



Randomised Controlled Trial

Ward based goal directed fluid therapy (GDFT) in acute pancreatitis (GAP) trial: A feasibility randomised controlled trial



Farid Froghi^{a,b,*}, Fiammetta Soggiu^a, Federico Ricciardiⁱ, Cecilia Vindrola-Padros^g, Lefteris Floros^h, Daniel Martin^{a,f}, Helder Filipe^e, Massimo Varcada^{a,b}, Kurinchi Gurusamy^a, Satya Bhattacharya^d, Angela Fanshawe^c, Bogdan Delcea^c, Pawan Mathur^c, Brian Davidson^{a,b}, GAP Collaborators

^a UCL Division of Surgery and Interventional Science, Royal Free Hospital, London, UK

^b General and Emergency Surgery Department, Royal Free Hospital, London, UK

^c General and Emergency Surgery Department, Barnet General Hospital, London, UK

^d Hepatopancreaticobiliary Surgery, Royal London Hospital, London, UK

^e Intensive Care Unit, Royal Free Hospital, London, UK

^f Peninsula Medical School, University of Plymouth, Plymouth, UK

^g Department of Targeted Intervention, University College London, London, UK

^h PHMR, Health Economics, Pricing & Reimbursement, London, UK

ⁱ Department of Statistical Science, University College London, London, UK

ARTICLE INFO

Keywords:

Fluid therapy
Acute pancreatitis
Cardiac output
Goal-directed fluid therapy

ABSTRACT

Background: Goal-directed fluid therapy (GDFT) reduces complications in patients undergoing major general surgery. There are no reports of cardiac output evaluation being used to optimise the fluid administration for patients with acute pancreatitis (AP) in a general surgery ward.

Method: 50 patients with AP were randomised to either ward-based GDFT (n = 25) with intravenous (IV) fluids administered based on stroke volume optimisation protocol or standard care (SC) (n = 25), but with blinded cardiac output evaluation, for 48-h following hospital admission. Primary outcome was feasibility.

Results: 50 of 116 eligible patients (43.1%) were recruited over 20 months demonstrating feasibility. 36 (72%) completed the 48-h of GDFT; 10 (20%) discharged within 48-h and 4 withdrawals (3 GDFT, 1 SC). Baseline characteristics were similar with only 3 participants having severe disease (6%, 1 GDFT, 2 SC). Similar volumes of IV fluids were administered in both groups (GDFT 5465 (1839) ml, SC 5211 (1745) ml). GDFT group had a lower heart rate, blood pressure and respiratory rate and improved oxygen saturations. GDFT was not associated with any harms. There was no evidence of difference in complications of AP (GDFT 24%, SC 32%) or in the duration of stay in intensive care (GDFT 0 (0), SC 0.7 (3) days). Length of hospital stay was 5 (2.9) days in GDFT and 6.3 (7.6) in SC groups.

Conclusion: Ward-based GDFT is feasible and shows a signal of possible efficacy in AP in this early-stage study. A larger multi-site RCT is required to confirm clinical and cost effectiveness.

1. Introduction

Acute pancreatitis (AP) affects approximately 30 per 100,000 of the UK population [1]. The principal causes include gallstones and alcohol excess with increasing age, male gender, and lower socioeconomic class being associated with a higher incidence of AP [1,2]. Although the majority of clinical presentation of AP is mild in severity, approximately

20% develop moderate to severe pancreatitis due to overwhelming systemic inflammatory response syndrome (SIRS) and multi-organ failure [3]. There is currently no effective pharmacological intervention in clinical practice for the treatment of this disease [4]. Supportive management in terms of maintenance of fluid and electrolyte balance remains the mainstay in the treatment of AP. Despite the key importance of fluid therapy there is a lack of information on the optimal fluid

* Corresponding author. UCL Division of Surgery & Interventional Sciences, 9th Floor, Royal Free Hospital, Pond Street, NW3 2QG, London, UK.
E-mail address: farid.froghi@nhs.net (F. Froghi).

<https://doi.org/10.1016/j.ijso.2022.106737>

Received 21 February 2022; Received in revised form 13 June 2022; Accepted 14 June 2022

Available online 12 July 2022

1743-9191/© 2022 The Author(s). Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

therapy [4,5]. There is some evidence supporting the use of lactated Ringer's solution [5], however, there is conflicting evidence from randomised controlled trials (RCT) regarding the rate and volume of fluid therapy for those with mild or moderate disease [3]. Given that the disease severity is variable and its assessment difficult at presentation, early goal-directed fluid therapy (GDFT) has been suggested to guide initial intravenous (IV) fluid resuscitation in acute pancreatitis until the resuscitation goals are reached [6].

GDFT in the peri-operative period using cardiac output monitoring during surgery (in the operating theatre) or on an intensive care unit (ICU) decreases complications in conditions associated with a SIRS response [7,8]. These trials were not conducted in a ward-based setting. For GDFT to be most effective in acute pancreatitis, the optimal timing for fluid therapy intervention is likely to be at the earliest opportunity following the onset of pancreatitis, which would equate with the time of admission to hospital and initial ward care in those not requiring immediate admission to ICU. Without invasive monitoring, GDFT trials in patients admitted to the ward with AP have had resuscitation goals based on biochemical markers (i.e. haematocrit) rather than haemodynamic measures as resuscitation goals and have failed to show a reduction in the inflammatory response or improved clinical outcomes [9]. Whilst other resuscitation goals such as heart rate (HR), urine output (UO) and central venous pressures have been suggested for fluid therapy in acute pancreatitis, it is the optimisation of intravascular volume guided by cardiac output measures that has been shown to be effective in decreasing morbidity after major surgery [10,11]. Clinical trials for fluid therapy in acute pancreatitis continue to evaluate aggressive versus moderate fluid therapy with complex biochemical or clinical markers to assess adequate resuscitation [12]. There is some evidence that Lactated Ringer's reduces SIRS response compared with normal saline for initial resuscitation and has therefore been recommended in the guidelines [6,9]. However, RCTs in AP have failed to show a clear benefit in terms of different rate and volume of fluid administration or the resuscitation goals [9,13–16]. In two RCTs of severe AP patients, both rapid haemodilution with a haematocrit >35% as resuscitation goal and rapid fluid expansion (10–15 ml/kg/h) were associated with significantly worse infection rates, abdominal compartment syndrome and need for mechanical ventilation [14,15]. Conversely, Buxbaum et al. demonstrated that aggressive (20 ml/kg bolus followed by 3 ml/kg/h) compared to standard (10 ml/kg bolus followed by 1.5 ml/kg/h) hydration with Lactated Ringer's solution was associated with a reduction in SIRS and early recovery in patients with mild acute pancreatitis [16]. There is currently no RCT investigating the role of ward based GDFT using cardiac output targets in patients with acute pancreatitis.

With the development of non-invasive cardiac output monitors, it is now possible to measure cardiac output as a guide for intravascular volume replacement in a ward setting [17]. Ward-based GDFT has the potential to correct the organ hypoperfusion resulting from inflammation and tissue damage which may result in decreased morbidity, improved health-related quality of life (HRQoL) and increased survival associated with AP. Reduced acute organ injury may also lead to a reduced need for ICU admission and overall hospital length of stay with a potential for significant healthcare cost savings.

The GDFT in AP (GAP) trial has been designed as a two-centre RCT to assess the feasibility of guiding the initial 48-h of IV fluid administration in patients with acute pancreatitis using a non-invasive ward based GDFT algorithm. The initial 48-h is considered the 'golden' period for interventions that may decrease the severity of acute pancreatitis [18]. Given the unique and novel nature of the study, it was important to assess feasibility of recruiting patients into a trial of patients with an emergency presentation as well as performing a preliminary assessment of associated healthcare costs. The safety and practicality of delivering ward based GDFT and secondary clinical outcome measures were also evaluated to identify potential endpoints and the trial recruitment numbers required for a subsequent multi-centre study to evaluate

efficacy. Health-related quality of life (HRQoL) assessment as well as preliminary health economic analysis of the indicative costs were also performed to inform the subsequent multi-centre trial of clinical and cost effectiveness.

2. Methods

2.1. Study design and setting

The GAP trial protocol has been published [19] and is summarised here. The trial protocol (V2) was reviewed and approved by the London Central Research Ethics Committee (REC ref: 17/LO/1235, project ID: 221,872). Informed consent was obtained from eligible patients after screening by a member of the research or clinical team trained in Good Clinical Practice (GCP). The trial was registered on ISRCTN (ISRCTN 36077283) on April 09, 2018 (<http://www.isrctn.com/ISRCTN36077283>). A two-centre randomised feasibility RCT was designed and conducted in accordance with the SPIRIT guidelines [20]. Feasibility was evaluated in the Royal Free Hospital (RFH) which is a specialist tertiary referral centre for pancreas disease management and Barnet General Hospital (BGH) which is a district general hospital providing secondary care for a large population of outer North London. Although the study was planned to recruit in two centres, due to changes in one of the sites, patients were recruited only at the Royal Free Hospital for the initial 6 months whilst the trial was set up at a new second site, Barnet General Hospital. The trial recruitment period was therefore extended for a further 6 months, and recruitment was completed within the revised timeline. The results are reported using Consolidated Standards of Reporting Trials (CONSORT) guidelines.

