

Very large treatment effects in randomised trials as an empirical marker to indicate whether subsequent trials are necessary: meta-epidemiological assessment

Appendix: ONLINE SUPPLEMENTAL DATA

Myura Nagendran, MA, MRCP¹

Tiago V Pereira, PhD²

Grace Kiew, BA³

Douglas G Altman, DSc⁴

Mahiben Maruthappu, MA, BM BCh⁵

John P A Ioannidis, MD, DSc⁶

Peter McCulloch, MD, FRCSEd⁷

1. Division of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, UK
2. Health Technology Assessment Unit, Institute of Education and Sciences, Hospital Alemão Oswaldo Cruz, Sao Paulo, Brazil
3. Gonville and Caius College, University of Cambridge, UK
4. Centre for Statistics in Medicine, Oxford, UK
5. North West Thames Foundation School, London, UK
6. Departments of Medicine, of Health Research and Policy, and of Statistics, and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, USA
7. Nuffield Department of Surgical Science, University of Oxford, UK

TABLE LEGENDS

Table S1. Intervention and comparator information for upheld index trial VLEs.

Abbreviations: ARD, absolute risk difference; CDSR ID, Cochrane database of systematic reviews identification; CI, confidence interval; RR, relative risk; VLE, very large effect.

Table S2. Intervention and comparator information for refuted index trial VLEs.

Abbreviations: ARD, absolute risk difference; CDSR ID, Cochrane database of systematic reviews identification; CI, confidence interval; RR, relative risk; VLE, very large effect.

Table S3. Number of large trials refuting index trial VLEs. Abbreviations: CDSR ID, Cochrane database of systematic reviews identification

NOTE REGARDING REFERENCES

References have been included in the supplement for the Cochrane reviews from which all index trials and subsequent large trials originate.

Individual references for index and large trials have not been listed here. When extracting data for analysis, Cochrane reviewers use every available source (published full text original article, published subsequent full-text analysis, published abstract, unpublished data).

In many cases, there are several sources for a single trial. Hence, it is best to locate the sources directly from the reference list of the Cochrane review and we have not duplicated this work here.

Table S1. Intervention and comparator information for upheld index trial VLEs.

Cochrane review information				Index trial				Large trial data				Reference
CDSR ID	Population	Intervention	Outcome	RR	95% CI	ARD	95% CI	RR	95% CI	ARD	95% CI	
CD004181	Patients at the stage of pre- exposure or post-exposure of hepatitis A (infectious hepatitis)	No intervention, placebo or control vs. immunoglobulins	Number with hepatitis A or infectious hepatitis at 6-12 months	5.03	3.18-7.94	0.01	0.00 to 0.01	1.94	1.74-2.17	0.00	0.00 to 0.01	1
CD004736	Pregnant women	Daily iron vs. placebo/no intervention	Haemoconcentration (i.e. Hb rise) during second or third trimester	5.08	1.87-14.64	0.15	0.07 to 0.24	5.66	4.26-7.52	0.57	0.52 to 0.63	2
CD001290	Asthmatic children at risk of asthma-related emergency department attendance	Control vs. education (any type)	Emergency Department visits	5.17	2.35-11.76	0.31	0.19 to 0.43	1.37	1.12-1.68	0.15	0.06 to 0.24	3
CD006936	Adult smokers	Motivational interviewing vs. brief advice/usual care	Abstinence at maximal follow up	5.28	1.75-17.92	0.15	0.07 to 0.23	1.21	1.05-1.39	0.03	0.01 to 0.05	4
CD001886	Adults requiring surgery	Control vs. aprotinin (anti-fibrinolytic)	No. exposed to allogeneic blood	5.33	1.10-90.83	0.54	0.16 to 0.93	1.47	1.31-1.66	0.17	0.12 to 0.23	5
CD004386	Patients with cancer and neutropenia	Intervention vs. quinolone antibiotic	Febrile episodes	5.33	2.04-17.49	0.62	0.38 to 0.85	1.39	1.11-1.74	0.05	0.02 to 0.09	6
CD007277	Adults with rheumatoid arthritis	Abatacept vs. placebo	ACR 50% improvement	5.40	2.32-14.04	0.17	0.11 to 0.22	2.37	1.72-3.26	0.23	0.16 to 0.30	7
CD006063	Adults with type 2 diabetes mellitus	Rosiglitazone vs. control	Oedema	5.61	1.79-18.36	0.09	0.04 to 0.14	1.65	1.34-2.04	0.06	0.03 to 0.08	8
CD003756	Children living in malaria endemic regions	Placebo vs. intermittent preventive treatment with antimalarial	Clinical malaria	5.64	4.10-7.76	0.34	0.29 to 0.39	1.13	1.01-1.26	0.07	0.01 to 0.13	9

