

1 **Effect of a peri-operative, cardiac output-guided, hemodynamic**
2 **therapy algorithm on outcomes following major gastrointestinal**
3 **surgery: A multi-center randomized controlled trial**

4
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34 **Summary**

35 **Importance**

36 Annually, over 230 million patients undergo surgery worldwide. Complications and death are
37 frequent among high-risk patients undergoing major gastrointestinal surgery. Pooled small trials
38 suggest outcomes may be improved by peri-operative, cardiac output-guided, hemodynamic
39 therapy.

40

41 **Objective**

42 To evaluate the clinical effectiveness of a peri-operative, cardiac output-guided, hemodynamic
43 therapy algorithm.

44

45 **Design**

46 Pragmatic, multi-center, randomized trial and updated systematic review.

47

48 **Setting**

49 17 acute hospitals in the UK.

50

51 **Participants**

52 734 high-risk patients; aged over 50 years undergoing major gastrointestinal surgery.

53

54 **Interventions**

55 Delivery of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm for intra-
56 venous fluid and inotrope (dopexamine) infusion during and for six hours following surgery,
57 compared with usual peri-operative care.

58

59 **Main outcome measures**

60 The primary outcome was a composite of pre-defined moderate or major post-operative
61 complications and mortality at 30 days following surgery. Secondary outcomes were morbidity on
62 day 7, infectious complications, critical care free days and all cause mortality at 30 days following
63 surgery, all cause mortality at 180 days following surgery and acute hospital length of stay.

64

65 **Results**

66 Baseline patient characteristics, clinical care and volumes of intra-venous fluid were similar
67 between groups. Allocated care was non-compliant for fewer than 10% of patients in each group.
68 The primary outcome was 36.6% for the intervention and 43.4% for usual care (RR 0.84 [0.71-
69 1.01], ARR 6.8% [-0.3% to 13.9%]; p=0.07). There was no significant difference for any of the
70 secondary outcomes. Five intervention patients (1.4%) experienced cardiovascular serious
71 adverse events within 24 hours compared with none in the usual care group. In pre-specified
72 analyses, the primary outcome treatment effect was strengthened after adjustment for protocol
73 compliance (RR 0.80 [0.61-0.99]) and exclusion of the first ten patients recruited at each site (RR
74 0.59 [0.41-0.84]). The findings of the updated systematic review suggest that patients receiving
75 the intervention are less likely to develop complications (Intervention 488/1548 [31.5%] vs
76 Controls 614/1476 [41.6%]; RR 0.77 [0.71-0.83]).

77

78 **Conclusions**

79 Whilst the cardiac output-guided, hemodynamic therapy algorithm was not associated with a
80 significant reduction in post-operative complications in this trial, the findings of the updated
81 systematic review suggest this intervention is associated with clinically important reductions in
82 complications rates.

83

84 **Trial registration:** <http://www.controlled-trials.com/ISRCTN04386758>

85 **Short summary**

86 Findings from small trials suggest post-operative outcomes may be improved by cardiac output-
87 guided, hemodynamic therapy but this remains unconfirmed. In a multi-center randomized trial,
88 we allocated 734 high-risk patients undergoing major gastrointestinal surgery to a hemodynamic
89 therapy algorithm for intra-venous fluid and inotrope (dopexamine) infusion during and six hours
90 following surgery, or usual care. The primary outcome of pre-defined moderate or major post-
91 operative complications was met by 36.6% of intervention patients and 43.4% of usual care
92 patients (RR 0.84 [0.71-1.01]; p=0.07). Whilst not statistically significant, these findings were
93 consistent with those of a recent Cochrane systematic review. When the systematic review was
94 updated to include our results, significantly fewer patients developed complications having
95 received this intervention (RR 0.70 [0.62-0.80]; p=0.01). The combined findings of the randomized
96 trial and systematic review suggest cardiac output-guided hemodynamic therapy may be
97 associated with a clinically important reduction in complications after surgery.

98

99

100 **Introduction**

101 Estimates suggest that over 230 million patients undergo surgery worldwide each year with
102 mortality reported between 1 and 4%.^{1,2} Complications and deaths are most frequent among
103 high-risk patients, those who are older or have co-morbid disease and undergo major
104 gastrointestinal or vascular surgery. Patients who develop complications, but survive to leave
105 hospital, suffer reduced functional independence and longer-term survival.³⁻⁵ Variation in
106 mortality indicates both the potential and the need to improve survival after major surgery.^{2,6}
107 Given the high volumes of surgery, even a low rate of avoidable harm will be associated with a
108 large number of preventable deaths.

109

110 It is generally accepted that intra-venous fluid and inotropic drugs have an important effect on
111 patient outcome, in particular following major gastrointestinal surgery. Yet, they are commonly
112 prescribed on subjective criteria leading to wide variation in clinical practice.⁷ One possible
113 solution is the use of cardiac output monitoring to guide intra-venous fluid and inotropic drug
114 therapy as part of a hemodynamic therapy algorithm. This approach has been shown to modify
115 inflammatory pathways, improve tissue perfusion and oxygenation,^{8,9} and possibly improve
116 clinical outcomes.¹⁰⁻¹⁶ The current evidence base consists of a number of small trials insufficient
117 to resolve controversies regarding potential harm associated with fluid excess, myocardial injury
118 and invasive forms of monitoring. As a result, this approach has not been widely adopted into
119 clinical practice. More recently, hemodynamic therapy algorithms have been adapted to utilize
120 less invasive forms of cardiac output monitoring and lower doses of inotropic therapy for shorter
121 periods.¹² These refinements have improved the feasibility, safety and costs but clinical
122 effectiveness remains unconfirmed. Despite this, use of hemodynamic therapy algorithms has
123 been recommended in a report commissioned by the Centers for Medicare and Medicaid Services
124 in the USA,¹⁷ and by the National Institute for Health and Care Excellence (NICE) in the UK,¹⁸

125 based on the findings of a number of small trials which suggest improved clinical outcomes. A
126 recent Cochrane review, however, has suggested that the treatment benefit may be more
127 marginal than previously believed.¹⁵ The mortality benefit has become less apparent in more
128 recent trials with lower control group mortality.¹⁴

129

130 In this context, we developed a peri-operative, cardiac output-guided, hemodynamic therapy
131 algorithm for the administration of intra-venous fluid and inotropic therapy, supported by solid
132 clinical and mechanistic evidence. Our objective was to evaluate the clinical effectiveness of this
133 algorithm in a large, pragmatic, multi-center randomized controlled trial in high-risk patients
134 undergoing major gastrointestinal surgery. We then conducted an updated systematic review
135 incorporating the findings of this trial.

136

137 **Methods**

138 ***Trial design***

139 OPTIMISE was a multi-center, randomized controlled trial conducted in seventeen acute hospitals
140 in the National Health Service in the United Kingdom. Adult patients, aged 50 years or over
141 undergoing major abdominal surgery involving the gastrointestinal tract of expected duration
142 greater than 90 minutes, were eligible for recruitment provided they satisfied one of the following
143 high-risk criteria: aged 65 years or over; presence of a defined risk factor for cardiac or respiratory
144 disease; renal impairment (serum creatinine ≥ 1.5 mg dl⁻¹); diabetes mellitus; or emergency surgery.
145 Exclusion criteria included refusal of consent, pregnancy, acute pulmonary edema (within prior
146 seven days), acute myocardial ischemia (within prior 30 days) and patients undergoing surgery for
147 palliative treatment only. Investigators were asked not to randomize patients where the clinician
148 intended to use cardiac output monitoring for clinical reasons. OPTIMISE was approved by the East
149 London & City Research Ethics Committee (09/H0703/23) and the Medical and Healthcare products
150 Regulatory Agency and registered with Controlled Trials (ISRCTN04386758). Written informed
151 consent was obtained from all patients prior to surgery. Site visits were performed by RP and AA
152 for training and for source data verification. The trial protocol was lodged and is available online at
153 www.perioperativemedicine.net/OPTIMISE.

