Supplement: Clinical trials in critical care: can a Bayesian approach enhance clinical and scientific decision making?

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Systematic Review Details

From Abrams et al (2020)[1]:

"Studies eligible for inclusion were multicenter randomized clinical trials of critically ill adult patients in which mortality was the main endpoint. For inclusion, the publication must have appeared between January 1, 2008 and December 31, 2018 in one of five journals: New England Journal of Medicine, Journal of the American Medical Association (JAMA), The Lancet, American Journal of Respiratory and Critical Care Medicine, or Lancet Respiratory Medicine. Trials were excluded if not designed as superiority trials or if patient-level randomization was not employed."

"Journals were selected by considering impact factor and content relevance in effort to identify trials most influential to future trial design and clinical practice."

"Tables of contents for each journal issue were screened independently by two study physicians to identify articles for inclusion. A PubMed search was also conducted to ensure eligible articles were not missed (Supplementary Appendix). Results from all search strategies were combined with discordance resolved by review from a third study physician to create the final study list. Data were extracted in duplicate by study physicians blinded to each other's data entry, and discordance resolved by an independent third reviewer."

"Trials with more than two parallel groups or 2x2 factorial design were reviewed to identify the main prespecified comparison per protocol. When only a single comparison was pre-specified, that sole comparison was included in this analysis. For factorial trials in which more than one comparison was prespecified as the main analysis of the primary endpoint, each pairwise comparison was entered as a separate trial for all analyses."

"Studies involving patients who underwent an elective procedure, were not critically ill prior to the procedure, and rapidly recovered post-procedure without high probability of life-threatening deterioration, were excluded. For final arbitration of discordance regarding what constituted critical illness, the Centers for Medicare and Medicaid Services definition of critical illness was applied, as illness or injury that "acutely impairs one or more vital organ systems such that there is a high probability of imminent or life threatening deterioration in the patient's condition."

"To identify articles for inclusion, tables of contents for each journal issue were screened independently by two study physicians. To ensure studies of key topics were not missed during manual screening, a PubMed search was also conducted for each journal using the following Medical Subject Headings: critical illness or shock or acute respiratory distress syndrome or respiratory failure; and either randomized controlled trial or clinical trial. The final study list was compiled combining results from all search strategies. Discordance in studies identified for possible inclusion was resolved by review by a third study physician."

Trials with three arms or factorial designs were individually assessed to determine which arms would be included in the primary analysis (Table E1). The number of patients and events in each treatment group were extracted from the manuscripts.

Table E1: Trials Evaluating Multiple Interventions

Trial Name	First Author	Interventions	Decision	Rationale
Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial	Annane	1. Intensive vs conventional insulin therapy 2. Fludricortisone with hydrocortisone vs hydrocortisone alone	Include only intensive insulin versus conventional insulin	Fludricortisone arm described as a secondary objective
Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium	Van de Boogard	Three times per day IV administration of: 1. Haloperidol 2mg 2. Haloperidol 1mg 3. Saline placebo	Include only comparison between haloperidol 2mg and placebo	Haloperidol 1mg arm stopped early, and the two arms differ only in dose
Multiple-dose activated charcoal in acute self-poisoning	Eddleston	1. Multi-dose charcoal 2. Single-dose charcoal 3. No charcoal	Include only multi-dose charcoal vs no charcoal	Described as the purpose of the trial in the introduction
Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial	Asfar	1. FiO2 of 1.0 vs FiO2 titrated to maintain saturation 88-95% 2. Boluses of hypertonic (3%) vs normal (0.9%) saline for fluid resuscitation	Include both interventions	The two therapies could exert independent effects
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis	Brunkhorst	1. Intensive versus conventional insulin therapy 2. Hydroxyethyl starch versus Ringer's lactate	Include both interventions	The two therapies could exert independent effects
Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest	Kudenchuk	1. Amiodarone 2. Lidocaine 3. Placebo	Include only amiodarone versus placebo	Lidocaine used as an alternate control based on previous data.
A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients	Heyland	1. Glutamine vs placebo 2. Antioxidants vs placebo	Include both	The two therapies could exert independent effects
A Randomized Trial of Protocol-Based Care for Early Septic Shock	The ProCESS Investigators	1. Early Goal-Directed Therapy 2. Standard protocolised care 3. Usual care	Include both protocolised arms compared with usual care	This is described as the primary outcome
Prednisolone or Pentoxyfilline for Alcoholic Hepatitis	Thursz	1. Pentoxifylline versus placebo 2. Prednisolone versus placebo	Include both	The two therapies could exert independent effects
Recombinant Tissue Factor Pathway Inhibitor in Severe Community-acquired Pneumonia	Wunderink	1. Tifacogin high dose 2. Tifacogin low dose 3. Placebo	Include low-dose and placebo arms only	High-dose arm stopped for futility and the two arms differ only in dose

Minimum Clinically Important Differences

The minimum clinically important difference was estimated by asking 10 clinicians to read the background and methods section of the abstract for each study and note what they judged to be the minimum clinically important difference. The MCID was explained to participating clinicians as "the smallest treatment size that would cause you to use this intervention." Clinicians were instructed to avoid considering the cost of treatment in estimating the MCID, and to avoid perceiving the MCID as either the estimate of the true effect or an estimate of what the trial will show. A training session was held to ensure all clinicians understood the task. Each clinician was presented with the trials in a different randomized order. A separate minimum clinically important difference was estimated for each intervention (a departure from the usual approach where an MCID is associated only with an outcome measure, not an outcome and an intervention) because interventions for critical illness are associated with variable degrees of morbidity.

Each clinician was a coauthor in this project (Authors LM, EF, EG, RF, HW, DA, MB, MH, PM, DB). Training background of clinicians was internal medicine for 8 (80%) of whom 4 had pulmonary training in addition to critical care medicine training. The remaining 2 (20%) had anesthesiology training. Median year of medical school graduation was 2005 with 80% graduating between 1999 and 2007. The median duration since finishing fellowship training was 9 years, with 80% having between 7 and 14 years of post-fellowship clinical experience. Four (40%) of clinicians were female.

The expert opinion-based method to determining MCIDs in this study is similar to previous studies where clinicians were asked to estimate minimum clinically important differences based on hypothetical randomized trials or clinical vignettes.[2–6] Alternative approaches to generating estimates of minimum clinically important differences include anchor-based and distributional approaches, which were not feasible in this study because mortality was the target measure. A more rigorous approach would use a Delphi method, but given (1) the goal of our analysis was to explore possible discordance between Bayesian and frequentist analyses, not to offer definitive judgments on the efficacy of treatments and (2) our estimates were similar to other estimates of minimum clinically important differences we felt that going through a full Delphi process for all 82 interventions would not add value to the investigation.

Table E2: Minimum Clinically Important Differences by Study

ID	Title	Author	MCID (%)	NNT of MCID	Anticipated Effect (%)
1	Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome.	Kesecioglu	3.0	33	10
2	Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial	Jansen	2.0	50	15
3	Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury.	Spragg	3.0	33	8
4	Recombinant human activated protein C for adults with septic shock: a randomized controlled trial	Annane	5.0	20	10
5	Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery	Combes	4.5	22	12
6	Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.	Meade	4.0	25	9
7	Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.	Mercat	2.5	40	10
8	Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial.	Taccone	4.0	25	15
9	Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial	Annane	4.0	25	12
10	Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe SepsisThe ACCESS Randomized Trial	Opal	3.5	29	8
11	Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition	Doig	3.5	29	8
12	Effect of Early vs Late Tracheostomy Placement on Survival in Patients Receiving Mechanical VentilationThe TracMan Randomized Trial	Young	4.5	22	8
13	Prednisolone With vs Without Pentoxifylline and Survival of Patients With Severe Alcoholic HepatitisA Randomized Clinical Trial	Mathurin	2.0	50	14
14	Effect of Statin Therapy on Mortality in Patients With Ventilator-Associated PneumoniaA Randomized Clinical Trial	Papazian	2.0	50	8
15	Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial	Annane	2.0	50	5
16	Mechanical Chest Compressions and Simultaneous Defibrillation vs Conventional Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac ArrestThe LINC Randomized Trial	Rubertsson	4.5	22	6
17	Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe TraumaThe PROPPR Randomized Clinical Trial	Holcomb	3.0	33	12

18	Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial	Lemiale	3.0	33	15
19	Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With SepsisA Randomized Clinical Trial	Kawazoe	2.5	40	20
20	Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial.	Cavalcanti	3.0	33	8
21	Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium	van den Boogaard	2.0	50	8
22	Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level: The EUPHRATES Randomized Clinical Trial	Dellinger	4.0	25	15
23	Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure: The HIGH Randomized Clinical Trial.	Azoulay	3.0	33	10
24	Multiple-dose activated charcoal in acute self-poisoning	Eddleston	2.0	50	3
25	CPR with Chest Compression Alone or with Rescue Breathing	Rea	2.0	50	4
26	Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial	Shakur	3.0	33	2
27	Effect of intravenous Beta-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial	Smith	3.5	29	9
28	Compression-Only CPR or Standard CPR in Out-of-Hospital Cardiac Arrest	Svensson	2.0	50	2
29	Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial	Sierink	2.0	50	5
30	Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2).	Reignier	4.0	25	5
31	Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial	Moore	3.5	29	19
32	Hyperoxia (and hypertonic saline) in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial.	Asfar	4.0	25	10
33	Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial	Alam	2.0	50	6
34	Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial	Itenov	5.0	20	12
35	Intensive insulin therapy (and pentastarch resuscitation) in severe sepsis	Brunkhorst	3.0	33	10
36	Hydrocortisone therapy for patients with septic shock	Sprung	2.5	40	10
37	Vasopressin versus norepinephrine infusion in patients with septic shock	Russell	2.5	40	10
38	Home use of automated external defibrillators for sudden cardiac arrest.	Bardy	3.0	33	2
39	Intensity of renal support in critically ill patients with acute kidney injury	VA/NIH Acute Renal Failure Trial Network	4.0	25	10

