 32:1739-1744.
[21] Anderson et al. (2013). Rapid blood-pressure lowering in patients with acute intracerebral haemorrhage. N Engl J Med 368:2355-65.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Functional outcomes at 3 months (Rankin scale score)	Service cost: -$713 QALY: -$13,906	Functional outcomes are measured through two of the trial's outcome measures: functional outcomes at 3 months, as measured by the modified Rankin scale score, and Health-related quality of life, as measured by the EQ-5D questionnaire. To avoid duplication, only functional outcomes as measured by the modified Rankin scale are costed. This captures the clinically significant outcome of death or disability. Incremental differences between functional outcomes at 3 months are translated into treatment costs and QALYs preserved. Treatment costs for stroke are based on cost breakdown by functional outcome in Tan Tanny at al. (2013). Life expectancies for these patients range from an additional 0 to 10.15 years, based on the average age of patients in the study. Additional reference is taken from Harald Hannerz et al. (2001). Cross-checked with Slot et al. (2008) and Hong et al. (2010). Each Rankin Scale score was assigned to a different WHO disability weight, where a Rankin Scale score of 0 is equivalent to a full, healthy life, with no disability, and a Rankin Scale score of 6 is equivalent to death, and a disability weight of 1.	Tan Tanny et al. (2013). Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke. Stroke. 44:2269-2274. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease Slot et al. (2008). Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. Hong et al. (2010). Years of Optimum Health Lost Due to Complications after Acute Ischemic Stroke: Disability-Adjusted Life Years Analysis. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Intervention costs	Service cost: +$195	Intervention (intensive blood pressure lowering) is said to be low additional cost compared to what is already done now. Costs are estimated based on clinician time and intravenous agents used.	Anderson et al. (2013). Statistical analysis plan analysis plan for the second INTensive blood pressure Reduction in Acute Cerebral hemorrhage trial (INTERACT2): a large-scale investigation to solve longstanding controversy over the most appropriate management of elevated blood pressure in the hyperacute phase of intracerebral haemorrhage. International Journal of Stroke. Vol 8: 327-328.

1.4 PROGRESS Trial (2001) – Randomised trial of a perindopril-based blood-pressure lowering previous stroke or transient ischaemic attack[22]

Context

- **The risk of recurrent stroke among those who survive a stroke or a transient ischaemic attack is 6 times greater than the risk of first-ever stroke.**
- Prior to the trial, there was some evidence that hypertension was associated with an increased risk of stroke recurrence.
- While studies had shown that treatment to lower blood pressure reduced the risk of initial stroke, there was little convincing evidence that blood pressure-lowering treatment would reduce the incidence of recurrent stroke.
- The PROGRESS trial found that fewer patients treated with ACE inhibitors and diuretics (blood pressure-lowering treatments) suffered a stroke (8% vs 14%).
- The risk of total major vascular events is also lower across all studied demographic subgroups for these patients.
- The trial changed international clinical guidelines, including in Australia, and changed practice to recommend use of blood pressure-lowering treatments to avoid stroke recurrence.
- The PROGRESS trial received sizeable, unrestricted funding from pharmaceutical company Servier.

[22]PROGRESS Collaborative Group (2001). Randomised trial of a perindopril-based blood-pressure lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358:1033-41. Hardie et al. (2004). Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke 35:731-735. Correspondence with senior trial investigators. Donnan (2003). PROGRESS results: implementation in stroke guidelines. J Hypertens 21 (suppl 5):S25-S28.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Fewer patients in the treatment group suffered a stroke, and the risk of total major vascular events was also lower, irrespective of patient's blood pressure, type of initial event, time since last event, or geographic region. The trial provided evidence for blood pressure lowering for the prevention of stroke particularly in those with known Cerebrovascular Disease irrespective of baseline blood pressure.	Adults with stroke or transient ischaemic attack = 64,249[23,24] Proportion eligible = 86%[28] N = 55,254	Total stroke (fatal or non-fatal).	Fatal or disabling stroke; total major vascular events (non-fatal stroke, non-fatal MI, or death due to any vascular cause); total and cause-specific deaths; and hospital admissions.	Before the results of PROGRESS were published in 2001, there was little convincing evidence that BP-lowering treatment would reduce the incidence of recurrent stroke in patients with cerebrovascular disease.[25]	Costing combination therapy only (not single therapy).[26] Prevented vascular deaths preserve an impaired life. Average cost of stroke treatment based on Tan Tanny et al. (2013).[27]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Total stroke	-44%	-2,289	-$65,654	-$150m	-$75,344	-$172m	-$323m
Secondary	Non-fatal myocardial infarction	-41%	-484	-$15,818	-$8m	-$1,246	-$0.6m	-$8m
	Vascular death (excluding fatal stroke)	-22%	-442	-$3,321	-$1m	-$80,171	-$35m	-$37m
Change in intervention costs		+$21m						
Totals					-$159m		-$209m	-$347m

Columns may not sum due to rounding. Negative values are savings in the calculations. **Senior trial investigators have reported that per patient drug costs were covered by a commercial drug supplier. This was said to be $80m. If included, the net benefit of the PROGRESS study is $242m, and the consolidated BCR is 4:1.

[23] Access Economics (2013). The economic impact of stroke in Australia.
[24] AIHW (2013). Stroke and its management in Australia: an update. Cardiovascular disease series no. 37. Cat. no. CVD 61. Canberra: AIHW. Note, this could be an underestimate as many are unclassified.
[25] Arima & Chalmers (2011). PROGRESS: Prevention of recurrent stroke. Journal of Clinical Hypertension. Vol 13 (9).
[26] Commentaries indicate that combination therapy is indicated to reduce risk, while monotherapy could be less effective because of the decreased effect on blood pressure lowering, or because the trial was not powered to assess the difference in combination therapy versus monotherapy. Consolidated outcomes for combination therapy assumed to apply uniformly across patient subgroups.
[27] Tan Tanny et al. (2013). Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke. Stroke. 44:2269-2274.
[28] PROGRESS Collaborative Group (2001). Randomised trial of a perindopril-based blood-pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 358:1033-41.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Total stroke	Service cost: -$65,654 QALY: -$75,344	Total stroke refers to fatal strokes, non-fatal, disabling strokes and non-fatal, non-disabling strokes. Service cost of stroke based on average costs by functional outcome scores by Tan Tanny et al. (2013). Estimate cross checked with Gloede (2014). Patients who had a fatal stroke would have otherwise been impaired with a disability weight equivalent to the average WHO disability weight for mild, moderate and severe long-term consequences of stroke (0.237), and would have been expected to live for an additional 4.1 years, based on Harald Hannerz et al. (2001). Patients who have a non-fatal, disabling stroke are expected to be impaired with mild, moderate or severe long-term consequences of stroke, average disability weight 0.237 (WHO) and average 2.1-year additional years' survival. Harald Hannerz et al. (2001). Major/intermediate treatment complexity expected (Rankin scale score 4-5). Patients with non-fatal, non-disabling strokes have no long-term consequences. Minor treatment complexity only.	Tan Tanny et al. (2013). Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke. Experience from Australian Stroke Centre. Stroke 44:2269:2274. Gloede et al. (2014). Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. Stroke 45:3389-3394. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease. WHO (2013) WHO. methods and data sources for global burden of disease estimates 2000-2011.
Non-fatal myocardial infarction	Service cost: -$15,818 QALY: -$1,246	Casemix costs for myocardial infarction (AR-DRG F10A and F10B, minor and major complexity). Majority of costs borne in hospital (Ioannides-Demos et al.). Impairment from myocardial infarction is acute, with no lasting symptoms (based on Moran et al. 2014). Disability weight based on WHO.	IHPA National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16. Ioannides-Demos et al. (2010). Cost of myocardial infarction to the Australian community: a prospective, multicentre survey. Clin Drug Investig. 30(8):533-43. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011. Moran et al. (2014) The Global burden of ischemic heart disease in 1990 and 2010: The Global burden of disease 2010 study.

Vascular death (excluding fatal stroke)	Service cost: -$3,321 QALY: -$80,171	Casemix costs for vascular death (AR-DRG B70D for stroke and other cerebrovascular disorders, transferred <5 days). Patients who survive a vascular episode that would have led to death are more impaired than the rest of the cohort (i.e. are a subgroup), and would likely not have survived longer than a year (Allen et al. 2008). Disability weight based on combined WHO weights for severe heart failure and moderate stroke (0.560).	IHPA National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011. Allen et al. (2008). Discordance between patient-predicted and model-predicted life expectancy among ambulatory patients with heart failure. JAMA. 2008 Jun 4;299(21):2533-42.

1.5 AVERT Trial (2015) – Efficacy and safety of very early mobilisation within 24 hours of stroke onset[29]

Context

- **Early mobilisation after stroke, comprising out-of-bed sitting, standing, and walking, is thought to improve patient outcomes.**
- Prior to the trial, early mobilisation was recommended in many guidelines, despite a lack of evidence. The guidelines rarely specified how and when the intervention should be delivered.
- An Australian practice survey showed that 40% of professionals were in favour of mobilising patients within the first 24 hours of stroke onset. Other clinicians were less certain about the optimal time point to start mobilisation however, and concerned that early mobilisation was harmful.
- The AVERT trial shows that fewer patients in the very early mobilisation group (within 24 hours of stroke onset) have a favourable outcome at 3 months than those in the usual care group (46% vs. 50%). Clinical guidelines in the US, UK and Canada have since been updated to stop delivery of early intensive intervention in stroke.
- Australian guidelines have not yet been updated. The trial investigators intend to analyse the remaining data collected before an implementation message is distributed.
- The AVERT implementation study highlighted key success factors to delivering complex intervention in clinical practice. Successful implementation strategies included interdisciplinary teamwork, education and strong leadership. Inadequate staffing, various organisational barriers, and patient-related barriers could prevent successful implementation. While there were no stroke rehabilitation trial sites in Australia prior to the AVERT trial, 24 Acute Stroke Units across Australia participated in the trial.

[29] The AVERT Trial Collaboration Group (2015). Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet; 386: 46–55. Luker et al. (2016). Implementing a complex rehabilitation intervention in a stroke trial: a qualitative process evaluation of AVERT. BMC Medical Research Methodology 16:52. Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
The higher dose, very early mobilisation protocol (starting, on average, 5 hours' earlier than usual care) is associated with a reduction in the odds of a favourable outcome at 3 months. The data shows that high-dose, frequent mobilisation protocol within 24 h of stroke onset is not better than usual care.	Adults with stroke = 49,067[30] Eligible population = 18% [33] N= 8,590	A favourable outcome 3 months after stroke, defined as a modified Rankin Scale sore of 0-2.	Modified Rankin score; time taken to achieve unassisted walking over 50m; unassisted walking by 3 months; deaths; non-fatal serious adverse events at 3 months: immobility related (PE, DVT, UTI, pressure sores or pneumonia) or neurological (stroke progression, recurrent strokes).	Clinicians will now not deliver intensive intervention very early in stroke. Some international clinical guidelines have changed, and others will also change as they are updated.[31]	Economic benefit modelled on functional outcomes at 3 months, which is expected to sustain for at least 1 year. Life expectancy based on Harald Hannerz et al. (2001).[32]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Functional outcomes at 3 months (Rankin scale score).	Based on $ difference for treatment and QALY between treatment and control groups.	-5,584	-$65	-$0.4m	-$9,953	-$56m	-$56m
Secondary	None statistically significant.	-	-	-	-	-	-	-
Change in intervention costs		-$2m						
Totals					-$0.4m		-$56m	-$58m

Columns may not sum due to rounding. Negative values are savings in the calculations. PE = pulmonary embolism. DVT = deep vein thrombosis. UTI = urinary tract infection.

[30] Access Economics (2013). The economic impact of stroke in Australia.
[31] Correspondence with senior trial investigators.
[32] Harald Hannerz et al. (2001). Life expectancies among survivors of acute cerebrovascular disease. Stroke 32:1739-1744.
[33] The AVERT Trial Collaboration Group (2015). Efficacy and safety of very early mobilisation within 24 hours of stroke onset (AVERT): a randomised controlled trial. Lancet; 386: 46–55.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Functional outcomes at 3 months (Rankin scale score)	Service cost: -$65 QALY: -$9,953	Incremental difference between functional outcomes at 3 months are translated into treatment costs and QALYs preserved. Treatment costs for stroke are based on cost breakdown by functional outcome in Tan Tanny (2013). Life expectancies for these patients range from an additional 0 to 6.4 years, based on average age of patients in the study. Additional reference is taken from Harald Hannerz et al. (2001). Cross-checked with Slot et al. (2008) and Hong et al. (2010). Each Rankin Scale score was assigned to a different WHO disability weight, where a Rankin Scale score of 0 is equivalent to a full, healthy life, with no disability, and a Rankin Scale score of 6 is equivalent to death, and a disability weight of 1.	Tan Tanny et al. (2013). Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke. Stroke. 44:2269-2274. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease. Slot et al. (2008). Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. Hong et al. (2010). Years of Optimum Health Lost Due to Complications after Acute Ischemic Stroke: Disability-Adjusted Life Years Analysis. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Intervention costs	Service cost: -$408	Average cost of intervention is based on additional physiotherapy and nursing time (131.5 mins physiotherapy and 35 mins nursing). This was estimated with senior trial investigators.	Informal estimate from community nursing provider sources $135 per hour.

1.6 QASC Trial (2011) – Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing (FeSS) dysfunction in acute stroke[34]

Context

- **Organised stroke unit care significantly reduces death and disability from cerebrovascular events. Hyperglycaemia, fever, and swallowing dysfunction are poorly managed however, despite their importance for long-term recovery.**
- There are international guidelines for the management of the three stated physiological variables, however, care is not always consistent with these recommendations. Audit data shows only 21% of patients received paracetamol at their first febrile event, and 24% received a swallowing screening within the first 24 hours of admission to hospital. All three involve multidisciplinary teamwork, a priority for stroke care.
- The QASC trial found that the implementation of multidisciplinary team supported evidence-based protocols for the three variables delivered better patient outcomes - 42% were dead or dependent at 90 days compared to 58% for patients treated in stroke care units who received an abridged version of the guidelines.
- Following the trial, the intervention has been successfully implemented into 36 stroke services in NSW. The National Stroke Foundation (NSF) clinical audit now includes variables for fever and glucose.
- The guidelines for use of paracetamol in NSW were adjusted to allow its use in stroke patients with a temperature of >37.5°C (updated from >38°C).
- Furthermore, the QASC Implementation Project found that participating trial sites were more likely to adhere to the hyperglycemia protocol (the protocol requiring the most amount of multidisciplinary teamwork) than sites that had not participated in the trial.