154

155 ***Randomization and procedures to minimize bias***

156 Randomization was performed through a dedicated, secure, web-based system. Participants were
157 allocated to treatment groups using a computer-generated, dynamic procedure (minimization) with
158 a random component. Participants were allocated, with an 80% probability, to the group that
159 minimized between group differences in trial site, urgency of surgery and surgical procedure
160 category among all participants recruited to date. This was a pragmatic effectiveness trial and it
161 was not possible to blind all investigators to study group allocation. To minimize bias, investigators

162 were instructed not to reveal study group allocation unnecessarily. Patients were followed up by
163 another investigator who, wherever possible, was unaware of allocation. Investigators performing
164 follow-up self-assessed the extent to which they remained blinded. Outcomes were verified
165 according to pre-defined criteria by the principal investigator or designee at each site, who was
166 always blinded to allocation. The decision to admit a trial patient to critical care was made by
167 clinical staff and recorded prior to randomization and surgery, allowing comparison with actual
168 location of post-operative care.

169

170 ***Clinical management***

171 The intervention period commenced with induction of anesthesia and continued until six hours
172 following completion of surgery.

173

174 *All patients*

175 Peri-operative care for all patients was loosely defined to avoid extremes of clinical practice and
176 practice misalignment.¹⁹ All patients received standard measures to maintain oxygenation (SpO₂
177 ≥94%), hemoglobin (>80 g l⁻¹), core temperature (37 °C) and heart rate (<100 beats min⁻¹). 5%
178 dextrose was administered at 1 ml kg⁻¹ hr⁻¹ to satisfy maintenance fluid requirements. Additional
179 fluid was administered at the discretion of the treating clinician guided by pulse rate, arterial
180 pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess.
181 Mean arterial pressure was maintained between 60 and 100 mmHg using an alpha adrenoceptor
182 agonist or vasodilator, as required. Post-operative analgesia was provided by epidural infusion
183 (bupivacaine and fentanyl) or intra-venous infusion (morphine or fentanyl). With the exception of
184 the interventions below, all other treatment decisions were at the discretion of, and taken by,
185 senior clinicians.

186

187

188 *Hemodynamic therapy algorithm group patients*

189 Intervention group patients received intra-venous fluid and inotropes according to a cardiac
190 output-guided, hemodynamic therapy algorithm (supplementary file). The algorithm was
191 developed for OPTIMISE by an expert group. It was designed to be delivered in the operating
192 room/post-anesthetic care unit by both medical and nursing staff, ensuring that admission for
193 critical care was not necessary for compliance. A cardiac output monitor was chosen which could
194 be used in conscious (extubated) patients (LiDCOrapid, LiDCO Ltd, UK). This technology has been
195 extensively evaluated and in clinical use for more than ten years.²⁰ The hemodynamic therapy
196 algorithm was supported by solid clinical and mechanistic evidence and had a good cardiovascular
197 safety profile.^{8-16,21-23} Intra-venous colloid solution was administered in 250ml boluses in order to
198 achieve and maintain a maximal value of stroke volume; no attempt was made to standardize
199 choice of colloid. Dopexamine was administered at a fixed, low dose of $0.5 \mu\text{g kg}^{-1} \text{min}^{-1}$ either
200 through a peripheral or a central venous catheter (Cephalon Ltd, Welwyn Garden City, UK). The
201 choice and dose of inotrope was based on the findings of a previous meta-regression analysis.¹³ The
202 dose of dopexamine was reduced if the heart rate increased to 120% of baseline or $100 \text{ beats min}^{-1}$
203 (whichever was greater) for more than 30 minutes despite adequate anesthesia and analgesia. If
204 the heart rate did not decrease despite dose reduction, then the infusion was discontinued.

205

206 *Usual care group patients*

207 These patients received usual peri-operative care although the use of a dynamic central venous
208 pressure target was recommended. Cardiac output monitoring was not used in the usual care
209 group unless specifically requested by clinical staff because of patient deterioration.

210

211 ***Trial endpoints***

212 The primary effect estimate was the relative risk of a composite of pre-defined moderate or major
213 post-operative complications and mortality at 30 days following surgery (supplementary file).

214 Secondary outcomes were: Post-Operative Morbidity Survey (POMS) defined morbidity on day 7;²⁴
215 infectious complications, critical care free days (number of days alive and not in critical care) and all
216 cause mortality at 30 days following surgery; all cause mortality at 180 days following surgery; and
217 acute hospital length of stay. Level of post-operative critical care was categorized according to
218 standard criteria.²⁵ Patients were followed for 30 days by visit and through local computerized
219 records while in hospital. All patients were contacted at 30 days either by telephone for those who
220 had left hospital or by visit for those who had not. Where necessary, investigators contacted
221 community physicians or other hospitals, by telephone and in writing, for outstanding information
222 describing the primary outcome. All cause mortality at 180 days was assessed through the Office
223 for National Statistics. Data entry was performed through a dedicated, secure, web-based system.
224 Automated validation checks included plausibility ranges and cross checks between data fields.
225 Further data checks were performed centrally and through source data verification.

226

227 ***Statistical analysis***

228 Assuming a type I error rate of 5%, 345 patients per group (690 total) were required to detect, with
229 90% power, a reduction in the composite of pre-defined moderate or major post-operative
230 complications and mortality at 30 days following surgery from 50% in the usual care group to 37.5%
231 in the hemodynamic therapy algorithm group (absolute risk reduction 12.5%; relative risk reduction
232 25%).¹² Allowing for a 3% one-way, cross-over rate due to use of cardiac output monitoring in the
233 usual care group, this was increased to 367 per group (734 total). A planned interim analysis was
234 performed at halfway. Pre-defined stopping guidelines permitted early termination of the trial for
235 harm but not effectiveness.

236

237 Analyses were performed according to an a priori statistical analysis plan including all patients on
238 an intention to treat basis (supplementary file). Categorical data were compared using Fisher's

239 exact test. Differences in critical care free days and acute hospital length of stay were tested using
240 the Wilcoxon rank-sum test. Kaplan-Meier curves were plotted for all cause mortality up to 180
241 days following surgery. Adjustment for baseline data was made using a logistic regression model
242 including age, gender, urgency of surgery, surgical procedure category, ASA grade, planned location
243 following surgery, renal impairment, diabetes mellitus, risk factors for cardiac or respiratory
244 disease and random effect of site. Baseline variables were selected for inclusion in the adjusted
245 analysis according to anticipated relationship with outcome, including all variables used in the
246 minimization algorithm. Results for primary and secondary outcomes are reported as relative risks
247 (RR) with 95% confidence intervals (CI). Results for the primary outcome are additionally reported
248 as absolute risk reduction (ARR) with 95% CI. Results of the logistic regression model are reported
249 as adjusted odds ratios (OR) with 95% CI, with unadjusted OR for comparison.

250

251 Pre-specified secondary analyses were: a modified intention to treat analysis excluding patients
252 who did not undergo surgery; a compliance-adjusted analysis in which patients whose treatment
253 did not comply with allocation were assumed to have the same outcome as if they had been
254 assigned to the alternative treatment group;²⁶ and scenario-based sensitivity analyses for missing
255 primary outcomes (a best cases analysis assuming all missing outcomes in the intervention group
256 were favorable and all missing outcomes in the usual care group were unfavorable and a worst
257 case analysis assuming the reverse). Pre-specified sub-group analyses were performed: by urgency
258 of surgery; by surgical procedure category; and by timing of recruitment (comparing the first ten
259 patients recruited at each site with those recruited subsequently (sites recruiting fewer than ten
260 patients were excluded). Continuous variables are presented as mean (SD) where normally
261 distributed or median (quartiles) where not. Categorical variables are presented as n (%). Analyses
262 were performed using Stata SE version 10.1. Significance was set at $p < 0.05$ (two-tailed).