40	Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema	Gray	2.0	50	6
41	Intensive versus conventional glucose control in critically ill patients	NICE-SUGAR Study Investigators	3.5	29	4
42	Intensity of continuous renal-replacement therapy in critically ill patients	RENAL Replacement Therapy Study Investigators	2.0	50	8
43	Comparison of dopamine and norepinephrine in the treatment of shock	De Backer	1.5	67	8
44	Neuromuscular blockers in early acute respiratory distress syndrome	Papazian	4.0	25	15
45	Drotrecogin alfa (activated) in adults with septic shock	Ranieri	4.5	22	7
46	Intraaortic balloon support for myocardial infarction with cardiogenic shock	Thiele	3.5	29	12
47	Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care	Myburgh	2.0	50	4
48	High-frequency oscillation in early acute respiratory distress syndrome	Ferguson	5.0	20	7
49	High-frequency oscillation for acute respiratory distress syndrome	Young	5.0	20	9
50	A randomized trial of glutamine (and antioxidants) in critically ill patients	Heyland	2.0	50	8
51	Prone positioning in severe acute respiratory distress syndrome	Guerin	4.0	25	15
52	Targeted Temperature Management at 33C versus 36C after Cardiac Arrest	Nielsen	2.5	40	11
53	Albumin replacement in patients with severe sepsis or septic shock	Caironi	2.0	50	8
54	High versus low blood-pressure target in patients with septic shock	Asfar	3.0	33	10
55	A randomized trial of protocol-based care for early septic shock (protocolized vs usual care)	ProCESS Investigators	2.5	40	6
56	Rosuvastatin for sepsis-associated acute respiratory distress syndrome	National Heart, Lung, and Blood Institute ARDS Clinical Trials Network	2.0	50	9
57	Lower versus higher hemoglobin threshold for transfusion in septic shock	Holst	3.5	29	9
58	Goal-directed resuscitation for patients with early septic shock	ARISE Investigators	2.5	40	8
59	Trial of the route of early nutritional support in critically ill adults	Harvey	3.0	33	6
60	Trial of early, goal-directed resuscitation for septic shock	Mouncey	3.0	33	8
61	Age of transfused blood in critically ill adults	Lacroix	2.0	50	5
62	Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults	Arabi	1.5	67	8

63	Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit	Gaudry	4.5	22	15
64	Age of red cells for transfusion and outcomes in critically ill adults	Cooper	3.0	33	4
65	Hydrocortisone plus Fludrocortisone for Adults with Septic Shock	Annane	2.5	40	10
66	Adjunctive Glucocorticoid Therapy in Patients with Septic Shock	Venkatesh	2.0	50	5
67	Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome	Combes	5.5	18	20
68	Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis	Barbar	4.0	25	10
69	Energy-Dense versus Routine Enteral Nutrition in the Critically Ill	TARGET Investigators	1.5	67	4
70	Pantoprazole in Patients at Risk for Gastrointestinal Bleeding in the ICU	Krag	2.0	50	5
71	Recombinant Tissue Factor Pathway Inhibitor in Severe Community-acquired Pneumonia: A Randomized Trial	Wunderink	4.0	25	6
72	Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction	Frobert	3.0	33	1
73	Prednisolone (or Pentoxifylline) for Alcoholic Hepatitis	Thursz	2.5	40	9
74	Amiodarone, (Lidocaine), or Placebo in Out-of-Hospital Cardiac Arrest	Kudenchuk	2.0	50	6
75	Levosimendan for Hemodynamic Support after Cardiac Surgery	Landoni	3.0	33	5
76	A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest	Perkins	2.0	50	2
77	Vasopressin and Epinephrine vs. Epinephrine Alone in Cardiopulmonary Resuscitation	Gueugniaud	2.0	50	5
78	Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest	Bottiger	4.5	22	7
79	(Hyperoxia and) hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial.	Asfar	4.0	25	10
80	(Intensive insulin therapy and) pentastarch resuscitation in severe sepsis	Brunkhorst	3.0	33	10
81	A randomized trial of (glutamine and) antioxidants in critically ill patients	Heyland	2.0	50	8
82	(Prednisolone or) Pentoxifylline for Alcoholic Hepatitis	Thursz	2.5	40	9

Table E3: Characteristics of MCID and Anticipated Effects

Characteristics of treatment effects	MCID	Anticipated Effect
Median absolute risk reduction (Interquartile range)	3 (2-4)	8 (6-10)
Effect estimates – number (%) in each interval of ARR		
0 ≤ effect < 2	3 (4%)	2 (2%)
2 ≤ effect < 4	56 (68%)	8 (10%)
4 ≤ effect < 7	23 (28%)	16 (20%)
7 ≤ effect < 10	0 (0%)	25 (30%)
Effect ≥ 10	0 (0%)	31 (38%)

This table shows the characteristics of the minimum clinically important differences and anticipated effects from trial sample size calculations (median and number in each range of absolute risk reduction).

Prior Distributions

Table E4: Features of Prior Distributions

	Skeptical	Enthusiastic
Prior distribution parameters		
Mean of the distribution	ARR = 0%	ARR = 2*MCID
Effective sample size of the prior distribution	400 subjects	400 subjects
Median (IQR) of quantities for the prior distributions		
Probability of harm (ARR less than 0%)	50% (50-50)	8% (5-14)
Probability of clinical benefit (ARR greater than MCID)	26% (21-31)	74% (69-79)
Frequentist p-value of equivalent trial	1.0 (1.0-1.0)	0.21 (0.1-0.32)

This table shows characteristics of the prior distributions. Because each prior distribution was calculated using the particular study's control group mortality and adjudicated estimate of minimum clinically relevant effect, the prior distributions vary slightly across studies.
ARR = Absolute Risk Reduction in mortality.
MCID = Minimum Clinically Important Difference.

Iatrogenic Prior and Probability of Harm

Using the iatrogenic prior distribution centered at an absolute mortality increase of magnitude equal to the minimum clinically important difference and variance equivalent to a trial of 100 people, there were 2 trials deemed positive by frequentist criteria that had less than 50% probability of exceeding the MCID and 9 trials deemed negative by frequentist criteria that had greater than 50% probability of exceeding the MCID.

Equipoise is a prerequisite for a therapy to be evaluated in a large multicenter randomized trial, and equipoise implies that the probability of benefit and harm are approximately equal. The iatrogenic prior distribution likely represents a minority view in the scientific community and so we have decreased the certainty of the prior to a 100 person trial. Additional priors can always be explored through the interactive app referenced in the main text.

The rate of reversal with respect to harm was also assessed. Shifting the prior from enthusiastic to skeptical reversed the probability of harm (increase in absolute risk of mortality > 0%) from improbable (≤ 50%) to more probable than not (> 50%) in 24 (29%) of trials. Results were similar using the iatrogenic prior (27 or 33% of trials).

Table E5: Trials with Reversal in Bayesian Analyses Comparing Skeptical and Enthusiastic Priors

Manuscript Name	Unadjusted Mortality Result (intervention versus control)	Minimum Clinically Important Difference	Number Needed to Treat implied by MCID	Posterior Mean ARR (Probability of ARR exceeding MCID)	
				Skeptical	Enthusiastic
Intraaortic balloon support for myocardial infarction with cardiogenic shock[7]	30-day mortality 40% vs. 41%	3.5%	29	1.0% (0.21)	3.8% (0.53)
Intensive insulin therapy (and pentastarch resuscitation) in severe sepsis[8]	28-day mortality 25% vs 26%	3%	33	0.7% (0.21)	3.3% (0.54)
Prednisolone With vs Without Pentoxifylline and Survival of Patients With Severe Alcoholic Hepatitis: A Randomized Clinical Trial[9]	6-month mortality 30% vs. 31%	2%	50	0.2% (0.31)	2.6% (0.57)
Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults[10]	90-day mortality 27% vs. 29%	1.5%	67	1.2% (0.45)	2.1% (0.59)
Compression-Only CPR or Standard CPR in Out-of-Hospital Cardiac Arrest[11]	30-day mortality 92% vs. 93%	2%	50	1.3% (0.28)	2.3% (0.59)
Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock[12]	30-day mortality 36% vs. 36%	4.5%	22	0% (0.12)	5.8% (0.63)
Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial.[13]	28-day mortality 31% vs 33%	4%	25	0.8% (0.18)	5.1% (0.63)
Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome[14]	Hospital mortality 36% vs 40%	4%	25	2.8% (0.33)	5.1% (0.66)
Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure[15]	28-day mortality 24% vs. 27%	3%	33	1.6% (0.33)	4.6% (0.70)
Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.[16]	28-day mortality 28% vs. 31%	2.5%	40	2.2% (0.46)	3.9% (0.70)
Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma[17]	30-day mortality 22% vs. 26%	3%	33	2.5% (0.42)	4.6% (0.73)
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome[18]	60-day mortality 35% vs. 46%	5.5%	18	4.0% (0.35)	10.1% (0.91)

Additional Figures

Figure E1: Posterior Probability of Absolute Risk Reduction by Prior Distribution

Posterior Probability of Absolute Risk Reduction
Grouped by Study, Ordered by P-value and Coloured by Probability of Achieving MCID

