Randomized clinical trial

Randomized multicentre feasibility trial of intermediate care *versus* standard ward care after emergency abdominal surgery (InCare trial)

M. Vester-Andersen[1], T. Waldau[1], J. Wetterslev[3], M. H. Møller[4], J. Rosenberg[2], L. N. Jørgensen[5], J. C. Jakobsen[3] and A. M. Møller[1], on behalf of the InCare trial group*

Departments of [1]Anaesthesiology and Intensive Care Medicine and [2]Surgery, Herlev Hospital, University of Copenhagen, Herlev, and [3]Copenhagen Trial Unit, Centre for Clinical Intervention Research, and [4]Department of Intensive Care Medicine – 4131, Rigshospitalet, University of Copenhagen, [5]Digestive Disease Centre, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

Correspondence to: Dr M. Vester-Andersen, Department of Anaesthesiology and Intensive Care Medicine, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark (e-mail: drvester@dadlnet.dk)

Background: Emergency abdominal surgery carries a considerable risk of death and postoperative complications. Early detection and timely management of complications may reduce mortality. The aim was to evaluate the effect and feasibility of intermediate care compared with standard ward care in patients who had emergency abdominal surgery.

Methods: This was a randomized clinical trial carried out in seven Danish hospitals. Eligible for inclusion were patients with an Acute Physiology And Chronic Health Evaluation (APACHE) II score of at least 10 who were ready to be transferred to the surgical ward within 24 h of emergency abdominal surgery. Participants were randomized to either intermediate care or standard surgical ward care after surgery. The primary outcome was 30-day mortality.

Results: In total, 286 patients were included in the modified intention-to-treat analysis. The trial was terminated after the interim analysis owing to slow recruitment and a lower than expected mortality rate. Eleven (7·6 per cent) of 144 patients assigned to intermediate care and 12 (8·5 per cent) of 142 patients assigned to ward care died within 30 days of surgery (odds ratio 0·91, 95 per cent c.i. 0·38 to 2·16; $P = 0·828$). Thirty (20·8 per cent) of 144 patients assigned to intermediate care and 37 (26·1 per cent) of 142 assigned to ward care died within the total observation period (hazard ratio 0·78, 95 per cent c.i. 0·48 to 1·26; $P = 0·310$).

Conclusion: Postoperative intermediate care had no statistically significant effect on 30-day mortality after emergency abdominal surgery, nor any effect on secondary outcomes. The trial was stopped prematurely owing to slow recruitment and a much lower than expected mortality rate among the enrolled patients. Registration number: NCT01209663 (http://www.clinicaltrials.gov).

*Members of the InCare trial group are collaborators in the trial and co-authors of this article, and can be found under the heading Collaborators

Paper accepted 14 November 2014

Published online 18 March 2015 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9749

Introduction

Emergency major abdominal surgery is associated with a short-term mortality rate of 15–20 per cent[1–4], which is among the highest in non-cardiac surgery[5]. The annual incidence of emergency major abdominal surgery has been estimated at 92 per 100 000 population[6]. Patients undergoing emergency abdominal surgery have a high risk of postoperative complications, in particular cardiopulmonary complications and sepsis, which are the most frequent causes of death after surgery[7–9]. Surgical patients who develop postoperative medical complications are at increased risk of death[10,11]; once complications have developed, timely and effective management may reduce mortality[12,13]. Thus, early routine postoperative admission of high-risk surgical patients to intensive or intermediate care units may be beneficial. Over the past decade, there has been a growing concern that many high-risk surgical patients may not

receive appropriate postoperative care, because of inadequate allocation of critical care resources[4,5,14,15]. Recently, the European Surgical Outcome Study (EuSOS)[16] confirmed this as a challenge in many European countries. Likewise, patients undergoing emergency abdominal surgery are often treated in standard surgical wards with limited resources for monitoring and advanced treatment methods[2,3].

Intermediate care (high-dependency care) may be an appropriate level of postoperative care for stable patients with an *a priori* high risk of complications and death. Intermediate care is generally defined as a level of care between that provided by a standard ward and an intensive care unit. An intermediate care unit monitors and supports patients with, or likely to develop, acute single-organ failure[17–19]. However, according to the authors' knowledge, the effect of postoperative intermediate care compared with standard ward care has never been evaluated in a randomized clinical trial[20,21].

The aim of this trial was therefore to evaluate the effect and feasibility of intermediate care following high-risk emergency abdominal surgery. The hypothesis was that postoperative intermediate care would reduce mortality by avoidance, or timely recognition and effective management, of postoperative complications, and that postoperative intermediate care would reduce the need for intensive care admissions and length of hospital stay.

Methods

The Copenhagen Capital Region Ethics Board (H-3-2010-010) and the Danish Data Protection Agency (HEH.afd.I.750.16-18) approved the trial, which adhered to the International Conference on Harmonization Good Clinical Practice standards. Written informed consent was obtained from the patients or a legal representative if the patient was incapable. The trial was designed to comply with the Consolidated Standards of Reporting Trials (CONSORT) statement for non-pharmacological trials[22,23], and fulfilled the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement[24]. An independent Data Monitoring Committee monitored safety and efficacy at a scheduled interim analysis after 200 patients had been included[20].

Trial design and patients

The InCare trial was a multicentre randomized clinical trial with postoperative 1 : 1 allocation to either intermediate care for 48 h or standard surgical ward care. Patients were enrolled between 4 October 2010 and 30 November 2012 at seven Danish university-affiliated secondary referral hospitals. The trial protocol, including details of the rationale and design, has been published previously[20]. Patients were eligible if they: had undergone emergency abdominal laparotomy or laparoscopy; were ready to be transferred to a standard ward after their postoperative stay in a postanaesthesia care, intermediate care or intensive care unit for less than 24 h; and had a perioperative Acute Physiology And Chronic Health Evaluation (APACHE) II score of 10 or above. Emergency surgery was defined as surgery to be undertaken within 24 h. The APACHE II index was used to select high-risk surgical patients[25–30]. A score of 10 or above reflects the presence of perioperative sepsis, cardiovascular and/or respiratory failure (index range in emergency surgical patients 5–71)[20]. To increase the enrolment rate, the APACHE II score threshold was lowered from the original limit of at least 12 to 10 or more on 23 May 2012 after enrolment of 192 patients[31].