2.2. Patient population

Patients (>16 years) admitted to hospital as an emergency with a diagnosis of acute pancreatitis confirmed by the international consensus criteria were eligible for this study [21]. Acute pancreatitis diagnosis was confirmed with two of the following three features: 1. Abdominal pain consistent with acute pancreatitis; 2. Serum amylase or lipase activity at least three times greater than the upper limit of normal; and 3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasound (US). Exclusion criteria were tertiary referrals of patients transferred from another hospital for the management of complications of acute pancreatitis, those requiring immediate admission to the ICU, known chronic pancreatitis in whom an acute exacerbation cannot be confirmed, a history of cardiac failure in the past three months and those unable to provide fully informed consent.

2.3. Recruitment, randomisation & blinding

Patients with suspected or confirmed acute pancreatitis were screened by the emergency department (ED) physicians, general surgical team on-call or trial research nurses, and screening information was recorded in a recruitment log. Diagnosis of acute pancreatitis was confirmed by the general surgical registrar on call. Eligible patients were provided with both an abbreviated and an in-depth patient information sheet (PIS). Those wishing to be included in the GAP trial were consented by a member of the clinical or research team trained in Good Clinical Practice (GCP) [22]. The trial nursing staff were contacted through a GAP trial telephone hotline, set up in each site, within 4 h of diagnosis. Consenting patients were randomised on a 1:1 basis stratified by site of admission using the 'Sealed Envelope' (www.sealedenvelope.com) internet-based randomisation system by trial nursing staff. Following admission to the ward trial participants received either GDFT or Standard of Care (SC) which was commenced within 6 h of the diagnosis and was continued for the next 48-h of inpatient stay. It was

not possible to blind the research nurses delivering GDFT or the treating clinicians to the treatment group. However, the participants, outcome assessors of health-related quality of life, health economics and statisticians were blinded to the treatment groups. Patient blinding was aided by cardiac output monitoring of both intervention and control groups at the same time points but performing GDFT in the intervention group alone. Cardiac output data from the SC group were not available to the treating clinicians but was included in the outcome analysis.

2.4. Intervention (GDFT)

GDFT was carried out for the initial 48-h of admission. A ward-based stroke volume (SV) optimisation algorithm was designed (Fig. 1) using a non-invasive cardiac output measuring device (NICOM). The Cheetah NICOM™ device (Cheetah Medical Ltd, Maidenhead, Berkshire, UK) was used on the ward for guiding GDFT by the GAP trial research nurses. Trial nursing staff were experienced ICU nurses who had received training in Cheetah NICOM measurements and delivering the intervention. The IV fluid administration regimen in the GDFT group consisted of maintenance IV fluid (balanced crystalloid solution) at a rate of 1.5 ml/kg/hr. Every 4 h for 48-h cardiac output studies were performed, and the SV optimised as follows:

After randomisation SV was recorded and an initial bolus of 250 ml of IV balanced crystalloid was administered over 5–10 minutes. A sustained rise in SV of greater than 10% for 15 minutes or more was taken to indicate fluid responsiveness and a repeat 250 ml bolus was administered. If SV did not rise greater than 10% then the patient was deemed fluid unresponsive and no further fluid boluses were administered. SV was monitored four hourly and a drop in SV by

more than 10% from the previous reading initiated a further fluid bolus. All fluid boluses in the GDFT group were balanced crystalloid solution (Fig. 1).

2.5. Standard of care (SC)

In the SC group, IV fluid therapy (rate, volume and type) was at the discretion of the clinical team caring for the patient. Patients in SC group had haemodynamic monitoring using the Cheetah NICOM™ every 4 h by trial nursing staff, however the readings were not made available to the clinical team.

2.6. Primary outcome measures

The primary outcome of the trial was an assessment of feasibility. In the trial protocol we suggested the following criteria would support progression to a full trial:

- a) the ability to identify and recruit 50 patients at the selected sites to a study of acute pancreatitis over the 17-month study period;
- b) a recruitment target of 30% of eligible patients;
- c) availability of the study team to recruit into this study for a condition presenting as an emergency 24/7;
- d) ability to randomise and commence ward GDFT within 6 h of admission;
- e) completion rate of 48-h of GDFT;
- f) withdrawal rate from GDFT protocol (aim was <20%).

A complication rate in the intervention group not more than 10% higher than that of the control group at 90 days was decided as a measure of safety of the intervention.

2.7. Secondary outcome measures

Total IV fluid administration volumes (crystalloids, colloids and others including blood products), vital signs (temperature, heart rate, blood pressure, respiratory rate and oxygen saturation) and haemodynamic monitoring (CO and SV) during the intervention period were recorded. Severity of pancreatitis was assessed by serum C-reactive protein (CRP), modified Glasgow score and modified Marshall score for assessment of organ failure. Modified Glasgow score is a composite score for predicting severity of acute pancreatitis which is performed on admission and repeated at 48 h [23]. The parameters include PaO2 <7.9 kPa, age >55 years, white cell count >15 × 10⁹/L, calcium <2 mmol/L, urea >16 mmol/L, lactate dehydrogenase >600 IU/L, serum albumin <32 g/L, and blood glucose >10 mmol/L. A score of 3 or above is considered as high risk (>20%) for severe pancreatitis with a positive predictive value of 79% [23].

The modified Marshall score was used to assess organ dysfunction in three systems: respiratory, renal and cardiovascular [24,25]. Organ failure was defined as presence of Marshall score of 2 or more in any given organ system. As the study was conducted in non-ventilated ward patients, serial arterial partial pressures of oxygen (PaO₂) and functional inspired oxygen (FiO₂) ratios were derived from peripheral oxygen saturations (SpO₂)/FiO₂ ratios to assess respiratory failure [26]. Indication for ICU admission and critical care outreach (CCOT) review were as per hospital policy for invasive monitoring or organ support. Severe acute pancreatitis was defined as the presence of organ failure as per modified Marshall score which persisted for more than 48-h [25]. All predefined complications of pancreatitis were recorded up to discharge and at follow-up at 30- and 90-days post randomisation.

2.8. Sub-studies

A qualitative study was conducted to explore the reasons for

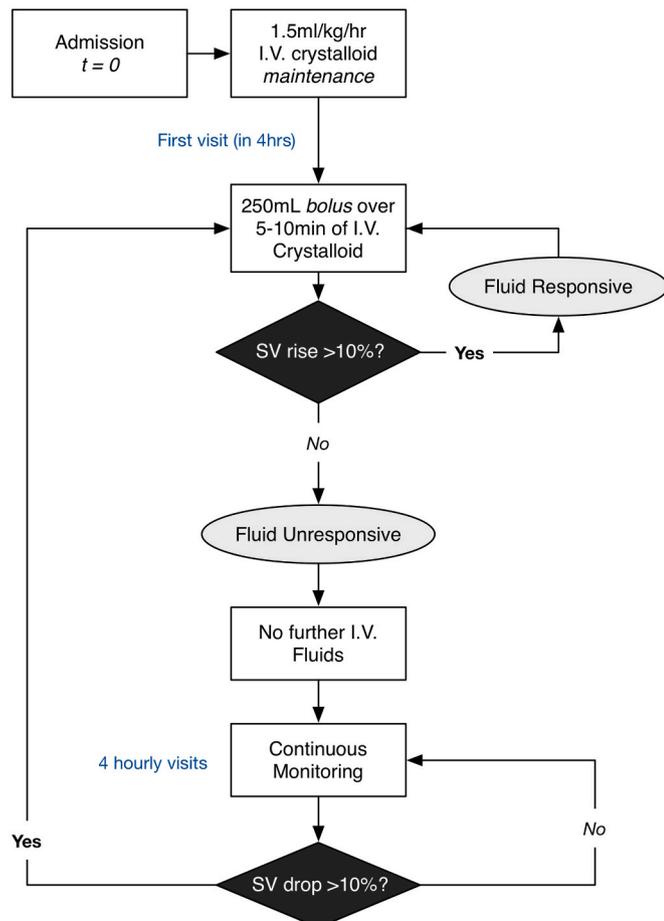


Fig. 1. SV optimisation protocol for GDFT.

participation and non-participation of eligible patients and patients' and clinicians' acceptability of the trial to assist in optimisation of recruitment strategies employed for the definitive trial. Interviews with a sample of eligible patients were held to explore patient perspectives of fluid therapy treatment, their understanding of the two treatments, reasons for taking part or refusing the trial, and the acceptability of randomisation between the procedures. Interviews with clinical staff were conducted to explore their views about the trial, clinical equipoise, and their understanding of the recruitment challenges. Semi-structured interviews informed by a topic guide were developed in conjunction with the trial management group.