Studies on y-axis are ordered by p-value (lower p-values closer to x-axis). MCID = minimum clinically important difference. ARR = absolute risk reduction. Pr(ARR > MCID) = probability that ARR exceeds MCID. Shaded grey area indicates p-value < 0.05.
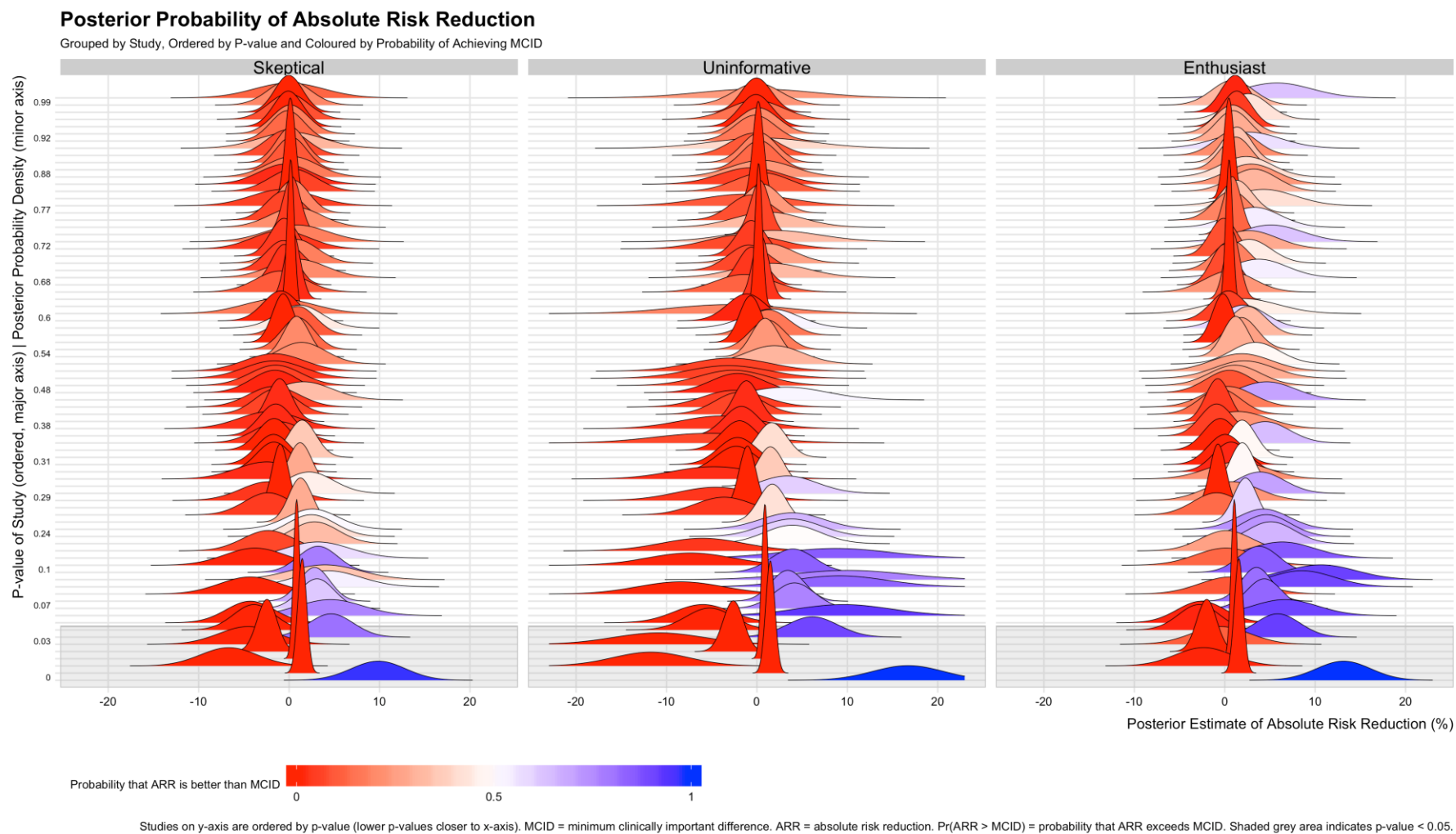
Figure E1: This figure shows the posterior probability distributions of treatment effects for every intervention included in the review using skeptical (left), uninformative (center) and enthusiastic (right) priors. Each contour represents the distribution for a separate trial. The y axis for each contour is the probability density, such that the

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area within each contour between two values of the absolute risk reduction (ARR) on the x-axis is the probability that the posterior treatment effect lies between those two values. For example, the area within each contour to the left of the line drawn through ARR = 0 gives the posterior probability of harm for each intervention. The contours are coloured according to the posterior probability that the ARR is greater than the MCID, with red denoting probabilities less than 50%, blue denoting probabilities greater than 50%, and white denoting the transition between the two extremes. The contours are arranged by p-value, with the lowest p-values at the bottom and the highest p-values at the top. Contours with their base within the shaded gray area correspond to trials with p-values less than 0.05. This complex construction allows the reader to see how the posterior probability distributions and probability of exceeding the MCID change across prior distributions, p-values, and studies.

**Figure E2: Prior-Dependent Shift in Posterior Probability versus Sample Size**
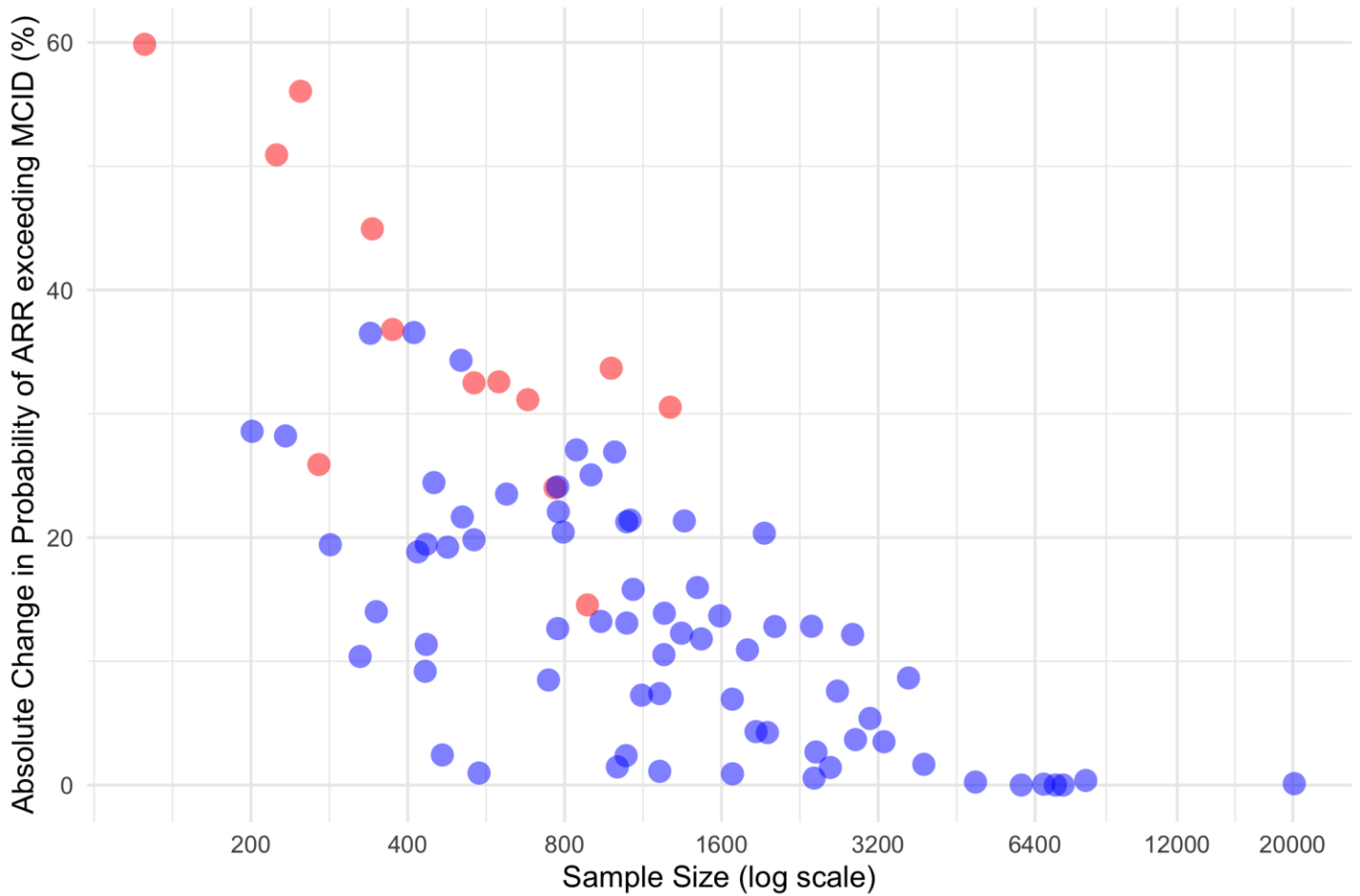
Change in probability refers to the difference in posterior probability of ARR exceeding MCID changing from skeptical to enthusiastic priors.
ARR = absolute risk reduction. MCID = minimum clinically important difference.
Reversal: posterior probability of ARR > MCID changes from less than 50% to greater than 50% when changing from skeptical to enthusiastic priors.