263

264 ***Systematic review***

265 Using identical methods, we updated the previous Cochrane systematic review (SR) of published
266 randomized trials of 'Peri-operative increase in global blood flow to explicit defined goals and
267 outcomes following surgery' with the findings of the OPTIMISE Trial and other published trials
268 identified by an updated search.¹⁵ CENTRAL (Cochrane Library 2014), MEDLINE (1966 to February
269 2014) and EMBASE (1982 to February 2014) were searched for randomized trials involving adult
270 patients (≥ 16 years) undergoing surgery in an operating room where the intervention met the
271 following criteria: Peri-operative administration of fluids, with or without inotropes/vasoactive
272 drugs, targeted to increase blood flow (relative to control) against explicit measured goals. 'Peri-
273 operative' was defined as: initiated within 24 hours before surgery and lasting up to 6 after surgery.
274 'Explicit measured goals' were defined as: cardiac index, oxygen delivery, oxygen consumption,
275 stroke volume, mixed venous oxygen saturation, oxygen extraction ratio or lactate. We selected the
276 following key outcomes: number of patients with complications (primary outcome variable for the
277 OPTIMISE trial), number of infections, length of postoperative hospital stay, mortality at longest
278 follow-up (primary outcome variable of Cochrane SR) and 28 day/30 day/hospital mortality.
279 Treatment effects were reported as relative risks (RR) with 95% CI for clinical variables or weighted
280 mean differences (SD) for length of hospital stay. Analyses were performed using Review Manager
281 (RevMan 5.2.8) using fixed effects models.

282

283 **Results**

284 A total of 734 patients were enrolled between June 2010 and November 2012; 368 patients were
285 allocated to the cardiac output-guided, hemodynamic therapy algorithm, and 366 to usual care. In
286 the usual care group, one patient was randomized in error and excluded from the study (eFigure 1).
287 Baseline patient characteristics were similar between the groups (Table 1). Most patient types
288 were well represented with the exception of those having emergency surgery (25 patients) and
289 those having urological or gynecological surgery involving the gut (nine patients). Clinical care
290 outside the trial intervention was also similar (Table 2), including admission for critical care. Overall
291 volumes of intra-venous fluid (colloid and crystalloid combined) administered during the
292 intervention period were similar (intervention 4190 ml versus usual care 4024 ml). For usual care
293 group patients, more intra-venous fluid was administered during than after surgery, while for
294 intervention group patients similar volumes were administered during surgery and during the six
295 hours following surgery. Intervention group patients received more colloid and less crystalloid than
296 usual care group patients. With the exception of dopexamine, use of vasopressor and inotropic
297 agents was similar between the groups. Fewer than 10% of patients in each group were non-
298 compliant with their allocated treatment (eTable 1). This was achieved through the presence of
299 trained investigators, where necessary, to observe, advise or deliver the intervention (eTable 2).
300 Investigator self-assessment of blinding for determination of outcomes also indicated a high rate of
301 compliance with trial procedures (Table 3).

302

303 The primary outcome, a composite of pre-defined moderate or major post-operative complications
304 and mortality at 30 days following surgery, was met by 36.6% (134 of 366) of patients in the
305 intervention group and by 43.4% (158 of 364) of patients in the usual care group (RR 0.84 [0.71-
306 1.01], ARR 6.8% [-0.3% to 13.9%]; p=0.07) (Table 3). Following adjustment for baseline risk factors,
307 the observed treatment effect remained non-significant with an adjusted OR of 0.73 [0.53-1.00];

308 p=0.05 (unadjusted OR 0.75 [0.56-1.01]; p=0.07). The pre-specified, modified, intention to treat
309 analysis, in which three patients (all in the usual care group) who did not undergo surgery were
310 excluded, had little effect on the primary outcome (RR 0.84 [0.70-1.00]; p=0.06). In the pre-
311 specified, compliance-adjusted analysis conducted using established methodology,²⁶ the observed
312 treatment effect was strengthened when the 65 patients whose care was non-compliant (eTable 1)
313 were assumed to experience the same outcome as if they had been allocated to the alternative
314 group (RR 0.80 [0.61-0.99]; p=0.037). Scenario-based sensitivity analyses demonstrated that the
315 very small number of patients with missing primary outcome data had minimal influence on
316 treatment effect (RR 0.84 [0.70-1.00] to 0.85 [0.71-1.02]).

317

318 Five patients in the intervention group experienced serious adverse cardiac events within 24 hours
319 of the end of the intervention period (two tachycardia, two myocardial infarction and one
320 arrhythmia) compared with none in the usual care group (p=0.062). At 30 days following surgery,
321 however, the incidence of cardiovascular events was similar between the groups (Table 3). There
322 were no significant differences for any of the secondary outcomes: POMS defined morbidity on day
323 7; infectious complications, critical care free days and all cause mortality at 30 days following
324 surgery; all cause mortality at 180 days following surgery; and duration of acute hospital length of
325 stay (Table 4, Figure 1). No interaction was found for urgency of surgery, the intervention was
326 associated with a slight reduction in the primary outcome for the elective surgery sub-group. No
327 interaction was found for surgical procedure category, the intervention was associated with a slight
328 reduction in the primary outcome for patients undergoing small bowel +/- pancreas surgery. A
329 significant interaction (p=0.019) was found for timing of recruitment, the intervention was
330 associated with a reduction in the primary outcome for patients recruited later (RR 0.59 [0.41-0.84]
331 compared with earlier at each site (RR 1.51 [0.75-3.01] (Table 5).

332

333

334 ***Systematic review***

335 The updated literature search identified seven additional trials including OPTIMISE, to provide a
336 total of 38 trials that included 6595 participants with 23 trials including 3024 participants providing
337 data describing our primary outcome. Fewer patients receiving the intervention developed
338 complications (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0.77 [0.71-0.83])
339 (Figure 2). The intervention was associated with a reduced incidence of post-operative infection
340 (Intervention 182/836 patients [21.8%] vs Controls 201/790 patients [25.4%]; RR 0.81 [0.69-0.95])
341 and a reduced duration of hospital stay (mean reduction 0.80 days (0.97-0.62)) (eFigures 2 and 3).
342 There was no significant reduction in hospital / 28 day / 30 day mortality (Intervention 159/3215
343 deaths [4.9%] vs Controls 206/3160 deaths [6.5%]; RR 0.82 [0.67-1.01]) and borderline evidence of
344 a reduction in mortality at longest follow-up (Intervention 267/3215 deaths [8.3%] vs Controls
345 327/3160 deaths [10.3%]; RR 0.86 [0.74-1.00]) (eFigures 4 and 5).

346

347

348 **Discussion**

349 The findings of the OPTIMISE trial were that in high-risk patients undergoing major abdominal
350 surgery involving the gastrointestinal tract, when compared with usual care, use of this peri-
351 operative, cardiac output-guided, hemodynamic therapy algorithm was not associated with a
352 significant reduction in the composite primary outcome of pre-defined moderate or major post-
353 operative complications and mortality at 30 days following surgery. However, after incorporating
354 the results of this large clinical trial into an updated systematic review of published trials, there was
355 evidence that cardiac output-guided, hemodynamic therapy is associated with a clinically
356 important reduction in the number of patients who develop complications after surgery.¹⁵ In the
357 OPTIMISE trial, there was no difference in the secondary outcomes of POMS defined morbidity at
358 day 7; infectious complications, critical care-free days or all cause mortality at 30 days; all cause
359 mortality at 180 days; or acute hospital length of stay. However, the findings of the updated
360 systematic review suggest this treatment approach is associated with a significant reduction in the
361 number of patients who develop post-operative infection as well as in duration of hospital stay.
362 The findings of the mortality analyses provide borderline evidence but remain consistent with
363 benefit.