Exclusion criteria

Exclusion criteria were: appendicectomy, laparoscopic cholecystectomy, negative diagnostic laparoscopy, intensive care not indicated (patients receiving palliative care or with irreversible organ failure), previous participation in the trial, age below 18 years, trauma, and no intermediate care bed available.

Randomization

Randomization was performed by the Copenhagen Trial Unit remote from the participating trial sites, through a centralized, interactive voice-response system in accordance with a concealed, computer-generated allocation sequence using varying block sizes unknown to the investigators. The randomization was stratified by trial site, APACHE II score (10–14 or at least 15), and perforated viscera (yes or no). The attending anaesthetists randomized the patients when they were ready to be transferred to the surgical ward in accordance with Danish national recommendations[20]. The interventions were initiated immediately after randomization.

Interventions

Patients allocated to intermediate care were admitted for at least 48 h. Patients were at a minimum monitored with continuous electrocardiography and pulse oximetry when not mobilized, and BP and respiratory rate were measured every other hour when not asleep. More details can be found in *Table S1* (supporting information)[20]. If the patient deteriorated, the monitoring and treatment level

was increased. Patients were transferred to an intensive care bed if invasive arterial BP monitoring, invasive ventilation, emergency renal replacement therapy or parallel sympathomimetic drug infusion was needed. Surgeons and intensivists made protocol-based rounds on a daily basis using a standard form[20]. Forty-eight hours after randomization, patients with stable vital signs were transferred to the surgical ward.

Patients allocated to standard surgical ward care were transferred with a protocol-based discharge note by the attending anaesthetist, using a standard form[20]. A written plan for monitoring and treatment over the first 24 h in the ward was stated in the medical record. All other interventions were as standard for the individual ward (*Table S2*, supporting information). In brief, the surgical wards had the resources to monitor vital signs every 8 h, and continuous monitoring of vital signs was not possible. Any patient who deteriorated was transferred to an intensive care unit when appropriate.

For all patients, medical treatments and investigations were initiated at the discretion of the clinicians based solely on medical indications, and were not determined by the trial protocol.

Adherence to trial protocol

Two or three investigators managed the implementation of the trial at each hospital by teaching and supervising key healthcare staff in patient enrolment, intermediate care patient monitoring, and conducting protocol-based evaluations. Adherence to the protocol was enhanced by repeated staff educational sessions, which were recorded in a log, and by monitoring data from the intervention period. This was assessed by both the coordinating investigator and the monitors of good clinical practice[20].

Outcomes

The primary outcome was all-cause mortality within 30 days after surgery. Secondary outcomes were time to death within the total observation period (from the index surgical procedure until 30 days after randomization of the last patient), percentage of days alive without intensive care within 30 days of randomization, and percentage of days alive and out of the hospital within 30 days of randomization.

Mortality data were retrieved from the Danish Civil Registration System by the Copenhagen Trial Unit at interim analyses and 30 days after the trial had been completed[32]. The Danish Civil Registration System contains the exact dates of death of all Danish citizens through a unique personal identification number. Data on intensive care admissions and hospital admission were obtained from patient files by the trial investigators and the Danish National Patient Registry, not limited to the index admission[33]. An intensive care day was counted if the patient was present in the intensive care unit at 08.00 hours.

Postoperative complications and reoperations

To describe the postoperative course, the rate of abdominal surgical reoperations and postoperative complications requiring treatment within 14 days of index surgery and randomization were registered. The predefined complications were obtained from patient files by the investigators or their delegates. For definitions, refer to *Appendix S1* (supporting information).

Blinding

Patients, staff and investigators were not blinded to the group allocation. A data manager, external to the participating trial sites, retrieved the mortality data centrally from the Danish Civil Registration System. The InCare trial Steering Committee approved the statistical plan before the outcome data were assessable. Data were analysed by a statistician not involved in the trial during randomization and follow-up, who was blinded to the group allocation.

Sample size estimation

The estimated 30-day mortality rate of 38 per cent in the ward care group was based on previously reported rates of 28–45 per cent after emergency major abdominal surgery in patients with an APACHE II score of 10 or above[20,26–30]. A relative risk reduction of 34 per cent was anticipated, in accordance with previous results of optimized care in patients with perforated peptic ulcer[34]. Based on these assumptions, it was calculated that 400 patients were needed to detect or reject a reduction in 30-day mortality rate from 38 to 25 per cent, with 80 per cent power and a 5 per cent risk of type I error[35].

Statistical analysis

The outcome measures were analysed in accordance with a predefined statistical plan (*Appendix S1*, supporting information)[36]. The primary analyses were performed on data from the modified intention-to-treat population adjusted for stratification variables (*Fig. 1*)[37,38].

The primary outcome, 30-day mortality, was analysed by univariable and multivariable logistic regression adjusted for the stratification variables, and a fully adjusted analysis

