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Restrictive versus liberal fluid therapy in major abdominal surgery (RELIEF): rationale and design for a multicentre randomised trial

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ABSTRACT

Introduction: The optimal intravenous fluid regimen for patients undergoing major abdominal surgery is unclear. However, results from many small studies suggest a restrictive regimen may lead to better outcomes. A large, definitive clinical trial evaluating perioperative fluid replacement in major abdominal surgery, therefore, is required.

Methods/analysis: We designed a pragmatic, multicentre, randomised, controlled trial (the RELIEF trial). A total of 3000 patients were enrolled in this study and randomly allocated to a restrictive or liberal fluid regimen in a 1:1 ratio, stratified by centre and planned critical care admission. The expected fluid volumes in the first 24 hour from the start of surgery in restrictive and liberal groups were ≤3.0 L and ≥5.4 L, respectively. Patient enrolment is complete, and follow-up for the primary end point is ongoing. The primary outcome is disability-free survival at 1 year after surgery, with disability defined as a persistent (at least 6 months) reduction in functional status using the 12-item version of the World Health Organisation Disability Assessment Schedule.

Ethics/dissemination: The RELIEF trial has been approved by the responsible ethics committees of all participating sites. Participant recruitment began in March 2013 and was completed in August 2016, and 1-year follow-up will conclude in August 2017. Publication of the results of the RELIEF trial is anticipated in early 2018.

Trial registration number: ClinicalTrials.gov identifier NCT01424150.

Strengths and limitations of this study

- This is the first large randomised trial evaluating the impact of perioperative intravenous fluid volumes.
- The multicentre, multinational design and broad inclusion criteria will support external validity.
- The primary end point is disability-free survival, a novel and patient-centred outcome measure.
- While the treating anaesthetists could not be blinded, all research staff collecting postoperative outcome data are blinded to the treatment group.

INTRODUCTION

Major abdominal surgery is associated with many risks, and the personal, social and economic consequences of postoperative complications are substantial. Strategies to mitigate these risks, therefore, are keenly sought, and recently attention has turned to the influence that intravenous fluid administration might have on outcomes.

Historically perioperative intravenous fluid administration has been liberal. Since the 1950s, when it was first claimed that fluids are redistributed to a theoretical 'third space' perioperatively,[1] intravenous fluid administration has included replacement of such third-space losses with crystalloid. In addition, clinicians administer liberal volumes of intravenous fluids during and after surgery because of concerns related to preoperative dehydration, circulatory instability associated with general and regional anaesthesia, inadequate tissue oxygen delivery (especially to the bowel), unnecessary blood transfusion and low urine output.[2–4]

However, traditional perioperative intravenous fluid regimens in abdominal surgery can lead to patients receiving 3–7 L of fluid on the day of surgery and more than 3 L per day for the following 3–4 days, leading to a 3–6 kg weight gain.[5 6] In addition liberal fluid administration causes oedema, with increased pulmonary morbidity,[7] impaired

coagulation,[8] bacterial translocation and sepsis[9] and poor wound healing.[10]

Early randomised trials suggested positive benefits with a restrictive fluid regimen in abdominal surgery, with faster return of bowel function, fewer complications and shorter hospital stay.[5 11 12] Even though these findings were not always replicated,[13–15] several recent expert guideline/consensus statements on perioperative fluid therapy have supported more restrictive fluid regimens.[16 17] However if fluid administration is restrictive it is more likely that hypotension will be treated with vasopressor therapy. Such vasopressor therapy may impair organ perfusion, threaten local tissues at the site of intravenous administration, cause cardiac arrhythmias or be mistakenly used when hypovolaemia is the underlying cause.[18 19]

A meta-analysis of perioperative fluid trials up to 2007 found that restrictive regimens reduced overall complications, OR 0.41 (95% CI 0.22 to 0.77), p=0.005;[20] but the authors noted the heterogeneity of fluid regimens and outcome definitions. More recently, we undertook an updated meta-analysis (12 trials, 1160 patients) to evaluate the overall effect of fluid restriction on mortality and some morbidities.[21] However, we could not pool overall complications because of their variability and inconsistency of definitions.