Health-related quality of life (HRQoL) was assessed using EQ5D -5L questionnaire [27] on admission and subsequently on day 7, day 30 and day 90. Resource use data for health economic analysis on length of hospital stay, length of ICU stay, and number of days ventilated, time to return to pre-pancreatitis activities, number of work-days lost (in those who work), and costs (NHS and personal social services (PSS) perspectives) were collected. The additional costs for the intervention arm were accounted for in the form of device cost, consumables and additional nurse time per fluid challenge. All clinical and HRQoL outcomes were measured up to discharge and subsequently at 30 days and 90 days post randomisation by face-to-face or telephone follow-up.

2.9. Statistical analysis

A pragmatic sample size of 50 patients was chosen for this feasibility study. Data was recorded in a secure online database using the RedCap (Research Electronic Data Capture) platform hosted at University College London (UCL) [28]. The two groups were compared using descriptive statistics to ensure they had similar baseline characteristics. As this was a feasibility study, all analyses other than recruitment rate and withdrawal rates were considered exploratory. For the primary outcome, the proportion of patients who consented to be randomised and the rate of withdrawal from GDFT protocol were calculated. The median number of complications in each group were presented. The secondary outcomes were presented for each group using the mean and standard deviation (SD) or frequencies and proportions as appropriate. Mean profile plots, by arm, were also used to graphically to describe secondary outcomes. The mean difference in quality-of-life scores between the two groups at 7 days is presented with a 95% CI. All other secondary outcomes collected over time will be summarised for each group using mean profile plots. The frequency and nature of adverse events were reported for each group.

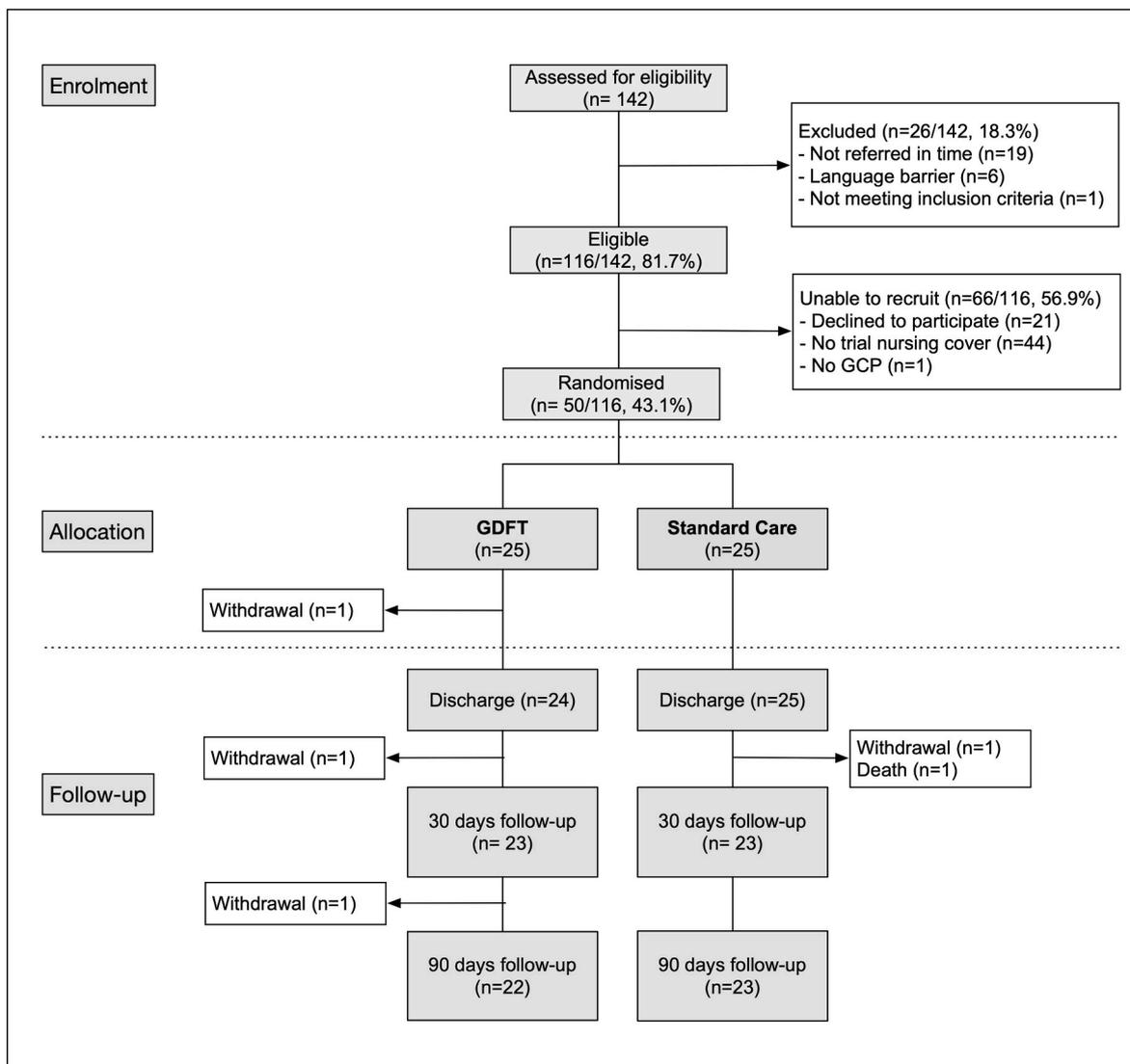


Fig. 2. CONSORT diagram.

3. Results

3.1. Patient recruitment

Overall, 142 patients were screened for eligibility of which 26 patients (26/142, 18.3%) were excluded. Reasons for exclusion were: not referred to trial team in the appropriate time (within 4 h of diagnosis of AP) (n = 19), unable to provide informed consent due to language barrier (n = 6), and not meeting inclusion criteria after further scrutiny (n = 1). A total of 116 patients were eligible of the 142 screened (116/142, 81.7%) of whom 50 patients were randomised to either GDFT (n = 25) or SC (n = 25) during the study period from January 2018 to October 2019 between the two sites (Royal Free Hospital and Barnet Hospital) (Fig. 2). Hence, the recruitment rate for the trial was 43.1% (n = 50/116) over the study period. The median recruitment was 2 patients per calendar month. Reasons for not being able to recruit eligible patients (n = 66/116, 56.9%) were: no research staff availability (n = 44), patient declined (n = 21), recruiting physician not trained in Good Clinical Practice (GCP) (n = 1).

The baseline characteristics are shown in Table 1. The mean age (SD) for the overall study cohort was 50.4 (18.0) years. There two groups were similar in age, gender or ethnicity. None of the patients recruited had a past medical history of heart failure and only 2 (4%) patients (GDFT 1 vs SC 1) had a history of chronic renal failure. 30% (15/50) of patients had suffered previous episodes of acute pancreatitis. Previously known gallstones disease was present in 7 GDFT (28%) and 8 SC (32%) patients. The cause of acute pancreatitis requiring hospital admission was predominantly unknown across both groups (46%), followed by gallstones (32%), alcohol (26%) and others (6%). GDFT had a higher proportion of patients with gallstone related pancreatitis, whilst SC had more patients with alcohol as a cause (Table 1). Patients in the GDFT

Table 1
Baseline characteristics.

	GDFT (n = 25)	Standard Care (n = 25)
Centre		
Royal Free Hospital (N)	18/25 (72%)	19/25 (76%)
Barnet Hospital (N)	7/25 (28%)	6/25 (24%)
Demographics		
Age (SD)	50.48 (19.64)	50.48 (16.62)
Sex (%)		
Female	12 (48%)	7 (28%)
Male	13 (52%)	18 (72%)
Ethnicity (%)		
White British	13 (54.17%)	15 (60%)
White Other	4 (16.67%)	7 (28%)
White & Black Caribbean	0 (0%)	1 (4%)
White & Black African	2 (8.33%)	0 (0%)
White & Asian	1 (4.17%)	0 (0%)
Indian	2 (8.33%)	1 (4%)
Caribbean	1 (4.17%)	0 (0%)
Other (please specify)	1 (4.17%)	1 (4%)
Past Medical History		
Pancreatitis	7 (28%)	8 (32%)
Gallstones	7 (28%)	8 (32%)
Renal failure	1 (4%)	1 (4%)
Heart failure	0	0
Onset of symptoms prior to admission in days (SD)	3.78 (4.9)	1.56 (1.53)
Presumed cause of AP		
Unknown	12 (48%)	11 (44%)
Alcohol	3 (12%)	10 (40%)
Gallstones	10 (40%)	6 (24%)
Other	1 (4%)	2 (8%)
IV fluids given prior to intervention	19 (76%)	24 (96%)
Volume (ml) of IV fluid given prior to intervention	1333 (993)	1167 (713)

Continuous variables are summarised using mean and standard deviations (SD), binary and categorical variables are shown as frequency and percentage (%).

group had a longer period between symptom onset and hospital admission delay (GDFT 3.75 (4.9) vs SC 1.56 (1.53) days). Intravenous (IV) fluids were administered following hospital admission but prior to randomisation in 87% (n = 43) of participants. The volume of IV fluids received prior to trial intervention in GDFT group was 1332 (993) ml versus 1167 (713) ml in SC group.