[34] Middleton et al. (2011). Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. The Lancet. Published online 12. QASC Presentation by Sandy Middleton, NSW Agency for Clinical Innovation. [34] Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Treatment delivers better patient outcomes after discharge.	Adults with stroke = 49,067[35] Proportion of patients excluded = 69%[38] N= 15,211	90 days after hospitalisation: death or dependency; functional dependency; mean SF-36 mental & physical components.	Processes of care: mean temperature; mean finger-prick blood glucose; proportion with swallowing screening undertaken; discharge diagnosis of aspiration pneumonia; LOS in hospital.	The Fever, Sugar, Swallowing (FeSS) intervention has since been successfully implemented into 36 stroke services in NSW. The NSF clinical audit was also changed, and the NSW guidelines for paracetamol updated.[36]	Expect functional outcomes as based on Rankin score will capture the QALY impact of Barthel and SF-36 indices. Costing is based on Rankin score. Life expectancy based on Harald Hannerz et al. (2001).[37]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Functional outcomes at 3 months (Rankin scale score).	Based on $ difference for treatment and QALY between treatment and control groups.	-9,887	-$1,865	-$18m	-$26,580	-$263m	-$281m
Change in intervention costs		+$0.6m						
Totals					-$18m		-$263m	-$281m

Columns may not sum due to rounding. Negative values are savings in the calculations. LOS = length of stay. NSF = National Stroke Foundation.

[35] Access Economics (2013). The economic impact of stroke in Australia.
[36] Correspondence with senior trial investigators.
[37] Harald Hannerz et al. (2001). Life expectancies among survivors of acute cerebrovascular disease. Stroke 32:1739-1744.
[38] Middleton et al. (2011) Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. The Lancet. Published online 12 October 2011.

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Functional outcomes at 3 months (Rankin scale score)	Service cost: -$1,865 QALY: -$26,580	Incremental difference between functional outcomes at 3 months are translated into treatment costs and QALYs preserved. Treatment costs for stroke are based on cost breakdown by functional outcome in Tan Tanny (2013). Life expectancies for these patients range from an additional 0 to 6.4 years, based on average age of patients in the study. Additional reference is taken from Harald Hannerz et al. (2001). Cross-checked with Slot et al. (2008) and Hong et al. (2010). Each Rankin Scale score was assigned to a different WHO disability weight, where a Rankin Scale score of 0 is equivalent to a full, healthy life, with no disability, and a Rankin Scale score of 6 is equivalent to death, and a disability weight of 1.	Tan Tanny et al. (2013). Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke. Stroke. 44:2269-2274. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease. Slot et al. (2008). Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. Hong et al. (2010). Years of Optimum Health Lost Due to Complications after Acute Ischemic Stroke: Disability-Adjusted Life Years Analysis. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Intervention costs	Service cost: +$11,400	Average cost of intervention based on implementation cost per acute stroke unit (87 in total in Australia). Includes workshops, travel and audit. Confirmed through interview.	https://www.strokefoundation.com.au/~/media/strokewebsite/resources/treatment/nsf1221_audit_final.ashx?la=en Informal estimate from community nursing provider sources $135 per hour.

1.7 ENCHANTED Trial (2016) – Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke[39]

Context

- **Thrombolytic therapy with intravenous alteplase at a dose of 0.9 mg/kg of body weight is an effective treatment to dissolve the clots causing acute ischemic stroke. Evidence exists however that the treatment increases the risk of intracerebral haemorrhage.**
- The average cost of alteplase has doubled over the last decade.
- Variable dose regimens of alteplase are used across Asia without any reliable or established evidence.
- An uncontrolled, open-label study in Japan showed that a dose of 0.6 mg/kg of alteplase resulted in equivalent clinical outcomes, and a lower risk of intracerebral haemorrhage compared to a 0.9 mg/kg dose.
- The ENCHANTED trial shows that low-dose alteplase is not inferior to standard-dose alteplase for death and disability at 90 days.
- In addition, fewer patients treated with low-dose alteplase have symptomatic intracerebral haemorrhage compared with standard-dose (1% vs. 2%).
- The trial was recently published (May 2016).
- The uptake on the results of the trial are expected to be variable, however, most clinicians are expected to be influenced by the strong trend towards improved survival with lower dose treatment, based on reduced risk of major intracerebral haemorrhage.

[39] Anderson et al. (2016). Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. N Engl J Med online. Sharma et al. (2011). Current status of intravenous thrombolysis for acute ischemic stroke in Asia. International Journal of Stroke Vol 6, 523-530. Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Low-dose intravenous alteplase is not inferior to standard-dose. There are significantly fewer symptomatic intracerebral haemorrhages with low-dose alteplase.	Ischaemic strokes per year = 23,552[40,41] Proportion eligible to be treated with alteplase = 85%[45] N= 19,925	Death or disability at 90 days (scores of 2 to 6 on mRS).	Intracerebral haemorrhage (ICH); distribution of mRS scale scores at 90 days; neurologic deterioration, admission to a long-term residential care facility at 90 days, and use of health services.	After this study, clinicians will consider using lower dose or standard dose depending on expectation of outcome.	Hospital and ongoing rehabilitation costs are broadly similar for ischemic and haemorrhagic stroke.[42] An ICH after a previous ischaemic stroke within 90 days' results in incremental impairment beyond baseline.[43] Life expectancy based on Harald Hannerz et al. (2001).[44]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Death or disability at 90 days	No statistically significant difference	-	-	-	-	-	-
Secondary	Major intracerebral haemorrhage	-52%	-143	-$65,654	-$9m	-$0.2m	-$27m	-$37m
Change in intervention costs		-$13m						
Totals					-$9m		-$27m	-$50m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[40] Access Economics (2013). The economic impact of stroke in Australia.
[41] AIHW (2013). Stroke and its management in Australia: an update. Cardiovascular disease series no. 37. Cat. no. CVD 61. Canberra: AIHW. Note, this could be an underestimate as many are unclassified.
[42] Confirmed with Gloede et al. (2014). Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. Stroke 45:3389-3394. While patients with intracerebral haemorrhage were found to have lower treatment costs than patients with ischemic stroke in years 3 to 5, these patients had considerably greater direct service costs at 10 years. Therefore, would expect similar service costs to ischemic stroke.
[43] Confirmed with senior trial investigators.
[44] Harald Hannerz et al. (2001). Life expectancies among survivors of acute cerebrovascular disease. Stroke 32:1739-1744.
[45] Sharma et al. (2011). Current status of intravenous thrombolysis for acute ischemic stroke in Asia. International Journal of Stroke Vol 6, 523-530.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Major intracerebral haemorrhage	Service cost: -$65,654 QALY: -$192,100	Hospital and ongoing rehabilitation costs are broadly similar for ischemic and haemorrhagic stroke. Confirmed with Gloede et al. (2014). Service cost of intracerebral haemorrhage based on average cost by Tan Tanny et al. (2013). Subsequent stroke will add additional impairment (from a moderate stroke disability weight, 0.312, to a severe weight, 0.539) for the remainder of survival (a further 6 years, based on Harald Hannerz et al.).	Tan Tanny et al. (2013). Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke. Experience from Australian Stroke Center. Stroke 44:2269:2274. Gloede et al. (2014). Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. Stroke 45:3389-3394. Harald Hannerz et al. (2001). Life Expectancies Among Survivors of Acute Cerebrovascular Disease. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Intervention costs	Service cost: -$1,000	Average cost of intervention is based on $1,000 incremental cost difference of alteplase doses. Clinician time is same or minimal.	Scuffham et al. (2008). The Cost-Effectiveness of Thrombolysis Administered by Paramedics. Kleindorfer et al. (2017). The cost of alteplase has more than doubled over the past decade. Stroke 2016;47: Suppl 1: AWP78-AWP78). http://www.homepharmacy.com.au/products/products_view.cfm?ProductID=17725

2 The IMPACT Network – Trial level results

2.1 ICE Trial (2011) – Whole body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy[46]

Context

- **Hypoxic-ischemic encephalopathy (HIE) is a condition that occurs when the entire brain is deprived of an adequate oxygen supply.**
- Perinatal HIE is an important cause of brain injury in the newborn and can result in devastating long-term consequences.
- Accumulating evidence suggests that therapeutic hypothermia (low core body temperature) may be of benefit to term newborns with HIE.
- Commencing therapeutic hypothermia before 6 hours of age is considered critical, however, most neonates are not transferred to neonatal intensive care before this time.
- The ICE trial found that a simple, inexpensive method of whole-body hypothermia (using refrigerated gel packs) is effective and safe for term or near-term newborns with HIE, significantly reducing the risk of death or major sensorineural disability at 2 years of age (51.4% vs. 66.3%).
- The ICE method of whole-body hypothermia has since been incorporated into Australian guidelines.

[46] Jacobs et al. (2011). Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy. Arch Pediatr Adolesc Med. 165(8):692-700. Correspondence with senior trial investigators. https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/perinatal-reproductive/neonatal-ehandbook/procedures/initiation-hypothermia-scn

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Therapeutic hypothermia reduces the risk of death or major sensorineural disability at 2 years of age. Adverse effects of hypothermia are negligible.	Newborns of ≥35 weeks' gestation = 307277 [47] Proportion of infants with indicators of peripartum hypoxia-ischaemia and moderate to severe clinical encephalopathy (1.2 per 1000)[49] N= 369	**Infants:** Composite of mortality and major sensorineural impairment at 2 years.	**Infants:** Mortality; major sensorineural impairment at 2 years.	The trial shows that the inexpensive ICE method of therapeutic hypothermia is effective and safe.[48]	Inexpensive intervention treatment. No statistically significant impact of sensorineural outcomes, therefore not included. Benefit is primarily due to decreased mortality. No impairment in survivors, standard life expectancy.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Composite outcome – individually costed below.	-	-	-	-	-	-	-
Secondary	Mortality	-35%	-32	-	-	-$4.2m	-$136m	-$136m
	Sensorineural impairment	No statistically significant difference.	-	-	-	-	-	-
Change in intervention costs		+<$0.1m			-			
Totals							-$136m	-$136m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[47] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[48] Confirmed with senior trial investigators.
[49] South Australian Clinical Guidelines.
http://www.sahealth.sa.gov.au/wps/wcm/connect/3beb3b0042abf6c09e57bfad100c470d/Hypoxic+inc+neonatal+hypothermic+neuroprotection_May2014.pdf?MOD=AJPERES&CACHEID=3beb3b0042abf6c09e57bfad100c470d

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Mortality	QALY: -$4,200,000	Incremental gain is extra survivors, who are not impaired or disabled. Survivors have full life expectancy. Confirmed through interview.	Office of Best Practice Regulation, value of statistical life year. https://www.dpmc.gov.au/sites/default/files/publications/Value_of_Statistical_Life_guidance_note.pdf
Intervention costs	Service cost: +$288	Average cost of intervention is based on cost of standard gel packs and 2 hours nursing oversight.	http://www.health.vic.gov.au/neonatalhandbook/procedures/initiation-hypothermia-scn.htm http://www.pharmacyonline.com.au/first-aid/hot-cold-packs/blue-healer-hot-cold-pack-regular; https://www.priceline.com.au/health/home-health-aids/heat-and-ice-packs/medi-ice-pak-reusable-cold-or-hot-pack-1-ea Informal estimate from community nursing provider sources $135 per hour.

2.2 VIBES+ Trial (2010) – Preventive care at home for very preterm infants improves infant and caregiver outcomes at 2 years[50]

Context

- **While survival rates for very preterm infants born less than 32 weeks' gestation have stabilised, high rates of neuro-behavioural disabilities are recorded among survivors.**
- The benefits of early intervention for very preterm infants are not fully established.
- Some evidence suggests that intervention programs should focus on parents, because caregivers of preterm infants are at increased risk of emotional distress, which is associated with short- and long-term consequences for their children.
- The VIBES+ trial assesses outcomes of a home-based preventive care program for very preterm infants and their families, comprising 9 visits by a psychologist and physiotherapist.
- Preventive care was found to be effective – it improves behavioural outcomes for infants (less externalising and dysregulation behaviours) and reduces anxiety and depression for primary caregivers.
- Due to the costs involved in providing preventive care at home (particularly for families who live in rural and remote areas), the trial findings are not believed to have been widely implemented. Investigators are currently focussed on finding an effective, cheaper option for delivery, using web-based care.