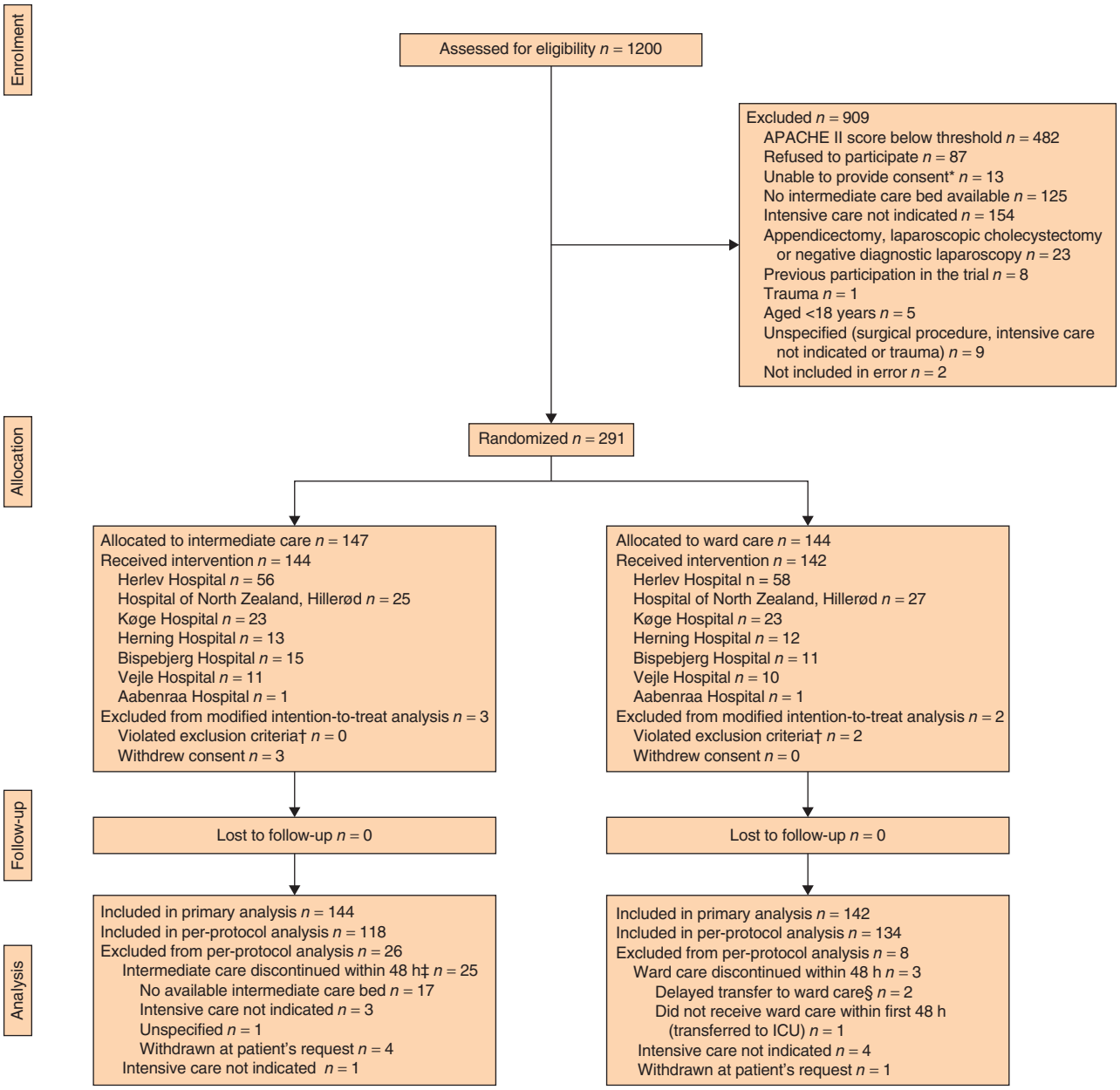

Fig. 1 Patient enrolment and follow-up. *Because of language barrier. †Excluded from the modified intention-to-treat analysis as specified by the predefined statistical plan; one patient had undergone a negative diagnostic laparoscopy and one had experienced trauma. ‡In 14 patients, the intermediate care was discontinued within 24 h (2 patients did not receive intermediate care at all). §One patient was not ready to be transferred to ward care and one patient received the wrong intervention for 6 h. APACHE, Acute Physiology And Chronic Health Evaluation; ICU, intensive care unit

with stratification and other design variables including age, American Society of Anesthesiologists fitness grade (I–II *versus* III or more), cancer (yes/no) and nature of surgery (reoperation or not).

Time to death within the total observation period was analysed by means of Cox regression analyses, with and without adjustment for the stratification variables, and a fully adjusted analysis with stratification and other design variables. The Cox regression model produced survival curves adjusted for the stratification variables.

The percentage of days alive without intensive care, and alive and out of hospital were analysed using the

Table 1 Preoperative baseline characteristics

	Intermediate care ($n = 144$)	Ward care ($n = 142$)
Age (years)*	73 (48–95)	73 (23–93)
Sex ratio (M : F)	66 : 78	75 : 67
ASA physical status grade		
I	13 (9·0)	17 (12·0)
II	65 (45·1)	62 (43·7)
III	61 (42·4)	58 (40·8)
IV	5 (3·5)	5 (3·5)
Current smoker	36 (25·0)	35 of 141 (24·8)
Alcohol abuse†	10 of 140 (7·1)	10 of 139 (7·2)
Home care‡	17 (11·8)	9 of 141 (6·4)
Co-morbidity		
Preoperative cancer	35 (24·3)	43 (30·3)
Metastatic cancer	6 (4·2)	14 (9·9)
Cardiovascular disease	81 (56·3)	67 (47·2)
Chronic obstructive pulmonary disease	34 (23·6)	18 (12·7)
Requiring renal replacement therapy	4 (2·8)	1 (0·7)
Dementia	4 (2·8)	3 (2·1)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †More than 36 g/day (men) or 24 g/day (women). ‡Need for assistance with personal hygiene before admission. ASA, American Society of Anesthesiologists.