3.2. Intervention period

Overall, 36 patients (72%) completed the 48-h intervention period in both groups. GDFT for the intervention period was completed in 20 patients (80%) and monitoring was completed in 16 patients (64%) in the SC group. The reason for 14 patients (28%) who did not complete the intervention period was predominantly due to early recovery and discharge from hospital prior to 48-h (n = 10). Other reasons included patient withdrawal from the study prior to 48-h (n = 2), transferred to another hospital due to cerebrovascular accident (n = 1), patient death (n = 1).

3.3. Withdrawal rate and completion of follow up

The total number of patients with complete data at the end of 90 day follow up was 45/50 (90%). There was one death in SC and none in the GDFT group. The number of patients who withdrew from the study before the end of follow up period was 4 (3 in GDFT group and 1 in SC group). The overall withdrawal rate was 8.9%. The reasons for withdrawal were available for three patients and reported as "concerned about fluids" (n = 1), "does not want to be called again" (n = 1), "no reason given" (n = 1).

3.4. Fluid administration

The total mean (SD) fluid input for GDFT group was 7611 (3012) ml and for SC 7184 (2557) ml over the initial 48-h of intervention which included oral, crystalloids and other infusions such as intravenous medications (Table 3). No colloids were administered to patients. The mean profile plots for IV fluid administration and urine output are demonstrated in Fig. 3 and Fig. 4 respectively.

3.5. Monitoring during intervention

The stroke volume (SV) readings in GDFT group appear approximately 10% higher than SC group (Fig. 5). This trend was not demonstrated in the cardiac output readings. GDFT group also appeared to have a lower heart rate than the SC group over the intervention period.

Table 2
Admission observations and blood gases.

	GDFT (n = 25)	Standard Care (n = 25)	Missing N
Vital signs			
Heart Rate (b/min)	80.52 (20.21)	82.76 (20.24)	0
Systolic blood pressure (SBP) (mmHg)	127.12 (22.48)	138.88 (23.63)	0
Diastolic blood pressure (DBP) (mmHg)	78.92 (16.46)	82.48 (13.32)	0
FiO ₂ (%)	21 (0.00)	21 (0.00)	0
Blood gases			
pH	7.41 (0.07)	7.41 (0.08)	17
pO ₂ (kPa)	7.81 (4.59)	8.08 (4.03)	21
pCO ₂ (kPa)	5.27 (1.19)	5.16 (1.44)	20
Haemoglobin (g/L)	137.18 (21.35)	150.56 (16.17)	17
Lactate (mmol/L)	1.43 (0.67)	1.53 (0.83)	17
Base Excess (mmol/L)	0.30 (2.41)	-0.49 (1.64)	19
HCO ₃ ⁻ (mmol/L)	24.96 (2.39)	23.73 (1.31)	18

Continuous variables are summarised using mean and standard deviations (SD).

Table 3
Fluid input/output during the intervention period.

	GDFT (n = 25)	Standard Care (n = 25)	Missing N
Intravenous fluids			
Crystalloid infusion	5465 (1839)	5211 (1745)	0
Colloid infusion	0 (0)	0 (0)	6
Other infusion	252 (249)	368 (414)	4
Oral intake	2042 (1697)	1965 (1324)	0
Total Fluid Input	7611 (3012)	7184 (2557)	0
Total Fluid Output	4021 (2271)	3332 (1641)	2

Fluid volumes in ml.

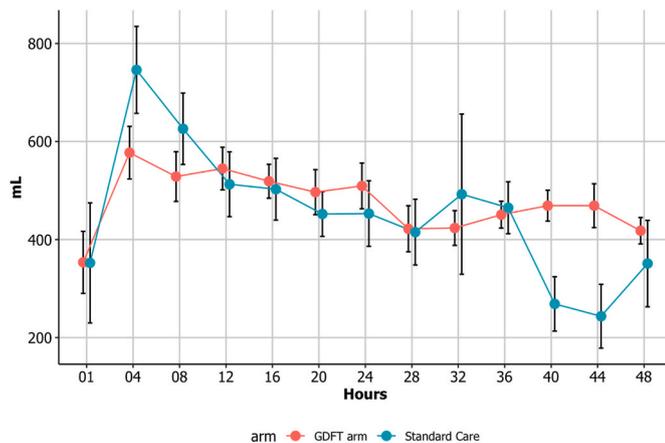


Fig. 3. Total intravenous fluids infusion trend during the intervention period Mean (SE) total intravenous fluids infusion over 48 h.

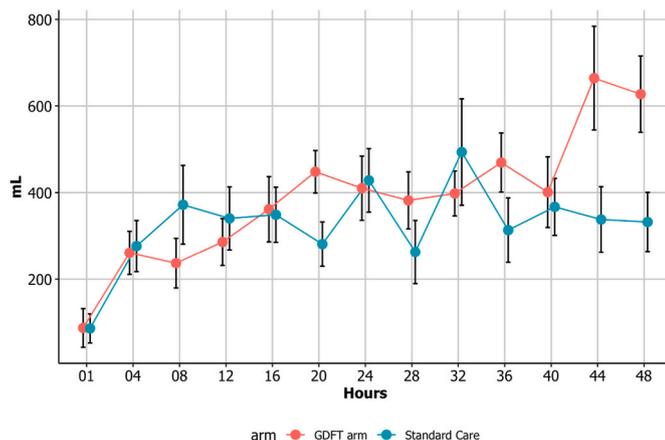


Fig. 4. Urine output trend during the intervention period Mean (SE) urine output over 48 h.

Systolic blood pressure was similar between the two groups (Fig. 6). A lower respiratory rate and higher oxygen saturation was also observed in the GDFT group (Fig. 6).

3.6. Secondary outcomes

The admission vital signs and blood gas measures are shown in Table 2. An arterial blood gas (ABG) was not performed on admission in 21 of the 50 patients. The majority of patients in both groups had mild acute pancreatitis based on prognostic (Glasgow) and organ failure (Marshall) scores. (Fig. 7).

A Glasgow severity score was performed on 26 patients (52%) on admission and only 17 patients (34%) at 48-h. Of those who had a Glasgow score on admission, two patients had a predicted severe score

(3 or more) in SC and one in GDFT group (Table 4). The Marshall scores on admission are presented in Table 5. There was no evidence of organ failure in 98% of patients (n = 49) on admission. For those who remained inpatient at 48-h, there was evidence of organ failure in four patients (GDFT 2 vs SC 2). In the GDFT group, the two patients had a transient oxygen requirement due to bi-basal atelectasis and small pleural effusions on chest x-ray which resolved in less than 48-h. Organ failure was observed in two patients in SC group; these were due to acute kidney injury and type 1 respiratory failure as well as local complications of pancreatitis which persisted for more than 48-h. Both patients required admission to intensive care unit. Progression to severe acute pancreatitis (as defined by the revised Atlanta criteria) was observed in two patients in SC (8%) and none in GDFT group (Table 6 and Fig. 7). The median (IQR) levels of CRP on admission were 10 (19.5) mg/L for GDFT and 6 (15.5) for SC group. At day 7 post randomisation, the median (IQR) CRP levels GDFT group was 70 (39) mg/L and 289 (45) mg/L for SC group (Fig. 8).

3.7. Complications and outcome

At least one pre-defined complication occurred during the hospital stay in five patients in the GDFT group (23.8%) and eight in SC group (32%). The median (range) of complication per patient was 0 (0–3) for GDFT vs 0 (0–7) for SC. None of the patients in GDFT group developed persistent organ failure and progression to severe acute pancreatitis whilst this was observed in 2 (8%) patients in SC group. Documented SIRS occurred in GDFT (n = 2, 8.3%) compared to SC (n = 6, 24%). Four patients underwent ERCP (GDFT 3 (12.5%) vs SC 1 (4%)) with one post-ERCP complication in the GDFT arm. At 30- and 90-day follow-up, patients experiencing new complications related to pancreatitis were rare (Table 6). One patient in SC arm died after 15 days in ICU due to severe necrotising pancreatitis developing infected pancreatic necrosis, mesenteric venous thrombosis, pancreatic pseudocyst and multi-organ failure. The mean (SD) length of hospital stay was lower by one day in GDFT at discharge and at 30- and 90-day time points which would include any re-admissions (Table 6).

3.8. Health related quality of life

Complete QoL data were available for 47/50 at baseline, 37/50 at 7 days, 35/50 at 30 and 90 days. Complete case analysis was adopted to estimate incremental quality adjusted life year (QALY) for each patient. This approach reduced the sample size to 16 and 10 patients in the GDFT and SC group, respectively. A summary of utility estimates for the two arms over the trial period is provided in Table 7. Differences between treatment arms were not significant at a 95% confidence level. The mean (95% CI) incremental QALYs in the GDFT group was marginally lower than the control group (GDFT 0.191 (0.17–0.21) versus SC 0.2 (0.17–0.02)), mean difference –0.0096).