Given the above uncertainties and the ubiquity of fluid therapy in major abdominal surgery, we planned and executed a large definitive trial to generate the reliable and robust evidence needed to guide practice around the world (the Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery [RELIEF] trial).

OUTCOME MEASURES AFTER MAJOR ABDOMINAL SURGERY

Outcome measures should reflect the personal, social and economic consequences of adverse events after major abdominal surgery. However, most of the above studies pooled a variety of postoperative adverse outcomes into a single composite outcome ('complications'), for which there was questionable long-term relevance to patients. In addition, there was often an imbalance in severity and duration of complications included in the outcome. While mortality is a commonly measured 'hard' end point after surgery, none of the above studies were sufficiently powered to detect a clinically important difference. In any case mortality is low after most types of surgery and so is a problematic primary end point on which to base a sample size calculation in perioperative outcome trials.

There is a strong argument to use outcome measures that are relevant to patients. Quality of life is often used, but the available instruments were not designed to be responsive after major surgery. Survival with avoidance of long-term disability ('disability-free survival') is likely to be the most important and most highly valued outcome for patients undergoing major surgery,[22] and a validated instrument is available (the World Health Organisation Disability Assessment Schedule [WHODAS]).[22 23] We, therefore, measured disability-free survival up to 1 year after surgery as the primary outcome in the RELIEF trial.

FEASIBILITY: PILOT STUDY

We undertook a pilot study in three hospitals to test the feasibility of the proposed trial. After ethics approval, patient consent and surgeon, anaesthetist and intensivist support, we demonstrated that we could successfully implement the protocolised fluid regimens intraoperatively and postoperatively (table 1).

STUDY HYPOTHESES

Our primary hypothesis is that a restrictive fluid regimen for adults undergoing major abdominal surgery leads to reduced complications and improved disability-free survival when compared with a liberal fluid regimen. Our secondary hypotheses are: (1) the effects of fluid restriction are similar whether or not goal-directed therapy is used (assessed as a statistical test of interaction), (2) a

Table 1 Results of our feasibility pilot study.

Variable	Restrictive (n=41)	Liberal (n=41)	p Value
Patient age, years	65 (12)	67 (12)	–
Intravenous fluid (crystalloid+colloid), mL			
Intraoperative	1746 (748)	2730 (1309)	<0.001
Total at 24 hour postoperative	3167 (1625)	5133 (2138)	<0.001
Postoperative			
Haemoglobin, g/L	110 (18)	101 (17)	0.014
Albumin, g/L	31 (6.7)	27 (7.0)	0.030
C reactive protein, mg/L	108 (80)	128 (75)	0.33
QoR-40 score	159 (20)	154 (26)	0.34
Median (IQR) ICU stay, h	0 (0–15)	0 (0–19)	0.86
Median (IQR) hospital stay, days	8.1 (5.6–14)	8.4 (6.9–16)	0.30

Mean (SD) unless otherwise specified.
ICU, intensive care unit; IQR, interquartile range; QoR-40, 40-item quality of recovery scale (range 0 [very poor] to 200 [excellent recovery])[50].

restrictive fluid regimen will reduce a composite of 30-day septic complications and mortality.

METHODS AND ANALYSIS

The RELIEF protocol was submitted to the responsible ethics committees (or relevant regulatory bodies) for all participating sites, and their approval was obtained.

Study design

RELIEF is a large, multicentre, randomised, international, single blind, pragmatic trial, with patients randomly assigned to either restrictive or liberal fluid groups, stratified by site and by planned high dependency unit (HDU) or intensive care unit (ICU) admission.

Participants and enrolment

We targeted at-risk patients undergoing planned major abdominal or pelvic surgery with an expected operative duration of at least 2 hours. All patients provided informed consent after explanation of the trial and provision of written information by a research nurse or clinician.