Table 2 Perioperative baseline characteristics

	Intermediate care ($n = 144$)	Ward care ($n = 142$)
Surgical procedure		
Gastroduodenal	23 (16·0)	18 (12·7)
Small bowel	53 (36·8)	49 (34·5)
Colorectal	42 (29·2)	51 (35·9)
Surgery for anastomotic dehiscence	6 (4·2)	2 (1·4)
Other†	20 (13·9)	22 (15·5)
Reoperative procedure‡	20 (13·9)	14 (9·9)
Laparoscopic surgery	8 (5·6)	6 (4·2)
Surgical pathology		
Perforated viscera§	55 (38·2)	51 (35·9)
Ischaemic intestine¶	21 (14·6)	13 (9·2)
Cancer surgery#	20 (13·9)	31 (21·8)
Duration of surgery (min)*	122 (25–491)	133 (17–655)
Anaesthesia care		
Type of anaesthesia		
Inhalational	92 of 143 (64·3)	80 of 141 (56·7)
Total intravenous	51 of 143 (35·7)	61 of 141 (43·3)
Epidural analgesia	60 (41·7)	50 (35·2)
Sympathomimetic infusion**	37 (25·7)	30 (21·1)
Duration of postanaesthesia care (h)*	6 (2–23)	6 (1–22)
Fluid management††		
Estimated blood loss (ml)*	100 (0–5000) ($n = 142$)	100 (0–4700) ($n = 140$)
Crystalloid infusion (ml)*	3000 (0–9100)	3175 (500–16 500)
Colloid infusion (ml)*	225 (0–3500)	500 (0–3100)
Received blood products‡‡	36 (25·0)	30 (21·1)
Amount per transfused patient (units)*	2 (1–21)	2 (1–12)
Perioperative morbidity scores		
APACHE II score*§	16 (10–31)	16 (10–27)
≥ 15	90 (62·5)	90 (63·4)
Sepsis score§§		
No SIRS or sepsis	90 of 140 (64·3)	105 of 142 (73·9)
SIRS	28 of 140 (20·0)	21 of 142 (14·8)
Sepsis, severe sepsis or septic shock	22 of 140 (15·7)	16 of 142 (11·3)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Includes hernia repair, open cholecystectomy, laparotomy without intervention, peritoneal adhesion surgery, peritoneal drainage or lavage, intraperitoneal infection and haemorrhage, and stoma revision surgery. ‡Index surgical procedure within 14 days of the primary procedure (elective surgery or emergency surgery with Acute Physiology And Chronic Health Evaluation (APACHE) II score below threshold). §Stratification variable. ¶Defined by the surgeon. #Cancer visible in the surgical field. **Infused continuously for more than 15 min during surgery or in the postanaesthesia care unit. ††During surgery and in the postanaesthesia care unit. ‡‡Red blood cell concentrate, platelet concentrate or fresh frozen plasma. §§Evaluated just before randomization. SIRS, systemic inflammatory response syndrome.

Mann–Whitney *U* test. The proportions of patients with one or more intensive care admissions, postoperative complications and abdominal surgical reoperation were analysed with the χ^2 test. Two per-protocol analyses were performed: one excluding patients with one or more major protocol violations, and another including patients who received 24 h or more of intermediate care. Additionally, the mortality outcome measures were analysed in subgroups with APACHE II score 15 or above, cancer or perforated viscera.

An independent Data Monitoring Committee monitored safety and efficacy at a scheduled interim analysis after 200 patients had been included. The interim analysis was conducted on 30-day mortality data blinded to group allocation. In the event that the interim analysis was significant ($P < 0{\cdot}001$) for benefit or harm of the intervention, an additional interim analysis was planned after the inclusion of 300 patients[20]. SPSS® version 19.0 (IBM, Armonk, New York, USA) was used for statistical analysis. Two-sided $P < 0{\cdot}050$ was considered statistically significant.

Results

The scheduled interim analysis revealed a very low 30-day all-cause mortality rate compared with the pretrial estimate. This precluded the possibility of detecting or rejecting the anticipated relative risk reduction of 34 per cent with the planned sample size, and the trial was therefore terminated.

A total of 291 patients were randomized, and 286 were included in the modified intention-to-treat analysis (*Fig. 1*).

Table 3 Monitoring and treatment levels during the first 48 h after randomization relative to trial protocol in the intermediate care group, and to standard ward care in the ward care group

	Intermediate care ($n = 144$)	Ward care ($n = 142$)
Duration of allocated intervention		
Patients receiving the allocated intervention for ≥ 48 h	115 (79·9)	131 (92·3)
Patients with intervention discontinued within 48 h	29 (20·1)	11 (7·7)
Step up to intensive care	4 (2·8)	7 (4·9)
Discharged*	25 (17·4)	1 (0·7)
Wrong intervention	0 (0)	3 (2·1)
Monitoring level at allocated intervention		
Level of consciousness – complying with standards†	97 of 133 (72·9)	42 of 138 (30·4)
Respiratory rate – complying with standards‡§	117 of 136 (86·0)	45 of 137 (32·8)
Continuous pulse oximetry	139 of 142 (97·9)	16 of 137 (11·7)
BP – complying with standards‡	115 of 134 (85·8)	49 of 133 (36·8)
Continuous ECG monitoring	138 of 142 (97·2)	0 of 140 (0)
Hourly urinary output registration for more than 24 h	89 of 141 (63·1)	4 of 133 (3·0)
24-h fluid balance calculations on days 1–2	120 of 142 (84·5)	65 of 127 (51·2)
Temperature – complying with standards†	71 of 134 (53·0)	49 of 135 (36·3)
Pain visual assessment score – complying with standards†	87 of 135 (64·4)	7 of 134 (5·2)
Standard blood samples taken at least twice	110 of 137 (80·3)	92 of 139 (66·2)
Use of early warning score system monitoring¶	20 of 140 (14·3)	74 of 141 (52·5)
Treatment level at allocated intervention		
Received sympathomimetic infusion	2 of 138 (1·4)	0 of 140 (0)
≥ 2 litres supplemental oxygen for 2 nights	75 of 141 (53·2)	53 of 102 (52·0)
Received PEP therapy		
Self-management	87 of 128 (68·0)	34 of 84 (40)
Assistance	39 of 129 (30·2)	11 of 91 (12)
Received non-invasive ventilation	3 of 143 (2·1)	0 of 141 (0)
Postoperative nutrition plan initiated within 24 h	107 of 140 (76·4)	63 of 140 (45·0)
Mobilized to chair within 24 h	105 of 135 (77·8)	84 of 125 (67·2)
Mobilized with or without walker within 24 h	41 of 130 (31·5)	56 of 123 (45·5)
Two or more surgeon evaluations	96 of 142 (67·6)	115 of 141 (81·6)
Two or more intensivist or anaesthetist evaluations	119 of 142 (83·8)	1 of 141 (0·7)
Protocol-based discharge note written in the postanaesthesia care unit before transfer to ward	n.a.	126 of 142 (88·7)
Two or more protocol-based rounds by a surgeon	59 of 143 (41·3)	n.a.
Two or more protocol-based rounds by an intensivist or anaesthetist	105 of 143 (73·4)	n.a.