[50] Spittle et al. (2010). Preventive care at home for very preterm infants improves infant and caregiver outcomes at 2 years. Pediatrics 126:e171-e178. Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Preventive care at home leads to Improved behavioural outcomes for infants, and reduces anxiety and depression for primary caregivers.	Infants born at <30 weeks' gestation with no major congenital brain anomalies associated with poor neurodevelopmental outcomes = 1.7% [51] Live births = 307277, mothers = 304777 [53] Infants, N = 5224, Mothers, N = 5181	**Infants:** Cognitive, language and motor development at age 2. **Mothers:** and mental health of primary care-giver at same time-point.	**Infants:** Child behaviour and emotional regulation at age 2.	Prior to the trial, there was little existing evidence for the effectiveness for preventive care at home for newborns. It is unlikely the trial results will be implemented due to the cost of intervention.	Main impact is through maternal outcomes rather than those for infants.[52] Dysregulation will not be treated in clinical practice at this stage. Dysregulation may be predictive of longer term neurodevelopmental outcomes (e.g. autism), however, it is not costed here as the predictive association is not part of this study. Impairment for maternal anxiety and depression is for two years in parents of very preterm infants.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Cognitive, language and motor development	No statistically significant difference.	-	-	-	-	-	-
Secondary	Anxiety (maternal)	-43%	-326	-$2,000	-$0.7m	-$60,979	-$20m	-$21m
	Depression (maternal)	-35%	-1027	-$2,000	-$2m	-$57,033	-$59m	-$60m
Change in intervention costs		+$6m						
Totals					-$3m		-$78m	-$75m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[51] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[52] Confirmed with senior trial investigators.
[53] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Anxiety (maternal)	Service cost: -$2,000 QALY: -$60,979	Cost of treating perinatal anxiety is approximately $1,000 per year, based on Deloitte 2012 paper on Perinatal Depression and Anxiety (estimate that includes government, private health insurance and personal costs – productivity costs not included). The majority of cases are dealt with in primary care. Confirmed through interview. Anxiety is more prevalent and lasts longer in parents with a very preterm infant. Parents of very preterm infants may still experience anxiety up to 7 years after birth (Treyvaud et al. 2010 and 2014). Two years' impairment and treatment included for a conservative estimate. Based on clinical heuristic and confirmed through interview. AIHW disability weight for Generalised Anxiety Disorder, 0.170.	Deloitte Access Economics (2012). The cost of perinatal depression in Australia. Treyvaud et al. (2010). Parental mental health and early social-emotional development of children born very preterm. Journal of Pediatric Psychology 35(7):768-777. Treyvaud et al. (2014). Very preterm birth influences parental mental health and family outcomes seven years after birth. The Journal of Pediatrics 164:515-21. Mathers et al.1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW.
Depression (maternal)	Service cost: -$2,000 QALY: -$57,033	Cost of treating perinatal depression is approximately $1,000 per year, based on Deloitte 2012 paper on Perinatal Depression and Anxiety (estimate that includes government, private health insurance and personal costs – productivity costs not included). The majority of cases are dealt with in primary care. Confirmed through interview. Depression is more prevalent and lasts longer in parents with a very preterm infant. Parents of very preterm infants may still experience depression up to 7 years after birth (Treyvaud et al. 2010 and 2014). 2 years' impairment and treatment included for a conservative estimate. Based on clinical heuristic and confirmed through interview. AIHW disability weight for major depressive episode (mild), 0.140.	Deloitte Access Economics 2012. The cost of perinatal depression in Australia. Treyvaud et al. (2010). Parental mental health and early social-emotional development of children born very preterm. Journal of Pediatric Psychology 35(7):768-777. Treyvaud et al. (2014). Very preterm birth influences parental mental health and family outcomes seven years after birth. The Journal of Pediatrics 164:515-21. Mathers et al.1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW.
Intervention costs	Service cost: +$1,823	Average cost of intervention is based on 9 home visits of physiotherapist and psychologist, 90min duration at $135/hour.	Informal estimate from community nursing provider sources $135 per hour.

2.3 COSMOS Trial (2012) – Effects of continuity of care by a primary midwife (caseload midwifery) on caesarean section rates in women of low obstetric risk[54]

Context

- **There is international concern about the growing proportion of women giving birth by caesarean section (18% in 1991; 32% in 2011).**
- Evidence from RCTs shows that midwife-led care is associated with fewer interventions in pregnancy and birth (e.g. analgesia during labour, episiotomy and instrumental births) and increased satisfaction for women.
- Caseload midwifery is a model where women are cared for by a primary midwife throughout pregnancy, birth and the postnatal period.
- The COSMOS trial shows that women at low obstetric risk in early pregnancy who were allocated to caseload midwifery care are less likely to have a caesarean section than women who had usual care (19% vs. 25%).
- Since the first model was established in 1995, the number of services offering caseload midwifery care has increased nationally. A recent survey shows a third of hospitals offer this model. Only 8% of women however were found to have accessed it. Access was most likely for women living in metropolitan areas and considered to be at low obstetric risk.
- The trial site (Royal Melbourne Hospital) has since continued and grown their caseload midwifery program. The hospital is in the process of applying for a new grant to focus on vulnerable populations (e.g. Aboriginal and Torres Strait Islander mothers).
- The IMPACT network disseminated findings, garnering interest from the obstetric community, in what was an otherwise midwifery specific trial.

[54] McLachlan et al. (2012). Effects of continuity of care by a primary midwife (caseload midwifery) on caesarean section rates in women of low obstetric risk: the COSMOS randomised controlled trial. BJOG 119:1483-1492. Australian Institute of Health and Welfare 2014 Australia's health 2014. Australia's health series no. 14. Cat. no. AUS 178. Canberra: AIHW. [54] Correspondence with senior trial investigators. Dawson et al. (2015). Implementing caseload midwifery: Exploring the views of maternity managers in Australia: A national cross-sectional survey. Women and Birth 29:214-222.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
In low risk women, caseload midwifery care shows a reduction in unplanned caesarean section as well as epidural pain relief, episiotomy, postpartum length of stay. For infants, caseload midwifery leads to reduced admission to special care nurseries, and fewer low birth weight babies, without any adverse impact.	Singleton pregnancies = 98.5% [55] Low-risk pregnant women = 63%[57] N = 189,621	**Mothers:** Caesarean section.	**Infants:** NICU admission **Mothers:** Epidural analgesia in labour; Episiotomy; Postpartum LOS; Antenatal visits; Analgesia administration; Spontaneous labour; Breastfeeding on hospital discharge.	The trial confirms caseload midwifery as the approach of choice for low risk pregnant women. There has been substantial growth in caseload midwifery since the trial.	Most of the differences in intervention costs are due to; labour and birth characteristics, mode of birth, admission to NICU/SCN episiotomy and Apgar score. Episiotomy disability weight equivalent to maternal haemorrhage disability weight.[56]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Caesarean section (planned and unplanned)	-22%	-9,078	-$5,014	-$46m	-	-	-$46m
Secondary	Episiotomy	-21%	-3,030	-$1,797	-$5m	-$2,002	-$6m	-$11m
	SCN or NICU admission	-37%	-2,933	-$20,500	-$60m	-	-	-$60m
Change in intervention costs		-$70m						
Totals					-$111m		-$6m	-$187m

Columns may not sum due to rounding. Negative values are savings in the calculations. NICU = neonatal intensive care unit. SCN = special care nursery.

[55] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[56] WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
[57] McLachlan et al. (2012). Effects of continuity of care by a primary midwife (caseload midwifery) on caesarean section rates in women of low obstetric risk: the COSMOS randomised controlled trial. BJOG 119:1483-1492.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Caesarean section (planned and unplanned)	Service cost: -$5,014	Costed as the incremental difference between caesarean delivery and vaginal delivery. Casemix costing for caesarean sections (AR-DRG codes O01A, O01B, O01C) and uncomplicated vaginal delivery (AR-DRG codes O02B, O60C). Caesarean section costing is weighted based on the frequency of occurrence of minor and major complexities, as reported in AIHW data (2013-14).	http://www.aihw.gov.au/hospitals-data/ar-drg-data-cubes/ IHPA National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16.
Episiotomy	Service cost: -$1,797 QALY: -$2,002	Based on Tracy et al.(2003), which describes a birth ending in a forceps or vacuum extraction and an episiotomy as 1.3 times the cost of a straightforward (uncomplicated) vaginal birth. Casemix costing for uncomplicated vaginal delivery (AR-DRG codes O02B or O60B). QALY impairment based on AIHW maternal haemorrhage disability weight (0.011).	Tracey et al. (2003). Costing the cascade: estimating the cost of increased obstetric intervention in childbirth using population data. BJOG 110:717-724. IHPA National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16. AIHW (2016). Australian Burden of Disease Study: Impact and causes of illness and death in Australia 2011. Australian Burden of Disease Study series no. 3. BOD 4. Canberra: AIHW.
SCN or NICU admission	Service cost: -$20,500	Driven by SCN stay as there is no statistically significant difference in NICU stay. Estimates from Royal Women's Hospital – casemix costs ($2,971 per day). Includes overheads, clinician time and materials. Cross checked with NICU report QLD Health. The average length of stay in a Special Care Nursery is 6.9 days (as outlined in the QLD Health report).	https://www.thewomens.org.au/patients-visitors/patient-fees/ 2016 fees & Beckmann et al. 2016 https://www.health.qld.gov.au/caru/networks/docs/NICU_report.pdf

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Intervention costs	Service cost: -$567	The average cost of intervention is based on the costing study for the M@NGO trial (Tracy et al. 2013). Both the COSMOS and the M@NGO trials use the same intervention, but in different patient cohorts. The M@NGO costing study determined the difference between the intervention costs and costs of standard care. The intervention was found to be $567 less costly than standard care. The estimate has been cross-matched with statistically significant findings from the COSMOS trial. It is assumed that the estimate includes costs for epidural analgesia in labour and postpartum stay. Some outcomes that were not statistically significant in the M@NGO trial are statistically significant for the COSMOS trial. These are caesarean section, episiotomy and SCN admission. The costs for these outcomes are over and above the difference in costs calculated in the M@NGO study, and are therefore costed separately.	Tracy et al. (2013). Caseload midwifery versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial. Lancet. Costing approach confirmed with IMPACT stakeholders and senior trial investigators.

2.4 M@NGO Trial (2013) – Caseload midwifery care versus standard maternity care for women of any risk [58]

Context

- **As with the COSMOS trial, the M@NGO trial came about due to growing concern at the increasing level of intervention and consequent morbidity among childbearing women.**
- Caseload midwifery care, a model where women are cared for by a primary midwife throughout pregnancy, birth and the postnatal period, is intended to improve continuity of care, and improve outcomes for both childbearing women and their infants.
- The M@NGO trial shows that for women of any risk, caseload midwifery care is safe and cost-effective, saving $567 per woman, despite no significant difference in the health outcomes found to be improved in the COSMOS Trial.
- The cost difference is driven primarily by direct service costs of antenatal visits, post-natal hospital length of stay, analgesia, and greater proportion of spontaneous (not induced) deliveries.
- Since the first model was established in 1995, the number of services offering caseload midwifery care has increased nationally. A recent survey shows a third of hospitals offer this model. Only 8% of women however were found to have accessed it. Access was most likely for women living in metropolitan areas and considered to be at low obstetric risk.

[58] Tracy et al. (2013). Caseload midwifery versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial. Lancet. Dawson et al. (2015). Implementing caseload midwifery: Exploring the views of maternity managers in Australia: A national cross-sectional survey. Women and Birth 29:214-222.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
In women of any risk, caseload midwifery is cheaper than standard care, with the same outcomes.	Singleton pregnancies = 98.5% [59] Exclude 34% with planned caesarean section.[61] **Note overlap in population with COSMOS. N = 75,467	**Mothers:** Caesarean section.	**Mothers:** Instrumental vaginal birth or unassisted vaginal birth, and the proportion who had epidural analgesia during labour.	The trial confirms caseload midwifery as the approach of choice for low risk pregnant women. There has been growth in use of caseload midwifery since the trial.	The trial paper includes information on costs.[60] There are no additional cost savings for caesarean section and NICU (contrary to COSMOS). Median differences in intervention costs used due to large outliers (outliers due to non-obstetric causes).

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Median antenatal visits	-1	-49,053	-$567	-$28m	-	-	-$28m
	Post-natal stay (days)	-0.4	-19,621					
	No pharmacological analgesia	+56%	+4,415					
	Spontaneous labour	+20%	+3,434					
Change in intervention costs		Included in costing study					-	
Totals					-$28m			-$28m

Columns may not sum due to rounding. Negative values are savings in the calculations. NICU = neonatal intensive care unit.

[59] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[60] Tracy et al. (2013). Caseload midwifery versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial. Lancet.
[61] Tracy et al. (2013). Caseload midwifery versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial. Lancet.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Median antenatal visits	Service cost: -$567	The average cost of intervention is based on Tracy et al. (2013) (the costing paper for M@NGO). This is assumed to include all relevant cost differences. It is assumed that most of the cost difference is driven by difference in labour and birth characteristics, mode of birth, admission to NICU, SCN, episiotomy and Apgar score. It is assumed there are no additional cost savings for caesarean section and SCN admission (as in COSMOS).	Tracy et al. (2013). Caseload midwifery versus standard maternity care for women of any risk: M@NGO, a randomised controlled trial. Lancet.
Post-natal stay (days)			
No pharmacological analgesia			
Spontaneous labour			
Intervention costs	Included in costing study	-	-

2.5 MAP Trial (2011) – Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide[62]

Context

- **Approximately 12% of pregnant women in Australia have asthma. Asthma exacerbations during pregnancy are common and can be associated with substantial maternal and foetal morbidity.**
- Maintenance treatment with inhaled corticosteroids can effectively reduce the frequency and severity of asthma exacerbations.
- Treatment can be guided by symptoms and lung function. Results improve when therapy is adjusted according to direct measures of airway inflammation.
- Studies have shown variable benefit when fraction of exhaled nitric oxide (F_ENO) is used to guide therapy.
- Testing a management algorithm based on F_ENO, the MAP trial shows that there are fewer exacerbations in the F_ENO group compared to usual care (0.288 vs. 0.615 exacerbations per pregnancy). There are also fewer neonatal hospitalisations.
- While there is limited evidence of change of practice since the trial, awareness of asthma as a problem in pregnancy has improved.
- Guidelines now include the trial intervention as an option.
- The MAP trial was a single site study. The investigators are now undertaking a large multi-centre trial, the Breathing for Life trial, to provide further evidence for the F_ENO algorithm.