Inclusion criteria

We included the following patients:

1. Adults (≥18 years) undergoing elective major surgery and providing informed consent.
2. All types of open or laparoscopic-assisted abdominal or pelvic surgery with an expected duration of at least 2 hours, and an expected hospital stay of at least 3 days (eg, oesophagectomy, gastrectomy, pancreatectomy, colectomy, aortic or aorto-femoral vascular surgery, nephrectomy, cystectomy, open prostatectomy, radical hysterectomy and abdominal incisional hernia repair).
3. At increased risk of postoperative complications, defined by at least one of the following criteria:
   i. age ≥70 years
   ii. known or documented history of coronary artery disease
   iii. known or documented history of heart failure
   iv. diabetes currently treated with an oral hypoglycaemic agent and/or insulin
   v. preoperative serum creatinine >200 µmol/L (>2.8 mg/dL)
   vi. morbid obesity (body mass index [BMI] ≥35 kg/m^2)
   vii. preoperative serum albumin <30 g/L
   viii. anaerobic threshold (if performed) <12 mL/kg/min
   ix. or two or more of the following risk factors:
      – American Society of Anesthesiologists (ASA) physical status 3 or 4
      – chronic respiratory disease
      – obesity (BMI 30–35 kg/m^2)
      – aortic or peripheral vascular disease
      – preoperative haemoglobin <100 g/L
      – preoperative serum creatinine 150–199 µmol/L (>1.7 mg/dL)
      – anaerobic threshold (if performed) 12–14 mL/kg/min.

Exclusion criteria

We applied the following exclusion criteria:

1. Urgent or time-critical surgery
2. ASA physical status 5
3. Chronic renal failure requiring dialysis
4. Pulmonary or cardiac surgery
5. Liver resection
6. Minor or intermediate surgery, such as laparoscopic cholecystectomy, transurethral resection of the prostate, inguinal hernia repair, splenectomy and closure of colostomy.

After enrolment, on the day of surgery, patients were randomly assigned (1:1) to groups via a web-based service using a computer-generated code. All other perioperative clinical care was undertaken in accordance with standard practice. All relevant factors were recorded on a trial case report form.

Perioperative management

Enhanced recovery after surgery (ERAS) perioperative care principles were emphasised in all participating centres. All patients received prophylactic antibiotics in accordance with established guidelines.[24] Preoperative medications were continued perioperatively or at the clinicians discretion, but we recommended withholding ACE inhibitors and angiotensin receptor blockers on the day of surgery. We recorded preoperative use of bowel preparation, fasting times, medications and biochemistry and haematology results on the case report form. All diabetic patients were to have their haemoglobin A1C measured before surgery.

The use of advanced monitoring techniques, such as central venous pressure (CVP) monitoring, oesophageal Doppler, pulse contour analysis or other goal-directed device, to identify fluid responsiveness was left to the discretion of the anaesthetist. Such use was recorded, and general guidelines were provided to guide fluid boluses in such circumstances according to treatment group allocation (see online supplementary appendix).

Selection of anaesthetic agents and perioperative analgesia was left to the discretion of the anaesthetist, and such data were recorded. We emphasised the need to avoid hypothermia (<36°C) by employing routine intraoperative patient warming strategies. Epidural analgesia was recorded as this can increase the risk of hypotension and need for intravenous fluids,[25] although such effects are expected to be small.[26]

The acceptable lower limits of low blood pressure (BP) and the definition of 'hypotension' vary widely[27] and probably should be modified by older age, preexisting hypertension and cerebrovascular disease. We used a general guideline of systolic BP <90 mm Hg for more than 5 min, but also asked the attending

anaesthetist to modify their acceptable lower limit of systolic BP at the initiation of surgery based on their assessment of the patient. This lower limit was used to trigger treatment, depending on the randomly assigned group protocol, with additional intravenous fluid or vasopressor therapy (see below). Such modification to the acceptable lower systolic BP was recorded. For patients managed in HDU/ICU after surgery, hypotension was similarly managed for the first 24 hour after surgery.