Values in parentheses are percentages. *Intermediate care group: discharged to ward because of no available intermediate bed (17 patients), intensive care not indicated (3), not specified (1) or withdrawn at patient's request (4); ward care group: discharged home (1). †Intermediate care group: six or more registrations; ward care group: six or more registrations (3 times a day for 2 days). ‡Intermediate care group: 16 or more registrations (every other hour during the day and evening shifts for 2 days); ward care group: six or more registrations. §At Vejle Hospital, Bispebjerg Hospital and Herlev Hospital (from 7 June 2012), the respiratory rate was monitored continuously and registered as 99 per min. ¶Not a trial protocol element. ECG, electrocardiography; PEP, positive expiratory pressure; n.a., not applicable.

Five patients were excluded because they withdrew consent or because a surgical procedure criterion was not fulfilled. Preoperative and perioperative baseline characteristics are presented in *Tables 1* and *2* respectively.

Table 3 details adherence to the trial protocol in the intermediate care group, and the level of monitoring in the ward care group relative to standard surgical ward treatment. The intervention was discontinued more often in the intermediate care group than in the ward care group, predominantly because of lack of intermediate care beds.

Outcomes

The primary outcome, death within 30 days of surgery, occurred in 11 (7·6 per cent) of 144 patients in the intermediate care group and 12 (8·5 per cent) of 142 in the ward care group (odds ratio 0·91, 95 per cent c.i. 0·38 to 2·16; $P = 0·828$) (*Table 4*). Death within the total observation period occurred in 30 (20·8 per cent) of 144 patients in the intermediate care group and 37 (26·1 per cent) of 142 in the ward care group (hazard ratio (HR) 0·78, 95 per cent c.i. 0·48 to 1·26; $P = 0·310$) (*Table 4* and *Fig. 2*). Thirteen (9·0 per cent) of 144 patients in the intermediate care group and 23 (16·2 per cent) of 142 in the ward care group required admission to intensive care ($P = 0·068$). The percentage of days alive without intensive care, and alive and out of hospital did not differ significantly between the groups (*Table 4*).

Similar results were obtained in per-protocol analyses. Intermediate care had no effect on mortality outcomes in

Table 4 Primary and secondary outcomes

	Intermediate care* ($n = 144$)	Ward care* ($n = 142$)	Univariable OR/HR†	*P*	Adjusted OR/HR†‡	*P*	Fully adjusted OR/HR†§	*P*
Primary outcome								
Death within 30 days	11 (7·6)	12 (8·5)	0·90 (0·38, 2·10)	0·801	0·91 (0·38, 2·16)	0·828	0·73 (0·29, 1·82)	0·498
Secondary outcomes								
Death within total observation period	30 (20·8)	37 (26·1)	0·80 (0·49, 1·29)	0·360	0·78 (0·48, 1·26)	0·310	0·82 (0·50, 1·34)	0·420
Alive without intensive care within 30 days								
Median no. of days	30	30						
Median % of days	100	100	n.a.	0·193¶	n.a.	n.a.	n.a.	n.a.
Alive and out of hospital within 30 days								
Median no. of days	17	17						
Median % of days	56.7	56.7	n.a.	0·534¶	n.a.	n.a.	n.a.	n.a.

Values in parentheses are *percentages and †95 per cent c.i. The ward care group is the reference value for interpretation of odds ratios (ORs) for death within 30 days and hazard ratios (HRs) for death within the total observation period. ‡Adjusted for stratification variables (primary analysis): study site, Acute Physiology And Chronic Health Evaluation (APACHE) II score (10–14, ≥ 15) and perforated viscera (yes/no). §Adjusted for stratification variables and other design variables: age, American Society of Anesthesiologists fitness grade (I–II, ≥ III), cancer (yes/no) and nature of surgery (reoperation or not). n.a., Not applicable. ¶Mann–Whitney *U* test.

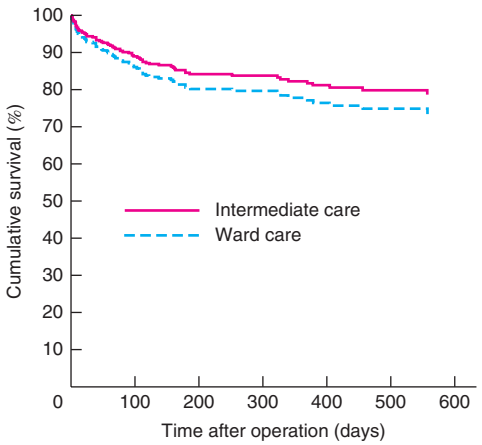

Fig. 2 Survival curves created from the Cox regression model with adjustment for stratification variables

the prespecified subgroups with an APACHE II score of 15 or above, cancer or perforated viscera. Among those with perforated viscera, 12 (22 per cent) of 55 patients in the intermediate care group and 20 (39 per cent) of 51 in the ward care group died within the total observation period (univariable HR 0·51, 95 per cent c.i. 0·25 to 1·05; $P = 0·068$; test for interaction, $P = 0·102$).

Complications and reoperations

Postoperative complications were recorded in 73 (50·7 per cent) of 144 patients in the intermediate care group and 62 (43·7 per cent) of 142 in the ward care group ($P = 0·234$) (*Table S3*, supporting information). Cardiovascular complications were frequently detected and treated in the intermediate care group, especially cardiac arrhythmias during the intervention period (20 patients in intermediate care group, 6 in ward care group). The rate of one or more abdominal surgical reoperations was similar in the intervention groups.