Prior-Dependent Shift in Posterior Mean versus Sample Size
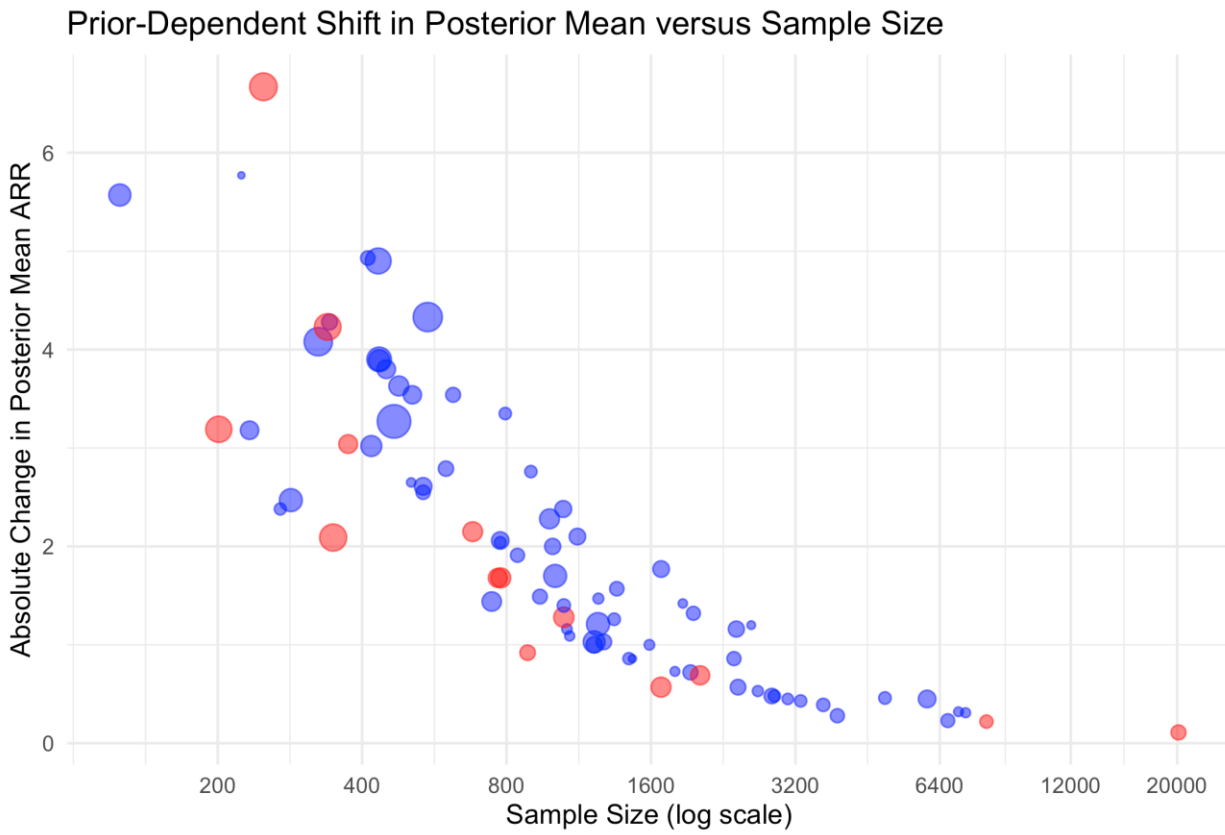
Change in posterior mean refers to the difference in posterior mean comparing enthusiastic and skeptical priors.
ARR = absolute risk reduction. MCID = minimum clinically important difference.
Agreement: Bayesian probability of 50% or more that ARR > MCID and trial is positive by frequentist criteria,
or Bayesian probability of less than 50% that ARR > MCID and trial is negative by frequentist criteria.
Size of point corresponds to absolute value of observed mean.

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Posterior Mean of Absolute Risk Reduction

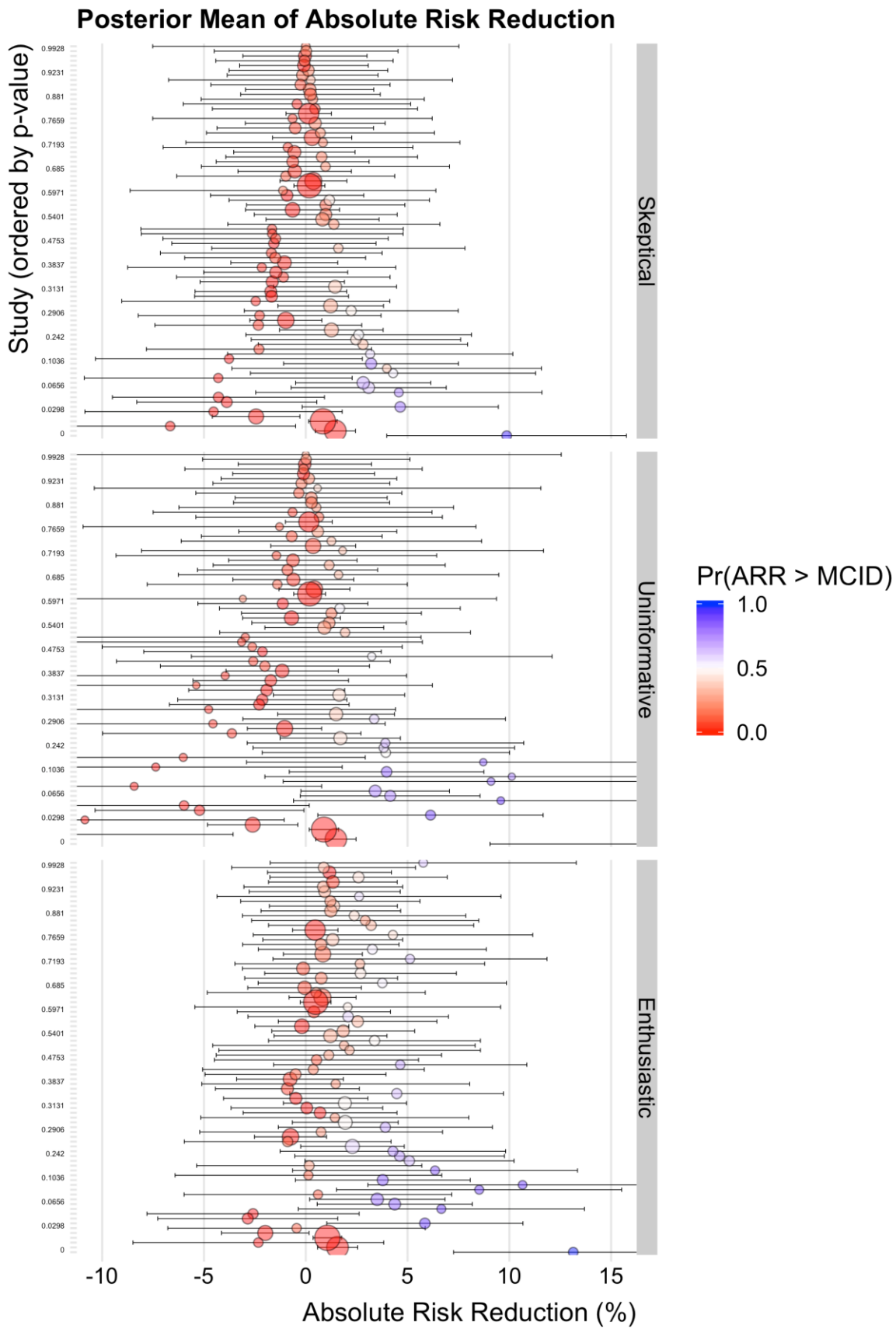Minimum Clinically Important Difference by Study
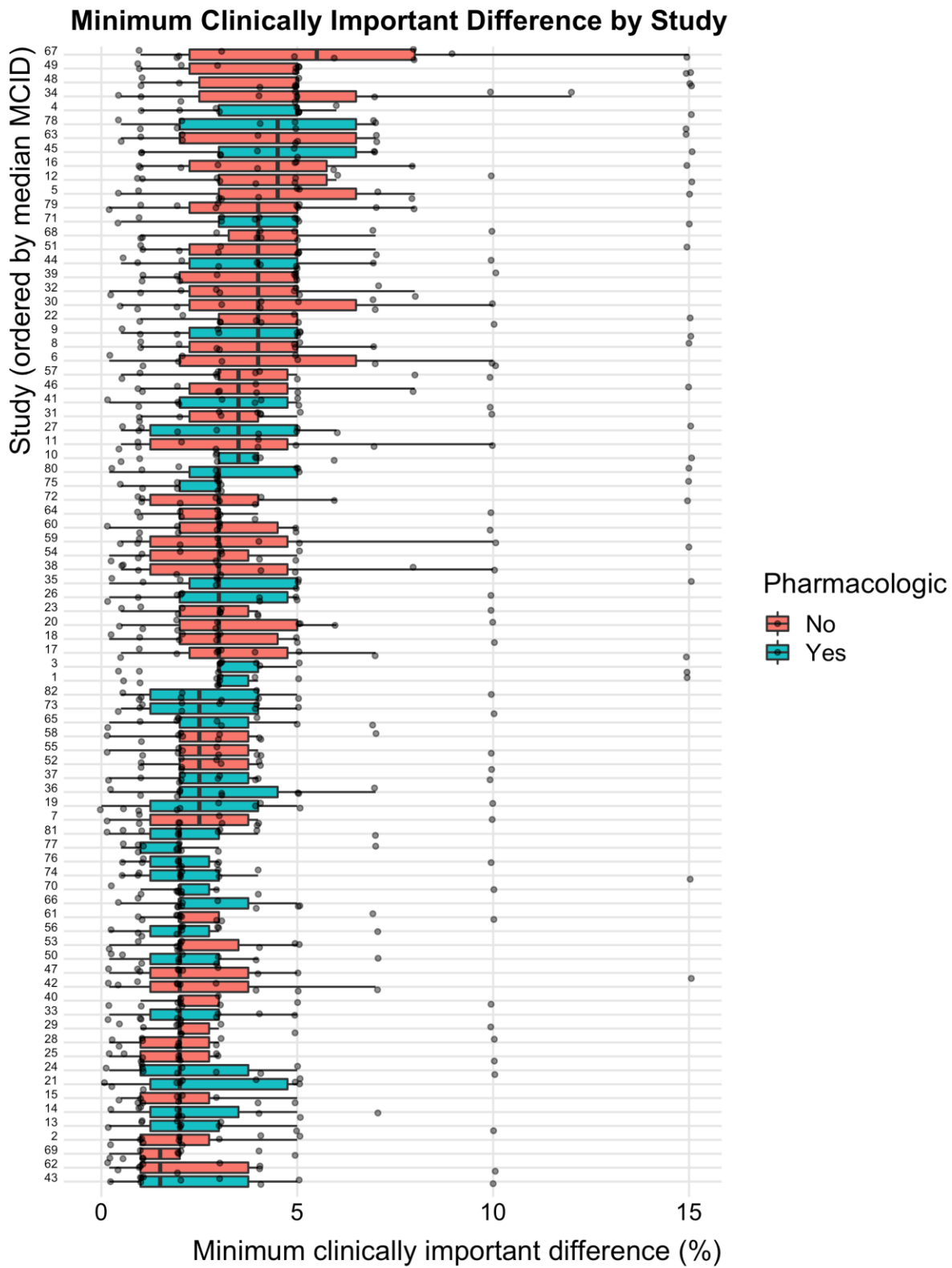
Figure E5: Posterior Probability of Clinical Benefit by MCID
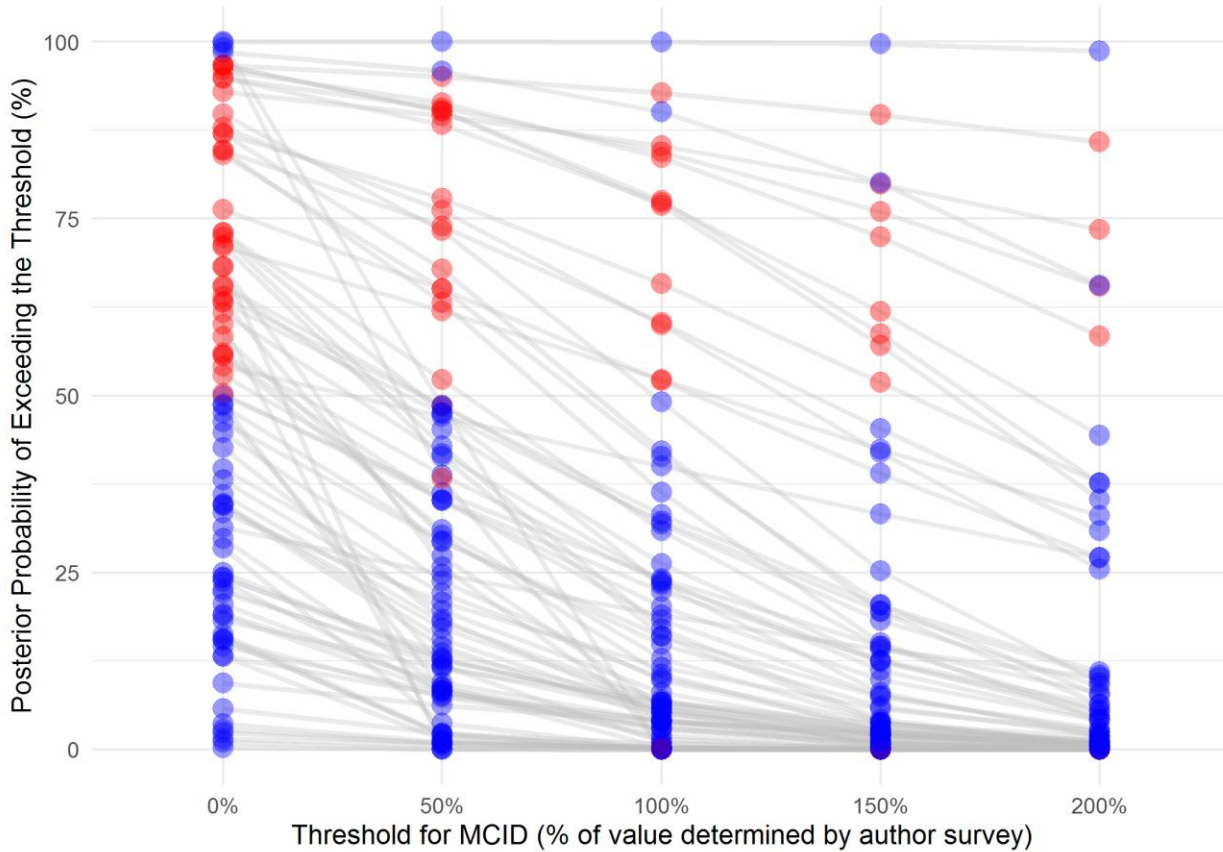
This plot shows the sensitivity of calculations of posterior probability of achieving the MCID for different values of MCID. Each point shows the posterior probability of exceeding an effect equal to the indicated percentage of the MCID. Lines connect estimates from the same trial.
MCID = minimum clinically important difference.