[62] Powell et al. (2011). Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. Lancet 378:983-90. Vanders & Murphy (2015). Maternal complications and the management of asthma in pregnancy. Womens Health (Lond) 11(2):183-91. Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Women in the intervention group have fewer unplanned GP visits, and reduced oral corticosteroid use. Quality of life is also better (for the mental summary component of the Short Form health survey). There was no difference for ED attendance or hospital admission, or for lung function.	Non-smoking pregnant women aged ≥18 years with asthma = 12%[63] Total no. of mothers = 304777[65] N= 32,550	**Mothers:** Total asthma exacerbations (moderate and severe).	**Infants:** neonatal hospitalisation. **Mothers:** Quality of life.	The trial has increased awareness of asthma in pregnancy, and has changed some guidelines, management through the algorithm is now a supported option.[64]	The results of the mental health component of the Short Form health survey (SF-12) did not affect ongoing treatment (as this was measured at the end of trial). Neonatal hospitalisations were admissions to special care nurseries. The average length of stay is based on data from the Breathing for Life trial (4 days). Most exacerbations are treated in primary care. No QALY impairment for moderate asthma exacerbations resolved with oral corticosteroid use.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Unplanned doctors visit (mean)	-0.3	-6,347	-$130	-$0.8m	-	-	-$0.8m
	Oral corticosteroid use (mean)	-0.09	-2,327	-$9	<-$0.1m	-	-	<-$0.1m
Secondary	Neonatal hospitalisation	-53%	-1,920	-$11,884	-$23m	-	-	-$23m
Change in intervention costs		+$2m					-	
Totals					-$24m			-$22m

Columns may not sum due to rounding. Negative values are savings in the calculations. ED = emergency department.

[63] Vanders & Murphy (2015). Maternal complications and the management of asthma in pregnancy. Womens Health (Lond) 11(2):183-91.
[64] Correspondence with senior trial investigators.
[65] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Unplanned doctor visits	Service cost: -$130	Unscheduled doctor visits were in primary care. Confirmed through interview. The cost is based on MBS 597, out of hours cost, to offset some of the missed savings in additional nursing and ancillary support.	http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=597&qt=item&criteria=597
Oral corticosteroid use	Service cost: -$9	Costs of B2 agonists balance out due to overall different treatment profile, and are not thought to be economically salient. Cost of oral corticosteroids included as a primary outcome (raw material cost $9, PBS). No additional clinical costs (beyond GP visits). No QALY impairment for moderate asthma exacerbations resolved with oral corticosteroids.	http://www.asthmahandbook.org.au/acute-asthma/clinical/corticosteroids http://www.aafp.org/afp/2011/0701/p40.html http://www.pbs.gov.au/medicine/item/1916W-1917X-3152X
Neonatal hospitalisations	Service cost: -$11,884	Neonatal hospitalisation is driven primarily by SCN stay. Confirmed through interview. Estimates from Royal Women's Hospital – casemix costs ($2,971 per day) includes overheads, clinician time and materials. Cross checked with NICU report QLD Health. The value is based on a median length of stay (4 days) from the Breathing for Life trial (unpublished, estimates provided by senior trial investigators).	https://www.thewomens.org.au/patients-visitors/patient-fees/ 2016 fees & Beckmann et al. 2016 https://www.health.qld.gov.au/caru/networks/docs/NICU_report.pdf
Intervention costs	Service cost: +$94	Intervention includes questionnaire, measurement of F_ENO and entry of data into algorithm spreadsheet. Usual care is questionnaire only. Cost of equipment provided by senior trial investigators. 15 mins clinician time estimated by senior trial investigators.	Informal estimate from community nursing provider sources $135 per hour.

2.6 COIN Trial (2008) – Nasal CPAP or intubation at birth for very preterm infants [66]

Context

- **Approximately 0.5% of babies in Australia are born at 25 to 28 weeks' gestational age. These very preterm infants will often require life-saving respiratory support at birth.**
- For two decades, the standard treatment was with assisted ventilation and surfactant.
- However, evidence suggests that ventilation may damage the lungs, resulting in bronchopulmonary dysplasia (chronic lung disease), a major cause of mortality and morbidity in very preterm infants.
- Observational studies suggested that nasal continuous positive airway pressure (CPAP), a less invasive method of providing respiratory support, could reduce the need for intubation, and reduce the incidence of bronchopulmonary dysplasia.
- Despite showing no significant difference in the rate of death or bronchopulmonary dysplasia when comparing CPAP with intubation, the COIN trial shows that CPAP is safe and effective for very preterm infants.
- CPAP is expected to be preferable to mothers and infants, despite minimal cost difference, as it is a less invasive treatment.
- CPAP use among neonates ≤32 weeks slowly increased from 2001 to 2008. While there is a lack of data on current CPAP rates, it is expected that rates will be higher as the results of the trial have been incorporated into guidelines.

[66] Morley et al. (2008). Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 358:700-8. Correspondence with senior trial investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
In very preterm infants, early nasal CPAP does not significantly reduce the rate of death or bronchopulmonary dysplasia. Even though the CPAP group have more incidences of pneumothorax, fewer infants receive oxygen at 28 days, and they have fewer days of ventilation.	Infants born at 25 to 28 weeks' gestation 0.50% [67] Proportion excluded= 19.4% [70] N= 1,244	**Infants:** Death or bronchopulmonary dysplasia at 36 weeks' gestational age.	**Infants:** Intubation at 28 days of age, need for oxygen treatment, fraction of inspired oxygen, incidence of air leaks and intracranial haemorrhages, ventilation and CPAP duration, days in hospital.	The trial provides evidence that even very small babies can be treated with CPAP from birth.[68] This has reduced the rate of intubation and ventilation and expenditure on surfactant.	Reduction in days on intubation/ ventilation is more clinically relevant than the increase in risk of pneumothorax which is thought to be transient, and was not replicated in other trials (such as the SUPPORT Trial).[69] International guidelines have changed to include CPAP as an option. No ongoing QALY impact for intubation, ventilation or pneumothorax.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Death or bronchopulmonary dysplasia	No statistically significant difference.	-	-	-	-	-	-
Secondary	Surfactant treatment	-51%[71]	-356	-$500	-$0.2m	-	-	-$0.2m
	Methylxanthine treatment	+18%	+105	+$95	<+$0.1m	-	-	<+$0.1m
	Received intubation or ventilation (days)	-25%	-809	-$2,491	-$2m	-	-	-$2m
	Pneumothorax	+203%[72]	+60	+$3,571	+$0.2m	-	-	+$0.2m
Change in intervention costs		-$0.1m						
Totals					-$2m			-$2m

Columns may not sum due to rounding. Negative values are savings in the calculations. CPAP = Continuous Positive Airway Pressure.

[67] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[68] Correspondence with senior trial investigators.
[69] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. (2010). Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 362:1970–9.
[70] Morley et al. (2008). Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 358:700-8.
[71] Control prevalence used is from Bolisetty et al. 2015.
[72] Control prevalence used is from Bolisetty et al. 2015.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Surfactant treatment	Service cost: -$500	The surfactant treatment, Survanta, is indicated for use in preterm infants in clinical guidelines and in the Western Australian and Victorian neonatal handbook of procedures. The cost relates to the cost of materials, and minimal ($100) clinician time, as confirmed through interviews with senior trial investigators.	Survanta (per vial, Beractant, Suspension;25mg/Ml;8ml;Vial) https://www.contractswa.finance.wa.gov.au/resources/Price_Matrix_-_HCNS110709.xls
Methylxanthine treatment	Service cost: +$95	Caffeine citrate (as a methylxanthine treatment) is indicated for use in the NSW John Hunter Children's Hospital guidelines. Confirmed through interviews with senior trial investigators. Costing based on Dukhovny et al. (2011). It is assumed that there is negligible clinician time.	http://www.hnekidshealth.nsw.gov.au/site/content.cfm?page_id=534813&current_category_code=8338 Dukhovny et al. (2010) Economic evaluation of caffeine for apnea of prematurity. Pediatrics 2011;127:e146–e155.
Received intubation or ventilation (days)	Service cost: -$2,491	Costing estimate is based on NSW per hour average. It is expected that there is no additional cost for neonates compared to standard care costs. Confirmed through interview.	http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_007.pdf
Pneumothorax	Service cost: +$3,571	The majority of cases of pneumothorax are acute and resolve within a few days (as outlined in the study and confirmed through interviews with senior trial investigators). Casemix costing (AR-DRG E68B and E72Z) to account for any treatment costs, and increased length of stay. Confirmed through interviews with senior trial investigators. No QALY impairment. Confirmed through interview with senior trial investigators.	IHPA NWAU calculator for acute activity 2016-17.
Intervention costs	Service cost: -$160	Average incremental cost of intervention of CPAP versus ventilation/intubation. Cost of CPAP based on Dukhovny et al. 2011. Crosschecked with Buckmaster et al. (2007). Cost of ventilation/intubation based on NSW Cost of Care 2011. Assumption of no additional cost for neonates compared to standard care costs, confirmed through interview. Overall estimate cross checked with senior trial investigators.	http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_007.pdf Dukhovny et al. (2010) Economic evaluation of caffeine for apnea of prematurity. Pediatrics 2011;127:e146–e155. Buckmaster et al. (2007) Continuous Positive Airway Pressure therapy for infants with respiratory distress in non-tertiary care centers: a randomised, controlled trial. Pediatrics 120(3).

2.7 ACTORDS Trial (2006) – Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids[73]

Context

- **Babies born preterm are at high risk of neonatal lung disease and its sequelae. Respiratory distress syndrome, as a result of immature lung development, is the main cause of early neonatal mortality, and causes substantial morbidity in survivors.**
- A single course of prenatal corticosteroids given to the mother remains the most effective known prenatal strategy for reducing the adverse results of preterm birth.
- Prior to the trial, a practice survey showed that 44% of obstetricians and 21% of neonatologists recommended use of repeat corticosteroids for women who remained at risk of preterm birth. This practice almost ceased while the ACTORDS trial was being undertaken, due to concerns around harm.
- The ACTORDS trial shows that repeat doses of antenatal corticosteroids reduce short-term neonatal morbidity, with fewer infants having severe lung disease (12% vs. 20%).
- Repeat antenatal corticosteroids are now recommended in Australian guidelines.
- There is, however, widespread variation in practice: trial findings have been implemented at trial sites. The Cochrane review indicates however, that there is uncertainty about potential longer term risks.

[73] Crowther et al. (2006). Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet 367:1913-19. McLaughlin et al. (2003). Repeat prenatal corticosteroids: Who still recommends their use and why? Australian and New Zealand Journal of Obstetrics and Gynaecology 43:199-202. Correspondence with senior trial investigators. Crowther et al. (2015). Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD003935. DOI: 10.1002/14651858.CD003935.pub4.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Exposure to repeat doses of antenatal corticosteroids reduces neonatal morbidity.	Proportion of preterm births before 32 weeks' gestation 3.7% of total 307,277 [74] Women who remained at risk of preterm birth after receiving a first course of prenatal corticosteroids 40%[76] N= 4,548	**Infants:** Neonatal respiratory distress syndrome; lung disease; oxygen therapy; mechanical ventilation via an endotracheal tube; weight, length & head circumference at birth and at discharge from hospital.	**Infants:** Neonatal morbidity. **Mothers:** Clinical chorioamnionitis, postpartum pyrexia, side-effects of the injection.	Provides evidence that repeat doses of antenatal corticosteroids are safe and effective to reduce respiratory morbidity associated with prematurity. Use of repeat doses would have ceased without the trial.[75]	Babies with severe lung disease will also have respiratory distress syndrome (there is overlap between the two outcomes). Service costs (e.g. for surfactant use and mechanical ventilation) represent the costs to treat severe lung disease and respiratory distress syndrome. QALY impairment for severe lung disease babies only, short-term impairment. Minor maternal side effects, thought to be negligible. Oxygen therapy cost is negligible.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Severe lung disease	-40%	-236	(included elsewhere)	-	-$5,460	-$1m	-$1m
	Mechanical ventilation (hours)	-24	-70,944	-$104	-$7m	-	-	-$7m
Secondary	Surfactant use	-25%	-236	-$500	-$0.1m	-	-	-$0.1m
	Patent ductus arteriosus	-42%	-148	-$4,182	-$0.6m	-$5,460	-$0.8m	-$1m
	Caesarean sections	+16%	+151	+$5,014	+$0.8m	-	-	+$0.8m
Change in intervention costs		+$0.5m						
Totals					-$7m		-$2m	-$9m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[74] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[75] Correspondence with senior trial investigators.
[76] Crowther et al. (2006). Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet 367:1913-19.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Severe lung disease	QALY: -$5,460	Cost is captured in mechanical ventilation and surfactant use (no difference in average length of stay or NICU admission rates). Confirmed through interview with senior trial investigators. AIHW disability weight 0.03 equivalent to surgically treated congenital atrial or ventricular septal defect. Impairment is for one year.	Mathers et al.1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW.
Mechanical ventilation (hours)	Service cost: -$104	Costing estimate is based on NSW per hour average. It is expected that there is no additional cost for neonates compared to standard care costs. Confirmed through interview.	http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_007.pdf
Surfactant use	Service cost: -$500	The surfactant treatment, Survanta, is indicated for use in preterm infants in clinical guidelines and in the Western Australian and Victorian neonatal handbook of procedures. The cost relates to the cost of materials, and minimal ($100) clinician time, as confirmed through interview.	Survanta (per vial, Beractant, Suspension;25mg/Ml;8ml;Vial) https://www.contractswa.finance.wa.gov.au/resources/Price_Matrix_-_HCNS110709.xls
Patent ductus arteriosus	Service cost: -$4,182 QALY: -$5,460	Service cost estimated on weighted average of most common treatments (medication and surgery). Most (90%) treated with medication only ($2.5k, ibuprofen course). Surgery is to be considered where first line therapy has failed. 10% treated surgically (Evans 2015) ($16k-18k based on MSAC). AIHW disability weight 0.03 equivalent to surgically treated congenital atrial or ventricular septal defect. Impairment is for one year.	http://www.slhd.nsw.gov.au/rpa/neonatal/html/docs/pda.pdf http://www.msac.gov.au/internet/msac/publishing.nsf/content/6F852E27F39ECC3FCA257AAF0073BB52/$File/1330-ContractedAssessmentReport%20accessibility.pdf Evans (2015). Preterm patent ductus arteriosus: A continuing conundrum for the neonatologist? Seminars in Fetal & Neonatal Medicine 20:272-277. Mathers et al.1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Caesarean sections	Service cost: +$5,014	Costed as the incremental difference between caesarean delivery and vaginal delivery. Casemix costing for caesarean sections (AR-DRG codes O01A, O01B, O01C) and uncomplicated vaginal delivery (AR-DRG codes O02B, O60C). Caesarean section costing is weighted based on the frequency of occurrence of minor and major complexities, as reported in AIHW data (2013-14).	http://www.aihw.gov.au/hospitals-data/ar-drg-data-cubes/ IHPA National Hospital Cost Data Collection Australian Public Hospitals Cost Report 2011-2012, Round 16.
Intervention cost	Service cost: +$167	PBS listing for corticosteroid (Celestone Chronodose). Maximum three doses administered. 20 minutes' midwifery administration time per dose. Confirmed through interview.	http://www.pbs.gov.au/medicine/item/2694T-5034Y Informal estimate from community nursing provider sources $135 per hour.