Discussion

In this randomized clinical feasibility trial, the effect of postoperative intermediate care was compared with standard surgical ward care among high-risk patients undergoing emergency abdominal surgery. Postoperative intermediate care did not reduce mortality, the need for intensive care, or length of hospital stay in these patients. However, the trial was stopped early owing to a very low mortality rate, which precluded evaluation of the primary endpoint at the planned enrolment of 400 patients. Despite this, the authors believe that the trial may provide data to inform design adjustments and sample size estimates for future trials.

The strengths of this study are that it is a multicentre, randomized clinical trial with a low risk of bias compared with previous studies[39–45]. The complex intervention was described thoroughly before the start, good clinical practice monitors assessed adherence to the trial protocol, and the actual monitoring and treatment levels in the intervention groups were reported clearly, as recommended for non-pharmacological trials[23]. Follow-up was complete and validated by national registers[32,33].

However, this trial has several limitations. First, it was terminated after inclusion of 72·8 per cent of the planned sample, because the interim analysis revealed a very low overall 30-day mortality compared with the pretrial estimate. Thus, the trial was not powered to show the anticipated relative risk reduction with a sample of 400 patients. Nevertheless, because this is the first randomized trial investigating the effect of intermediate *versus* standard ward care after emergency abdominal surgery, the point estimates are the least biased so far and can be used for the design of future trials on this topic. It was not possible to blind the patients, staff or investigators to the group allocation. However, the mortality data were retrieved centrally from national registers by a data manager outwith the participating trial sites who was blinded to the interventions. Finally, this trial had to rely on the availability of intermediate care beds in intensive care units. Limited bed availability challenged both the patient enrolment rate and implementation of the intermediate care intervention. To increase the enrolment rate, the APACHE II score threshold was lowered from the original 12 to 10, as it was impossible to increase the number of trial sites. The change in APACHE II score threshold and the inability to include all principally eligible patients, owing to a limited number of free beds, may have caused the trial population to become less representative of the future target population. The intermediate care intervention was discontinued in 25 (17·4 per cent) of 144 patients, with the majority discharged to the ward prematurely owing to limited availability of beds (*Fig. 1*). This may affect the internal validity of the trial. Nevertheless, relying on availability of intermediate care beds may, to some extent, reflect everyday clinical practice in many healthcare settings.

No effect of postoperative intermediate care on short-term mortality was found. In the present trial, the short-term mortality rate in the ward care group was much lower than the pretrial estimate (8·5 *versus* 38 per cent), based on cohort studies of patients with an APACHE II score of 10 or above undergoing emergency abdominal surgery[26–30]. This deviation may relate to differences in case mix, as patients admitted to the intensive care unit for more than 24 h after surgery and those for whom intensive care was not indicated were excluded. The latter comprised a larger proportion of patients having emergency abdominal surgery than predicted.

Previous studies[4,39–45] of the effects of postoperative intermediate care are comparative observational studies with a high risk of bias. They have reported conflicting mortality results. In the present trial, the HR for death within the total observation period was 0·78 (95 per cent c.i. 0·48 to 1·26), possibly in favour of intermediate care, an outcome that has not been investigated in previous studies. Likewise, the HR was 0·51 (0·25 to 1·05), possibly in favour of intermediate care, among patients with perforated viscera. These point estimates may inform a hypothesis that intermediate care can reduce mortality and that patients with perforated viscera may be the most important to include in a future larger trial.

In keeping with previous studies[39,40,43,44], the trial results indicate that intermediate care does not reduce length of hospital stay. One previous study[41] reported that postoperative intermediate care may reduce unplanned intensive care admissions. In the present trial, 9·0 per cent of patients in the intermediate care group and 16·2 per cent in the ward care group were transferred to an intensive care bed after surgery ($P = 0{\cdot}068$). However, this event was rare, and the trial was not powered to assess the secondary outcome days alive without intensive care.

The present trial confirmed that patients undergoing emergency abdominal surgery are at high risk of cardiopulmonary complications and sepsis[7,8]. Two previous studies[39,40] have suggested that postoperative intermediate care is associated with fewer cardiac complications after major abdominal surgery than ward care. The present trial indicated the opposite, possibly because of an increased recognition of complications owing to a higher level of monitoring in the intermediate care group[20].

The rationale for postoperative intermediate care for 48 h is that extra and prolonged monitoring, extra specialist attention and additional resources for more advanced treatments might lead to a reduction in mortality by avoidance, or timely recognition and effective management, of postoperative complications[12,46]. However, a larger trial is required to assess the potential efficacy of this intervention on mortality. The authors believe that the InCare trial design is feasible, but the following adjustments are recommended. First, the participating trial sites should guarantee available beds for the intermediate care intervention, thereby guaranteeing a high enrolment rate and limited discontinuation of the intermediate care intervention. This could be achieved by securing dedicated funding for research beds. Second, if the effect on mortality is to be evaluated, the primary outcome should be time to death within the total observation period, preferably with a final assessment date later than used in the present trial. This is a more comprehensible outcome to the patients than short-term landmark mortality with an arbitrary censoring date. Third, the APACHE II score could be replaced with a more simple and transparent way of selecting high-risk patients. Based on the present results, a future trial should enrol at least 2000 patients if the primary outcome measure is time to death within the total observation period, with a

2-year enrolment period and 1 year of additional follow-up, addressing an anticipated HR reduction of 22 per cent, a control group mortality rate of 26 per cent within the total observation period, 80 per cent power and a 5 per cent type I error risk[35]. If postoperative intermediate care proves beneficial, it may potentially save one in 20 high-risk patients undergoing emergency abdominal surgery in the future[47].