3.9. Cost analysis

The mean inpatient length of stay was lower in the GDFT group compared to SC group although this was not statistically significant. Unit prices are available in the supplementary material. The difference in resource use was not statistically significant at any time point. The average cost of inpatient stay up to 90-day follow up for GDFT was £4857.82, which was lower than the SC group (£5312.92). The estimated cost difference was £1,610, £159, £455 in favour of the GDFT group at discharge, 30 days and 90 days respectively (Table 8). However, differences were not statistically significant.

3.10. Qualitative study

The qualitative study was conducted during the trial recruitment period and was able to identify and mitigate factors that may hinder

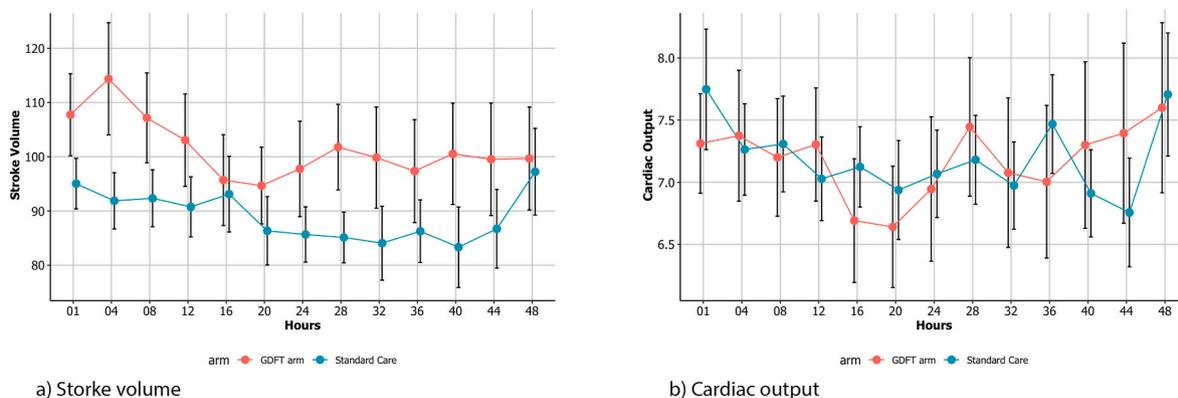


Fig. 5. Stroke volume and cardiac output during the intervention period
Mean (SE) profile plots of a) Stroke volume (SV), b) Cardiac output (CO) during the 48-h intervention period.

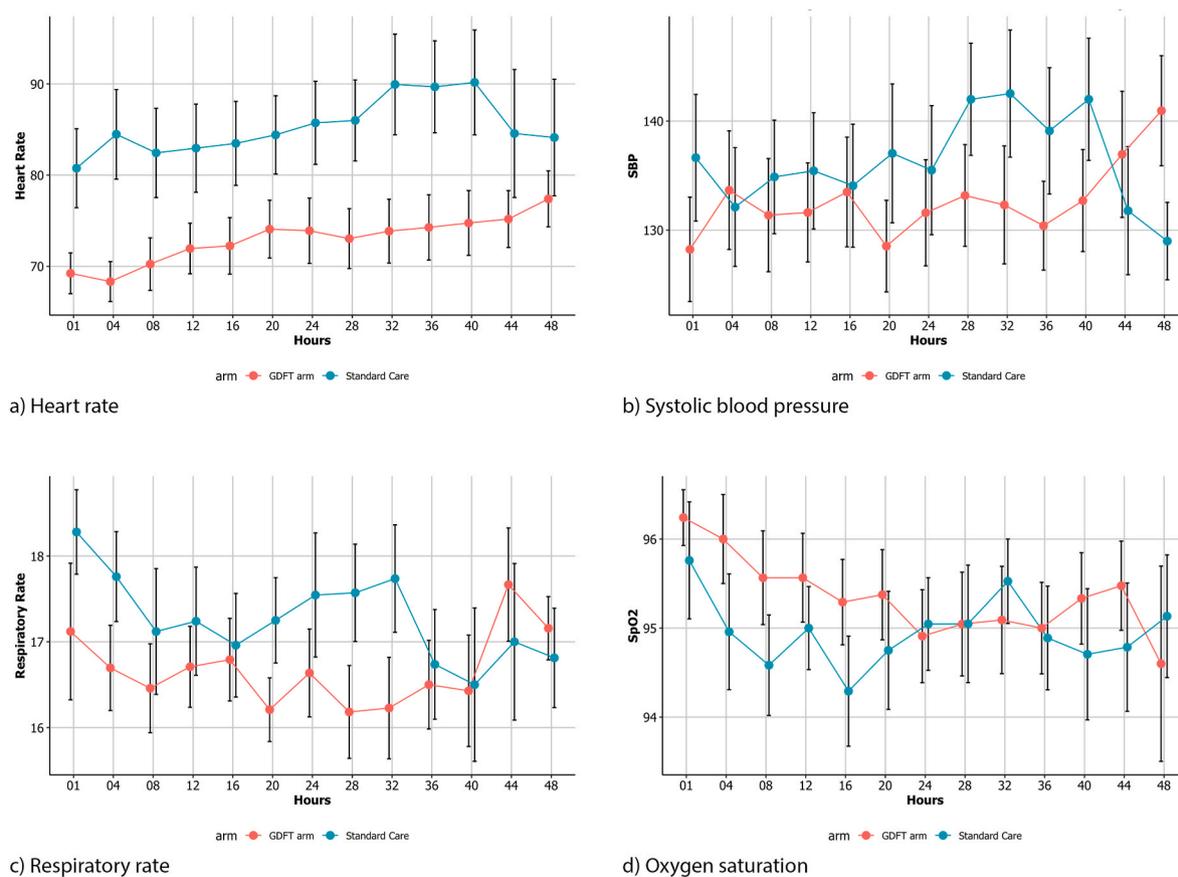


Fig. 6. Vital signs during the intervention period
Mean (SE) profile plots of a) Heart rate (HR), b) Systolic blood pressure (SBP), c) Respiratory rate (RR), d) Oxygen saturation (SpO₂) during the 48-h intervention period.

recruitment. An executive summary of the qualitative study report is presented as supplementary material as the full qualitative evaluation has been submitted for publication (Appendix 1). Problems were identified with cross-site working. The need for additional research nurses to cover night and weekend cover at both sites were highlighted. During initial trial set-up stages, issues with site initiation at the second site were mainly due to lack of capacity within the hospital: space on wards, ward staff time, research nurse time. Patient screening was identified as a difficult process as patients needed to be identified rapidly as having acute pancreatitis by the ED staff who needed trial awareness and to contact the trial team in the appropriate time window. Doctor change-

over contributed to missing recruitment across all stages of the trial. The trial team found it is easier to screen patients during office hours and to identify potential trial participants at the RFH (as the team were based there).

Patient acceptance and participation in the trial was good with a common belief that the intervention could benefit other patients with the same condition. Severe pain and feeling unwell was identified as reasons for patients declining participation in the trial. All patients interviewed felt the information provided during informed consent process was clear. In relation to delivery of treatment during the trial, two patients complained about visits made by staff at night for

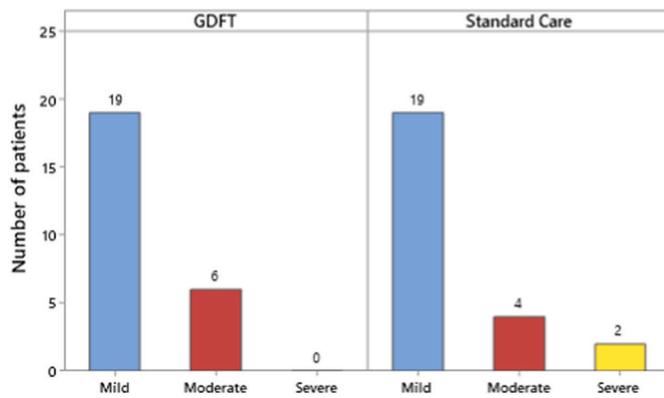


Fig. 7. Clinical grade of severity of acute pancreatitis
Clinical severity of acute pancreatitis as scored by the 2010 revised Atlanta criteria [25]: Mild acute pancreatitis: No organ failure and No local or systemic complications; Moderately severe acute pancreatitis: Organ failure that resolves within 48 h (transient organ failure) and/or Local or systemic complications without persistent organ failure; Severe acute pancreatitis: Persistent organ failure (>48 h) – Single or multiple organ failure.

Table 4
Glasgow Severity Score for predicted severity of AP.