CD000022	Adults receiving intensive care	No prophylaxis vs. topical plus systemic antibiotic	Respiratory tract infections	6.46	2.86-15.87	0.56	0.40 to 0.72	1.66	1.36-2.02	0.23	0.14 to 0.31	10
CD003611	Adults undergoing heart surgery	Control vs. all treatments	Post operative atrial fibrillation	7.32	2.08-35.41	0.34	0.19 to 0.50	1.25	1.05-1.48	0.08	0.02 to 0.14	11
CD003221	Adults with migraine pain of moderate to severe intensity	Rizatriptan vs. placebo	Pain-free response at 2 hours	7.32	2.45-25.79	0.22	0.12-0.32	4.23	2.96-6.03	0.32	0.26 to 0.38	12
CD000262	Adult pregnant women	Placebo/control vs. any antibiotic	Failure of test of cure of bacterial vaginosis	7.58	3.47-18.72	0.75	0.60 to 0.89	2.87	2.54-3.24	0.37	0.34 to 0.41	13
CD001478	Children at risk of whooping cough	Whole cell vaccine vs. acellular vaccine	Primary series non-completion due to adverse events	7.59	1.63-42.27	0.05	0.00 to 0.11	1.82	1.43-2.33	0.00	0.00 to 0.00	14
CD006743	Patients with acute cardiovascular event	Control vs. nitrates	All-cause mortality at 2 days	7.90	1.27-99.80	0.04	0.01 to 0.08	1.22	1.11-1.35	0.00	0.00 to 0.01	15
CD000146	Adult smokers	Nicotine replacement therapy (patch) vs. placebo/control	Smoking cessation at >6 months follow up	8.21	2.18-39.39	0.18	0.08 to 0.28	1.54	1.34-1.77	0.07	0.05 to 0.09	16
CD003897	Kidney transplant recipients	Placebo or no treatment vs. IL2Ra	Biopsy-proven acute rejection at 1 year	8.80	1.17-∞	0.36	0.09 to 0.63	1.43	1.14-1.79	0.08	0.03 to 0.13	17
CD008521	Children	Placebo vs. rotarix (RV1) vaccine	Rotavirus diarrhoea of any severity up to 1 year	9.08	2.41-42.30	0.15	0.07 to 0.23	2.15	1.75-2.63	0.06	0.05 to 0.08	18
CD004352	Pregnant women in spontaneous preterm labour	Placebo vs. all betamimetics	Birth within 48 hours of treatment	10.00	1.99-183.52	0.60	0.33 to 0.87	1.66	1.30-2.12	0.14	0.08 to 0.21	19
CD001841	Adults requiring first line anti-hypertensive treatment	Placebo vs. high dose thiazide	Total cardiovascular events	11.47	1.97-204.42	0.14	0.05 to 0.23	1.25	1.03-1.51	0.01	0.00 to 0.01	20
CD004125	Patients undergoing general anaesthesia, regional anaesthesia or sedation	Placebo vs. ondansetron	Nausea	13.00	2.57-224.97	0.60	0.37 to 0.83	1.24	1.02-1.52	0.10	0.01 to 0.19	21
CD004604	Adults with moderate to severe postoperative pain	Rofecoxib vs. placebo	>50% pain relief over 4 to 6 hours	23.00	4.42-393.80	0.69	0.52 to 0.85	8.40	5.48-12.87	0.55	0.50 to 0.61	22

CD007223	Women being treated for spontaneous miscarriage	Surgery vs. misoprostol	Surgical evacuation	24.79	9.79-67.48	0.89	0.82 to 0.96	18.00	10.39-31.21	0.94	0.90 to 0.97	23
CD006060	Adults with type 2 diabetes mellitus	Pioglitazone vs. control	Oedema	30.98	3.93-∞	0.04	0.02 to 0.06	1.67	1.47-1.88	0.09	0.07 to 0.11	24
CD003775	Patients with chronic renal failure who are seronegative for HBsAg	Plasma vaccine vs. placebo	Seroconversion to anti-HBs	48.64	6.47-∞	0.36	0.25 to 0.47	21.43	11.83-38.84	0.35	0.31 to 0.38	25

Table S2. Intervention and comparator information for refuted index trial VLEs.