Collaborators

The following members of the InCare trial group contributed to the trial as principal site investigators, and are co-authors of this article: I. E. Gillesberg, H. L. Jakobsen, E. G. Hansen (Herlev Hospital, Herlev); L. M. Poulsen, J. Skovdal, E. K. Søgaard (Køge Hospital, Køge); M. Bestle, J. Vilandt, I. Rosenberg, T. S. Itenov (Hospital of North Zealand, Hillerød); J. Pedersen, M. R. Madsen (Herning Regional Hospital, Herning); C. Maschmann, M. Rasmussen (Bispebjerg Hospital, Copenhagen); C. Jessen, L. Bugge (Lillebælt Hospital, Vejle).

Acknowledgements

The authors thank the following, who also helped as site investigators but do not fulfil authorship criteria: P. B. Larsen, H. Jørgensen, A. Fischer (Herlev Hospital, Herlev); J. Jacobsen, L. Höegh, R. E. Berthelsen (Hospital of North Zealand, Hillerød); M. L. Rasmussen (Herning Hospital, Herning), T. Feurstein, M. J. Busse, J. D. H. Andersen, A.-M. Ulrik, L. Kaag (Aabenraa Hospital, Aabenraa); K. Møller, M. Krag, C. Strøm (Bispebjerg Hospital, Copenhagen); S. Kähler, H. Ørding (Lillebælt Hospital, Vejle). They also thank the participants, staff (anaesthetists, intensivists, surgeons, nurses and secretaries) and department heads at the participating sites who made this trial possible; and T. Faber for programming the APACHE II calculator. Quality assessment and good clinical practice monitoring: T. Thomsen (Department of Anaesthesiology, Abdominal Centre, Rigshospitalet, University of Copenhagen, Copenhagen) and U. T. Jensen (Research Unit, Department of Anaesthesiology and Intensive Care Medicine, Herlev Hospital, University of Copenhagen, Herlev). Data monitoring committee: L. S. Rasmussen (Department of Anaesthesiology, Rigshospitalet, University of Copenhagen, Copenhagen) and I. Gögenur (Department of Surgery, Koege Hospital, University of Copenhagen, Koege). Randomization and data management: J. Engstrøm (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, University of Copenhagen, Copenhagen). Statistical expertise: J. C. Jakobsen (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen).

The trial was funded by the Herlev Hospital Research Council, the Danish Capital Region's Medical Research Foundation, the Health Insurance Foundation (2010B053), A. P. Møller Foundation for the Advancement of Medical Science, the Danish Council for Independent Research in Medical Science (11-108561), the Research Council of Hospital of Southern Jutland Aabenraa, the Lundbeck Foundation (R118-A11357) and the Department of Anaesthesiology and Intensive Care Medicine, Herlev Hospital. None of the funding sources influenced the trial design, data collection, data management, data analysis or reporting.

Disclosure: The authors declare no conflict of interest.

References

1 Al-Temimi MH, Griffee M, Enniss TM, Preston R, Vargo D, Overton S *et al.* When is death inevitable after emergency laparotomy? Analysis of the American College of Surgeons National Surgical Quality Improvement Program database. *J Am Coll Surg* 2012; **215**: 503–511.

2 Saunders DI, Murray D, Pichel AC, Varley S, Peden CJ; UK Emergency Laparotomy Network. Variations in mortality after emergency laparotomy: the first report of the UK Emergency Laparotomy Network. *Br J Anaesth* 2012; **109**: 368–375.

3 Vester-Andersen M, Lundstrøm LH, Møller MH, Waldau T, Rosenberg J, Møller AM *et al.*; Danish Anaesthesia Database. Mortality and postoperative care pathways following emergency gastrointestinal surgery in 2904 patients: a population-based cohort study. *Br J Anaesth* 2014; **112**: 860–870.

4 Symons NR, Moorthy K, Almoudaris AM, Bottle A, Aylin P, Vincent CA *et al.* Mortality in high-risk emergency general surgical admissions. *Br J Surg* 2013; **100**: 1318–1325.

5 Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A *et al.* Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care* 2006; **10**: R81.

6 Shapter SL, Paul MJ, White SM. Incidence and estimated annual cost of emergency laparotomy in England: is there a major funding shortfall? *Anaesthesia* 2012; **67**: 474–478.

7 Awad S, Herrod PJ, Palmer R, Carty HM, Abercrombie JF, Brooks A *et al.* One- and two-year outcomes and predictors of mortality following emergency laparotomy: a consecutive series from a United Kingdom teaching hospital. *World J Surg* 2012; **36**: 2060–2067.

8 Sorensen LT, Malaki A, Wille-Jørgensen P, Kallehave F, Kjaergaard J, Hemmingsen U *et al.* Risk factors for mortality and postoperative complications after gastrointestinal surgery. *J Gastrointest Surg* 2007; **11**: 903–910.

9 Harten J, McCreath BJ, McMillan DC, McArdle CS, Kinsella J. The effect of gender on postoperative mortality after emergency abdominal surgery. *Gend Med* 2005; **2**: 35–40.

10 Iversen LH, Bulow S, Christensen IJ, Laurberg S, Harling H; Danish Colorectal Cancer Group. Postoperative medical complications are the main cause of early death after emergency surgery for colonic cancer. *Br J Surg* 2008; **95**: 1012–1019.

11 Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ; Participants in the VA National Surgical Quality Improvement Program. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg* 2005; **242**: 326–341.

12 Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. *N Engl J Med* 2009; **361**: 1368–1375.

13 Almoudaris AM, Burns EM, Mamidanna R, Bottle A, Aylin P, Vincent C *et al.* Value of failure to rescue as a marker of the standard of care following reoperation for complications after colorectal resection. *Br J Surg* 2011; **98**: 1775–1783.

14 National Confidential Enquiry into Patient Outcome and Death (NCEPOD). *Knowing the Risk. A Review of the Peri-operative Care of Surgical Patients*; 2011. http://www.ncepod.org.uk/2011report2/downloads/POC_fullreport.pdf [accessed 7 November 2014].

15 Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, Pearse RM. Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. *Anaesthesia* 2008; **63**: 695–700.