364

365 This is the largest trial of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm,
366 to date. OPTIMISE was designed to address several limitations in the previous evidence base.²⁷ The
367 large sample size allowed for comparison of the cardiac output-guided hemodynamic therapy
368 algorithm with usual peri-operative care, avoiding problems associated with alternative 'control'
369 treatment algorithms which do not reflect typical practice.¹⁹ A large number of algorithms for
370 cardiac output guided hemodynamic therapy have been published describing a variety of options in
371 terms of hemodynamic end-points, use of inotropic agents and cardiac output monitoring. We used
372 an algorithm suited to the care of patients during and after major gastrointestinal surgery, that was

373 supported by solid clinical and mechanistic evidence and a good cardiovascular safety profile.^{8,9,10-15,}
374 ²⁴⁻²⁶ The β_2 -agonist dopexamine has mild inotropic and vasodilator effects and is the most widely
375 studied agent in this context. The findings of a meta-regression analysis suggested that
376 dopexamine infusion at low dose is associated with improved outcomes following major surgery.¹⁵
377 Further modifications were made by an expert group to allow delivery in the operating room and
378 post-anesthetic care unit by both medical and nursing staff and in particular to ensure admission to
379 critical care was not necessary for compliance with the intervention. Importantly, the high rate of
380 compliance with the hemodynamic therapy algorithm used in this trial suggests this treatment
381 approach is feasible for use in routine clinical practice. A widely used cardiac output monitoring
382 technology was employed (although our findings are not specific to this device). In keeping with the
383 pragmatic nature of the trial, no attempt was made to standardize the choice of colloid in either
384 group. Recent evidence has suggested an increased incidence of acute kidney injury in critically ill
385 patients receiving starch-based, colloid solutions.^{28,29} While we do not have individual patient data
386 describing the use of starch, a post-hoc survey of investigators suggested few patients received
387 this. A recent systematic review identified no evidence of acute kidney injury associated with the
388 use of starch solutions in surgical patients.³⁰

389

390 A potential weakness of OPTIMISE may be the use of a primary outcome that was a composite of
391 moderate or major post-operative complications and mortality. The components of this outcome
392 measure may reflect benefit, no effect or harm associated with the intervention. We controlled for
393 bias by assessing and grading this outcome according to pre-defined criteria and, although it is not
394 possible to blind all clinical staff administering complex interventions, our data suggest excellent
395 compliance with blinding for patient outcome assessment. Finally, the event rate in the usual care
396 arm was slightly lower than expected and cross-over in terms of cardiac output monitoring in the
397 usual care group was more frequent than predicted. These factors reduced the power of the trial,
398 perhaps resulting in failure to achieve statistical significance for the primary outcome. Although

399 emergency surgery was one of our inclusion criteria, we were only able to recruit a small number of
400 these patients. The approach to recruiting elective and emergency patients is quite different and
401 the design of future trials should take this into account. Whilst additional research staff were often
402 present during the trial, anesthesia and critical care staff would be able to deliver such algorithms
403 of care with minimal training. Myocardial injury is the most important adverse effect of
404 hemodynamic therapy algorithms; there was a low rate of cardiovascular serious adverse events
405 within 24 hours of the intervention and the incidence of cardiovascular events was similar between
406 the groups at 30 days following surgery. The trial findings also suggests that cardiac output-guided
407 fluid therapy need not result in excessive fluid administration but may lead to a more individualized
408 approach to achieving the correct dose of fluid, as and when required. Finally, a pre-specified
409 analysis of timing of recruitment suggested that a learning curve may have existed, consistent both
410 with an expectation for trials of complex interventions and from previous experience from
411 implementation in this field, and this warrants consideration in future research in this area.³¹

412 **Conclusion**

413 In this large multi-center trial, the use of a peri-operative, cardiac output-guided, hemodynamic
414 therapy algorithm for the administration of intra-venous fluid and a low-dose inotrope
415 (dopexamine) was not associated with a significant reduction in a composite primary outcome of
416 pre-defined moderate or major post-operative complications and mortality at 30 days following
417 surgery. However, when incorporated into an updated systematic review, these findings
418 contributed to a clinically important reduction in the number of patients who developed
419 complications.

420

421

422 **Author contributions**

423 Prof Pearse had full access to all of the data in the study and takes responsibility for the integrity
424 of the data and the accuracy of the data analysis.

425 *Study concept and design:* Pearse, Harrison, Hinds, Rowan.

426 *Acquisition of data:* Pearse, MacDonald, Gillies, Blunt, Ackland, Ahern, Scott.

427 *Analysis and interpretation of data:* All authors.

428 *Drafting of the manuscript:* Pearse, Harrison, Hinds, Rowan.

429 *Critical revision of the manuscript for important intellectual content:* All authors.

430 *Statistical analysis:* Griggs, Harrison.

431 *Systematic review:* Grocott, Pearse, Harrison, Rowan.

432 *Obtained funding:* Pearse, Harrison, Hinds, Rowan.

433 *Administrative, technical, or material support:* Pearse, Hinds, Rowan.

434 *Study supervision:* Pearse.

435

436 **Conflict of interest disclosures**

437 All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of
438 Interest. RP has received equipment loans from LiDCO Ltd, a research grant from Circassia Holdings
439 Ltd. and has performed consultancy work for Edwards Lifesciences, Covidien and Massimo Inc. CH
440 and RP are named inventors on a lapsed patent application relating to the peri-operative use of
441 dopexamine. MG has received an honorarium from LiDCO Ltd for organizing a teaching workshop.

442 All other authors declare they have no conflicts of interest. MPWG has received unrestricted grant
443 funding from Deltex Medical Ltd, and fees for lecturing from Fresenius Kabi and Edwards
444 Lifesciences.

445

446

447 **OPTIMISE Study group: (*denotes principal investigator)**

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540

541

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543 The funding bodies had no role in the design and conduct of the study; collection, management,
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546

547 **References**

- 548 1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a
549 modelling strategy based on available data. *Lancet*. 2008;372(9633):139-144.
- 550 2. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet*.
551 2012;380(9847):1059-1065.
- 552 3. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term
553 survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*.
554 2005;242(3):326-341.
- 555 4. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-
556 service program. *N Engl J Med*. 2009;360(14):1418-1428.
- 557 5. Head J, Ferrie JE, Alexanderson K, Westerlund H, Vahtera J, Kivimaki M. Diagnosis-specific sickness
558 absence as a predictor of mortality: the Whitehall II prospective cohort study. *BMJ*. 2008;337:a1469.
- 559 6. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery.
560 *N Engl J Med*. 2009;361(14):1368-1375.
- 561 7. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in
562 patients undergoing high risk surgery: a survey among North American and European
563 anesthesiologists. *Critical Care*. 2011;15(4):R197.
- 564 8. Jhanji S, Vivian-Smith A, Lucena-Amaro S, Watson D, Hinds CJ, Pearse RM. Haemodynamic
565 optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised
566 controlled trial. *Crit Care*. 2010;14(4):R151.
- 567 9. Bangash MN, Patel NS, Benetti E, et al. Dopexamine can attenuate the inflammatory response and
568 protect against organ injury in the absence of significant effects on haemodynamics or regional
569 microvascular flow. *Critical Care*. 2013;17(2):R57.
- 570 10. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative
571 increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA*. 1993;270(22):2699-2707.
- 572 11. Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled
573 trial of preoperative optimisation of oxygen delivery. *BMJ*. 1999;318(7191):1099-1103.

- 574 **12.** Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after
575 major surgery reduces complications and duration of hospital stay. A randomised, controlled trial
576 [ISRCTN38797445]. *Crit Care*. 2005;9(6):R687-693.
- 577 **13.** Pearse RM, Belsey JD, Cole JN, Bennett ED. Effect of dopexamine infusion on mortality following
578 major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care*
579 *Med*. 2008;36(4):1323-1329.
- 580 **14.** Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive
581 hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical
582 patients. *Anesth Analg*. 2011;112(6):1392-1402.
- 583 **15.** Grocott MP, Dushianthan A, Hamilton MA, Mythen MG, Harrison D, Rowan K. Perioperative increase
584 in global blood flow to explicit defined goals and outcomes following surgery. *Cochrane Database of*
585 *Systematic Reviews*. 2012;11:CD004082.
- 586 **16.** Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of
587 hospital stay after major surgery. *Anesthesiology*. 2002;97(4):820-826.
- 588 **17.** Esophageal Doppler ultrasound based cardiac output monitoring for real time therapeutic
589 management of hospitalized patients. 2007;
590 <http://www.cms.gov/determinationprocess/downloads/id45TA.pdf>.
- 591 **18.** CardioQ-ODM oesophageal doppler monitor. 2011;
592 <http://www.nice.org.uk/nicemedia/live/13312/52624/52624.pdf>.
- 593 **19.** Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies:
594 unintended consequences of using fixed treatment protocols. *Critical care medicine*. 2007;35(6):1509-
595 1516.
- 596 **20.** Marquez J, McCurry K, Severyn DA, Pinsky MR. Ability of pulse power, esophageal Doppler, and
597 arterial pulse pressure to estimate rapid changes in stroke volume in humans. *Crit Care Med*.
598 2008;36(11):3001-3007.
- 599 **21.** Pearse RM, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett D. The incidence of myocardial
600 injury following post-operative Goal Directed Therapy. *BMC Cardiovasc Disord*. 2007;7:10.