2.8 ACHOIS Trial (2005) – Effect of treatment of gestational diabetes mellitus on pregnancy outcomes [77]

Context

- **Gestational diabetes mellitus (GDM) occurs in approximately 15,000 pregnancies in Australia each year.**
- Prior to the trial, there were two extreme views influencing care:
  1. GDM is not a disease, and all forms of testing in pregnancy should stop until there is evidence of benefit
  2. GDM is a major cause of poor maternal and infant outcomes, and needs detection and treatment.
- The majority (87%) of Australian hospitals provided screening for GDM.
- The ACHOIS Trial established, for the first time in a RCT, that treatment of women with even mild degrees of GDM reduces the risks of serious complications for their babies (1% vs. 4% in the control group).
- This knowledge has been taken up into clinical practice with recommendations to treat women identified with GDM.
- Clinical practice guidelines have changed worldwide, and there is widespread uptake of trial findings throughout Australia.
- A costing paper for this study was published in 2007. This costed the outcomes: serious perinatal complications (treatment only), admission to neonatal nursery, induction of labour, antenatal clinic visits, physician clinic visits, visit with a dietician, visits with a diabetes educator, and insulin therapy.

[77] Crowther et al. (2005) Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477-86. AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW. Correspondence with senior trial investigators. Rumbold et al. (2001). Guideline use for gestational diabetes mellitus and current screening, diagnostic and management practices in Australian hospitals. Aust NZ J Obstet Gynaecol 41; 1:86-90. Moss et al. (2007) Costs and consequences of treatment for mild gestational diabetes mellitus – evaluation from the ACHOIS randomised trial. BMC Pregnancy and Childbirth 7:27

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Treatment of gestational diabetes mellitus (GDM) reduces serious perinatal morbidity and may also improve women's health-related quality of life.	Prevalence of gestational diabetes in pregnant women 5% [78] Total no. of mothers per year 304,777[80] N= 15,239	**Infants:** Serious complications, admission to SCN, jaundice. **Mothers:** induction of labour, caesarean birth, maternal anxiety, depression, and health status.	**Infants:** components of the primary outcome, gestational age at birth, birth weight. **Mothers:** visits to a health professional, mode of birth, weight gain, antenatal admissions, pregnancy-induced hypertension	The trial has established that treatment for GDM is beneficial without harm. Without the results of this trial there would still be two extreme views of best practice care.	The ACHOIS costing paper is used for intervention costs (insulin, antenatal visits, physician visits and visits with a diabetes educator) and treatment of significant outcomes (perinatal complications, special care nursery and induction of labour). [79] QALY impairments were not included in the paper, and therefore have been calculated separately. Treatment of postpartum depression was also not included in the paper. Minimal ongoing QALY impact for serious perinatal complications (single event). Average duration of postpartum depression (based on EPDS > 12) is 1 year. SF-36 QALY impairment based on 3 months' duration.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Any serious perinatal complication	-68%	-298	Included in cost of intervention	Included in cost of intervention	-$20,020	-$6m	-$6m
	SF-36 score (3 months)	-0.038	-9905	-	-	-$1,729	-$17m	-$17m
	EPDS score > 12 (3 months)	-51%	-859	-$1,000	-$0.9m	-$25,480	-$22m	-$23m
Change in intervention costs		+$8m						
Totals					-$0.9m		-$45m	-$38m

Columns may not sum due to rounding. Negative values are savings in the calculations. EPDS refers to the Edinburgh Postnatal Depression Scale, a screening questionnaire for postnatal depression. SCN = special care nursery.

[78] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.
[79] Moss et al. (2007) Costs and consequences of treatment for mild gestational diabetes mellitus – evaluation from the ACHOIS randomised trial. BMC Pregnancy and Childbirth 7:27.
[80] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Any serious perinatal complication	QALY: -$20,020	Any serious perinatal complication includes death, shoulder dystocia, bone fracture and nerve palsy. Health service costs for serious perinatal complications are included in the overall intervention cost based on Moss et al.(2007) (within hospital costs). AIHW disability weight 0.110, lowest unit within birth trauma category. Impairments for 1 year.	Mathers et al.1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW.
SF-36 score (3 months)	QALY: -$1,729	SF-36 score collected at 3 months postpartum is more clinically significant than SF-36 score collected at 6 weeks. Confirmed with senior trial investigators. SF-36 score converted to utility value (-0.038 lower in treatment group). No data is available on duration of impairment. The follow-up period for this study was 3 months, therefore the disability impairment is applied for 3 months. Confirmed through interview.	Communication with senior trial investigator.
EPDS score >12 (3 months)	Service cost: -$1,000 QALY: -$25,480	Cost of treating perinatal depression is approximately $1,000 per year, based on Deloitte 2012 paper on Perinatal Depression and Anxiety (estimate that includes government, private health insurance and personal costs – productivity costs not included). The majority of cases are dealt with in primary care. Average duration of postpartum depression is one year. Confirmed through interview. AIHW disability weight for major depressive episode (mild), 0.14.	Deloitte (2012). Perinatal Depression and Anxiety.
Intervention cost	Service cost: +$770	Moss et al. (2007) ACHOIS costing paper found additional $53,985 direct costs incurred at the obstetric hospital for every 100 women offered treatment for mild gestational diabetes ($539 per woman in 2002 dollars). This included: antenatal clinic, specialist clinic, dietician, diabetes educator, insulin therapy, and hospital costs. Costs adjusted to 2014 dollars.	Moss J, Crowther C, Hiller J, Willson K, Robinson J for the ACHOIS Trial Group 2007. Costs and consequences of treatment for mild gestational diabetes mellitus – evaluation from the ACHOIS randomised trial. BMC Pregnancy and Childbirth 7:27.

2.9 ACTOMgSO4 Trial (2003) – Effect of magnesium sulfate given for neuroprotection before preterm birth [81]

Context

- **Infants born very preterm (less than 30 weeks' gestation) have increased risks of mortality, or of surviving with neurosensory impairments and disabilities, such as cerebral palsy.**
- Observational studies showed that maternal administration of magnesium sulfate ($MgSO_4$) could be effective as a neuroprotective agent, and could reduce the risk of cerebral palsy in preterm infants.
- $MgSO_4$ had not previously been used in this way.
- The ACTO$MgSO_4$ Trial was the first multicentre RCT to suggest benefit from administering intravenous $MgSO_4$ to women immediately prior to very preterm birth. It was one of four trials being conducted worldwide around the similar time.
- The combined meta-analysis shows the overall benefit of reduction in cerebral palsy and death.
- Within two years of the systematic review, estimates of uptake changed from 0% to up to 90% across tertiary hospitals (Bain et al. 2013). Active implementation was via the WISH (Working to Improve Survival and Health for babies born preterm) Project, an ongoing project, funded by the Cerebral Palsy Alliance, comprising a package of active implementation strategies to guide the introduction and local adaptation of guideline recommendations.
- Trial findings were included in the 2010 Australian and New Zealand guidelines, endorsed by NHMRC, and were also included in the 2015 WHO Preterm Birth Guidelines.

[81] Crowther et al. (2003). Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomised controlled trial. JAMA November 26, 2003. Vol 290. No. 20. Correspondence with senior trial investigators. Doyle et al. (2009). Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database of Systematic Reviews, Issue 1. Bain et al. (2013). Implementation of a clinical practice guideline for antenatal magnesium sulphate for neuroprotection in Australia and New Zealand. Australian and New Zealand Journal of Obstetrics and Gynaecology 2013; 53: 86–89.

Outcome	Eligible population if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Magnesium sulfate (MgSO4) may prove important to paediatric outcomes in preterm infants. No serious harmful effects are seen.	Proportion of babies born <30 weeks' gestation 1.2% [82] Total no. of babies 309,489[83] N= 3,714	**Infants:** Total paediatric mortality, cerebral palsy, and the combined outcome of death or cerebral palsy at a corrected age of 2 years.	**Infants:** rates of major IVH, and neurosensory disability. **Mothers**: adverse cardiovascular and respiratory effects of the infusion, primary postpartum haemorrhage, and major postpartum haemorrhage.	Prior to the trial, MgSO4 was not being used as a neuroprotective agent. The trial, and combined meta-analysis, established the significance of the overall benefit of MgSO4 in reducing cerebral palsy and death in infants born very pre-term.	While not statistically significant, the outcome of death or cerebral palsy is clinically significant. Cerebral palsy is difficult to diagnose in infants. Therefore, the statistically significant outcome for substantial gross motor dysfunction (GMD) (believed to be an indicator for cerebral palsy) is used to support the significance of death or cerebral palsy. All patients with substantial GMD are captured by the numbers for patients with cerebral palsy. Average life expectancy of patients with cerebral palsy ~36 years.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Combined death or cerebral palsy	-18%	-103	-$17,633	-$2m	-$1,545,338	-$158m	-$160m
Change in intervention costs		+$1m						
Totals					-$2m		-$158m	-$159m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[82] Australian Research Centre for Health of Women and Babies 2010 https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp128_mag_sulphate_child.pdf
[83] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Combined death or cerebral palsy	Service cost: -$17,633 QALY: -$1,545,338	Combined outcome based on frequency of events. Of total 123 deaths or cerebral palsy, 87 (71%) were deaths, and 36 (29%) were cerebral palsy. No incremental service costs expected to be saved for deaths. Inclusion of ongoing care costs required would negate the value of saving a life. Treatment costs per year for cerebral palsy (~$1700) are based on the Access Economics (2008) report. Includes GP, medication, specialists, pathology, imaging, outpatient, aged care, allied health and aids and equipment. Costs are adjusted to 2014. Average life expectancy for cerebral palsy patients is 35.5 years based on Strauss et al. (2008) and Cumpston Sarjeant Consulting Actuaries (2014). Confirmed through interview. Combined disability weight for cerebral palsy (0.436) from Access Economics (2008) report Mathers et al. (1999) and WA CP Register (2006). Cerebral palsy is used as the baseline for infant deaths, such that infants who died would have otherwise had cerebral palsy (combined cerebral palsy disability weight used).	Access Economics (2008). The Economic Impact of Cerebral Palsy in Australia in 2007. Strauss D et al. (2008). Life expectancy in cerebral palsy: an update. Developmental Medicine & Child Neurology 50: 487-493. http://www.cumsar.com.au/docs/cerebral_palsy.pdf
Intervention cost	Service cost: +$570	MgSO4 pack cost ($30) – estimate provided by senior trial investigators. 4 hours nursing time to provide loading dose (at $135 per hour).	Informal estimate from community nursing provider sources $135 per hour.

2.10 PPROMT Trial (2015) – Immediate delivery compared with expectant management after preterm pre-labour rupture of the membraness close to term [84]

Context

- **Rupture of the membranes before the onset of labour complicates 1–2% of all pregnancies.**
- The PPROMT study arose because of wide variation in practice. For women near term, half of obstetricians (50%) would offer immediate delivery, and half (50%) would deliver the babies at term.
- It had become normal practice to advocate early planned birth, with the Royal College of Obstetricians and the American Congress of Obstetricians and Gynaecologists stating this in guidelines.
- The PPROMT trial findings were contrary to recommendations at that time: while the risk of infection does not differ between the two groups, fewer babies born to women managed expectantly had respiratory disease, and fewer required respiratory support. Fewer days were spent in a special care baby unit and in hospital. Women managed expectantly had a lower incidence of delivery by caesarean section (19% vs. 26%). Findings are being incorporated in to updated international guidelines.
- The trial was awarded the inaugural ACTA Clinical Trial of the Year Award in 2016. Professor Jonathan Morris, advocated for research, "…if we want a great health care system... an ever improving health system…it is clinical trials not clinical services that will effect most change…it is the application of trial findings not the application of technology that will guide a reduction in variation."
- Professor Morris noted the importance of the IMPACT network, which was "instrumental" in ensuring the PPROMT study was funded and commenced in Australia.

[84] Morris et al. (2015). Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. The Lancet Volume 387, No. 10017, p444–452, 30 January 2016. http://www.clinicaltrialsalliance.org.au/wp-content/uploads/2016/06/ACTA-acceptance.pdf Correspondence with senior trial investigators.

Outcome	Eligible population if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Expectant management should be followed except in signs of infection or foetal compromise. There are fewer C-section deliveries while immediate delivery increases risk of respiratory distress, mechanical ventilation and NICU length of stay in babies. . This must be balanced with greater ALOS in expectant deliveries and higher risk of intrapartum haemorrhage & fever.	Prevalence of preterm prelabour rupture of membranes 2% [85] Total no. of singleton births 300,148 [86] N= 6,003 (34-36wks and 6 days) singleton pregnancies. Aged over 16.	Incidence of neonatal sepsis.	**Infant:** Composite neonatal morbidity and mortality indicator; respiratory distress syndrome; any mechanical ventilation; NICU/SCN LOS. **Mothers:** antepartum or intrapartum haemorrhage, fever, postpartum treatment with antibiotics, and mode of delivery.	Meta-analysis conducted by trial authors found that immediate delivery does not reduce neonatal sepsis. Previous studies had sufficient power, and therefore applicability in the specific gestational period. Maternal sepsis outcome (even if no difference in comparative effectiveness) in addition to infant respiratory outcomes were key decision making drivers.	No increase in intervention costs of expectant management as this is absorbed in the average length of stay. No long-term impact of respiratory distress in babies. Birthweight outcome is a process/predictive measure. No difference in spontaneous versus induced births. Respiratory distress Rx with surfactant.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	No difference		-	-	-	-	-	-
Secondary	Respiratory distress	+60%	-121	-$500	<-$0.1m	-	-	<-$0.1m
	Mechanical ventilation	+36%	-127	-$2491	-$0.3m	-	-	-$0.3m
	Hospital LOS (baby) (days)	+2	-7,804	-$1183	-$9m	-	-	-$9m
	SCN or NICU LOS (days)	+2	-7,804	-$2971	-$23m	-	-	-$23m
	Ante/intrapartum haemorrhage	-42%	+83	+$6737	+$0.5m	+$2002	+$0.2m	+$0.2m
	Intrapartum fever	-62%	+47	-$205	<-$0.1m	-	-	<-$0.1m
	Hospital LOS (mother) (days)	-1	+3,902	+$2016	+$8m	-	-	+$8m
	Caesarean delivery	+40%	-287	-$7532	-$2m	-	-	-$2m
Change in intervention costs		Captured in study outcomes						
Totals					-$27m		+$0.2m	-$26m

Columns may not sum due to rounding. Negative values are savings in the calculations. Rx = Treatment. LOS = length of stay. SCN or NICU = Special care nursery or neonatal intensive care unit.