	GDFT (n = 25)	Standard Care (n = 25)	Missing N
Admission			
Mild	7 (58.33)	8 (57.14)	24
Moderate	4 (33.33)	4 (28.57)	
Severe	1 (8.33)	2 (14.29)	
48 h			
Mild	7 (77.78)	3 (37.50)	33
Moderate	2 (22.22)	3 (37.50)	
Severe	0 (0.00)	2 (25.00)	

Modified Glasgow score is a composite score for predicting severity of acute pancreatitis which is performed on admission and repeated at 48 h [23]. The parameters include PaO₂ <7.9 kPa, age >55 years, white cell count >15 × 10⁹/L, calcium <2 mmol/L, urea >16 mmol/L, lactate dehydrogenase >600 IU/L, serum albumin <32 g/L, and blood glucose >10 mmol/L. A score of 3 or above is considered as high risk (>20%) for severe pancreatitis with a positive predictive value of 79% [23].

Table 5
Marshall Score for organ failure.

	GDFT (n = 25)	Standard Care (n = 25)	Missing N
Admission			
0	24 (96.00)	21 (84.00)	0
1	1 (4.00)	3 (12.00)	
2	0 (0.00)	0 (0.00)	
3	0 (0.00)	1 (4.00)	
48 h			
0	18 (85.71)	10 (62.50)	13
1	1 (4.76)	4 (25.00)	
2	2 (9.52)	1 (6.25)	
3	0 (0.00)	1 (6.25)	

A score of 2 or more in any organ system defines the presence of organ failure. The score has been adjusted for those with pre-existing chronic renal failure.

monitoring. They felt it was disruptive for patients who wanted to sleep when in the main ward.

According to members from the trial team, the main reasons why patients decided to withdraw from the study included: the family did not agree with the study, the patient was discharged prior to 48-h, and the patient was worried about “getting too much fluid”. There were concerns of missing follow up data as some patients did not answer follow up telephone calls.

4. Discussion

The GAP trial is the first randomised trial of ward-based fluid therapy in acute pancreatitis guided by cardiac output optimisation.

The primary outcome of the trial was feasibility. We have demonstrated that it is feasible to recruit patients with acute pancreatitis to a randomised study of ward-based fluid therapy determined by cardiac output evaluation. As regards the feasibility end points, we defined these in the published protocol. The trial recruitment target was >30% and this was achieved with 43% of eligible patients being recruited over the trial period. The study team was also able to recruit patients and commence the ward based GDFT intervention within 6 h of diagnosis in patients presenting as an emergency 24/7 in both a district general hospital (BGH) setting and a tertiary referral centre for management of pancreatic disorders (RFH). However, there were important difficulties related to recruitment as identified by the contemporaneously conducted qualitative study. The majority of the patients excluded from the trial were not referred to the trial staff in the appropriate time for the intervention to commence. Screening the ED presentations 24/7 for a time-based trial has been a challenge. Clinical teams in the ED and on-call general surgical team played an essential role in identifying patients presenting with suspected acute pancreatitis. A possible solution to increase recruitment in a subsequent trial on efficacy would include a better education and engagement of the clinical teams especially around the time when junior staff rotate from their placements. The referrals system to the research trial staff can also be made simpler through electronic messaging systems and remote consent processes. In hospitals with electronic medical records, this process can even be automated to alert research staff of a biochemical diagnosis of pancreatitis (lipase or amylase levels), or radiological results would alert the trial team of potential subjects with a diagnosis of AP. As for the language barrier, the consent form and information leaflet could be translated into the languages prevalent in the population that a specific hospital serves.

The withdrawal rate was low at 9% but many patients did not complete the planned 48-h duration of the intervention (28%). The main reason was patient discharge within 48-h, occurring in 14 patients (28%) which perhaps reflects that the majority of patients in the trial had mild acute pancreatitis (76%) and had a rapid recovery and discharge. This issue could be dealt with in a future trial either by increasing the recruitment to cover the trial dropout rate or excluding those with mild disease. Increasing the trial size may be the better option as the severity of pancreatitis may be difficult to determine at the time of admission [29] and there is no certainty as to whether there will be more or less benefit of GDFT in those with mild, moderate or severe disease.

The completeness of follow up was an additional aspect of feasibility to address complications and quality of life. This was achieved with complete follow up information in 90% of participants at 90 days.

The secondary end points of the study aimed to assess signals of efficacy and to identify whether ward based GDFT in acute pancreatitis was a cause of harm or clinical benefit. Feasibility studies are not powered to evaluate efficacy of the intervention and hence statistical analysis of secondary outcomes are not recommended.

Fluid therapy in the initial phase of hospitalisation remains the cornerstone of management in AP. In our study, there was no evidence that GDFT altered the total volume of intravenous fluids received during the 48-h intervention. However, there were clear differences in the timing of intravenous fluid administration. Patients in SC received more fluids in the first 4 h of intervention and less in the last 8 h whilst IV fluid administration was more consistent in the GDFT group over the 48-h intervention period. Although early aggressive fluid administration has been advocated in AP [30] this is of unproven value and may be associated with significant harms in some patient groups [14,15]. This study raises the possibility that a personalised strategy is required providing a targeted fluid volume only when required [31]. One patient in the GDFT group developed pleural effusion on chest x-ray compared to three patients in the SC group. The relationship to fluid therapy in

Table 6

Predefined complications of acute pancreatitis, mortality and cumulative length of stay at discharge, 30 days and 90 days follow-up.

Follow-up time point	Discharge			30 Days			90 days		
	GDFT arm	SC	Missing	GDFT arm	SC	Missing	GDFT arm	SC	Missing
Number (%) of patients who experienced at least one pre-defined complication	5 (23.81%)	8 (32%)	-	1 (4.55%)	1 (4.76%)	-	0 (0%)	1 (4.76%)	-
Median (range) pre-defined complication per patient	0 (0–3)	0 (0–7)	-	0 (0–1)	0 (0–2)	-	0 (0)	0 (0–1)	-
Frequency (%) of pre-defined complications									
Severe Acute Pancreatitis	0 (0%)	2 (8%)	0	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Necrotising pancreatitis	0 (0%)	1 (4%)	1	0 (0%)	0 (0%)	5	0 (0%)	0 (0%)	6
Infected pancreatic necrosis	0 (0%)	1 (4%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Mesenteric venous thrombosis	0 (0%)	1 (4%)	2	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Pancreatic pseudocyst	0 (0%)	1 (4%)	3	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Requiring ITU stay	0 (0%)	2 (8%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	5
Was the patient ventilated	0 (0%)	1 (4%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Persistent organ failure (>48 h)	0 (0%)	2 (8%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Renal replacement therapy	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
SIRS	2 (8.33%)	6 (24%)	1	0 (0%)	1 (4.35%)	5	0 (0%)	0 (0%)	6
Positive blood cultures	0 (0%)	2 (8%)	1	0 (0%)	1 (4.35%)	4	0 (0%)	0 (0%)	7
Pulmonary oedema	1 (4.35%)	0 (0%)	2	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	7
ARDS	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	5	0 (0%)	0 (0%)	6
Underwent ERCP	3 (12.5%)	1 (4%)	1	1 (4.35%)	0 (0%)	4	0 (0.00)	1 (4.35%)	5
Complication related to ERCP	1 (4.17%)	0 (0%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	5
Surgical intervention related to pancreatitis	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Surgical intervention NOT related to pancreatitis	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)	4	0 (0%)	0 (0%)	6
Death of patient	0 (0%)	1 (4%)	1	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Cumulative mean (SD) LOS in hospital days	5 (2.9)	6.32 (7.62)	1	6.7 (4.77)	7.09 (7.52)	4	7.55 (5.39)	8.61 (11.44)	5
Cumulative mean (SD) LOS in ITU days	0 (0)	0.68 (3.01)	1	0 (0)	0 (0)	4	0 (0)	0 (0)	5

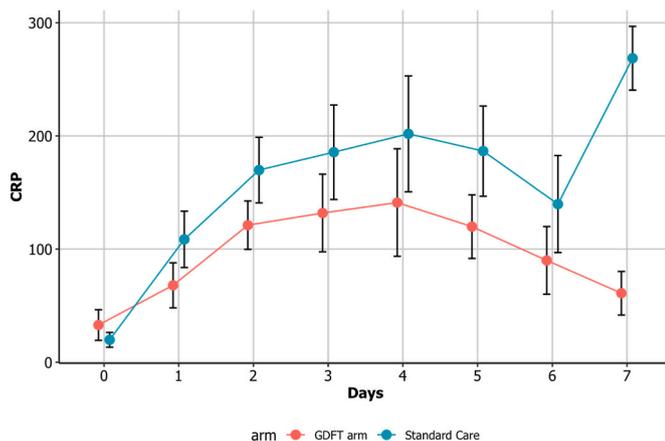


Fig. 8. C-reactive protein (CRP) levels (mg/l) Mean (SE) CRP levels over 7 days.

these patients was not clear as they were not clinically overloaded and transient hypoxia and pleural effusion is a recognised complication of acute pancreatitis. Overall, the rate of complication in the GDFT was similar to that of SC group and the intervention was considered safe. Possible benefits of improved fluid management in acute pancreatitis

Table 7

Quality of life measured by EQ-5D-5L index scores by treatment group.