- 601 **22.** Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome
602 after major abdominal surgery: a prospective, randomized, controlled multicenter study. European
603 Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med.*
604 2000;28(10):3417-3423.
- 605 **23.** Stone MD, Wilson RJ, Cross J, Williams BT. Effect of adding dopexamine to intraoperative volume
606 expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth.* 2003;91(5):619-
607 624.
- 608 **24.** Grocott MP, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated
609 and used to describe morbidity after major surgery. *J Clin Epidemiol.* 2007;60(9):919-928.
- 610 **25.** Eddleston J, Goldhill D, Morris J. *Levels of Critical Care for Adult Patients.* London: Intensive Care
611 Society;2009.
- 612 **26.** Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized
613 clinical trials. *Statistics in medicine.* 1997;16(9):1017-1029.
- 614 **27.** MacDonald N, Pearse RM. Peri-operative hemodynamic therapy: only large clinical trials can resolve
615 our uncertainty. *Critical Care.* 2011;15(3):122.
- 616 **28.** Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in
617 severe sepsis. *The New England Journal of Medicine.* 2012;367(2):124-134.
- 618 **29.** Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive
619 care. *The New England Journal of Medicine.* 2012;367(20):1901-1911.
- 620 **30.** Gillies MA, Habicher M, Jhanji S, et al. Incidence of postoperative death and acute kidney injury
621 associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. *Br J Anaesth.*
622 2013.
- 623 **31.** Kuper M, Gold SJ, Callow C, et al. Intraoperative fluid management guided by oesophageal Doppler
624 monitoring. *BMJ.* 2011;342:d3016.

625

626 **Figure legends**

627

628 **Figure 1. Kaplan-Meier cumulative incidence plots for mortality by treatment allocation**
629 **to 180 days from start of surgery**

630 **Log rank test p-value: 0.093.**

631

632

633 **Figure 2. Forest plot of meta-analysis for number of patients developing complications**
634 **after surgery.**

635

636

637 **Table 1: Baseline patient characteristics**

638 **All data presented as n (%)**

639 *** Eligibility criterion**

640 **† Minimization criterion**

641 **‡ Patients may have more than one risk factor**

642

	Cardiac output-guided hemodynamic therapy algorithm (n=368)	Usual care (n=365)
Age (years)	71.3 (8.4)	72.2 (8.6)
Age*		
50-64 years	68 (18.5)	57 (15.6)
≥ 65 years	300 (81.5)	308 (84.4)
Sex		
Male	237 (64.4)	229 (62.7)
Female	131 (35.6)	136 (37.3)
Urgency of surgery*†		
Elective	356 (96.7)	352 (96.4)
Emergency	12 (3.3)	13 (3.6)
Baseline risk factors*‡		
Renal impairment	26 (7.1)	12 (3.3)
Diabetes mellitus	57 (15.5)	65 (17.8)
Pre-defined risk factor for cardiac or respiratory disease	117 (31.8)	118 (32.3)
Planned surgical procedure category†		
Upper gastrointestinal	110 (29.9)	114 (31.2)
Lower gastrointestinal	167 (45.4)	163 (44.7)
Small bowel +/- pancreas	86 (23.4)	84 (23.0)
Urological or gynecological surgery involving gut	5 (1.4)	4 (1.1)
ASA grade		
1	21 (5.7)	24 (6.6)
2	200 (54.5)	174 (48.1)
3	143 (39.0)	155 (42.8)
4	3 (0.8)	9 (2.5)
Planned location following surgery		
Critical care unit (level 3)	275 (74.7)	276 (75.6)
Critical care unit (level 2)	33 (9.0)	33 (9.0)
Post-surgical recovery unit	4 (1.1)	7 (1.9)
Ward	56 (15.2)	49 (13.4)

643

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645

646 **Table 2: Clinical management of patients during intervention period (during surgery and**
 647 **six hours following surgery)**

648 Data presented as mean (SD) or n (%)

649 * Two patients (one in each group) missing data on anesthetic technique

650 † Two patients (both usual care) missing data on fluids both during surgery and during six hours following
 651 surgery; one patient (hemodynamic therapy algorithm) missing data on fluids during six hours following
 652 surgery; one patient (hemodynamic therapy algorithm) missing data on fluids during surgery; one patient
 653 (usual care) missing data on crystalloid during six hours following surgery; one patient (hemodynamic
 654 therapy algorithm) missing data on blood products during six hours following surgery

655 §Two patients (one in each group) missing data on vasopressor or inotrope agents both bolus and
 656 infusion; one patient (usual care) missing data on vasopressor or inotrope infusion

	Cardiac output-guided hemodynamic therapy algorithm (n=367)	Usual care (n=362)
Duration of surgery (minutes)	270 (200-350)	260 (195-360)
Anesthetic technique*		
General anesthetic only	107 (29.2)	105 (29.1)
General anesthetic plus epidural	259 (70.8)	256 (70.9)
Intravenous crystalloid (ml)†		
During surgery	1518 (1410)	2420 (1382)
During six hours following surgery	565 (254)	670 (367)
Intravenous colloid (ml)†		
During surgery	1465 (913)	708 (695)
During six hours following surgery	642 (498)	226 (361)
Blood products (ml)†		
During surgery	141 (723)	95 (542)
During six hours following surgery	80 (555)	10 (66)
Bolus vasopressor or inotrope agent used during intervention period§	301 (82.2)	270 (74.8)
Infusion of vasopressor or inotrope (other than dopexamine) used during intervention period§	103 (28.1)	108 (30.0)
Actual location of care following surgery		
Critical care unit (level 3)	258 (70.3)	246 (68.0)
Critical care unit (level 2)	42 (11.4)	40 (11.0)
Post-surgical recovery unit	10 (2.7)	9 (2.5)
Ward	57 (15.5)	67 (18.5)

658

659

660

661 **Table 3: Results for primary outcome**
662 **All data presented as n (%)**
663 ***Six patients (three hemodynamic therapy algorithm, three usual care) missing data on self-assessment**
664 **of blinding of outcome assessment**
665 **†Includes three patients (two hemodynamic therapy algorithm, one usual care) who died within 30 days**
666

	Cardiac output-guided hemodynamic therapy algorithm (n=366)	Usual care (n=364)	Relative risk (95% CI)	p- value
Composite				
Pre-defined moderate or major post-operative complications and mortality at 30 days following surgery	134 (36.6)	158 (43.4)	0.84 (0.71-1.01)	0.07
Individual elements				
Mortality	12 (3.3)	11 (3.0)		
Pulmonary embolism	4 (1.1)	1 (0.3)		
Myocardial ischemia or infarction	10 (2.7)	8 (2.2)		
Arrhythmia	39 (10.7)	40 (11.0)		
Cardiac or respiratory arrest	16 (4.4)	14 (3.8)		
Limb or digital ischemia	2 (0.5)	1 (0.3)		
Cardiogenic pulmonary edema	1 (0.3)	2 (0.5)		
Acute respiratory distress syndrome	3 (0.8)	4 (1.1)		
Gastrointestinal bleed	13 (3.6)	8 (2.2)		
Bowel infarction	2 (0.5)	5 (1.4)		
Anastomotic breakdown	12 (3.3)	16 (4.4)		
Paralytic ileus	20 (5.5)	27 (7.4)		
Acute psychosis	3 (0.8)	8 (2.2)		
Stroke	1 (0.3)	0 (0)		
Acute kidney injury	17 (4.6)	17 (4.7)		
Infection, source uncertain	11 (3.0)	9 (2.5)		
Urinary tract infection	9 (2.5)	9 (2.5)		
Surgical site infection	22 (6.0)	39 (10.7)		
Organ/space infection	20 (5.5)	36 (9.9)		
Bloodstream infection	6 (1.6)	15 (4.1)		
Nosocomial pneumonia	36 (9.8)	39 (10.7)		
Post-operative hemorrhage	6 (1.6)	4 (1.1)		
Self-assessment of blinding for outcome assessment*				
Assessor suitably blinded	342 (94.2)	349 (96.7)		
Assessor may have known allocation	9 (2.5)	6 (1.7)		
Assessor knew allocation†	12 (3.3)	6 (1.7)		