R Setup

Thank you to all the scientists and statisticians responsible for the many R packages upon which this project is based. It could not have been completed without their efforts.

R Packages Used:

Knitr, Tinytex, ggplot2, ggsci, Cairo, gridExtra, latex2exp, and the tidyverse environment including readxl, tidyr, dplyr, forcats, scales.[19–24]

```
# NB: to produce the preferred PDF output, LaTeX needs to be installed
# Some of the output may not typeset so well in HTML or Word.

# Flag for whether this is generating a report
report <- T
# Set seed so results are reproducible
set.seed(12345)
```

```r
# Load required R packages

library(knitr)
library(tinytex)
library(ggplot2)
library(ggsci)
library(Cairo)
library(gridExtra)
library(latex2exp)
library(readxl)
library(tidyr)
library(dplyr)

library(forcats)
library(scales)


# set the colour scheme
mypal <- pal_jama("default")(5)

# set default chunk options

opts_chunk$set(echo = T,
        message = F,
        warning = F,
        fig.height = 5,
        fig.width = 5,
        fig.align='center',
        fig.pos = '!h')

# load a function to calculate posterior probability
source('CalculatePosteriorProbability.R')
```

Data

Trial Data
```r
# read the data from Beitler et. al's systematic review
d <- data.frame(read.csv('mortendpoint final dataset all pairs.csv'))
```

MCID Data
```r
# read in the MCID data
MCID_data <- data.frame(read.csv('Master_MCID_Worksheet.csv')) %>%
    mutate(MCID = MCID/100) %>%
    filter(studyid != 25) %>%
    filter(studyid != 28) %>% # filter excluded studies
    mutate(studyid = ifelse(studyid == "79", "25", studyid)) %>% #recode
    mutate(studyid = ifelse(studyid == "80", "28", studyid)) %>%
    mutate(studyid = as.integer(studyid))

doubles <- filter(MCID_data, studyid %in% c(32,35,50,73)) %>%
    mutate(studyid = recode(studyid,  "32" = "79",
                          "35" = "80",
                          "50" = "81",
                          "73" = "82"))
```

```
MCID_data$studyid <- as.character(MCID_data$studyid)
doubles$studyid <- as.character(doubles$studyid)

MCID_data <- rbind(MCID_data, doubles) %>%
    mutate(studyid = as.integer(studyid))

e <- summarise(group_by(MCID_data, studyid), MCID = median(MCID))

d <- left_join(d,e, by = "studyid")

QuartL <- summarise(group_by(MCID_data, studyid), QL = quantile(MCID, 0.25, na.rm = TRUE))
QuartH <- summarise(group_by(MCID_data, studyid), QH = quantile(MCID, 0.75, na.rm = TRUE))

d <- left_join(d,QuartL, by = "studyid") %>%
    left_join(QuartH, by = "studyid")

# add in the predicted control group mortality for the van de Boogard study using their pilot study as they described in the
ir manuscript

d$pmortctrl[21] <- 100*(1-(0.5)^(28/18))

# add in the predicted control group mortality for the CPR with Chest Compression Alone or with Rescue Breathing study
. Using the targeted sample size from clinicaltrials.gov (1600), we can back-calculate that a predicted control group mort
ality of 0.88 or 0.15 with 1:1 ratio allocation between arms and 3.5% absolute mortality difference would generate a p-va
lue of slightly less than 0.05. Because of the nature of the clinical problem we will assume they intended the 88%.

#X <- matrix(nrow = 2, ncol = 2)
#cm <- 0.88
#X[,1] <- 800*c(cm, 1-cm)
#X[,2] <- 800*c(cm-0.035, 1-cm+0.035)
#prop.test(X)

d$pmortctrl[25] <- 88

d$pmortctrl <- d$pmortctrl/100
```

Analysis

Bayesian Analysis

The Bayesian analysis is driven by the script below called "CalculatePosteriorProbability." It contains within it code corresponding to the classical calculation of Bayesian analysis when priors and likelihood functions both take the form of normal distributions.

```
CalculatePosteriorProbability <- function(Z,
                        certainty = 100,
                        q = 0.975,
                        outlook = 0){
####################################################################################

# Takes the data Z with parameters ControlEvents = CE, ControlTotal = CT, TreatmtEvents = TE, TreatmtTotal = TT, M
CID, control mortality = CM
# and outputs a vector with posterior mean, MCID, standard deviation, p-value, and posterior probability of achieving M
CID.

# The outlook parameter runs from 0 (skeptic) to 1 (enthusiast) and adjusts where the center of the prior distribution falls.
# The certainty parameter adjusts the standard deviation (sd similar to a trial of size "certainty").
```

```r
# A positive Absolute Risk *Reduction* means the mortality rate
# has been reduced in the treatment group.

CE  <- Z[1]
CT  <- Z[2]
TE  <- Z[3]
TT  <- Z[4]
MCID<- Z[5]
CM  <- Z[6]


p1     <- CE/CT
p2     <- TE/TT


y.obs  <- p1 - p2


sd.obs <- sqrt(p1*(1-p1)/CT + p2*(1-p2)/TT)


low      <- y.obs - 1.96*sd.obs
high     <- y.obs + 1.96*sd.obs
pv       <- 2*pnorm(-abs(y.obs), 0, sd.obs)


# we use the certainty parameter to generate sd.prior
# where the integer value (usually 100 or 400)
# corresponds to the variance from a trial of that size
# with no difference between p1 and p2, equal group
# sizes of N/2 and p1 is set to the predicted control mortality.

# Var(p1-p2) = Var(p1) + Var(p2)
#            = 4*p1(1-p1)/N

sd.prior  <- sqrt(4*CM*(1-CM)/certainty)


tau.y     <- 1/sd.obs^2
tau.prior <- 1/sd.prior^2


posterior.precision <- tau.y+tau.prior
w         <- tau.y/posterior.precision

prior.mean <- 2*outlook*MCID

posterior.mean <- w*y.obs+(1-w)*prior.mean

posterior.sd  <- 1/sqrt(posterior.precision)

lo  <- posterior.mean - qnorm(q)*posterior.sd
hi  <- posterior.mean + qnorm(q)*posterior.sd

result <- c(Observed.Mean = y.obs,
        Posterior.Mean = posterior.mean,
        Low=lo,
        High=hi,
        PostProbMCID=1-pnorm(MCID,
                    posterior.mean,
                    posterior.sd),
```

```
        pvalue=pv,
        MCID=MCID,
        Posterior.SD = posterior.sd)

round(result,4)


}
```