Time point	GDFT			Standard Care			Diff (a-b)
	Obs.	Mean (a)	SD	Obs.	Mean (b)	SD	
Baseline	16	0.6312	0.2196	10	0.4691	0.3616	0.1622
7 days	16	0.7639	0.2134	10	0.807	0.1507	-0.0436
30 days	16	0.7893	0.1212	10	0.8227	0.2272	-0.0335
90 days	16	0.7738	0.2914	10	0.8414	0.1579	-0.0677

would be improved haemodynamics, a reduction in organ injury, fewer complications, and reduced admissions to the intensive care unit. Intervention fidelity was demonstrated by higher SV readings on an average of 10% in the GDFT group which would suggest that the GDFT was achieving the goal of improving systemic haemodynamics [32]. This is supported by cardio-respiratory parameters over the 48-h in the GDFT group showing a lower heart rate, blood pressure, respiratory rate and improved oxygen saturations. A major factor leading to cardio-respiratory instability in acute pancreatitis is the development of SIRS [33]. A further indication of efficacy of the ward GDFT is the reduction of SIRS from 24% in controls to 8.3% in the GDFT group as well as lower inpatient (7 days) CRP levels. Although, this could have been confounded by the fact that patients in the GDFT group presented on average 1.5 days later than SC group since the onset of symptoms. In a small sample size, this could simply be due to chance, which can be adjusted for by using continuous covariates in a definitive trial [34]. The delayed presentation can potentially under-estimate the effect of GDFT, as the inflammatory processes which would have been mitigated by the fluid therapy have already set in and the ‘golden period’ for intervention has passed. Equally, the delayed presentation could mean patients in the GDFT group had less acute presentation allowing patients to delay their hospital visit.

The number and severity of organ dysfunction is directly related to mortality in acute pancreatitis [33]. Whilst organ failure was observed equally in both groups, (GDFT 2 versus SC 2), patients in SC group had

Table 8
Total costs by treatment group.

Total costs (£)	GDFT			Standard Care			Diff (a-b)
	Obs.	Mean (a)	Std. Dev.	Obs.	Mean (b)	Std. Dev.	
Discharge	25	2998.96	1695.78	24	4608.78	6393.61	-1669.82
30 days	24	4131.11	2938.74	22	4290.23	4172.24	-159.13
90 days	23	4857.82	3199.21	22	5312.92	6273.80	-455.11

organ failure which persisted more than 48-h, requiring organ support in ICU. Severe AP was therefore observed in two cases in SC (8%) and none in the GDFT group who had transient organ failure. The lower rates of presentation with acute pancreatitis is partly due to the small sample size of the study, and part due to the exclusion of patients directly referred to ICU and inter-hospital transfers for tertiary care which are often severe AP requiring intervention. Whilst adequately powered studies to confirm association is required, this indicates that GDFT perhaps prevents the progression to severe disease by correcting organ failure as it occurs. The two patients in SC group developed AKI and type 1 respiratory failure which are directly related to the rate and timing of IV fluid administration. GDFT could therefore be beneficial in guiding fluid therapy in AP and further adequately powered studies of effectiveness are indicated.

The cumulative LOS in hospital was on average one day less in GDFT group compared to SC whilst the cumulative length of ICU stay was similar. In the context of this feasibility study, this could be a signal of early recovery and hospital discharge for patients with AP treated with GDFT.

Initial hospitalisation and subsequent complications of acute pancreatitis have been associated with significant and rising healthcare costs over the last two decades [35]. In the United States, the estimated total cost of acute pancreatitis admission was \$2.2 billion at a mean hospitalisation cost of \$9870 in 2003 [36]. This estimate is mirrored in Europe, costing €9762 for treating AP per patient [37]. In the trial a preliminary cost effectiveness evaluation was performed and the healthcare costs for managing a patients with acute pancreatitis was approximately £5000. This may be lower than previous costings as the majority of patients had mild AP and the hospital stay was short. The reduction in hospital stay by on average 1 day in the GDFT group was the major factor in reducing the healthcare costs associated with acute pancreatitis by approximately £500/patient in this study. Although these results may be biased by the small sample size of this analysis and difficulty in obtaining QoL information in sick patients. A further and more detailed study into cost-effectiveness would include staff training in GDFT and time to deliver fluid optimisation.

In this feasibility study, we have demonstrated that recruiting into a trial of this novel intervention was safe, feasible and acceptable by patients and clinicians. We have multiple signals of possible efficacy which would strongly support a subsequent larger multi-centre study of efficacy and cost effectiveness of ward based GDFT in acute pancreatitis.

Ethical approval

The study was approved by University College London Bloomsbury Research Ethics Committee (REC ref: 17/LO/1235, project ID: 221,872).

Sources of funding

This study is funded by the National Institute for Health Research (NIHR) Research for Patient Benefit Programme (RfPB) (Grant Reference Number PB-PG-0815-20002). This paper presents independent research funded by the (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0815-20002). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Research registration Unique Identifying number (UIN)

Name of the registry: ISRCTN.

Unique Identifying number or registration ID: ISRCTN (36077283).

Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://doi.org/10.1186/ISRCTN36077283>.

Trial registration

The GAP trial was registered on ISRCTN 36077283 (26-03-2018).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Guarantor

Professor Brian R Davidson.

CRedit authorship contribution statement

Farid Froghi: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Fiammetta Soggiu:** Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Project administration. **Federico Ricciardi:** Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Cecilia Vindrola-Padros:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Lefteris Floros:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Helder Filipe:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Satya Bhattacharya:** Conceptualization, Methodology, Investigation, Supervision. **Kurinchi Gurusamy:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Angela Fanshawe:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Bogdan Delcea:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Pawan Mathur:** Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Daniel Martin:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Massimo Varcada:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Brian Davidson:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Dimitris Tzelis:** Resources, Data

curation. **Christine Eastgate:** Resources, Data curation. **Maria Jose Ciaponi:** Resources, Data curation. **Margaret McNeil:** Resources, Data curation. **Sara Mingo Garcia:** Resources, Data curation. **Glykeria Pakou:** Resources, Data curation. **Otto Schwalowsky-Monks:** Resources, Data curation. **Atokoleka Osakanu:** Resources, Data curation. **Rebekkah Troller:** Resources, Data curation. **Nikolaos Dimitroklallis:** Resources, Data curation. **Stephanos Pericleous:** Resources, Data curation. **Amjad Khalil:** Resources, Data curation. **Aliza Abeles:** Resources, Data curation. **Charles Rees:** Resources, Data curation. **Khalid Abdulkareem:** Resources, Data curation. **Mavroudis Voultsos:** Resources, Data curation.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We are grateful for the support of our emergency surgical colleagues Mr Olegunju Ogunbiyi, Mr Massimo Varcada, Mr Pawan Mathur, Mr Jonathan Knowles, Mr Rován D'Souza, Mr Colin Hart, Mr Ahmad Hamad, the surgical registrars Ms Tanzeela Gala, Ms Karen Bosch, Ms Aliza Abeles, Mr Guillaume Lafaurie, Mr Tom Hanna, Mr Stephanos Pericleous, and our emergency department lead Dr Jonathan Costello, without whom the conduct of this trial would not be possible. We gratefully acknowledge the financial support of the Wellington hospital, London, in their HPB Surgery Fellowship funding for Mr Farid Froghi.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijvs.2022.106737>.