667

668 **Table 4: Results for secondary outcomes**

669 **Odds ratios for all cause mortality at 30 days following surgery: unadjusted 1.09 (0.48-2.45); adjusted**
 670 **1.20 (0.51-2.82); p=0.68**

671 **Odds ratios for all cause mortality at 180 days following surgery: unadjusted 0.63 (0.39-1.04); adjusted**
 672 **0.61 (0.36-1.04); p=0.071**

673 **Data presented as median (quartiles) or n (%)**

674 ***For patients alive and in hospital on day 7 following start of surgery**

675

676

	Cardiac output-guided, hemodynamic therapy algorithm	Usual care	Relative risk (95% CI)	p- value
Post-Operative Morbidity	182 (66.2)	195 (67.9)	0.97	0.72
Survey defined morbidity at 7 days following surgery*	(n=275)	(n=287)	(0.87-1.09)	
Infectious complications at 30 days following surgery	87 (23.8)	108 (29.7)	0.80	0.08
	(n=366)	(n=364)	(0.63-1.02)	
Critical care free days at 30 days following surgery	27 (26-29)	28 (25-29)	--	0.98
	(n=366)	(n=364)		
All cause mortality at 30 days following surgery	12 (3.3)	11 (3.0)	1.08	1.00
	(n=366)	(n=364)	(0.48-2.43)	
All cause mortality at 180 days following surgery	28 (7.7)	42 (11.6)	0.66	0.08
	(n=363)	(n=361)	(0.42-1.05)	
Duration of post-operative hospital stay	10 (7-14)	11 (7-17)	--	0.05
	(n=359)	(n=356)		
Survivors	10 (7-14)	11 (7-17)		
	(n=343)	(n=343)		
Non-survivors	7 (3-33)	16 (9-36)		
	(n=16)	(n=13)		

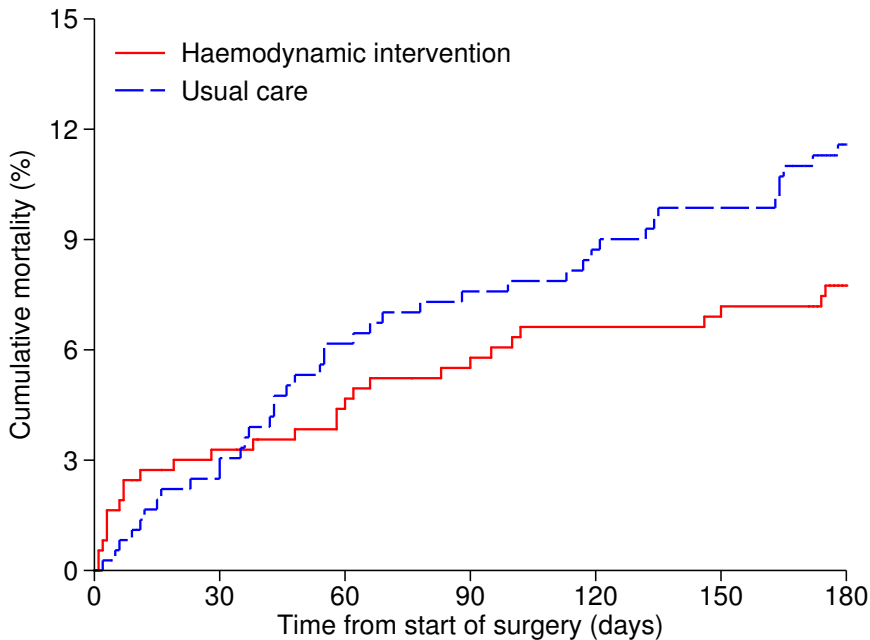
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Number at risk

Intervention	368	350	344	339	334	333	306
Usual care	365	348	331	325	321	317	286

Study or Subgroup	Protocol		Control		Weight	Risk Ratio		Year
	Events	Total	Events	Total		IV, Fixed, 95% CI	Year	
Shoemaker 1988	8	28	30	60	1.7%	0.57	[0.30, 1.08]	1988
Berlauk 1991	11	68	9	21	1.3%	0.38	[0.18, 0.79]	1991
Mythen 1995	0	30	6	30	0.1%	0.08	[0.00, 1.31]	1995
Sinclair 1997	1	20	1	20	0.1%	1.00	[0.07, 14.90]	1997
Ueno 1998	4	16	5	18	0.5%	0.90	[0.29, 2.78]	1998
Wilson 1999	38	92	28	46	6.2%	0.68	[0.48, 0.95]	1999
Lobo 2000	6	19	12	18	1.3%	0.47	[0.23, 0.99]	2000
Conway 2002	5	29	9	28	0.8%	0.54	[0.20, 1.40]	2002
Pearse 2005	27	62	41	60	6.3%	0.64	[0.46, 0.89]	2005
Wakeling 2005	24	67	38	67	4.8%	0.63	[0.43, 0.93]	2005
Noblett 2006	1	51	8	52	0.2%	0.13	[0.02, 0.98]	2006
Jerez 2001	53	181	65	209	7.6%	0.94	[0.70, 1.28]	2006
Donati 2007	8	68	20	67	1.3%	0.39	[0.19, 0.83]	2007
*Smetkin 2009	1	20	4	20	0.2%	0.25	[0.03, 2.05]	2009
Mayer 2010	6	30	15	30	1.1%	0.40	[0.18, 0.89]	2010
Jhanji 2010	57	90	30	45	10.4%	0.95	[0.73, 1.23]	2010
Cecconi 2011	16	20	20	20	12.8%	0.80	[0.64, 1.02]	2011
*Brandstrup 2012	23	71	24	79	3.1%	1.07	[0.66, 1.71]	2012
Challand 2012	10	89	13	90	1.2%	0.78	[0.36, 1.68]	2012
*Goepfert 2013	34	50	42	50	13.7%	0.81	[0.65, 1.01]	2013
*Salzwedel 2013	21	79	36	81	3.6%	0.60	[0.39, 0.93]	2013
*Optimise 2014	134	368	158	365	21.8%	0.84	[0.70, 1.01]	2014
Total (95% CI)		1548		1476	100.0%	0.77	[0.71, 0.83]	
Total events	488		614					
Heterogeneity: $\text{Chi}^2 = 30.44$, $\text{df} = 21$ ($P = 0.08$); $I^2 = 31\%$								
Test for overall effect: $Z = 6.22$ ($P < 0.00001$)								