The second part of the Bayesian analysis involves applying that function to the inputted data.

```
# Each trial has its own set of priors determined by the MCID.

# Standard deviation of the prior is set such that 45% of the density lies between the MCID and 0 when the mean is 0, and
the center of the prior shifts from 0 to 2*MCID depending on the balance of skepticism and enthusiasm. (5% chance of be
ing beyond either MCID or 0 depending on if the prior is skeptical or enthusiastic).

# A separate function "CalculatePosteriorProbability" takes the event rates from control and treatment arms, total patient
s in each arm, and MCID along with parameter determining the variance of the prior (threshprior) and the mean of the pr
ior (outlook) and outputs the observed mean, posterior mean, 95% credibility interval, posterior probability of attaining t
he MCID, MCID, pvalue, and posterior standard deviation.

# Based on the above rules for defining the prior, the prior is a normal distribution with variance MCID/(1-qnorm(thresh
prior)) and mean outlook*MCID.

ControlEvents <- as.numeric(as.character(d$deadctrl))
ControlTotal  <- as.numeric(as.character(d$sizectrl))
TreatmtEvents <- as.numeric(as.character(d$deadtx1))
TreatmtTotal  <- as.numeric(as.character(d$sizetx1))
MCID <- as.numeric(as.character(d$MCID))
CM   <- d$pmortctrl # predicted mortality of control group

MI = 0 # certainty of the Uninformative prior

X <- cbind(ControlEvents,
        ControlTotal,
        TreatmtEvents,
        TreatmtTotal,
        MCID,
        CM)

# function to apply the CalculatePosteriorProbability()
# function across all studies and consolidate in a table
BayesianTable <- function(X,outlook,certainty){
    A <- t(apply(X, 1,
        CalculatePosteriorProbability,
        outlook = outlook, certainty = certainty))
colnames(A) <- c("Observed.Mean",
        "Posterior.Mean",
        "Low",
        "High",
        "Posterior.Probability.MCID",
        "pvalue",
        "MCID",
        "Posterior.SD")
A <- as.data.frame(A) %>%
    mutate(Study = factor(seq(1:dim(A)[1])))
```

```r
}

SkeptResults <- BayesianTable(X,
                    outlook = 0,
                    certainty = 400)
MinInfResults <- BayesianTable(X,
                    outlook = 0,
                    certainty = MI)
EnthResults  <- BayesianTable(X,
                    outlook = 1,
                    certainty = 400)

Results = list(S = SkeptResults,
          M = MinInfResults,
          E = EnthResults)
```

Prior Distribution Characteristics

```r
certainty = 400
p1 <- d$deadctrl/d$sizectrl
sd.prior  <- sqrt(4*p1*(1-p1)/certainty)
prior.mean <- 2*MCID

summary(2*pnorm(-abs(prior.mean), 0, sd = sd.prior)) #p-values for enthusiastic prior

summary(1-pnorm(MCID, mean = prior.mean, sd = sd.prior)) # probability of exceeding MCRE for enthusiastic prior

summary(1-pnorm(MCID, mean = 0, sd = sd.prior)) # probability of exceeding MCRE for skeptical prior
```

Functions

Primary Outcome Analysis Function

```r
# Primary Outcome Analysis

# give this function an MCID threshold thresh and a dataframe of results of the format of TentSkeptResults (any of the items of the list Results). output is a 2 by 2 table with columns Pr(ARR > MCID) > 0.5 Yes / No  and rows pvalue <0.05 Yes / No
PrimaryOutcome <- function(X,t=0.5){
    A <- matrix(nrow = 2,ncol = 2)
    A[1,1] <- sum(
        (X$Posterior.Probability.MCID > t) &
        (X$pvalue < 0.05) &
        (X$Posterior.Mean > 0))
    A[1,2] <- sum(
        (X$Posterior.Probability.MCID <= t) &
        ((X$pvalue < 0.05) &
        (X$Posterior.Mean > 0)))
    A[2,1] <- sum(
        (X$Posterior.Probability.MCID > t) &
        !((X$pvalue < 0.05) &
        (X$Posterior.Mean > 0)))
    A[2,2] <- sum(
        (X$Posterior.Probability.MCID <= t) &
        !((X$pvalue < 0.05) &
        (X$Posterior.Mean > 0)))
    colnames(A) <- c(paste("Pr(ARR > MCRE) >",
```

```
                            as.character(t)),
                  paste("Pr(ARR > MCRE) <=",
                            as.character(t)))
      rownames(A) <- c("Pvalue < 0.05 and Posterior Mean > 0",
                  "Pvalue >= 0.05 or Posterior Mean < 0")
A
      }
```

MCID-based Sensitivity Analysis Function
 # MCID-based sensitivity analysis

 # recall that X is a matrix with five columns corresponding to control events, control total, treatment events, treatment total, and MCID. X is the input to the BayesianTables function that uses the CalculatePosteriorProbability function to give the results. WE will alter the MCIDs in X and redo the Bayesian analysis and primary outcomes.

 # function to do the primary analysis with MCIDs multiplied by a constant

```
MCID_SensitivityAnalysis <- function(X, constant){
      Y <- X
      Y[,5] <- Y[,5]*constant

SkeptResults2 <- BayesianTable(Y,
                  outlook = 0,
                  certainty = 400)
MinInfResults2 <- BayesianTable(Y,
                  outlook = 0,
                  certainty = MI)
EnthResults2  <- BayesianTable(Y,
                  outlook = 1,
                  certainty = 400)

Results2 = list(S = SkeptResults2,
          M = MinInfResults2,
          E = EnthResults2)

list(S2b2 = PrimaryOutcome(Results2$S),
     M2b2 = PrimaryOutcome(Results2$M),
     E2b2 = PrimaryOutcome(Results2$E))
}
```

Function for Calculating Reversal
 # this function takes arguments of the form ConfSkeptResults (X,Y) and a probability threshold t in [0,1] and calculates the number of trials that transition from posterior probability of ARR > MCID below t to above t. That is, the number of trials that transition from P(ARR > MCID) < t under skeptical prior to P(ARR > MCID) > t under enthusiast prior.
```
TransitionByPrior <- function(X,Y,t){
      sum((X$Posterior.Probability.MCID < t) & (
          Y$Posterior.Probability.MCID > t))
}

TransitionByPrior_Harm <- function(X,Y,t){
      sum( (pnorm(0, mean = X$Posterior.Mean, sd = X$Posterior.SD) < t)
        &(pnorm(0, mean = Y$Posterior.Mean, sd = Y$Posterior.SD) > t))
}

TransitionByPrior(SkeptResults,EnthResults,0.5)
```

```
## [1] 13
```

TransitionByPrior(SkeptResults,EnthResults,0.75)

```
## [1] 5
```

TransitionByPrior(SkeptResults,EnthResults,0.9)

```
## [1] 3
```

```
# This function identifies reversed trials
reverse <- function(X,Y){
    X <- cbind(X,EnthPostProb = Y$Posterior.Probability.MCID) %>%
        mutate(Reversal = (Posterior.Probability.MCID < 0.5 & EnthPostProb > 0.5))
    X}
```

Function for Subgroup Analyses
```
# this function takes an object analogous to SkeptResults and outputs a dataframe with just the rows identified in vector id
, usually corresponding to some subgroup. It can then be fed into the PrimaryOutcome function for subgroup analyses.
SubgroupX <- function(X, id){X[id,]}
```

```
IatroResults <- BayesianTable(X,
                    outlook = -0.5,
                    certainty = 100)
```

PrimaryOutcome(IatroResults)

```
##                              Pr(ARR > MCRE) > 0.5
## Pvalue < 0.05 and Posterior Mean > 0               2
## Pvalue >= 0.05 or Posterior Mean < 0               9
##                              Pr(ARR > MCRE) <= 0.5
## Pvalue < 0.05 and Posterior Mean > 0               2
## Pvalue >= 0.05 or Posterior Mean < 0              69
```

TransitionByPrior_Harm(EnthResults,IatroResults,0.5)

```
## [1] 30
```

This is the number of trials that transition from unlikely to likely harm as you go from enthusiastic to iatrogenic prior distributions.