Patients were followed daily and outcomes were recorded until discharge. We recommended that antihypertensive medications be withheld until BP was consistently at or above preoperative levels. A 12-lead ECG was ordered preoperatively, and serum electrolytes and haemoglobin/haematocrit were ordered preoperatively and on day 1 after surgery. C reactive protein was measured on postoperative day 3 and whenever sepsis was suspected. Additional laboratory tests were ordered if clinically indicated. On day 3, all patients were asked to complete the 15-item quality of recovery score (QoR-15).[28] At 30 days after surgery, all patients were contacted by phone to ascertain if they had experienced any outcomes, and if detected, further testing was arranged. Documentation for such events was sought in the hospital medical record and doctor's records. The QoR-15 was repeated on day 30 along with WHODAS, and the WHODAS was repeated at 3, 6 and 12 months after surgery to ascertain survival status and new-onset disability.

Blood transfusion and intravenous fluids: general guidelines

Excessive fluid resuscitation can cause haemodilution[25] and dilutional coagulopathy, and this may increase the need for red cell and other blood transfusion.[29] Blood transfusion is, of itself, associated with increased rates of sepsis and other postoperative complications.[30] All patients had the same red cell transfusion trigger of 70 g/L, but this could be modified by attending staff after assessment of cardiovascular risk[31 32] or concern for active bleeding. Normal saline, containing 154 mmol of sodium and 154 mmol of chloride per litre, is non-physiological and can lead to hyperchloraemic acidosis[33] and perhaps poorer outcome.[34 35] We protocolised a balanced salt solution as the routine fluid therapy for this reason. The questionable value of urine output as a measure of kidney or other tissue perfusion was emphasised.[36]

Our study group fluid regimens were aimed at distinct volume differences and were both consistent with most previous studies.[37 38] The group-assigned fluid regimens continued for at least 24 hours after surgery or until cessation of intravenous fluid therapy (whichever occurred first). If the patient's clinical condition warranted modification to the type or rate of fluid administration, then such modifications could be made. This did not imply that the patient should be removed from the trial because we plan to analyse according to the intention-to-treat principle, but we did collect such information for secondary per-protocol and sensitivity analyses.

Study interventions

Liberal ('traditional practice') intravenous fluid group

The liberal group fluid regimen reflects common contemporary practices in Australia[39] and is consistent with previous international trials.[38] At the initiation of surgery, a bolus of Hartmann's or comparable balanced salt crystalloid 10 mL/kg followed by 8 mL/kg/hour was administered until the end of surgery—the latter could be further downtitrated after 4 hours if clinically indicated. In patients exceeding a body weight of 100 kg, for the purposes of calculations of bolus and maintenance fluids, the maximal body weight was set at 100 kg. A maintenance infusion was then continued at 1.5 mL/kg/hour, for at least 24 hours, but this could be reduced postoperatively if there was evidence of fluid overload and no hypotension, and increased if there was evidence of hypovolaemia or hypotension. Alternative fluid types (crystalloid, dextrose, colloid) and electrolyte supplements were allowed postoperatively in line with local preferences and patient biochemistry, for which we collected data. For a 75 kg adult, the intraoperative volume (for a 4 hour operation) was expected to be 3150 mL (higher if colloid/blood replacement for blood loss), and then around 2700 mL per day. That is, the first (intraoperative+postoperative) 24-hour fluid administration was expected to be about 5400 mL (figure 1).

Restrictive ('zero balance') intravenous fluid group

The restrictive group fluid regimen was designed to provide <2.0 L water and 120 mmoL sodium per day. Induction of anaesthesia was accompanied by an intravenous fluid bolus limited to ≤5 mL/kg; no other intravenous fluids were used at the initiation of surgery (unless indicated by goal-directed device, where employed [see below]). Hartmann's solution or comparable balanced salt crystalloid at 5 mL/kg/hour was to be administered until the end of surgery, and bolus colloid/blood was used intraoperatively to replace blood loss (mL for mL); then a postoperative infusion rate of 0.8 mL/kg/hour until cessation of intravenous fluid therapy within 24 hours. The rate of postoperative fluid replacement could be reduced if there was evidence of fluid overload and no hypotension and could be increased if there was hypotension with evidence of hypovolaemia. For a 75 kg patient and 4 hour operation, intraoperative fluid volume was expected to be 1875 mL (higher if colloid/blood replacement for blood loss). The first 24-hour fluid administration was expected to be around half that of the liberal group (figure 1).