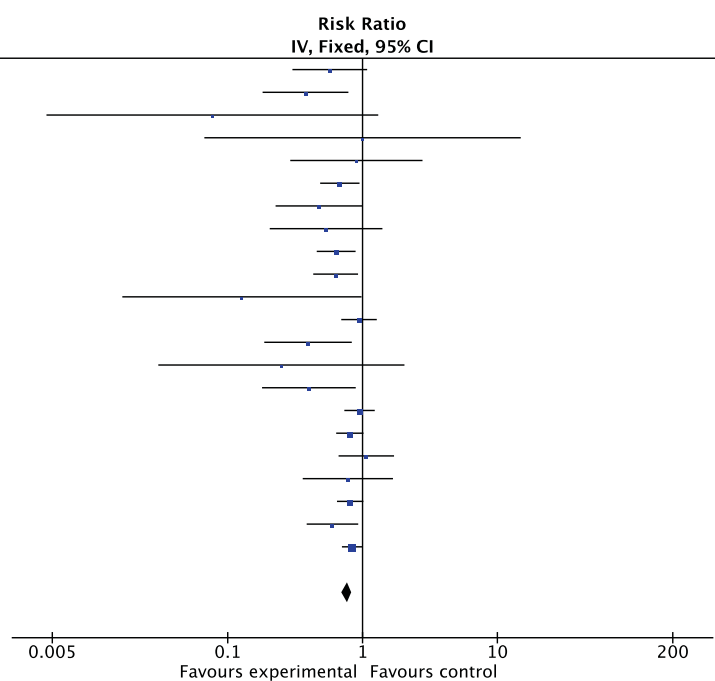
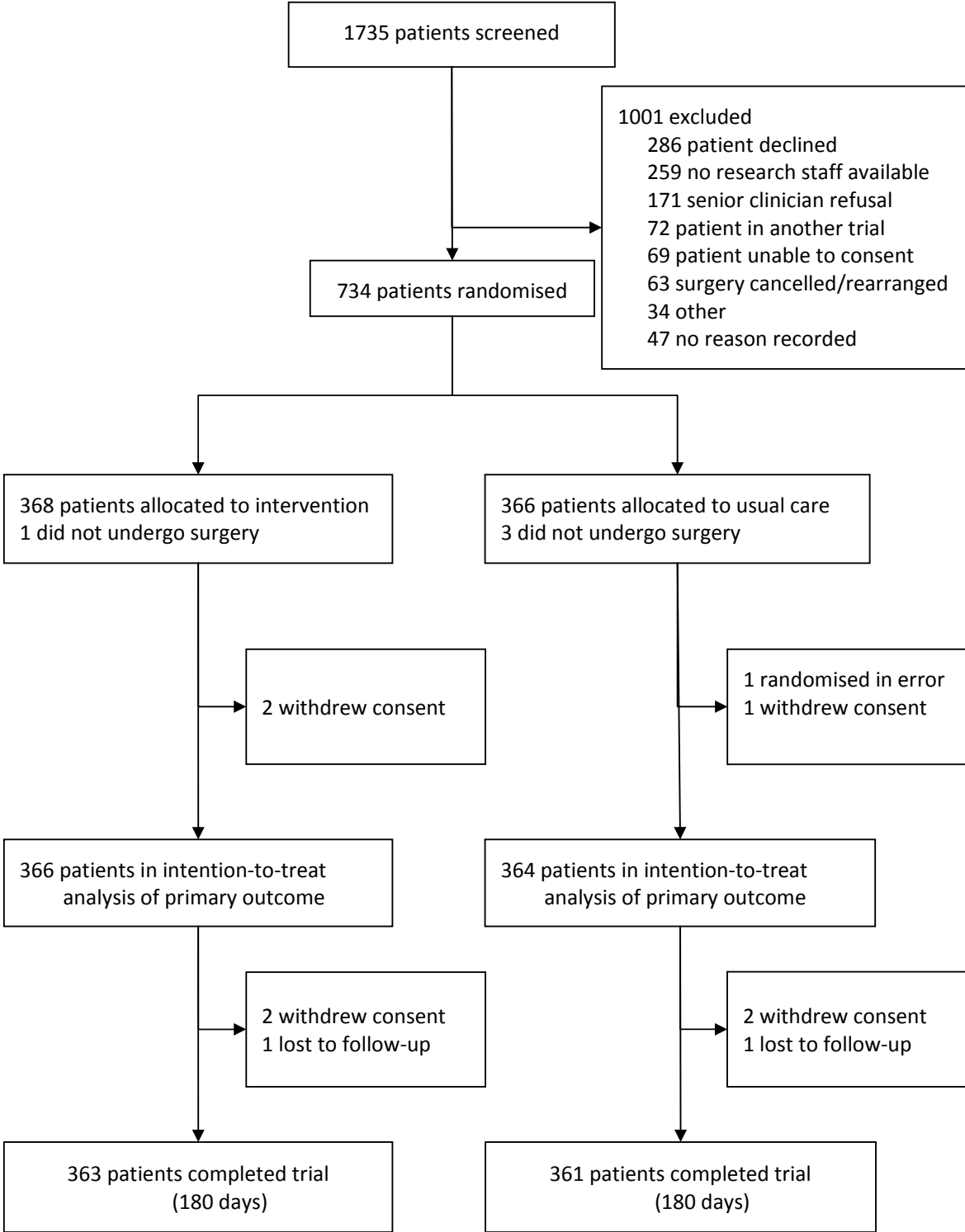
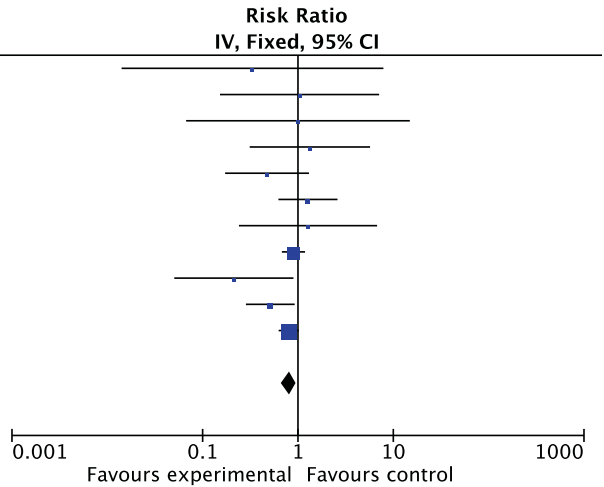


Figure 1. CONSORT flow diagram.



Study or Subgroup	Protocol		Control		Weight	Risk Ratio		Year
	Events	Total	Events	Total		IV, Fixed, 95% CI		
Mythen 1995	0	30	1	30	0.3%	0.33	[0.01, 7.87]	1995
Bender 1997	2	51	2	53	0.7%	1.04	[0.15, 7.10]	1997
Sinclair 1997	1	20	1	20	0.4%	1.00	[0.07, 14.90]	1997
Valentine 1998	4	60	3	60	1.3%	1.33	[0.31, 5.70]	1998
Lobo 2000	4	19	8	18	2.6%	0.47	[0.17, 1.30]	2000
Wakeling 2005	14	67	11	67	5.2%	1.27	[0.62, 2.60]	2005
Van der Linden 2010	3	20	2	17	1.0%	1.27	[0.24, 6.76]	2010
Jhanji 2010	52	90	29	45	34.1%	0.90	[0.68, 1.19]	2010
Pillai 2011	2	32	10	34	1.3%	0.21	[0.05, 0.90]	2011
*Salzwedel 2013	13	79	26	81	7.7%	0.51	[0.28, 0.92]	2013
*Optimise 2014	87	368	108	365	45.5%	0.80	[0.63, 1.02]	2014
Total (95% CI)		836		790	100.0%	0.81	[0.69, 0.95]	

Total events 182 201
Heterogeneity: Chi² = 9.90, df = 10 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)



Study or Subgroup	Protocol			Control			Weight	Mean Difference		Year	Mean Difference IV, Fixed, 95% CI [Days]
	Mean [Days]	SD [Days]	Total	Mean [Days]	SD [Days]	Total		IV, Fixed, 95% CI [Days]			
Shoemaker 1988	19.3	2.4	28	23.7	3.43	60	1.9%	-4.40	[-5.64, -3.16]	1988	
Berlauk 1991	18.9	11.7	68	15.4	7.5	21	0.2%	3.50	[-0.75, 7.75]	1991	
Boyd 1993	16	19	53	12.5	8.25	54	0.1%	3.50	[-2.07, 9.07]	1993	
Mythen 1995	6.4	1.1	30	10.1	9.4	30	0.3%	-3.70	[-7.09, -0.31]	1995	
Bender 1997	12.5	10	51	12	9.5	53	0.2%	0.50	[-3.25, 4.25]	1997	
Sinclair 1997	11.25	1.25	20	27.75	12.75	20	0.1%	-16.50	[-22.11, -10.89]	1997	←
Valentine 1998	13	2	60	13	2	60	5.8%	0.00	[-0.72, 0.72]	1998	
Wilson 1999	16	12	92	21.9	25.9	46	0.0%	-5.90	[-13.78, 1.98]	1999	
Lobo 2000	16	8	19	13.75	8.75	18	0.1%	2.25	[-3.16, 7.66]	2000	
Pölonen 2000	6	1.48	196	7	0.74	197	55.3%	-1.00	[-1.23, -0.77]	2000	
Bonazzi 2002	12	2	50	11	1.75	50	5.5%	1.00	[0.26, 1.74]	2002	
Conway 2002	12	24	26	11	5.75	28	0.0%	1.00	[-8.47, 10.47]	2002	
Gan 2002	5	3	50	7	3	50	2.1%	-2.00	[-3.18, -0.82]	2002	
Venn 2002	13.5	9.2	30	15.3	13.2	60	0.1%	-1.80	[-6.49, 2.89]	2002	
Sandham 2003	10	5.9	997	10	5.9	997	11.1%	0.00	[-0.52, 0.52]	2003	
Mckendry 2004	7	2.2	89	9	3.7	85	3.6%	-2.00	[-2.91, -1.09]	2004	
Pearse 2005	17.5	20.8	62	29.5	34.8	60	0.0%	-12.00	[-22.21, -1.79]	2005	←
Wakeling 2005	10.98	5.95	67	13.13	7.44	67	0.6%	-2.15	[-4.43, 0.13]	2005	
Noblett 2006	8	4.96	51	12.4	9.41	52	0.4%	-4.40	[-7.30, -1.50]	2006	
Donati 2007	11.3	3.8	68	13.4	6.1	67	1.0%	-2.10	[-3.82, -0.38]	2007	
Kapoor 2007	5.8	1.2	15	8.8	2.1	15	2.0%	-3.00	[-4.22, -1.78]	2007	
*Smetkin 2009	12	8.15	20	15	8.15	20	0.1%	-3.00	[-8.05, 2.05]	2009	
Jhanji 2010	20.8	13.3	90	18.5	11.5	45	0.2%	2.30	[-2.04, 6.64]	2010	
Mayer 2010	15	4.26	30	19	7.04	30	0.3%	-4.00	[-6.94, -1.06]	2010	
Van der Linden 2010	18.5	1.5	20	15	3.5	17	0.9%	3.50	[1.71, 5.29]	2010	
Cecconi 2011	10	0.74	20	10	1.48	20	5.6%	0.00	[-0.73, 0.73]	2011	
Pillai 2011	18	10.69	32	22	10.73	34	0.1%	-4.00	[-9.17, 1.17]	2011	
Challand 2012	8.8	4.37	89	6.7	6.3	90	1.2%	2.10	[0.51, 3.69]	2012	
Ramsingh 2013	5	4.5	18	7.5	5.5	20	0.3%	-2.50	[-5.68, 0.68]	2013	
*Zheng 2013	18	6.25	30	22	8	30	0.2%	-4.00	[-7.63, -0.37]	2013	
*Salzwedel 2013	11	8	79	10	11.8	81	0.3%	1.00	[-2.12, 4.12]	2013	
*Optimise 2014	14.4	23	359	15.1	14.3	356	0.4%	-0.70	[-3.50, 2.10]	2014	