R Code for Figures

Code For Figure E1: Posterior Distribution Plot

To generate the posterior distribution figure we first had to make the findings into a format that could be managed by ggplot.

```
# This block of code manipulates the data into a format that facilitates plotting with ggplot (tidy data).
```

```
n <- 1000 # number of points
boundaries <- c(-0.5,0.5) # range of ARR values over which to evaluate probability
```

```
# This function expands the dataframe so that each row represents one observation from one of the distributions. It create
s a total of n samples for each line of the dataframe A that it takes as input. The output is a dataframe that has n times as
many rows, a new column with samples from the posterior ARR distribution, and all other columns intact.
```

```
GenerateDensity <- function(A,n=1000,boundaries = c(-0.5,0.5)){
    x <- seq(from = boundaries[1],
        to = boundaries[2],
```

```r
        length.out = n)
    dnorm(x,
        mean = as.numeric(A[2]),
        sd = as.numeric(A[8]))}

# This function takes as input a dataframe outputted by the BayesianTable function and outputs a density ready for plotting

PosteriorDensity <- function(A,n=1000,boundaries=c(-0.5,0.5)){
    C <- as.data.frame(apply(A,1,
            GenerateDensity,n=n,
            boundaries=boundaries)) #calls function to generate the densities
    names(C) <- seq(1:dim(A)[1]) #makes sure study ids are in correct format
    C <- mutate(C, ARR = seq(from = boundaries[1],
        to = boundaries[2],
        length.out = n)) %>%  #adds column for x-axis / ARR
    gather(key = "Study", value = "Probability", -ARR) %>% # tidies the data
    mutate(Study = factor(Study)) %>%
    left_join(A,by = "Study")
}

SkeptDensity <- PosteriorDensity(SkeptResults,n,boundaries)
MinInfDensity  <- PosteriorDensity(MinInfResults,n,boundaries)
EnthDensity  <- PosteriorDensity(EnthResults,n,boundaries)

AllPriors <- rbind(mutate(SkeptDensity, Prior = "Skeptical"),
        mutate(MinInfDensity, Prior = "Uninformative"),
        mutate(EnthDensity, Prior = "Enthusiast")) %>%
    mutate(Prior = factor(
        Prior,
        levels = c("Skeptical",
                "Uninformative",
                "Enthusiast"))) %>%
    mutate(Benefit = (Posterior.Mean > 0)) %>%
    mutate(Benefit = factor(
        Benefit, levels = c(TRUE,FALSE),
        labels = c("Mortality benefit",
                "No mortality benefit")))
```

Next, the function for plotting.

```r
# Plotting function

PosteriorPlot <- function(data, name, w, h){

data$ARR <- data$ARR*100

pvalues <- sort(as.character(round(unique(data$pvalue),2))))
t1 <- seq(from = 2, to = 82, by = 5)
pvalues[t1] <- rep("",length(t1))
pvalues[t1+1] <- rep("",length(t1))
t2 <- seq(from = 4, to = 82, by = 5)
pvalues[t2] <- rep("",length(t2))
pvalues[t2+1] <- rep("",length(t2))

g <- ggplot(data,
```

```r
      aes(x = ARR,
        y = fct_reorder(Study,pvalue),
        group = Study,
        height = Probability)) +
      annotate(geom = "rect", xmin = -Inf, xmax = Inf,
            ymin = 0, ymax = 8.5, color = "grey",
            fill = "grey", alpha = 0.3) +
      geom_ridgeline(aes(fill = Posterior.Probability.MCID,
               min_height = 3e-2,
               scale = 0.2),
            size = 0.2) +
    theme_ridges() +
    labs(y = "P-value of Study (ordered, major axis) | Posterior Probability Density (minor axis)",
        x = "Posterior Estimate of Absolute Risk Reduction (%)",
        title = "Posterior Probability of Absolute Risk Reduction",
        subtitle = "Grouped by Study, Ordered by P-value and Coloured by Probability of Achieving MCRE",
        caption = "Studies on y-axis are ordered by p-value (lower p-values closer to x-axis). MCRE = minimum clinically r
elevant effect. ARR = absolute risk reduction. Pr(ARR > MCRE) = probability that ARR exceeds MCRE. Shaded grey ar
ea indicates p-value < 0.05.") +
    theme(title = element_text(size=10),
        plot.caption = element_text(size = 8),
        axis.title.x = element_text(size = 10),
        axis.title.y = element_text(size = 10),
        legend.title = element_text(size = 8),
        legend.text = element_text(size = 8),
        axis.text.x = element_text(size = 8),
        axis.text.y = element_text(size = 8)) +
    scale_fill_gradient2(
        midpoint = 0.5,
        high = "blue",
        low = "red",
        mid = "white",
        name = "Probability that ARR is better than MCRE",
        labels = c("0","0.5","1"),
        limits = c(0,1),
        breaks = c(0,0.5,1)) +
      scale_y_discrete(labels = pvalues) +
    facet_grid(cols = vars(Prior)) +
    xlim(-23,23) +
    theme(legend.position="bottom",
        legend.key.width = unit(2,"cm"))
g
}

PosteriorPlot(AllPriors, "PostProbARR_3Priors.png", w = 14, h = 8)
```

Code for Figure 2: Posterior Probability of Clinical Benefit by P-value
```r
Z <- rbind(mutate(Results$S, Prior = "Skeptical"),
      mutate(Results$M, Prior = "Uninformative"),
      mutate(Results$E, Prior = "Enthusiastic")) %>%
    mutate(Prior = factor(
        Prior,
        levels = c("Skeptical",
              "Uninformative",
              "Enthusiastic"))) %>%
```

```
    mutate(Low = 100*Low) %>%
    mutate(High = 100*High) %>%
    mutate(Posterior.Mean = 100*Posterior.Mean) %>%
    mutate(Contradictory =
            ((Posterior.Mean < 0 | pvalue > 0.05) &
            (Posterior.Probability.MCID < 0.5)) |
            ((Posterior.Mean > 0 & pvalue < 0.05) &
             (Posterior.Probability.MCID > 0.5)))

order <- sort(SkeptResults$pvalue, index.return = TRUE)

Z1 <- Z

Z1$pvalue[which(Z1$pvalue == 0)] <- 0.001

g <- ggplot(data = Z1, aes(y = Posterior.Probability.MCID,
          x = pvalue, color = Contradictory)) +
    geom_hline(yintercept = 0.5, color = "grey") +
    geom_vline(xintercept = 0.05, color = "grey") +
    geom_point(alpha = 0.5,
          size = 4,
          stroke = 0) +
    facet_grid(. ~ Prior) +
    theme_minimal() +
    scale_color_manual(values = c("red", "blue"),
                breaks = c(TRUE, FALSE),
                name = "Potential Discordance between Bayesian and Frequentist Analyses",
                labels = c("No", "Yes")) +
    guides(alpha = "none", size = "none") +
    theme(legend.position="bottom",
        plot.caption = element_text(hjust = 0)) +
    labs(title = "Probability of Clinical Benefit versus P-value for Randomized Trials in Critical Care Medicine",
        x = "P-value (log scale)",
        y = "Posterior probability of ARR exceeding MCRE",
        caption = "ARR = absolute risk reduction. MCRE = minimum clinically relevant effect. \nAgreement: Bayesian p
robability of 50% or more that ARR > MCRE and trial is positive by frequentist criteria, \n or Bayesian probability of less
than 50% that ARR > MCRE and trial is negative by frequentist criteria.") +
    scale_x_continuous(
        trans = "log",
        breaks = c(0.01,0.05, 0.2,1.0)) +
    scale_y_continuous(
        breaks = c(0,0.5,1))

g
```

Code for Figure E2: Prior-Dependent Shift in Posterior Probability versus Sample Size
```
reversed <- reverse(SkeptResults,EnthResults)$Reversal

Z1$SampleSize <- d$sizectrl + d$sizetx1

A <- select(filter(Z1, Prior == "Enthusiastic"), Posterior.Probability.MCID, SampleSize,Contradictory, Observed.Mean)
A$Reversed <- reversed
B <- select(filter(Z1, Prior == "Skeptical"), Posterior.Probability.MCID)
A <- mutate(A, ProbabilityShift = Posterior.Probability.MCID -
```

```r
        B$Posterior.Probability.MCID)

g <- ggplot(data = A,
        aes(x = SampleSize,
            y = ProbabilityShift,
            color = Reversed,
            alpha = 0.3)) +
      geom_point(size = 4,
            alpha = 0.5,
            stroke = 0) +
      theme_minimal() +
      scale_color_manual(values = c("blue", "red"),
                breaks = c(TRUE, FALSE),
                name = "Reversal from Improbable to Probable Clinical Benefit",
                labels = c("Yes", "No")) +
      scale_x_continuous(trans = "log",
                breaks = c(200,400,800,1600,3200,6400,12000,20000)) +
      guides(alpha = "none") +
      theme(legend.position="bottom",
          plot.caption = element_text(hjust = 0)) +
      labs(title = "Prior-Dependent Shift in Posterior Probability versus Sample Size",
        x = "Sample Size (log scale)",
        y = "Change in Probability of ARR exceeding MCRE",
        caption = "Change in probability refers to the difference in posterior probability of ARR exceeding MCRE compa
ring \n enthusiastic and skeptical priors. \nARR = absolute risk reduction. MCRE = minimum clinically relevant effect. \n
Reversal: posterior probability of ARR > MCRE changes from less than 50% to greater than 50% when \nchanging from s
keptical to enthusiastic priors.")

g
```

Code for Figure E3: Prior-Dependent Shift in Posterior Mean versus Sample Size

```r
Z1$SampleSize <- d$sizectrl + d$sizetx1

A <- select(filter(Z1, Prior == "Enthusiastic"), Posterior.Mean, SampleSize,Contradictory,Observed.Mean)
A$Contradictory <- filter(Z1, Prior == "Uninformative")$Contradictory
B <- select(filter(Z1, Prior == "Skeptical"), Posterior.Mean)
A <- mutate(A, MeanShift = Posterior.Mean -
      B$Posterior.Mean)

g <- ggplot(data = A,
        aes(x = SampleSize,
            y = MeanShift,
            color = Contradictory,
            size = abs(Observed.Mean),
            alpha = 0.3)) +
      geom_point() +
      theme_minimal() +
      scale_color_manual(values = c("red", "blue"),
                breaks = c(TRUE, FALSE),
                name = "Potential Discordance between Bayesian and Frequentist Analyses",
                labels = c("No", "Yes")) +
      scale_x_continuous(trans = "log",
                breaks = c(200,400,800,1600,3200,6400,12000,20000)) +
      guides(alpha = "none", size = "none") +
      theme(legend.position="bottom",
```

```
        plot.caption = element_text(hjust = 0)) +
    labs(title = "Prior-Dependent Shift in Posterior Mean versus Sample Size",
        x = "Sample Size (log scale)",
        y = "Absolute Change in Posterior Mean ARR",
        caption = "Change in posterior mean refers to the difference in posterior mean comparing enthusiastic and skeptic
al priors. \nARR = absolute risk reduction. MCRE = minimum clinically relevant effect. \nAgreement: Bayesian probabili
ty of 50% or more that ARR > MCRE and trial is positive by frequentist criteria, \n or Bayesian probability of less than 50
% that ARR > MCRE and trial is negative by frequentist criteria. \nSize of point corresponds to absolute value of observe
d mean.")

g
```