[85] SA Guidelines 2015. https://www.sahealth.sa.gov.au/wps/wcm/connect/2f46fd804eed9aacb052b36a7ac0d6e4/Preterm+Prelabour+Rupture+of+the+Membranes_Sept2015.pdf?MOD=AJPERES&CACHEID=2f46fd804eed9aacb052b36a7ac0d6e4

[86] AIHW (2015). Australia's mothers and babies 2013 in brief. Perinatal statistics series no. 31. Cat no. PER 72. Canberra: AIHW.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Respiratory distress	Service cost: -$500	The surfactant treatment, Survanta, is indicated for use in preterm infants in clinical guidelines and in the Western Australian and Victorian neonatal handbook of procedures. The cost relates to the cost of materials, and minimal ($100) clinician time, confirmed through interview.	Survanta (per vial, Beractant, Suspension;25mg/Ml;8ml;Vial) https://www.contractswa.finance.wa.gov.au/resources/Price_Matrix_-_HCNS110709.xls
Mechanical ventilation	Service cost: -$2,491	Costing estimate is based on NSW per hour average. It is expected that there is no additional cost for neonates compared to standard care costs. Confirmed through interview.	http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_007.pdf
Hospital LOS (baby) (days)	Service cost: -$1,183	Defined as total days from randomisation to delivery and from delivery to discharge – assuming no overlap with SCN/NICU. Costing from AR-DRG IHPA sources P67A to P68D.	ARDRG IHPA Version 7 Round 18.
SCN or NICU LOS (days)	Service cost: -$2,971	Casemix costs from Royal Women's Hospital. Includes overheads, clinician time and materials. Cross checked with NICU report QLD Health.	https://www.thewomens.org.au/patients-visitors/patient-fees/ 2016 fees & Beckmann et al. 2016 https://www.health.qld.gov.au/caru/networks/docs/NICU_report.pdf
Antepartum or intrapartum haemorrhage	Service cost: +$6,737 QALY: +$2,002	Expected incremental hospital costs of treatment while admitted. AR-DRG IHPA – 002A to 060C (complications versus counterfactual of none). Includes ICD-10-AM codes for intrapartum haemorrhage O67.0, O67.8 O67.9 and ICD-10-AM codes for antepartum haemorrhage O46.0, O46.8, O46.9. Disability weights for QALY based on AIHW 2010 data for maternal haemorrhage.	ARDRG IHPA Version 7 Round 18. OBPR VSLY guidance https://www.dpmc.gov.au/sites/default/files/publications/Value_of_Statistical_Life_guidance_note.pdf Mathers et al.1999. The burden of disease and injury in Australia. AIHW cat. no. PHE 17. Canberra: AIHW
Intrapartum fever	Service cost: -$205	Incremental costs expected to be negligible. Intrapartum antibiotics (benzylpenicillin or clindamycin). Cost of antibiotics, initial dose and 2 subsequent, materials (canula, saline flush etc.) 15 mins midwife time.	Cost-effectiveness of strategies to prevent infection http://www.thecie.com.au/wp-content/uploads/2014/08/CIE-Final-Report_-Economic-analysis-of-Group-B-streptococcus-screening.pdf
Hospital LOS (mother) (days)	Service cost: +$2016	From casemix funding O60A Vaginal Delivery with Complications. Highest costs per day taken here for conservatism. Cross checked with public sources (RWHOSP) for non-complicated deliveries.	ARDRG IHPA Version 7 Round 18 OBPR. https://www.thewomens.org.au/patients-visitors/patient-fees/

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Caesarean delivery	Service cost: -$7,532	Incremental difference between vaginal delivery (baseline) and caesarean delivery. Casemix funding.	ARDRG IHPA Version 7 Round 18. https://www.ihpa.gov.au/sites/g/files/net636/f/publications/ar-drg-v6_x-addendum.pdf
Intervention costs	Captured in trial outcomes	No incremental increase in intervention costs of expectant management as this will be absorbed in the average length of stay increase.	-

3 The ANZICS CTG – Trial level results

3.1 NICE-SUGAR Trial (2009) – Intensive versus conventional glucose control in critically ill patients [87]

Context

- **Hyperglycemia (high blood sugar) is common in acutely ill patients, including those treated in ICU.**
- Hyperglycemia is associated with increased morbidity and mortality in a variety of patient groups.
- Prior to the NICE-SUGAR trial, many professional organisations recommended tight glucose control for patients treated in ICU, though the evidence for this recommendation was not conclusive.
- While intensive glucose control was not standard practice in Australia prior to the trial, it was expected that international influence would have introduced it to Australia.
- The NICE-SUGAR trial shows that intensive glucose control increased mortality among adults in the ICU.
- Clinical guidelines have since changed worldwide, reflecting the results of the trial, and encouraging use of non-intensive glucose control in ICU patients.
- Non-intensive glycemic control remains in practice in Australia, with only minor changes in practice after the trial towards looser glycemic control.
- According to the implementation study by Kaukonen et al. (2013), ICUs who participated in the trial loosened their glucose control practice to a greater degree than ICUs who did not participate in the trial.

[87] NICE-SUGAR Study Investigators (2009). Intensive versus Conventional Glucose Control in Critically Ill Patients. N Engl J Med; 360:1283-97. Kaukonen et al. (2013). Glycaemic control in Australia and New Zealand before and after the NICE-SUGAR trial: a translational study. Critical Care 17:R215. Correspondence with senior ANZIC-RC investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
The trial shows a statistically significant difference in 90 -day mortality and survival time. No difference in ICU or hospital days, mechanical ventilation or morbidity is found.	Proportion of patients admitted to the ICU for at least 48 hours = 48%[88] Proportion excluded = 75%[89] Total number of adult ICU admissions = 123,564[92] N= 14,815[93]	Death from any cause within 90 days after randomisation .	Survival time during the first 90 days, cause-specific death and durations of mechanical ventilation, renal-replacement therapy and stays in the ICU and hospital.	Prior to the trial, many professional organisations recommended tight glucose control for patients treated in ICUs despite conflicting evidence. This trial shows that intensive glucose control increased mortality among ICU patients. Without this trial, tight glucose control would have been widely implemented in Australia.	Additional life expectancy for survivors is 4 years.[90] Survivors would not have ongoing costs of care. Lives saved are impaired.[91]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Death at day 90	-10%	-251	-	-	-$0.4m	-$110m	-$110m
Secondary	Severe hypoglycaemia	-1272%	-610	-$1,943	-$1m	-	-	-$1m
	Received corticosteroid	-9%	-277	-$7	<-$0.1m	-	-	<-$0.1m
Change in intervention costs		-$1m						
Totals					-$1m		-$110m	-$112m

Columns may not sum due to rounding. Negative values are savings in the calculations. ICU = intensive care unit.

[88] Correspondence with senior data managers from the ANZICS CORE.
[89] NICE-SUGAR Study Investigators (2009). Intensive versus Conventional Glucose Control in Critically Ill Patients. N Engl J Med; 360:1283-97. Note, this is assumed to be representative.
[90] Wright et al. (2003). Long-term survival following intensive care: Subgroup analysis and comparison with the general population. Anaesthesia. 58, pages 637–642.
[91] WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
[92] ANZICS CORE 2013/14 Annual Report http://www.anzics.com.au/Downloads/CORE%20Annual%20Report%202013-14.pdf
[93] Confirmed with senior ANZIC-RC investigators.

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Death at day 90	QALY: -$436,550	No incremental service costs are expected to be saved. Patients who would have otherwise died are impaired with moderate disability (estimated on age, APACHE II score and baseline characteristics). Many patients had respiratory or cardiovascular failure at baseline, and a high APACHE II score. For conservatism, it is assumed that these patients would have otherwise had a severe form of disability (equivalent to 0.37, the average WHO disability weight for stroke. 4-year additional life expectancy based on Wright et al. 2003 risk score estimates (for age group, APACHE II score and diagnosis hazard group). Confirmed through interview with senior trial investigators.	WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011. Wright et al. (2003) Long-term survival following intensive care: Subgroup analysis and comparison with the general population. Anaesthesia 58, pages 637–642.
Severe hypoglycaemia	Service cost: -$1,943	The incidence of severe hypoglycaemia is expected to increase costs (Krinsley et al. 2011). A UK study, McEwan et al. (2015), found that the total cost of an ICU patient with hypoglycaemia was 40% higher than an ICU patient without hypoglycaemia. For conservatism, 40% is applied to the ICU rate for 1 day rather than the full length of stay in ICU (median of 6 days), which was estimated by senior trial investigators to be too high in the Australian context. The national ICU rate of $200 per hour is based on IHPA 2015-16. “No long term sequelae of severe hypoglycaemia reported” stated in trial, therefore no QALY impact attributed. Confirmed through interview with senior trial investigators.	Krinsley et al. 2011 Mild hypoglycaemia is strongly associated with increased intensive care unit length of stay. Annals of Intensive Care 1:49. McEwan et al. (2015) Healthcare resource implications of hypoglycaemia-related hospital admissions and inpatient hypoglycaemia: retrospective record-linked cohort studies in England. BMJ Open Diabetes Research & Care. https://www.ihpa.gov.au/sites/g/files/net636/f/publications/national_pricing_model_technical_specifications_2015-16.pdf
Received corticosteroid	Service cost: -$7	Treatment with hydrocortisone sodium succinate based on NSW guidelines. PBS listing costs. Cost minimal. Confirmed through interview with senior trial investigators.	http://www.seslhd.health.nsw.gov.au/rhw/Newborn_Care/Guidelines/Medication/pdf/hydrosodium.pdf http://www.pbs.gov.au/medicine/item/1501B-1510L-3470P-5118J
Intervention costs	Service cost: -$146	Intervention cost is based on Van den Berghe study – a similar study of tight glycemic control in intensive care patients (excess treatment cost of intensive insulin therapy was 72 Euros per patient). Converted to Australian dollars. Confirmed through interview with senior trial investigators.	Van den Berghe et al. (2006) Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med. Vol. 34, No. 3.

3.2 DECRA Trial (2011) – Decompressive craniectomy in diffuse traumatic brain injury [94]

Context

- **Among patients who are hospitalised with severe traumatic brain injury (TBI), 60% either die or survive with disability. Approximately 1000 patients a year sustain a TBI.**
- Treatments minimise secondary brain injury such as intracranial hypertension caused by cerebral oedema.
- Where this first line medical therapy is not successful in reducing pressure, surgical intervention may be indicated.
- Decompressive Craniectomy (DC) is a neurosurgical process to remove part of the skull to reduce pressure on the brain.
- The use of this procedure was becoming more frequent.
- The DECRA trial shows that the treatment was potentially harmful.
- The current use of DC for diffuse TBI in clinical practice in Australia is unknown, because of the complexity of when it is and when it is not appropriate depending on individual circumstances and patient mix.
- The treatment is still indicated in some instances, but an increase in use is avoided and reduction in its use is generally expected.

[94] Cooper et al. (2011). Decompressive Craniectomy in Diffuse Traumatic Brain Injury. N Engl J Med 2011;364:1493-502. Myburgh et al. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862. Correspondence with senior ANZIC-RC investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Decompressive craniectomy (DC) decreases intracranial hypertension, but increases the risk of adverse events and poorer outcomes on the Extended Glasgow Outcome Scale (GOS-E) compared to standard care. ICU ALOS and days on mechanical ventilation are lower in DC.	Adults 15-59 TBI refractive intracranial hypertension = 956[95] Patients undergoing DC 12.1%[99] N= 116[100]	Death and Functional outcomes at 6 months on Extended Glasgow Outcome Scale (GOS-E).	ICU and Hospital Average Length of Stay (ALOS) medical or surgical complications days on mechanical ventilation.	The trial has resulted in a shift away from using Decompressive Craniectomy to reduce intracranial hypertension. In some instances, it is still indicated but a broad reduction is expected. Trial confirms control as approach of choice.	The analysis is based on functional outcomes, using GOS-E scores. Ongoing treatment costs are based on cost of services and equipment, by severity of disease.[96] Baseline of GOS-E 2-3 is used based on trial data and discussion with senior ANZIC-RC investigators. 10 years of survival/Rx.[97,98]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Death GOS-E 1	-1%	-1	-	-	-$599,652	-$0.6m	-$0.6m
	Functional outcomes GOS-E 2-4	+55%	-14	-$0.3m	-$4m	-$0.6m	-$9m	-$13m
Secondary	Mechanical Ventilation (days)	+27%	+301	+$2,491	+$0.7m	-	-	+$0.7m
	ICU Length of Stay (days)	+28%	+376	+$4,800	+$2m	-		+$2m
	Patients with complications	-94%	-15	-$13,118	-$0.2m	-$36,115	-$0.5m	-$0.7m
Change in intervention costs		-$3m						
Totals					-$2m		-$10m	-$15m

Columns may not sum due to rounding. Negative values are savings in the calculations. Rx = treatment

[95] Myburgh et al. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862.
[96] Access Economics Pty Limited for The Victorian Neurotrauma Initiative (2009). The economic cost of spinal cord injury and traumatic brain injury in Australia.
[97] Access Economics Pty Limited for The Victorian Neurotrauma Initiative (2009). The economic cost of spinal cord injury and traumatic brain injury in Australia.
[98] Brooks et al. (2015). Long-term survival after traumatic brain injury part II: life expectancy. Archives of Physical Medicine and Rehabilitation 96:1000-5.
[99] Myburgh et al. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862.
[100] Confirmed with senior ANZIC-RC investigators.