References

- [1] S.E. Roberts, A. Akbari, K. Thorne, M. Atkinson, P.A. Evans, The incidence of acute pancreatitis: impact of social deprivation, alcohol consumption, seasonal and demographic factors [Internet], *Aliment. Pharmacol. Ther.* 38 (5) (2013 Sep), 539–48, <http://www.ncbi.nlm.nih.gov/pubmed/23859492>. (Accessed 5 September 2018).
- [2] A. Pármiczky, B. Kúti, A. Szentesi, A. Balázs, Á. Szűcs, D. Mosztbacher, et al., Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis, *PLoS One* 11 (10) (2016) 1–19.
- [3] S.M. Van Dijk, N.D.L. Hallensleben, H.C. Van Santvoort, P. Fockens, H. Van Goor, M.J. Bruno, et al., Acute pancreatitis: recent advances through randomised trials, *Gut* 66 (11) (2017) 2024–2032.
- [4] E. Moggia, R. Koti, A.P. Belgaumkar, F. Fazio, S.P. Pereira, B.R. Davidson, et al., Pharmacological interventions for acute pancreatitis, *Cochrane Database Syst. Rev.* 2017 (2017) 1–14.
- [5] U. Iqbal, H. Anwar, M. Scribani, Ringer's lactate versus normal saline in acute pancreatitis: a systematic review and meta-analysis, *J Dig Dis* [Internet] 19 (6) (2018 Jun) 335–341, <https://doi.org/10.1111/1751-2980.12606>.
- [6] IAP/APA evidence-based guidelines for the management of acute pancreatitis, *Pancreatol* 13 (4 SUPPL. 2) (2013 Jul 1) e1–15.
- [7] R.M. Pearse, D.A. Harrison, N. MacDonald, M.A. Gillies, M. Blunt, G. Ackland, et al., Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery, *JAMA* 311 (21) (2014 Jun 4) 2181 [Internet], <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.5305>. (Accessed 11 October 2018).
- [8] M.A. Hamilton, M. Cecconi, A. Rhodes, A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients [Internet], *Anesth. Analg.* 112 (6) (2011 Jun), 1392–402, <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000539-201106000-00027>. (Accessed 27 August 2016).
- [9] B.U. Wu, J.Q. Hwang, T.H. Gardner, K. Repas, R. Delee, S. Yu, et al., Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis, *Clin. Gastroenterol. Hepatol.* 9 (8) (2011) 710–717.
- [10] E.P. Rivers, D.S. Ander, D. Powell, Central venous oxygen saturation monitoring in the critically ill patient, *Curr. Opin. Crit. Care* 7 (3) (2001) 204–211.
- [11] P. Bortolotti, F. Saulnier, D. Colling, A. Redheuil, S. Preau, New tools for optimizing fluid resuscitation in acute pancreatitis [Internet], *World J. Gastroenterol.* 20 (43) (2014 Nov 21), 16113–22. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25473163>. (Accessed 11 October 2018).
- [12] F. Bolado, J.L. Buxbaum, A. Vaillo-Rocamora, K. Cárdenas-Jaén, P. Maisonneuve, E. De-Madaria, Early weight-based aggressive vs. Non-aggressive goal-directed fluid resuscitation in the early phase of acute pancreatitis: an open-label multicenter randomized controlled trial (the WATERFALL trial), design, and rationale [Internet], *Front. Med.* 7 (2020 Sep 2) 440. Available from: <https://pubmed.ncbi.nlm.nih.gov/3492535/>. (Accessed 2 January 2021).
- [13] M.D. Wang, Y. Ji, J. Xu, D.H. Jiang, L. Luo, S.W. Huang, Early goal-directed fluid therapy with fresh frozen plasma reduces severe acute pancreatitis mortality in the intensive care unit, *Chin Med J (Engl.)* 126 (10) (2013) 1987–1988.
- [14] E.Q. Mao, J. Fei, Y.B. Peng, J. Huang, Y.Q. Tang, S.D. Zhang, Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis, *Chin Med J (Engl.)* 123 (13) (2010) 1639–1644.
- [15] E.Q. Mao, Y.Q. Tang, J. Fei, S. Qin, J. Wu, L. Li, et al., Fluid therapy for severe acute pancreatitis in acute response stage, *Chin Med J (Engl.)* 122 (2) (2009) 169–173.
- [16] J.L. Buxbaum, M. Quezada, B. Da, N. Jani, C. Lane, D. Mwendiga, et al., Early aggressive hydration hastens clinical improvement in mild acute pancreatitis [Internet], *Am. J. Gastroenterol.* 112 (5) (2017 May 1) 797–803. Available from: <http://journals.lww.com/0000434-201705000-00027>. (Accessed 2 January 2021).
- [17] C.M. Dunham, T.J. Chirichella, B.S. Gruber, J.P. Ferrari, J.A. Martin, B.A. Luchs, et al., Emergency department noninvasive (NICOM) cardiac outputs are associated with trauma activation, patient injury severity and host conditions and mortality, *J Trauma Acute Care Surg* 73 (2) (2012) 479–485.
- [18] J.M. Fisher, T.B. Gardner, The “golden hours” of management in acute pancreatitis [Internet], *Am. J. Gastroenterol.* 107 (8) (2012 Aug 3), 1146–50. Available from: <http://www.nature.com/articles/ajg201291>. (Accessed 11 October 2018).
- [19] F. Froghi, F. Soggiu, F. Ricciardi, K. Gurusamy, D.S. Martin, J. Singh, et al., Ward-based goal-directed fluid therapy (GDFT) in acute pancreatitis (GAP) trial: study protocol for a feasibility randomised controlled trial, *BMJ Open* 9 (10) (2019).
- [20] A.-W. Chan, J.M. Tetzlaff, P.C. Gotsche, D.G. Altman, H. Mann, J.A. Berlin, et al., SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials [Internet], *BMJ* 346 (jan08 15) (2013 Jan 9). e7586–e7586. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23303884>. (Accessed 25 October 2016).
- [21] S. Tenner, J. Baillie, J. Dewitt, S.S. Vege, American college of gastroenterology guideline: management of acute pancreatitis, *Am. J. Gastroenterol.* 108 (9) (2013) 1400–1415.
- [22] Good Clinical Practice (GCP) [Internet], Available from: <https://www.nih.ac.uk/our-faculty/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/>. (Accessed 14 September 2018).
- [23] S.L. Blamey, C.W. Imrie, J. O'Neill, W.H. Gilmour, D.C. Carter, Prognostic factors in acute pancreatitis [Internet], *Gut* 25 (1984), 1340–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23303884>. (Accessed 12 April 2018).
- [24] J.C. Marshall, D.J. Cook, N.V. Christou, G.R. Bernard, C.L. Sprung, W.J. Sibbald, Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome [Internet]. Vol. 23, *Critical Care Medicine, Crit. Care Med.* (1995), 1638–52. Available from: <https://pubmed.ncbi.nlm.nih.gov/7587228/>. (Accessed 19 December 2020).
- [25] P.A. Banks, T.L. Bollen, C. Dervenis, H.G. Gooszen, C.D. Johnson, M.G. Sarr, et al., Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus [Internet], *Gut* 62 (1) (2013 Jan 1), <https://doi.org/10.1136/gutjnl-2012-302779>, 102–11. Available from: (Accessed 19 December 2020).
- [26] Öztekin Long, M. Nicole, D. Badre, Pao 2 Fio2 derivation [Internet], *Bone* 23 (1) (2008) 1–7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/183624763/pdf/nihms412728.pdf>.
- [27] The EuroQol Group, EuroQol - a new facility for the measurement of health-related quality of life [Internet], *Health Pol.* 16 (3) (1990) 199–208. Available from: <https://pubmed.ncbi.nlm.nih.gov/10109801/>. (Accessed 7 June 2021).
- [28] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, et al., The REDCap consortium: building an international community of software platform partners, *J. Biomed. Inf.* 95 (2019), 103208. Academic Press Inc.
- [29] R. Mounzer, C.J. Langmead, B.U. Wu, A.C. Evans, F. Bishehsari, V. Muddana, et al., Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis [Internet], *Gastroenterology* 142 (7) (2012 Jun), 1476–82. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22425589>. (Accessed 12 April 2018).
- [30] A. Aggarwal, M. Manrai, R. Kochhar, Fluid resuscitation in acute pancreatitis [Internet], *World J. Gastroenterol.* 20 (48) (2014 Dec 28), 18092–103. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25561779>. (Accessed 15 September 2018).
- [31] J.A. Myburgh, M.G. Mythen, Resuscitation fluids [Internet], *N. Engl. J. Med.* 3369 (26) (2013 Sep 26), 1243–51. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMra1208627>. (Accessed 2 December 2016).
- [32] S.J. Davies, S. Minhas, R.J.T. Wilson, D. Yates, S.J. Howell, Comparison of stroke volume and fluid responsiveness measurements in commonly used technologies for goal-directed therapy, *J. Clin. Anesth.* 25 (6) (2013) 466–474.
- [33] J.P. Neoptolemos, M. Raraty, M. Finch, R. Sutton, Acute pancreatitis: the substantial human and financial costs [Internet], *Gut* 42 (1998), 886–91. Available from: <http://gut.bmj.com/>.
- [34] B.C. Kahan, H. Rushton, T.P. Morris, R.M. Daniel, A comparison of methods to adjust for continuous covariates in the analysis of randomised trials [Internet], *BMC Med. Res. Methodol.* 16 (1) (2016 Apr 11). Available from: <https://pubmed.ncbi.nlm.nih.gov/27068456/>. (Accessed 12 July 2021).

- [35] V. Wadhwa, S. Patwardhan, S.K. Garg, Y. Jobanputra, R. Lopez, M.R. Sanaka, Health care utilization and costs associated with acute pancreatitis [Internet], *Pancreas* 46 (3) (2017 Mar 1), 410–5. Available from: <https://journals.lww.com/00006676-201703000-00019>. (Accessed 7 January 2021).
- [36] P.J. Fagenholz, C. Fernández-del Castillo, N.S. Harris, A.J. Pelletier, C.A. Camargo, Direct medical costs of acute pancreatitis hospitalizations in the United States [Internet], *Pancreas* 35 (4) (2007 Nov), 302–7. Available from: <http://journals.lww.com/00006676-200711000-00002>. (Accessed 8 January 2021).
- [37] B. Andersson, B. Appलगren, V. Sjödin, D. Ansari, J. Nilsson, U. Persson, et al., Acute pancreatitis - costs for healthcare and loss of production [Internet], *Scand. J. Gastroenterol.* 48 (12) (2013), 1459–65. Available from: <https://www.tandfonline.com/doi/abs/10.3109/00365521.2013.843201>. (Accessed 8 January 2021).