Total (95% CI)

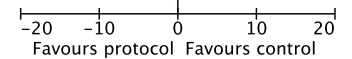
2909

2833 100.0%

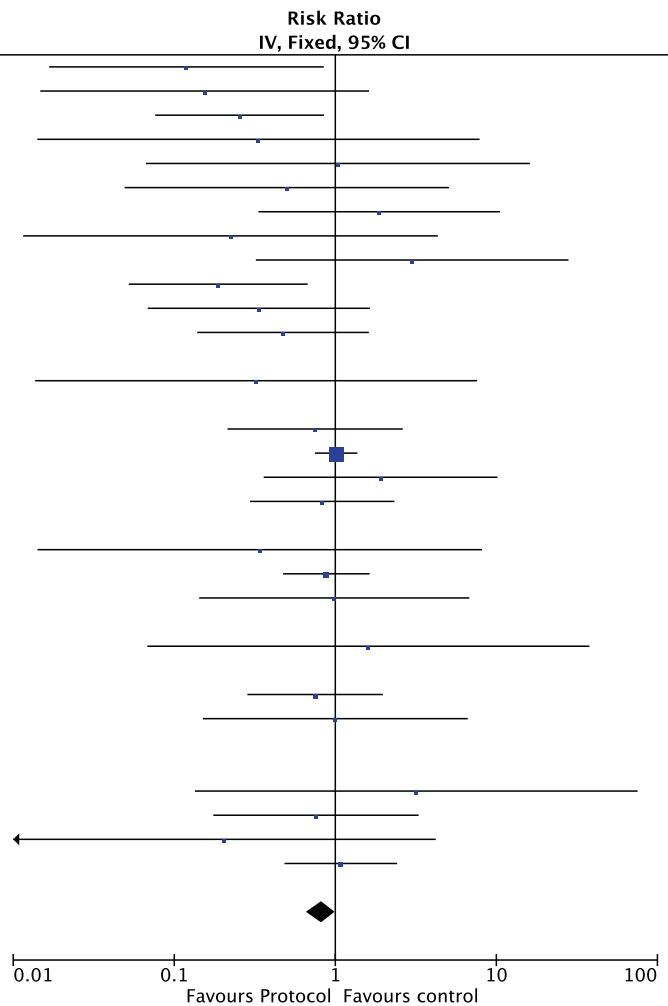
-0.80 [-0.98, -0.63]

Heterogeneity: $\chi^2 = 205.66$, $df = 31$ ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 9.15$ ($P < 0.00001$)



Study or Subgroup	Protocol		Control		Weight	Risk Ratio		Year
	Events	Total	Events	Total		IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Shoemaker 1988	1	28	18	60	1.1%	0.12 [0.02, 0.85]	1988	
Berlauk 1991	1	68	2	21	0.8%	0.15 [0.01, 1.62]	1991	
Boyd 1993	3	53	12	54	2.9%	0.25 [0.08, 0.85]	1993	
Mythen 1995	0	30	1	30	0.4%	0.33 [0.01, 7.87]	1995	
Bender 1997	1	51	1	53	0.6%	1.04 [0.07, 16.18]	1997	
Sinclair 1997	1	20	2	20	0.8%	0.50 [0.05, 5.08]	1997	
Ziegler 1997	3	32	2	40	1.4%	1.88 [0.33, 10.55]	1997	
Ueno 1998	0	16	2	18	0.5%	0.22 [0.01, 4.34]	1998	
Valentine 1998	3	60	1	60	0.9%	3.00 [0.32, 28.03]	1998	
Wilson 1999	3	92	8	46	2.6%	0.19 [0.05, 0.67]	1999	
Pölonen 2000	2	196	6	197	1.7%	0.34 [0.07, 1.64]	2000	
Lobo 2000	3	19	6	18	2.8%	0.47 [0.14, 1.62]	2000	
Bonazzi 2002	0	50	0	50		Not estimable	2002	
Conway 2002	0	29	1	28	0.4%	0.32 [0.01, 7.59]	2002	
Gan 2002	0	50	0	50		Not estimable	2002	
Venn 2002	3	30	8	60	2.7%	0.75 [0.21, 2.62]	2002	
Sandham 2003	78	997	77	997	46.6%	1.01 [0.75, 1.37]	2003	
Mckendry 2004	4	89	2	85	1.5%	1.91 [0.36, 10.16]	2004	
Pearse 2005	6	62	7	60	4.0%	0.83 [0.30, 2.33]	2005	
Wakeling 2005	0	67	0	67		Not estimable	2005	
Noblett 2006	0	51	1	52	0.4%	0.34 [0.01, 8.15]	2006	
Jerez 2001	16	181	21	209	11.1%	0.88 [0.47, 1.63]	2006	
Donati 2007	2	68	2	67	1.1%	0.99 [0.14, 6.79]	2007	
Kapoor 2007	0	15	0	15		Not estimable	2007	
Senagore 2009	1	42	0	22	0.4%	1.60 [0.07, 37.83]	2009	
*Smetkin 2009	0	20	0	20		Not estimable	2009	
Jhanji 2010	9	90	6	45	4.5%	0.75 [0.28, 1.98]	2010	
Mayer 2010	2	30	2	30	1.2%	1.00 [0.15, 6.64]	2010	
Van der Linden 2010	0	20	0	17		Not estimable	2010	
Cecconi 2011	0	20	0	20		Not estimable	2011	
Pillai 2011	1	32	0	34	0.4%	3.18 [0.13, 75.38]	2011	
Challand 2012	3	89	4	90	2.0%	0.76 [0.17, 3.29]	2012	
*Salzwedel 2013	0	79	2	81	0.5%	0.20 [0.01, 4.20]	2013	
*Optimise 2014	12	368	11	365	6.6%	1.08 [0.48, 2.42]	2014	
Total (95% CI)		3144		3081	100.0%	0.82 [0.67, 1.01]		



Total events 158 205
Heterogeneity: $\text{Chi}^2 = 25.61$, $\text{df} = 26$ ($P = 0.48$); $I^2 = 0\%$
Test for overall effect: $Z = 1.87$ ($P = 0.06$)