Hypotension was to be initially treated with fluid boluses in the liberal protocol group, and with a vasoconstrictor in the restrictive protocol group (table 2). The lower limit of acceptable systolic BP in the restrictive group could be further reduced by the attending

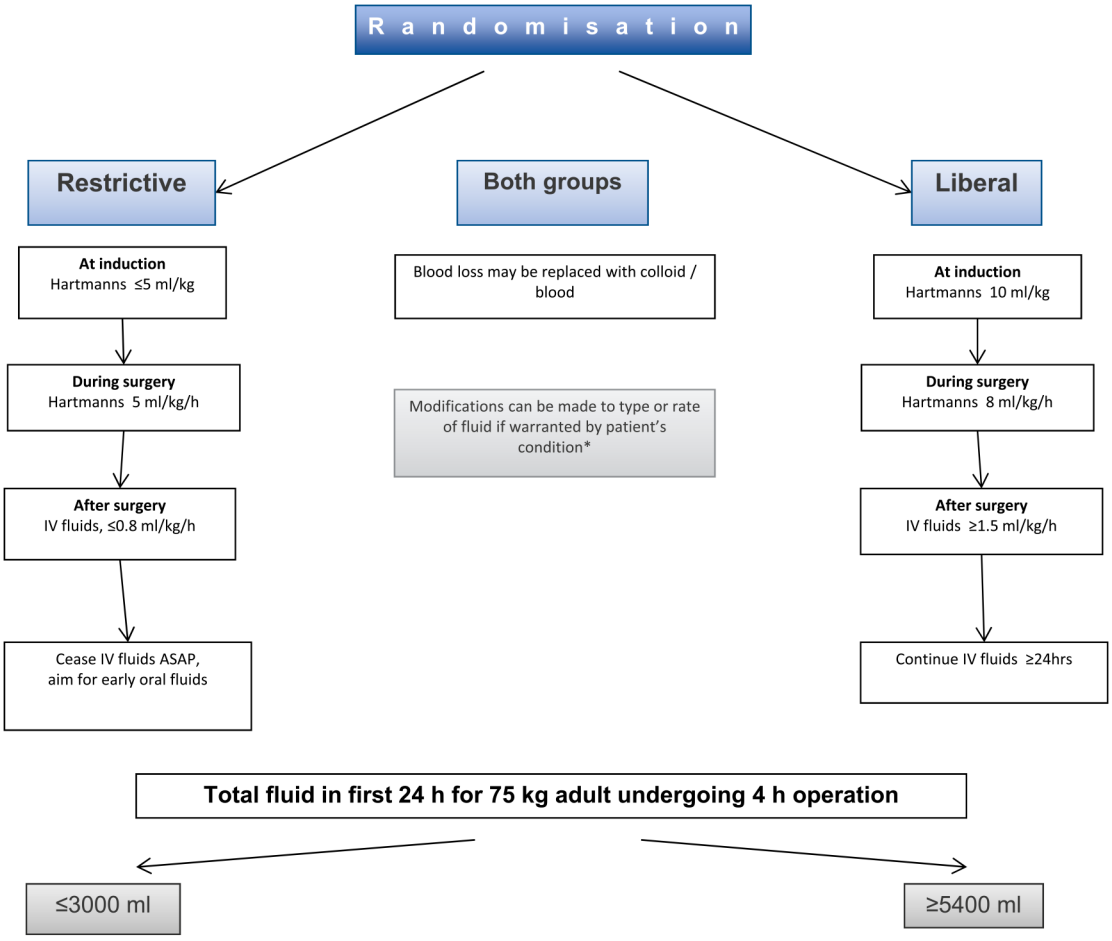

Figure 1 Fluid administration during surgery and up to 24 hours postoperatively in the restrictive and liberal groups.

anaesthetist or intensivist to limit fluid replacement or potentially unnecessary vasopressor support (see above). We provided instructional flow charts for the anaesthetists and postoperative (ward or HDU/ICU) medical and nursing staff caring for the study patients (see online supplementary appendix).