16 Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C *et al.* Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380**: 1059–1065.

17 Ridley SA. Intermediate care, possibilities, requirements and solutions. *Anaesthesia* 1998; **53**: 654–664.

18 Danish National Board of Health. *Intensive Care – Definitions, Documentation and Visitation*; 2006. http://sundhedsstyrelsen.dk/publ/publ2006/plan/intensiv_terapi/intensiv_terapi.pdf [accessed 7 November 2014].

19 Nasraway SA, Cohen IL, Dennis RC, Howenstein MA, Nikas DK, Warren J *et al.* Guidelines on admission and discharge for adult intermediate care units. American College of Critical Care Medicine of the Society of Critical Care Medicine. *Crit Care Med* 1998; **26**: 607–610.

20 Vester-Andersen M, Waldau T, Wetterslev J, Moller MH, Rosenberg J, Jorgensen LN *et al.* Effect of intermediate care on mortality following emergency abdominal surgery. The InCare trial: study protocol, rationale and feasibility of a randomised multicentre trial. *Trials* 2013; **14**: 37.

21 Turner J, Gemmell LW. Are high dependency units effective and efficient? A systemic review of the evidence. *Clin Intensive Care* 2003; **14**: 123–133.

22 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; **152**: 726–732.

23 Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P; CONSORT Group. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; **148**: 295–309.

24 Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; **346**: e7586.

25 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–829.

26 Wacha H, Hau T, Dittmer R, Ohmann C. Risk factors associated with intraabdominal infections: a prospective multicenter study. Peritonitis Study Group. *Langenbecks Arch Surg* 1999; **384**: 24–32.

27 Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgadari A, Gui D *et al.* Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. *Arch Surg* 1996; **131**: 641–645.

28 Kulkarni SV, Naik AS, Subramanian N Jr. APACHE-II scoring system in perforative peritonitis. *Am J Surg* 2007; **194**: 549–552.

29 Schein M, Gecelter G, Freinkel Z, Gerding H. APACHE II in emergency operations for perforated ulcers. *Am J Surg* 1990; **159**: 309–313.

30 Setti Carraro PG, Magenta A, Segala M, Ravizzini C, Nespoli A, Tiberio G. Predictive value of a pathophysiological score in the surgical treatment of perforated diverticular disease. *Chir Ital* 1999; **51**: 31–36.

31 ClinicalTrials.gov archive. *Changes to NCT01209663 on 2012_05_23.* http://clinicaltrials.gov/archive/NCT01209663/2012_05_23/changes [accessed 7 November 2014].

32 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**(Suppl): 22–25.

33 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**(Suppl): 30–33.

34 Møller MH, Adamsen S, Thomsen RW, Møller AM; Peptic Ulcer Perforation (PULP) trial group. Multicentre trial of a perioperative protocol to reduce mortality in patients with peptic ulcer perforation. *Br J Surg* 2011; **98**: 802–810.

35 Department of Biostatistics Vanderbilt University. *PS: Power and Sample Size Calculation*. 2009 (3.0). http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize [accessed 7 November 2014].

36 Lewis JA. Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline. *Stat Med* 1999; **18**: 1903–1942.

37 Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002; **325**: 652–654.

38 Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *BMJ* 2012; **345**: e5840.

39 Swart M, Carlisle JB. Case-controlled study of critical care or surgical ward care after elective open colorectal surgery. *Br J Surg* 2012; **99**: 295–299.
40 Jones HJ, Coggins R, Lafuente J, de Cossart L. Value of a surgical high-dependency unit. *Br J Surg* 1999; **86**: 1578–1582.
41 Eichenberger AS, Haller G, Cheseaux N, Lechappe V, Garnerin P, Walder B. A clinical pathway in a post-anaesthesia care unit to reduce length of stay, mortality and unplanned intensive care unit admission. *Eur J Anaesthesiol* 2011; **28**: 859–866.
42 McIlroy DR, Coleman BD, Myles PS. Outcomes following a shortage of high dependency unit beds for surgical patients. *Anaesth Intensive Care* 2006; **34**: 457–463.
43 Bellomo R, Goldsmith D, Uchino S, Buckmaster J, Hart G, Opdam H *et al.* A before and after trial of the effect of a high-dependency unit on post-operative morbidity and mortality. *Crit Care Resusc* 2005; **7**: 16–21.
44 Davies J, Tamhane R, Scholefield C, Curley P. Does the introduction of HDU reduce surgical mortality? *Ann R Coll Surg Engl* 1999; **81**: 343–347.
45 Turner M, McFarlane HJ, Krukowski ZH. Prospective study of high dependency care requirements and provision. *J R Coll Surg Edinb* 1999; **44**: 19–23.
46 Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002; **288**: 1987–1993.
47 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999; **319**: 1492–1495.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Definition of intermediate care (Word document)

Table S2 Surgical ward care: an overview of facilities (Word document)

Table S3 Postoperative complications and abdominal reoperations (Word document)

Appendix S1 Detailed statistical analysis plan (Word document)

Editor's comments

Reasons for conducting a feasibility trial may include the need to evaluate the features of a trial regarding the process, the resources needed and overall management, and to test the scientific rationale behind the question asked. The decision to stop the InCare trial was based on failure of at least three of these. First, the recruitment rate was much lower than expected. With an adaptive research design, the investigators widened the inclusion criteria (APACHE II score decreased to 10 or more from 12 or more) to include less sick patients. This may have affected the scientific rationale, as the observed mortality rate (less than 10 per cent) was much lower than expected (about 30 per cent), thus preventing the investigators from reaching the proposed power by aiming for about 400 included patients. Further, recruitment was delayed by a limitation of resources (available intermediate care beds). Feasibility trials are never conclusive, but the InCare trial has some important lessons and paves the way for the design of future trials. An effect on mortality may be seen only by including higher-risk patients, possibly from a larger catchment area (multicentre, international), while ensuring appropriate funding and availability of intermediate care beds. This should be suitable for collaboration across borders.

K. Søreide
Editor, BJS