Code for Figure E4: Alternative Forest Plot of Results Across Priors

```
pvalues <- sort(as.character(SkeptResults$pvalue))
t1 <- seq(from = 2, to = 82, by = 5)
pvalues[t1] <- rep("",length(t1))
pvalues[t1+1] <- rep("",length(t1))
t2 <- seq(from = 4, to = 82, by = 5)
pvalues[t2] <- rep("",length(t2))
pvalues[t2+1] <- rep("",length(t2))


g <- ggplot(data = Z, aes(y = Posterior.Mean, ymin = Low, ymax = High, x = fct_reorder(Study,pvalue))) +
    geom_errorbar(size = 0.2) +
    geom_point(aes(fill = Posterior.Probability.MCID, size = 1/Posterior.SD), alpha = 0.5, color = "black", shape = 21)
+
    labs(title = "Posterior Mean of Absolute Risk Reduction",
        y = "Absolute Risk Reduction (%)",
        x = "Study (ordered by p-value)") +
    theme_minimal() +
    facet_grid(Prior~.) +
    scale_x_discrete(labels = pvalues) +
    coord_flip(ylim = c(-10,15), expand = TRUE) +
    scale_size_area(guide = "none", max_size = 6) +
    scale_fill_gradient2(
        breaks = c(0,0.5,1),
        low = "red",
        mid = "white",
        midpoint = 0.5,
        high = "blue",
        limits = c(0,1),
        name = "Pr(ARR > MCRE)") +
    theme_ridges() +
    theme(axis.text.y = element_text(size = 4),
        panel.grid.major.y = element_blank())

g
```

Code for Figure E5: MCID Box-Plot

```
MCID_data$studyid <- factor(MCID_data$studyid)
MCID_data$MCID <- 100*MCID_data$MCID

pharmVec <- data.frame(studyid = d$studyid,pharma = d$pharmacologic)
pharmVec$studyid <- factor(pharmVec$studyid)

MCID_data <- left_join(MCID_data,pharmVec, by = "studyid")
```

```r
g <- ggplot(data = MCID_data,
       aes(x = fct_reorder(
           studyid,MCID, .fun = median),
         y = MCID,
         group = studyid,
         fill = factor(pharma))) +
     geom_boxplot(
         outlier.shape =  NA) +
     geom_jitter(alpha = 0.5, size = 1) +
     labs(title = "Minimum Clinically Relevant Effect by Study",
         x = "Study (ordered by median MCRE)",
         y = "Minimum clinically relevant effect (%)"
     ) +
     scale_fill_discrete(name = "Pharmacologic",
                 labels = c("No","Yes"))+
     coord_flip() +
     theme_ridges()
g
```

Code for Figure E6: Posterior Probability of Clinical Benefit by MCID

```r
# Plot of Posterior Probabilities by MCRE
library(dplyr)
# takes input of dataframe MinInfResults (or that type) and factor t that multiplies the MCIDs
ClinicalBenefitByMCID <- function(Z, t){
 tmp <- select(mutate(Z, PostProbMCID = 1-pnorm(t*MCID, mean = Posterior.Mean, sd = Posterior.SD)), PostProbMC
ID)
}

MCID_ts <- c(0.25, 0.5, 1, 1.5, 2)

Q <- select(MinInfResults, Posterior.Mean, Posterior.SD, Study, pvalue, Observed.Mean)

for (i in 1:length(MCID_ts)){
 Q <- cbind(Q, ClinicalBenefitByMCID(Q, MCID_ts[i]))
 names(Q)[5+i] <- paste0(round(MCID_ts[i]*100), "%")
}

Q <- gather(Q, key = "MCRE", value = "PosteriorProbability", -Posterior.Mean, -Posterior.SD, -Study, -pvalue, -Observe
d.Mean)
Q <- mutate(Q, MCRE = ordered(MCRE, levels = c("25%","50%","100%","150%","200%"))) %>%
 mutate(discordant = (pvalue < 0.05 & PosteriorProbability < 0.5 & Observed.Mean > 0) | (pvalue > 0.05 & PosteriorPro
bability > 0.5))

g <- ggplot(data = Q,
       aes(x = MCRE, y = PosteriorProbability, group = Study)) +
 geom_path(color = "grey",
       alpha = 0.3,
       size = 1) +
 geom_point(aes(color = discordant),
       alpha = 0.4,
       stroke = 0,
       size = 4) +
 theme_minimal() +
 scale_color_manual(values = c("blue", "red"),
```

```
                    breaks = c(TRUE, FALSE),
                    name = "Potential Discordance between Bayesian and Frequentist Analyses",
                    labels = c("Yes", "No")) +
    theme(legend.position="bottom",
            plot.caption = element_text(hjust = 0)) +
        labs(title = "Posterior Probability of Clinical Benefit by MCRE Value",
            x = "Percentage of Adjudicated Minimum Clinically Relevant Effect (MCRE)",
            y = "Posterior Probability of Exceeding the Modified* MCRE",
            caption = "This plot shows the sensitivity of calculations of posterior probability of achieving the MCRE for diffe
rent values \nof MCRE. Each point shows the posterior probability of exceeding an effect equal to the indicated percentag
e \nof the adjudicated MCRE. Lines connect estimates from the same trial.")

g
```

References

1. Abrams D, Montesi S, Moore S, et al. Design bias and clinically important treatment effects in randomized trials. *Crit Care Med*. 2020;In press.

2. McGlothlin AE, Lewis RJ. Minimal clinically important difference: Defining what really matters to patients. *JAMA - J Am Med Assoc*. 2014;312(13):1342-1343. doi:10.1001/jama.2014.13128

3. Van Walraven C, Mahon JL, Moher D, Bohm C, Laupacis A. Surveying physicians to determine the minimal important difference: Implications for sample-size calculation. *J Clin Epidemiol*. 1999;52(8):717-723. doi:10.1016/S0895-4356(99)00050-5

4. Cranston JS, Kaplan BD, Saver JL. Minimal clinically important difference for safe and simple novel acute ischemic stroke therapies. *Stroke*. 2017;48(11):2946-2951. doi:10.1161/STROKEAHA.117.017496

5. Perkins EM. Less morphine, or more?. *RN*. 2002;65(11):51-54. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12465527.

6. Nichol G, Brown SP, Perkins GD, et al. What change in outcomes after cardiac arrest is necessary to change practice? Results of an international survey. *Resuscitation*. 2016;107:115-120. doi:10.1016/j.resuscitation.2016.08.004

7. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. *N Engl J Med*. 2012;367(14):1287-1296. doi:10.1056/NEJMoa1208410

8. Brunkhorst FM, Engel C, Bloos F, et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. *N Engl J Med*. 2008;358(2):125-139. doi:10.1056/NEJMoa070716

9. Mathurin P, Louvet A, Duhamel A, et al. Prednisolone With vs Without Pentoxifylline and Survival of Patients With Severe Alcoholic Hepatitis. *JAMA*. 2013;310(10):1033. doi:10.1001/jama.2013.276300

10. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. *N Engl J Med*. 2015;372(25):2398-2408. doi:10.1056/NEJMoa1502826

11. Svensson L, Bohm K, Castrèn M, et al. Compression-Only CPR or Standard CPR in Out-of-Hospital Cardiac Arrest. *N Engl J Med*. 2010;363(5):434-442. doi:10.1056/NEJMoa0908991

12. Combes A, Bréchot N, Amour J, et al. Early High-Volume Hemofiltration versus Standard Care for Post–Cardiac Surgery Shock. The HEROICS Study. *Am J Respir Crit Care Med*. 2015;192(10):1179-1190. doi:10.1164/rccm.201503-0516OC

13. Taccone P, Pesenti A, Latini R, et al. Prone Positioning in Patients With Moderate and Severe Acute Respiratory Distress Syndrome. *JAMA*. 2009;302(18):1977. doi:10.1001/jama.2009.1614

14. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome. *JAMA*. 2008;299(6):637. doi:10.1001/jama.299.6.637

15. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure. *JAMA*. 2015;314(16):1711. doi:10.1001/jama.2015.12402

16. Mercat A, Richard J-CM, Vielle B, et al. Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome. *JAMA*. 2008;299(6):646. doi:10.1001/jama.299.6.646

17. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma. *JAMA*. 2015;313(5):471. doi:10.1001/jama.2015.12

18. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med*. 2018;378(21):1965-1975. doi:10.1056/NEJMoa1800385

19. Xie Y. knitr: A Comprehensive Tool for Reproducible Research in R. In: Stodden V, Leisch F, Peng RD, eds. *Implementing Reproducible Research*. Chapman and Hall/CRC; 2014:3-32. doi:xxx

20. Gómez-Rubio V. *Ggplot2 - Elegant Graphics for Data Analysis (2nd Edition)*. Vol 77. Springer-Verlag New York; 2017. doi:10.18637/jss.v077.b02

21. Urbanek S, Horner J. Cairo: R Graphics Device using Cairo Graphics Library for Creating High-Quality Bitmap (PNG, JPEG, TIFF), Vector (PDF, SVG, PostScript) and Display (X11 and Win32) Output. 2020. https://cran.r-project.org/package=Cairo.

22. Auguie B, Antonov A. gridExtra: Miscellaneous Functions for "Grid" Graphics. 2017. https://cran.r-project.org/package=gridExtra.

23. Meschiari S. latex2exp: Use LaTeX Expressions in Plots. 2015. https://cran.r-project.org/package=latex2exp.

24. Wickham et. al. Welcome to the Tidyverse. *J Open Source Softw*. 2019;4(43):1686. https://doi.org/10.21105/joss.01686.