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Death GOS-E 1	QALY: -$599,652	At baseline, patients are expected to have severe TBI (or an Extended Glasgow Outcomes Scale (GOS-E) score of 2-4). No incremental service costs are expected to be saved. Inclusion of ongoing care costs required would negate the value of saving a life and are not included for this reason unless explicitly measured. Survivors would have severe TBI, with 10-year survival, based on Brooks et al. (2015) and Access Economics report. Confirmed with senior ANZIC-RC investigators. Disability weight for severe, long-term TBI, 0.625 (WHO).	Access Economics for The Victorian Neurotrauma Initiative (2009). The economic cost of spinal cord injury and traumatic brain injury in Australia Brooks et al. (2015). Long-term survival after traumatic brain injury part II: life expectancy. Archives of Physical Medicine and Rehabilitation 96:1000-5. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Functional outcomes GOS-E 2-4	Service cost: -$305,078 QALY: -$641,228	Standard care incrementally moves patients from GOS-E 2-4 group (severe TBI) to GOS-E 5-8 group (moderate TBI) (when compared to decompressive craniectomy). Incremental service costs for severe TBI over moderate TBI based on healthcare, long term care, and aids and equipment for 10 years (Access Economics report 2009). Additional 10-year survival based on Brooks et al. (2015) and Access Economics report. Confirmed with senior trial investigators. Disability weight based on incremental difference between WHO disability weights for moderate, long-term TBI (0.224) and severe, long-term TBI (0.625), equivalent to 0.401.	Access Economics for The Victorian Neurotrauma Initiative (2009). The economic cost of spinal cord injury and traumatic brain injury in Australia. Brooks et al (2015). Long-term survival after traumatic brain injury part II: life expectancy. Archives of Physical Medicine and Rehabilitation 96:1000-5. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Mechanical Ventilation (days)	Service cost: +$2,491	Costing estimate is based on NSW per hour average. Confirmed through interview.	http://www0.health.nsw.gov.au/policies/gl/2011/pdf/GL2011_007.pdf
ICU Length of Stay (days)	Service cost: +$4,800	National ICU rate of $200 per hour based on IHPA 2015-16. Confirmed through interview.	https://www.ihpa.gov.au/sites/g/files/net636/f/publications/national_pricing_model_technical_specifications_2015-16.pdf
Patients with complications	Service cost: -$13,118 QALY: -$36,115	Occurrence of complications used to determine weighted treatment costs and disability weights. Majority of complications costed using casemix funding (AR-DRG 801C in ICU). Average cost of cerebral infarction based on average cost of stroke in Tan Tanny et al. (2013). Average disability weight (0.20) based on WHO. Impairment is for one year.	IHPA NWAU calculator for acute activity 2016-17. Tan Tanny et al. (2013). Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke. Stroke. 44:2269-2274. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Intervention costs	Service cost: -$42,294	Average cost of intervention based on casemix funding for 2 cranial procedures (first procedure is the craniectomy to remove part of the skull and the second procedure is the cranioplasty to repair the skull 2-3 months later). Average of AR-DRG B02A, B02B, B02C = $42,294 per patient. Comparable to Western Australian study by Ho et al. 2011, ~USD $28,000.	IHPA NWAU calculator for acute activity 2016-17. Ho et al. (2011). Cost-Effectiveness of Decompressive Craniectomy as a Lifesaving Rescue Procedure for Patients With Severe Traumatic Brain Injury.

3.3 SAFE Trial (2004) – The SAFE study: saline vs. albumin for fluid resuscitation in the critically ill[101]

Context

- **Fluid resuscitation, (the administration of intravenous fluids to maintain or increase intravascular volume), is a common intervention, used for around 35% of patients in the ICU.**
- There has been enduring controversy as to the impact of the choice of resuscitation fluid on patients' outcomes.
- The SAFE study compared patient outcomes when 4% albumin or 0.9% sodium chloride (normal saline) is used for intravascular fluid resuscitation in ICU.
- The SAFE study found that using 4% albumin and normal saline results in equivalent 28-day all-cause mortality, as well as similar use of mechanical ventilation and renal replacement therapy, and similar length of stays.
- While the cost of production for albumin is higher than saline ($133/L compared to $2/L), the actual use of albumin in Australia has not fallen drastically since the SAFE study (36.6% of patients receiving fluid resuscitation received albumin in 2007 compared to 31.6% in 2013).
- This may be because albumin is provided free-of-charge to public hospitals in Australia.
- The study has however likely prevented an increase in use of albumin.

[101] SAFE Study Investigators (2004). A comparison of albumin and saline for fluid resuscitation in the Intensive Care Unit, N Engl J Med 2004;350:2247-56. Hammond et al. (2015). Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Med 41:1611–1619. Correspondence with senior ANZIC-RC investigators.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Albumin and saline results in equivalent mortality, and mechanical ventilation use, renal replacement therapy, length of stay in ICU and hospital. There is some evidence that trauma patients benefit more from resuscitation with saline than non-trauma patients, but this requires further study.	Total adult ICU admissions per year 123,564[102] Proportion of ICU patients receiving albumin for fluid resuscitation = 35%[105] N= 42,415	Death from all causes at 28 days after randomisation.	Survival time during the first 28 days, new organ failures, mechanical ventilation use, renal replacement therapy and length of ICU and hospital stay.	Enduring controversy on the impact of resuscitation fluid on patient outcomes. No statistically significant difference shown. Use of albumin has remained consistent since the trial, possibly indicating a preference for albumin, which is provided free-of charge at the point of use, to Australian public hospitals.[103,104]	Cost based on study fluid administered (saline and albumin) and packed red blood cells. No cost differences required for process measures (net fluid balance, heart rate on day 1, central venous pressure and serum albumin).

Outcome	Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary & Secondary	No statistically significant difference		-	-	-	-	-
Change in intervention costs	-$16m			-		-	
Totals							-$16m

Columns may not sum due to rounding. Negative values are savings in the calculations.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Intervention costs	Service cost: -$563	Average cost of intervention based on fluid and packed red blood cells administered (volumes administered as reported in the trial manuscript).	CSL Behring via National Blood Authority (albumin 4% 500mL $66.68) http://www.blood.gov.au/national-product-list Baxter product catalogue ($2.43/L saline) Leahy et al. (2012). From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice. Internal Medicine Journal.

[102] ANZICS CORE 2013/14 Annual Report http://www.anzics.com.au/Downloads/CORE%20Annual%20Report%202013-14.pdf
[103] Hammond et al. (2015). Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Med 41:1611–1619.
[104] Correspondence with senior ANZIC-RC investigators.
[105] Hammond et al. (2015). Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Med 41:1611–1619.

3.4 RENAL Trial (2009) – Intensity of continuous renal-replacement therapy in critically ill patients[106]

Context

- **Acute kidney injury is a finding among patients in ICU (affecting 5% of patients) and is an independent predictor of mortality.**
- The optimal approach to continuous renal replacement therapy (CRRT) for these patients, including its intensity and timing, was unclear.
- Emerging evidence was showing that increased intensity of RRT resulted in improved survival. It is assumed that augmented treatment would have become the norm without the trial.
- In the pre-RENAL practice survey, no Australian or New Zealand ICU reported prescribing CRRT according to patient weight.
- In the USA and in Europe, most practitioners prescribed at least 35mL/kg/hour.
- The RENAL study tested the impact of high (40ml/kg/h) versus low (25ml/kg/h) intensity RRT on patient outcomes.
- The study found that high intensity RRT does not reduce mortality at 90 days.
- A practice survey conducted in 2013/2014 found that half of ICUs in Australia and New Zealand report a weight-based dosing prescription, with the most common dose of RRT being 16-25ml/kg/h, followed by >25mL/ kg/hour.

[106] RENAL Replacement Study Investigators (2009) Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients. N Engl J Med;361:1627-38. Uchino et al. (2005). Acute Renal Failure in Critically Ill Patients. JAMA 294:813-818. [106] RENAL Study Investigators (2008). Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. Crit Care Resusc 10:225-230. [106] Overberger et al. (2007). Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. Clin J Am Soc Nephrol 2:623-30. Jones & Devonald (2013). How acute kidney injury is investigated and managed in UK intensive care units – a survey of current practice. Nephrol Dial Transplant 28:1186-90.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Higher-intensity treatment does not decrease mortality compared to lower-intensity treatment. No significant differences in the rate of recovery (i.e., cessation of dialysis because it was no longer needed) or in the occurrence of organ failure, mechanical ventilation use, ICU or hospital length of stay was found.	ICU patients affected by acute renal failure per year = 5%[107] Adult ICU admissions = 123,564[109] N= 6,178	Death from any cause within 90 days after randomisation.	Death within 28 days, death in the ICU/ hospital, cessation of RRT, ICU and hospital LOS, duration of mechanical ventilation and RRT, dialysis status at day 90 and any new organ failures.	The trial showed that there is no significant difference between the control (cheaper) and the treatment. Without the trial, the treatment would have been implemented.	Main clinical outcome of difference between groups was the rate of hypophosphatemia (negligible cost). Hypophosphataemia episodes were acute and returned to normal within 24 hours in most cases.[108]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	No statistically significant difference	-	-	-	-	-	-	-
Secondary	Hypophosphatemia	+21%	+445	+$517	+<$0.2m	-	-	+<$0.2m
Change in intervention costs		-$7m					-	
Totals					+<$0.2m			-$7m

Columns may not sum due to rounding. Negative values are savings in the calculations. ICU = intensive care unit.

[107] Uchino et al. (2005). Acute Renal Failure in Critically Ill Patients. JAMA 294:813-818.
[108] Follow up of RENAL study trial patients in Bellomo et al. (2014) The relationship between hypophosphataemia and outcomes during low-intensity and high-intensity CRRT. Crit Care Resus 16:34-41.
[109] ANZICS CORE 2013/14 Annual Report http://www.anzics.com.au/Downloads/CORE%20Annual%20Report%202013-14.pdf

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Hypophosphatemia	Service cost: +$517	Treatment with IV potassium phosphate. Expected to be minimal cost, based on Xie et al. (2011). Additional 2 hours of clinician time to administer IV and monitor patient. French et al. (2004). No long-term or QALY impairment, as most resolved within 24 hours (Bellomo et al. 2014). Control prevalence is representative of the general population.	Xie et al. (2011), Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases. J Manag Care Pharm 17(8):621-34. French & Bellomo (2004). A rapid intravenous phosphate replacement protocol for critically ill patients. Crit Care Resusc 6:175-179. Bellomo et al (2014), The relationship between hypophosphataemia and outcomes during low-intensity and high-intensity CRRT. Crit Care Resusc 16:34-41.
Intervention costs	Service cost: -$1,200	Daily rate based on Bellomo (2006). Captures all differences in cost of treatment between intervention and control groups (e.g. consumables). Days on renal replacement therapy provided in the trial manuscript.	Bellomo (2006). Do we know the optimal dose for renal replacement therapy in the intensive care unit? Kidney International 70:1202-1204.

3.5 CHEST Trial (2012) – Hydroxyethyl starch or saline for fluid resuscitation in intensive care[110]

Context

- **The administration of intravenous fluids to maintain or increase intravascular volume is a common intervention in the ICU.**
- There has been enduring controversy as to the impact of the choice of resuscitation fluid on patients' outcomes.
- Prior to the trial, hydroxyethyl starch (HES) was not used widely in Australia due to the lack of evidence regarding its safety. Hydroxyethyl starch was not licensed in Australia until 2008.
- At the time, the CHEST trial received one the highest NHMRC grants ever awarded. The trial also received sizeable, unrestricted funding from pharmaceutical company Fresenius Kabi.
- The CHEST trial shows that there is no significant difference in 90-day mortality between patients who receive fluid resuscitation with hydroxyethyl starch compared to patients who receive normal saline. However, more patients who receive fluid resuscitation with hydroxyethyl starch are treated with renal replacement therapy.
- The use of hydroxyethyl starch remains low in Australia.
- National proprietary sales data was used to determine a 67% reduction in use of hydroxyethyl starch in Australia between 2012-2013 and 2013-2014.

[110] Myburgh et al. (2012). Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med;367:1901-11. Correspondence with senior trial investigators. Glassford et al. (2016). Changes in intravenous fluid use patterns in Australia and New Zealand: evidence of research translating into practice. Crit Care Resusc Hammond et al. (2015). Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Med 41:1611–1619.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
There is no significant difference in mortality between treatment and control groups.More patients in the treatment group however are treated with renal replacement therapy, and there are also more adverse events in the treatment group. Renal injury is more likely in the control group.	Patients receiving fluid resuscitation in ICU 35%[111]. Proportion excluded = 32%[112] Adult ICU admissions = 123,564[114] N= 29,566	Death within 90 days	Incidence of acute kidney injury, use of RRT, new organ failures, duration of mechanical ventilation and RRT; and cause-specific mortality.	The trial was undertaken in a starch-naïve society (starch not licensed until 2008 in Australia). There is now no use of starch in Australian ICUs. Without the trial, starch would have become standard practice in Australia.	Renal failure indicated by use of RRT. Pruritus not clinically significant (resolves and has other causes).[113]

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	No statistically significant differences	-	-	-	-	-	-	-
Secondary	Included as intervention cost	-	-	-	-	-	-	-
Change in intervention costs		-$38m			-		-	
Totals								-$38m

Columns may not sum due to rounding. Negative values are savings in the calculations. RRT = renal replacement therapy. ICU = intensive care unit. **If the unrestricted commercial funding amount described above is included, total funding to the CHEST trial will amount to approx. $10m, and the Net Profit will be $27m. The overall consolidated Benefit to Cost ratio will be 4.6:1 (if commercial funding from the PROGRESS trial within the ASTN is also included).