Cochrane review information				Index trial				Large trial data				Reference
CDSR ID	Population	Intervention	Outcome	RR	95% CI	ARD	95% CI	RR	95% CI	ARD	95% CI	
CD001960	Adults with dyspepsia symptoms	Placebo vs. prokinetic	Global symptom assessment	5.21	2.55-11.83	0.57	0.41 to 0.74	1.04	0.92-1.18	0.02	-0.04 to 0.07	26
CD001090	Patients with sepsis or septic shock	Placebo vs. IVIg	Mortality	5.34	1.41-26.16	0.26	0.08 to 0.43	1.05	0.86-1.29	0.02	-0.06 to 0.10	27
CD007176	Adult	Placebo vs. antioxidant	Mortality	5.44	1.38-21.96	0.03	0.00 to 0.06	1.05	1.03-1.08	0.01	0.00 to 0.01	28
CD004183	Adults at high risk of developing gastrointestinal cancer	Placebo vs. antioxidant	Gastrointestinal cancers at follow-up	5.46	1.18-30.09	0.08	0.01 to 0.16	1.09	0.95-1.25	0.00	-0.00 to 0.00	29
CD001928	Patients with presumed or definite acute ischemic stroke	Control vs. calcium antagonists	Poor outcome at end of follow up	5.61	1.56-25.19	0.32	0.12 to 0.51	1.01	0.94-1.09	0.01	-0.03 to 0.04	30
CD001090	Patients with sepsis or septic shock	Placebo vs. IVIg	Mortality	6.63	1.26-91.41	0.40	0.14 to 0.66	1.04	0.96-1.13	0.02	-0.02 to 0.05	27
CD001188	Adult smokers	Nursing interventions vs. control	Smoking cessation	7.54	2.48-24.62	0.15	0.08 to 0.21	1.12	0.90-1.41	0.03	-0.03 to 0.10	31
CD001150	Preterm infants	Control vs. topical ointment	Any bacterial infection	8.00	1.37-103.53	0.23	0.06 to 0.40	1.26	1.02-1.56	0.05	0.01 to 0.10	32
CD003180	Adults	Intervention vs. usual care	Self-reported physical activity	8.00	1.60-125.80	0.26	0.15 to 0.37	1.03	0.91-1.15	0.01	-0.04 to 0.06	33
CD002755	Patients with suspected or proven myocardial infarction	Placebo vs. magnesium	Mortality	8.49	1.43-139.72	0.15	0.04 to 0.26	1.01	0.97-1.07	0.00	-0.00 to 0.01	34
CD001141	Women intending to breastfeed their babies	Usual care vs. support	Cessation of breastfeeding	8.64	1.51-136.30	0.28	0.09 to 0.48	1.07	1.02-1.13	0.04	0.01 to 0.06	35
CD004227	Pregnant women at risk of developing pre-eclampsia	Placebo vs. antioxidant	Pre-eclampsia	9.73	1.08-∞	0.08	0.00 to 0.17	1.03	0.85-1.24	0.00	-0.02 to 0.03	36

CD001058	Women with preterm membrane rupture	Antibiotics vs. placebo	Perinatal death	12.55	1.58-∞	0.21	0.05 to 0.37	1.06	0.83-1.36	0.00	-0.02 to 0.01	37
CD003246	Pregnant women due for third trimester induction of labour	Oxytocin vs. placebo or expectant management	Caesarean section	13.00	1.66-∞	0.30	0.09 to 0.51	1.04	0.82-1.31	0.00	-0.02 to 0.03	38
CD002138	Adults undergoing coronary artery bypass grafting	Normothermia vs. hypothermia	Composite poor outcome	13.00	1.67-∞	0.27	0.08 to 0.47	1.08	0.94-1.24	0.02	-0.05 to 0.01	39
CD004659	Pregnant women at risk of developing pre-eclampsia	Placebo vs. antiplatelet	Proteinuric pre-eclampsia	13.85	1.70-∞	0.13	0.03 to 0.24	1.12	0.99-1.26	0.01	-0.00 to 0.02	40
CD000567	Critically ill patients	Colloids vs. crystalloids	Mortality	15.00	1.92-∞	0.26	0.09 to 0.43	1.00	0.92-1.09	0.00	-0.02 to 0.02	41
CD001287	Adults with chronic bronchitis	Mucolytic vs. placebo	No exacerbations in study period	16.23	2.14-∞	0.38	0.17 to 0.59	1.06	0.93-1.21	0.02	-0.02 to 0.06	42
CD005445	Adults with chronic hepatitis C	Ribavirin + interferon vs. interferon	Adverse events	17.00	2.17-∞	0.25	0.10 to 0.40	1.03	0.73-1.45	0.00	-0.04 to 0.04	43

Table S3. Number of large trials refuting index trial VLE.

CDSR ID	Index trial VLE refuted	No. of large trials	No. of large trials refuting index trial VLE
CD000022	No	1	0
CD000146	No	3	0
CD000262	No	2	0
CD000567	Yes	2	2
CD001058	Yes	1	1
CD001090	Yes	3	3
CD001090	Yes	1	1
CD001141	Yes	7	4
CD001150	Yes	1	1
CD001188	Yes	1	1
CD001287	Yes	2	2
CD001290	No	1	0
CD001478	No	1	0
CD001841	No	1	0
CD001886	No	2	0
CD001928	Yes	3	3
CD001960	Yes	3	2
CD002138	Yes	2	2
CD002755	Yes	4	2
CD003180	Yes	2	2
CD003221	No	1	0
CD003246	Yes	1	1
CD003611	No	1	0
CD003756	No	1	0
CD003775	No	1	0
CD003897	No	1	0
CD004125	No	1	0
CD004181	No	2	0
CD004183	Yes	2	2
CD004227	Yes	1	1
CD004352	No	1	0
CD004386	No	1	0
CD004604	No	1	0
CD004659	Yes	3	2
CD004736	No	1	0
CD005445	Yes	1	1
CD006060	No	1	0
CD006063	No	1	0
CD006743	No	2	0
CD006936	No	1	0
CD007176	Yes	9	9
CD007223	No	1	0
CD007277	No	1	0
CD008521	No	1	0

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