Goal-directed therapy

For anaesthetists employing advanced monitoring techniques, we allowed additional colloid fluid supplementation to augment a haemodynamic target. We expected that this would lead to additional colloid administration during and after surgery.[20 40 41] We plan to test the effectiveness of each approach against local availability and use. The statistical analysis will focus on a test for interaction, to determine whether the effects of a fluid regimen work differently in those with and without any advanced monitoring.

Management of Oliguria

It is a normal response of the body to attempt to conserve fluid in times of physiological stress. Oliguria is part of this homeostatic mechanism and is common in the first 24–48 hour after surgery: there is no evidence that it is harmful in the short term.[36] Nor is there any evidence that diuretics protect against acute kidney injury (AKI).[42] We did not mandate a specific management strategy for oliguria but did provide guidance to ward medical and nursing staff (see online supplementary appendix).

Blinding procedure

Patients were blinded to group allocation. Anaesthetists, and in many cases surgeons and intensivists, had knowledge of group identity. Similarly, it was expected that other surgical and nursing staff, and research staff conducting the in-hospital daily reviews, could not be properly blinded to group identity. However, we insisted that any research staff conducting the late follow-ups and primary end point data be blinded to group allocation.

Data collection: data entry and auditing

Study data were collected in a paper based case report form, for subsequent transcription onto a web database. We provided regular feedback to each participating centre via phone and the trial website, along with a monthly newsletter. A complete procedures manual was made available to each study site during site initiation.

Table 2 Suggested fluid challenges and use of vasoconstrictor therapy if there was evidence of fluid responsiveness

Colloid* (recommended) or crystalloid (3 mL/kg)	Liberal	Restrictive
Colloid/blood (using a transfusion threshold) bolus *if* acute bleeding	Yes	Yes
If normotensive but monitoring suggests hypovolaemia (eg, CVP<5 or oliguria)	Yes	No
If normotensive but goal-directed device suggests hypovolaemia (eg, FTc <0.33, ΔSV ≥10% or SVV≥13%)	Yes	Consider
If hypotensive		
(1) *and* hypovolaemia	Colloid*	Colloid* (but limit) +vasoconstrictor
(2) *but not* hypovolaemic	Colloid* ±vasoactive	vasoactive therapy

*Starch-based colloids were not recommended.
CVP, central venous pressure monitoring; FTc, flow time corrected; SVV, stroke volume variation.

All study personnel have 24-hour access to the study coordinating centre to resolve any questions that arise.

Random audits of centres were performed throughout the conduct of the trial, aiming to assess the accuracy and legitimacy of the trial data. Some statistical monitoring of the data completeness, data variance and risk-appropriate end point rates is also being performed.

End point Adjudication Committee

An End point Adjudication Committee consisting of experienced perioperative physicians was established at the initiation of the study. Its role is to resolve any uncertainty as to any of the trial outcomes. Confirmation reports of all detected outcomes are de-identified and re-labelled with a study case number and are sent to the Committee for adjudication. Additional advice can be sought by consultation with subspecialists.

Data monitoring

We established an independent Data Safety and Monitoring Committee (DSMC), consisting of an experienced academic intensive care physician (as chair), surgeon, anaesthetist, epidemiologist/trialist and independent statistician. The responsibilities of the DSMC were outlined in a DSMC charter and included review and providing advice on the trial protocol, review and interpretation of accruing data, and ensuring the safety of the trial participants and the integrity of the trial data.

Primary end point

The primary end point of the trial is disability-free survival at 1 year after surgery. Disability is defined as a persistent (at least 6 months) impairment in health status, as measured by the 12-item WHODAS score, of at least 24 points when using response scores of 1–5 for each item, reflecting a disability level of at least 25% and being the threshold point between 'disabled' and 'not disabled' as per WHO guidelines.[23]

A secondary sensitivity analysis will be performed to evaluate *new-onset* disability using a ≥4-point (8%) increase in the WHODAS score compared with the baseline (preoperative) score.

Timing of assessments

WHODAS was scheduled to be completed at five time points: baseline, and then 30 days, 3, 6 and 12 months after surgery. The onset of significant disability will be used to calculate a survival curve. A clinically significant elevated WHODAS score at 30 days will be assumed to be related to the surgery. Date of onset of any new disability will be collected at 3, 6 and 12 months postoperatively. This will typically be after an incident/illness in the postoperative follow-up period. If no such event is documented, then the current time point (interview date) will be used for calculation of disability-free survival.