[111] Hammond et al. (2015). Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Med 41:1611–1619.
[112] Myburgh et al. (2012). Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901-11. Note, this is assumed to be representative.
[113] Correspondence with senior trial investigators.
[114] ANZICS CORE 2013/14 Annual Report http://www.anzics.com.au/Downloads/CORE%20Annual%20Report%202013-14.pdf

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Intervention costs	Service cost: -$1,964	Average incremental cost of intervention based on fluid administered (PBS and Baxter costs), ICU stay and capital costs of service provision. Volume of fluid use and cost evens out at 4 to 1 saline to starch. ICU stay cost covers additional staffing, renal replacement therapy costs in particular, and organ failures, as these are treated in ICU and are resolved during ICU stay. Confirmed with senior trial investigators. Costing impact of pruritus is omitted as it is expected to be negligible and of questionable clinical significance to the intervention. Confirmed through interview. National ICU rate of $200 per hour based on IHPA 2015-16. Confirmed through interview.	Baxter product catalogue ($2.43/L saline) Hydroxyethyl starch 130/0.4 I.V. infusion 30 g per 500 mL ($38.50) mLhttp://www.pbs.gov.au/medicine/item/9487H https://www.ihpa.gov.au/sites/g/files/net636/f/publications/national_pricing_model_technical_specifications_2015-16.pdf

Addendum: A costing paper for CHEST was released after these results were finalised.[115] This paper indicated that, at 6 months, the mean total costs of resource use in the ICU were $2,721 higher in the hydroxyethyl starch group than the saline group. Using this per patient amount, the net benefit would be $43m. The results of the Taylor et al. (2016) paper were not statistically significant (p=0.08). Overall hospital costs were similar between the two groups. The results presented above have not been updated with the findings of the paper.

[115] Taylor et al. (2016). Hydroxyethyl starch versus saline for resuscitation of patients in intensive care: long-term outcomes and cost-effectiveness analysis of a cohort from CHEST. Lancet Respir Med.

3.6 ARISE Trial (2014) – Goal-directed resuscitation for patients with early septic shock[116]

Context

- **Despite decreasing mortality from severe sepsis in recent years, the risk of death remains high.**
- Management of sepsis requires early recognition, control of the source of infection, appropriate and timely administration of antimicrobial drugs, and resuscitation with intravenous fluids and vasoactive drugs.
- An randomised controlled trial in the USA showed that a specific protocol of early hemodynamic resuscitation, termed early goal-directed therapy (EGDT), could improve outcomes in patients presenting to ED with sepsis (Rivers et al. 2001).
- Globally, EGDT was becoming increasingly common, however, it had not yet been implemented in Australia and was not routinely used.
- There were concerns about its risks, the external validity of the original trial, and about the costs and resources required for its implementation.
- The ARISE trial shows that EGDT does not reduce all-cause mortality at 90 days.
- The trial provided evidence to shift away from implementation of EGDT, which carried additional costs, in Australia.

[116] ARISE Investigators (2014). Goal-directed resuscitation for patients with early septic shock. N Engl J Med 371:1496-506. Correspondence senior trial investigators. Peake et al. (2009). Australian resuscitation of sepsis evaluation (ARISE): A multi-centre, prospective, inception cohort study. Resuscitation 80:811-818. Rivers et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med;345:1368-77.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
There are no significant differences for mortality at 90 days, nor survival time, in-hospital mortality, duration of organ support, and length of hospital stay. There is a marginal reduction in time spent in the Emergency Department (ED), which is not considered to be sufficient to justify intervention with EGDT.	Patients admitted to ICU = 123,564[117] Proportion diagnosed with severe sepsis = 3%[119] N= 3,648	All-cause mortality within 90 days after randomisation.	Survival time to 90 days; mortality; LOS in the ED, ICU, or hospital; mechanical ventilation, vasopressor support, or RRT; adverse events.	The trial has resulted in a shift away from using Early Goal Directed Therapy for patients with early septic shock. Trial confirms control as approach of choice.	Increased treatment costs for EGDT driven by transfusions, dobutamine and intravenous fluids, time and materials.[118] ED time is costed separately to the intervention as it was a statistically significant finding. Change in ED time however, may be an artefact of patients from both groups being part of the trial (and therefore experiencing more efficient care coordination).

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	No statistically significant difference		-	-	-	-	-	-
Secondary	Duration in ED (hours)	+0.6	+1,423	+$200	+$0.3m	-	-	+$0.3m
Change in intervention costs		-$1.5m					-	
Totals					+$0.3m			-$1.2m

Columns may not sum due to rounding. Negative values are savings in the calculations. EGDT = early goal directed therapy. ED = emergency department. LOS = length of stay. ICU = intensive care unit. RRT = renal replacement therapy.

[117] ANZICS CORE 2013-2014 Annual Report http://www.anzics.com.au/Downloads/CORE%20Annual%20Report%202013-14.pdf
[118] Correspondence with senior trial investigators.
[119] Peake et al. (2009). Australian resuscitation of sepsis evaluation (ARISE): A multi-centre, prospective, inception cohort study. Resuscitation 80:811-818.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Duration in ED (hours)	Service cost: +$200	Average service cost based on IHPA Australian Public Hospitals Costs Report and AIHW average attendance cost and average ED stay. No QALY impairment attributed.	IHPA Australian Public Hospitals Cost Report 2013-2014 Round 18. https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc-round18.pdf http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129543146
Intervention costs	Service cost: -$632	Each individual component of the intervention has been costed to determine the overall incremental service cost of EGDT over usual care. Costs of catheters and clinician time estimates were obtained from current PhD level research being undertaken at Monash University Department of Epidemiology and Preventive Medicine. Volumes of fluids administered as reported in the trial. Total has been sense checked by senior trial investigators from the ANZIC-RC.	CSL Behring via National Blood Authority (albumin 4% 500mL $66.68) http://www.blood.gov.au/national-product-list Baxter product catalogue ($2.43/L saline) Leahy & Mukhtar (2012) From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice. Internal Medicine Journal. Informal estimate from community nursing provider sources $135 per hour.

3.7 EPO-TBI Trial (2015) – Erythropoietin in traumatic brain injury: a double-blind randomised controlled trial[120]

Context

- **Among patients who are hospitalised with severe traumatic brain injury (TBI), 60% either die or survive with disability. Approximately 1000 patients a year sustain a TBI.**
- Treatments can minimise secondary brain injury. It was hypothesised that erythropoietin (EPO) may improve functional outcomes, based on results in animal models with traumatic brain injury.
- The EPO-TBI trial shows that erythropoietin does not reduce the number of patients with severe neurological dysfunction.
- The EPO-TBI trial provides the evidence to disinvest in a treatment that would have otherwise been costly.
- Erythropoietin was not routinely used in Australia prior to the trial.
- The results of the trial have stopped widespread implementation of treatment with EPO in patients with traumatic brain injury.

[120] Nichol et al. (2015) Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 2015. 386: 2499-506. Myburgh et al. (2008) Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862. Correspondence with senior ANZIC-RC investigators. Bramlett HM et al. (2004). Pathophysiology of cerebral ischemia and brain trauma: similarities and differences. J Cereb Blood Flow Metab; 24: 133–50

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Compared with placebo, erythropoietin (EPO) does not reduce the proportion of patients with an Extended Glasgow Outcome Scale level of 1-4. Erythropoietin does not significantly affect 6-month mortality, or increase the occurrence of deep venous thrombosis of the lower limbs.	Severe and moderate TBI = 1671 [121] Proportion excluded = 78%[122] N= 360	Patients' neurological status at 6 months, in patients with moderate and severe traumatic brain injury.	Neurological outcome, 6-month mortality, proximal deep venous thrombosis, and an occurrence of a composite thrombotic outcome.	The EPO-TBI trial provides the evidence to disinvest in a treatment that would have otherwise been costly.	The trial does not support the use of EPO in TBI. While the adjusted mortality at 6 months is statistically significant, the trial manuscript highlights this was exploratory only, and the effect on mortality remains uncertain. The adjusted mortality at 6 months is not thought to influence an increase in EPO use. Intervention cost based on unit cost of erythropoietin and minimal administration time.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Not statistically significant	-	-	-	-	-	-	-
Change in intervention costs		-$0.3m			-		-	
Totals								-$0.3m

Columns may not sum due to rounding. Negative values are savings in the calculations.

Health Service or Outcome	Health service/ outcome cost per person or day	Explanation and costing assumptions	Reference
Intervention costs	Service cost: -$1,191	Average cost of intervention based on incremental cost of 2 doses of erythropoietin (Erythropoietin (epoetin alfa 40,000 units subcutaneously, Eprex Janssen-Cilag Pty Ltd) over saline. Minimal administration time. Confirmed through interview.	Baxter product catalogue ($2.43/L saline) http://www.pbs.gov.au/info/industry/pricing/pbs-items/f1-5percent-spr-1-april-2016

[121] Myburgh et al. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862.
[122] Nichol et al. (2015). Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 2015. 386: 2499-506. Note, this is assumed to be representative.

3.8 SAFE-TBI Trial (2007) – Saline or albumin for fluid resuscitation in patients with traumatic brain injury[123]

Context

- In patients with traumatic brain injury, resuscitation fluids are fundamental components of the restoration and maintenance of systemic and cerebral circulation.
- While the SAFE study showed no overall statistically significant difference in mortality among patients who received albumin compared to those who received saline, there was evidence to suggest higher mortality in the subset of patients from this study, that had suffered traumatic brain injury.
- The SAFE-TBI study was a post-hoc follow up study of patients from the SAFE study who had traumatic brain injury.
- The study found that patients with severe traumatic brain injury who are treated with albumin have a higher 28-day mortality rate.
- Work is being undertaken to determine the impact of the trial on current fluid practices in traumatic brain injury patients. It is expected that the trial has at least prevented an increase in use in this patient cohort, if not considerably reduced it.

[123] SAFE Study Investigators (2007). Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury. SAFE Study Investigators (2004). A comparison of albumin and saline for fluid resuscitation in the Intensive Care Unit, N Engl J Med; 350:2247-56. Correspondence with senior trial investigators. Hammond et al. (2015). Resuscitation fluid use in Australian and New Zealand Intensive Care Units between 2007 and 2013. Intensive Care Med 41:1611–1619.

Outcome	Eligible participants if implemented	Primary outcomes	Secondary outcomes	Clinical context	Main clinical assumptions
Fluid resuscitation with albumin is associated with higher mortality rates than resuscitation with saline.	Incidence of TBI = 1671 [124] Proportion severe TBI = 57% [125] N= 956	Mortality rate and functional neurologic outcome 24 months after randomisation.	Primary and secondary cause of death.	The trial showed that the control was better than treatment. Fluid resuscitation with albumin would have continued or increased without the trial. Work is underway to assess the actual change in uptake rates.	Survivors would have 10 years of impaired survival. Functional outcomes remain steady for 2 years (the follow up period for the study). Baseline Glasgow Coma Scale score of 7 is equivalent to an Extended Glasgow Outcomes Scale score of 2-4.

Outcome		Difference in risk between control and treatment	N if implemented at 65%	Health service cost per person or day	Economic Impact on health service costs if implemented	QALY impact per person	Economic impact on QALYS if implemented	Total Economic Impact
Primary	Death within 24 months	-56%	-74	-	-	-$0.6m	-$45m	- $45m
	Functional outcomes GOS-E 2-4	-22%	-83	-$0.3m	-$25m	-$0.1m	-$12m	-$37m
Change in intervention costs		-$0.4m						
Totals					-$25m		-$56m	-$82m

Columns may not sum due to rounding. Negative values are savings in the calculations.

[124] Myburgh et al. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862.
[125] Myburgh et al. (2008). Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. J Trauma 64:854-862.

Health Service or Outcome	Health service/outcome cost per person or day	Explanation and costing assumptions	Reference
Death within 24 months	QALY: -$599,652	At baseline, patients have a median Glasgow Coma Scale score of 7, which is broadly equivalent to severe TBI (or an Extended Glasgow Outcomes Scale (GOS-E) score of 2-4). No incremental service costs expected to be saved. Inclusion of ongoing care costs required would negate the value of saving a life and are not included for this reason unless explicitly measured. Survivors would have severe TBI, with 10-year survival, based on Brooks et al. (2015) and Access Economics report. Confirmed with senior ANZIC-RC investigators. Disability weight for severe, long-term TBI, 0.625 (WHO).	Access Economics for The Victorian Neurotrauma Initiative (2009). The economic cost of spinal cord injury and traumatic brain injury in Australia. Brooks et al. (2015). Long-term survival after traumatic brain injury part II: life expectancy. Archives of Physical Medicine and Rehabilitation 96:1000-5. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Functional outcomes GOS-E 2-4	Service costs: -$305,078 QALY: -$143,838	Resuscitation with saline incrementally moves patients from GOS-E 2-4 group (severe TBI) to GOS-E 5-8 group (moderate TBI). Incremental service costs for severe TBI over moderate TBI based on healthcare, long term care, and aids and equipment for 10 years (Access Economics report 2009). 2 years of steady functional outcomes used for QALY calculation in the absence of long-term functional outcomes for these patients. Patients expected to have longer life expectancy than DECRA and EPO-TBI cohorts. Incremental difference between WHO disability weights for moderate, long-term TBI (0.224) and severe, long-term TBI (0.625), equivalent to 0.401.	Access Economics for The Victorian Neurotrauma Initiative (2009). The economic cost of spinal cord injury and traumatic brain injury in Australia. Brooks et al. (2015). Long-term survival after traumatic brain injury part II: life expectancy. Archives of Physical Medicine and Rehabilitation 96:1000-5. WHO (2013). WHO methods and data sources for global burden of disease estimates 2000-2011.
Intervention costs	Service cost: -$587	Average cost of intervention based on fluid administered, packed red blood cells given and any relevant incremental increase in clinician time.	CSL Behring via National Blood Authority (albumin 4% 500mL $66.68) http://www.blood.gov.au/national-product-list Baxter product catalogue ($2.43/L saline) Leahy et al. (2012). From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice. Internal Medicine Journal.

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