Secondary end points

Planned secondary end points:

1. Death/survival: all-cause mortality at 90 days, and survival up to 12 months after surgery.
2. Composite (pooled) and individual incidence of septic complications: sepsis, surgical site infection, anastomotic leak and pneumonia.
3. Anastomotic leak.
4. AKI: according to the Kidney Disease: Improving Global Outcomes group criteria, but not urine output—for Stage 2 or worse AKI defined as at least twofold increase in creatinine, or estimated glomerular filtration rate decrease >50%.[43] Since a restrictive intravenous fluid regimen may artificially elevate serum creatinine due to a smaller dilutional effect from less intravenous fluids, we will calculate adjusted creatinine by first estimating the volume of distribution for creatinine as equal to total body water (assumed to be 60% of body weight, expressed in mL), and assuming that 50% of intravenous fluid was still accumulated as tissue oedema at the time of postoperative creatinine measurements.[44 45] That is, adjusted creatinine=serum creatinine×(1+[0.5×fluid balance/total body water]). We also plan to report the use of renal replacement therapy up to 90 days after surgery.

5. Pulmonary oedema: documented evidence of respiratory distress or impaired oxygenation and radiological evidence of pulmonary oedema.
6. Duration of mechanical ventilation: additive, for all episodes up to 90 days after surgery.
7. Inflammation: plasma C reactive protein concentration on day 3 after surgery.
8. Tissue perfusion marker: peak serum lactate concentration within 24 hours of surgery.
9. Any blood transfusion: including red cell, fresh frozen plasma or platelet transfusion, from the initiation of surgery.
10. Unplanned admission to HDU/ICU within 30 days of surgery.
11. Total HDU/ICU stay.
12. Total hospital stay, including any readmission(s) up to day 30.
13. Quality of recovery: QoR-15 score[28] on days 1, 3 and 30.

We will also report rates of serious adverse events, and severity of adverse events (mild, moderate, severe), classified by organ system.

Sample size

Our initial sample size calculation was based on our own data and other published studies. Our ENIGMA-II trial,[46] with a lower risk study population, had a disability-free survival rate of 70% at 1 year after surgery. The most recent large data comes from the UK, where the 1-year mortality for open colorectal surgery was 17% in the 31 847 patients with pre-existing comorbidity.[47] Reductions in serious complication rates have exceeded 25% in pooled analyses of similar studies,[20 34] and pre-existing major comorbidity increases mortality risk up to 16-fold.[48] Using a type I error of 0.05 and survival analysis, with an expected 1 year disability-free survival probability of 65%[49] and a HR of ≥1.25, 1300 patients in each group were estimated to provide 90% power. Target recruitment was set at 2800 patients to account for losses due to follow-up.

The Trial Steering Committee met on the 30 June 2016, to discuss the results of a data quality committee review and statistician's report of the accruing incidence of disability. With near-complete information on 2578 enrolled patients, there were 300 events (disability or death); that is, a 12-month event rate of ~14.6%. As this was lower than expected, an increase in the trial sample size to 3000 (≈380 events) was advised, aiming to provide 80% power to detect a HR of 0.75 or less. This protocol amendment was accepted by the Steering Committee and endorsed by the DSMC.

Statistical analysis

We will apply the intention to treat principle: all participants who are enrolled, randomised and undergo induction of general anaesthesia for eligible surgery are being followed for the duration of the trial (unless they withdraw consent), even if they did receive the randomised treatment for the full duration of the trial.

Interim analyses were performed after enrolment of 1445 patients, and results were made available to the DSMC. The DSMC recommended that the trial should continue as planned.

Statistical analyses will be undertaken after 1-year follow-up is completed for all patients. For analysis of the primary end point, we will use the Cox proportional hazards regression model with treatment as the only covariate to produce an unadjusted HR with a 95% CI, together with Kaplan–Meier survival curves for graphical display. Analysis of secondary outcomes measured on a binary scale will be performed using log-binomial regression to estimate RRs with 95% CIs, or exact logistic regression to approximate RRs if the number of events in either arm is fewer than 10. Time to event outcomes will use Cox proportional hazards regression as above.

Outcomes measured on a continuous scale with a right-skewed distribution will be log transformed and analysed using linear regression with robust SEs, and outcomes with a left-skewed distribution will be analysed with median regression with SEs estimated using 1000 bootstrap replications.

Sensitivity analyses for all outcomes will use regression models with additional adjustment for the stratification variables of site and planned HDU/ICU destination status, plus any variables exhibiting substantial imbalance across treatment arms at baseline.

Sensitivity to missing outcome data will be performed using multiple imputation if the proportion of missing outcome data is >5%. This will use baseline and auxiliary postbaseline information to inform the imputations under a *missing at random* assumption.

Subgroup analysis

Planned subgroup analyses will assess patient sex, age groups (approximate quintiles), country, bowel surgery (yes/no) and use of any goal-directed techniques (yes/no). The latter include invasive or non-invasive cardiac output, stroke volume or pulse pressure variation and oesophageal Doppler. For these analyses, we will undertake tests for interaction by adding treatment-by-covariate terms to the regression models.

Additional prespecified subgroups will be tested for heterogeneity of effect, and their results considered exploratory: country, BMI categories (underweight, normal, overweight, obese, ≥super obese), ASA physical status (1/2, 3, 4), planned HDU/ICU destination status and duration of surgery (approximate quintiles).

DISSEMINATION

The rationale and design of the RELIEF trial were presented at more than 10 international anaesthesia and surgical meetings over the past 5 years. There was very positive feedback and confirmation of the clinical importance of the trial results. Final results are expected

to be presented at one or more international scientific meetings in 2017 and 2018. The main results of the trial are expected to be published in a major medical journal in 2018. There are no plans to provide public access to the participant-level database.

CONCLUSIONS

There is preliminary supportive evidence of potential benefits of a restrictive fluid regimen for major abdominal surgery, but a large multicentre, multinational, randomised, controlled definitive trial is required to properly evaluate benefits and risks. The RELIEF trial is expected to provide the necessary evidence to guide fluid practice in these patients.

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Collaborators The RELIEF trial investigators.

Contributors PM, TC, AF, PP, DS, KL and RB contributed to the conception and design of the study. PM, SW, AF, TC, PP, DS, KL, SM, RP and RB contributed to the acquisition, analysis and interpretation of the data. PM wrote the first draft of the protocol. PM, RB, TC, AF, SW, PP, CC, DS, KL, JS, SM and RP revised the protocol critically for important intellectual content. PM and RB are the guarantors. All authors have read and approved the final version of the manuscript to be published.

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Competing interests RB has received grants and consultancy fees from two international fluid manufacturers (Baxter and BBraun). None of the other authors have any conflicts of interest.

Patient consent Obtained.

Ethics approval Ethics committee approvals were obtained from each of the responsible bodies for all trial sites: *Australia*: Alfred Hospital Ethics Committee, Human Research and Ethics Committee Epworth Healthcare, Western Sydney Local Health District Human Research Ethics Committee, Queensland Metro South Human Research Ethics Committee, Human Research Ethics Committee (Tasmania) Network, Central Adelaide Local Health Network (South Australia), Human Research Ethics Committee (Medical Sciences), Macquarie University, Government of Western Australia, Department of Health, South Metropolitan Area Health Service (Queensland); *UK*: Health Research Authority NRES Committee South West Exeter; *Hong Kong*: Joint Chinese University of Hong Kong—New Territories East Cluster, Clinical Research Ethics Committee; *New Zealand*: Health and Disability Ethics Committees; *Italy*: Ospendale San Raffaele; *Canada*: Queens University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (Kingston), Research Ethics Board (Toronto), University Health Network, SDR Research Ethics Board (McGill University); *USA*: Cleveland Clinic Foundation Institutional Review Board, Institutional Review Board Weill Cornell Medical College, Institutional Review Board Wake Forest University Health Science.

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