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# Ward based goal directed fluid therapy (GDFT) in acute pancreatitis (GAP) trial: a feasibility randomised controlled trial [ISRCTN 36077283]

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1 Abstract

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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.

8 **Method:** 50 patients with AP were randomised to either ward-based GDFT (n=25) with 9 intravenous (IV) fluids administered based on stroke volume optimisation protocol or standard 10 care (SC) (n=25), but with blinded cardiac output evaluation, for 48-hours following hospital 11 admission. Primary outcome was feasibility.

12

13 Results: 50 of 116 eligible patients (43.1%) were recruited over 20 months demonstrating 14 feasibility. 36 (72%) completed the 48-hours of GDFT; 10 (20%) discharged within 48-hours 15 and 4 withdrawals (3 GDFT, 1 SC). Baseline characteristics were similar with only 3 16 participants having severe disease (6%, 1 GDFT, 2 SC). Similar volumes of IV fluids were 17 administered in both groups (GDFT 5465 (1839) ml, SC 5211 (1745) ml). GDFT group had a 18 lower heart rate, blood pressure and respiratory rate and improved oxygen saturations. GDFT 19 was not associated with any harms. There was no evidence of difference in complications of 20 AP (GDFT 24%, SC 32%) or in the duration of stay in intensive care (GDFT 0 (0), SC 0.7 (3) 21 days). Length of hospital stay was 5 (2.9) days in GDFT and 6.3 (7.6) in SC groups.

22

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.

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27 Trial registration: ISRCTN 36077283 (26-03-2018).

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 ID: 221872)

31

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- 34
- Keywords: Fluid therapy, Acute Pancreatitis, Cardiac Output, Goal-directed Fluid Therapy
   36

#### 37 Introduction

38 Acute pancreatitis (AP) affects approximately 30 per 100,000 of the UK population (1). The 39 principal causes include gallstones and alcohol excess with increasing age, male gender, and 40 lower socioeconomic class being associated with a higher incidence of AP (1,2). Although the 41 majority of clinical presentation of AP is mild in severity, approximately 20% develop moderate 42 to severe pancreatitis due to overwhelming systemic inflammatory response syndrome (SIRS) 43 and multi-organ failure (3). There is currently no effective pharmacological intervention in 44 clinical practice for the treatment of this disease (4). Supportive management in terms of 45 maintenance of fluid and electrolyte balance remains the mainstay in the treatment of AP. 46 Despite the key importance of fluid therapy there is a lack of information on the optimal fluid 47 therapy (4,5). There is some evidence supporting the use of lactated Ringer's solution (5), 48 however, there is conflicting evidence from randomised controlled trials (RCT) regarding the 49 rate and volume of fluid therapy for those with mild or moderate disease (3). Given that the 50 disease severity is variable and its assessment difficult at presentation, early goal-directed 51 fluid therapy (GDFT) has been suggested to guide initial intravenous (IV) fluid resuscitation in 52 acute pancreatitis until the resuscitation goals are reached (6).

53

54 GDFT in the peri-operative period using cardiac output monitoring during surgery (in the 55 operating theatre) or on an intensive care unit (ICU) decreases complications in conditions 56 associated with a SIRS response (7,8). These trials were not conducted in a ward-based 57 setting. For GDFT to be most effective in acute pancreatitis, the optimal timing for fluid therapy 58 intervention is likely to be at the earliest opportunity following the onset of pancreatitis, which 59 would equate with the time of admission to hospital and initial ward care in those not requiring 60 immediate admission to ICU. Without invasive monitoring, GDFT trials in patients admitted to 61 the ward with AP have had resuscitation goals based on biochemical markers (i.e. 62 haematocrit) rather than haemodynamic measures as resuscitation goals and have failed to 63 show a reduction in the inflammatory response or improved clinical outcomes (9). Whilst other 64 resuscitation goals such as heart rate (HR), urine output (UO) and central venous pressures

65 have been suggested for fluid therapy in acute pancreatitis, it is the optimisation of 66 intravascular volume guided by cardiac output measures that has been shown to be effective 67 in decreasing morbidity after major surgery (10,11). Clinical trials for fluid therapy in acute 68 pancreatitis continue to evaluate aggressive versus moderate fluid therapy with complex 69 biochemical or clinical markers to assess adequate resuscitation (12). There is some evidence 70 that Lactated Ringer's reduces SIRS response compared with normal saline for initial 71 resuscitation and has therefore been recommended in the guidelines (6,9). However, RCTs 72 in AP have failed to show a clear benefit in terms of different rate and volume of fluid 73 administration or the resuscitation goals (9,13–16). In two RCTs of severe AP patients, both 74 rapid haemodilution with a haematocrit >35% as resuscitation goal and rapid fluid expansion 75 (10-15ml/kg/hr) were associated with significantly worse infection rates, abdominal 76 compartment syndrome and need for mechanical ventilation (14,15). Conversely, Buxbaum 77 et al. demonstrated that aggressive (20 ml/kg bolus followed by 3 ml/kg/h) compared to 78 standard (10 ml/kg bolus followed by 1.5 mg/kg/h) hydration with Lactated Ringer's solution 79 was associated with a reduction in SIRS and early recovery in patients with mild acute 80 pancreatitis (16). There is currently no RCT investigating the role of ward based GDFT using 81 cardiac output targets in patients with acute pancreatitis.

82

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). Wardbased 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.

90

91 The GDFT in AP (GAP) trial has been designed as a two-centre RCT to assess the feasibility
92 of guiding the initial 48-hours of IV fluid administration in patients with acute pancreatitis using

93 a non-invasive ward based GDFT algorithm. The initial 48-hours is considered the 'golden' 94 period for interventions that may decrease the severity of acute pancreatitis (18). Given the 95 unique and novel nature of the study, it was important to assess feasibility of recruiting patients 96 into a trial of patients with an emergency presentation as well as performing a preliminary 97 assessment of associated healthcare costs. The safety and practicality of delivering ward 98 based GDFT and secondary clinical outcome measures were also evaluated to identify 99 potential endpoints and the trial recruitment numbers required for a subsequent multi-centre 100 study to evaluate efficacy. Health-related quality of life (HRQoL) assessment as well as 101 preliminary health economic analysis of the indicative costs were also performed to inform the 102 subsequent multi-centre trial of clinical and cost effectiveness.

#### 103 Methods

# 104 Study design and setting

105 The GAP trial protocol has been published (19) and is summarised here. The trial protocol 106 (v2) was reviewed and approved by the London Central Research Ethics Committee (REC 107 ref: 17/LO/1235, project ID: 221872). Informed consent was obtained from eligible patients 108 after screening by a member of the research or clinical team trained in Good Clinical Practice 109 (GCP). The trial was registered on ISRCTN (ISRCTN 36077283) on 09 April 2018 110 (http://www.isrctn.com/ISRCTN36077283). A two-centre randomised feasibility RCT was 111 designed and conducted in accordance with the SPIRIT guidelines (20). Feasibility was 112 evaluated in the Royal Free Hospital (RFH) which is a specialist tertiary referral centre for 113 pancreas disease management and Barnet General Hospital (BGH) which is a district general 114 hospital providing secondary care for a large population of outer North London. Although the 115 study was planned to recruit in two centres, due to changes in one of the sites, patients were 116 recruited only at the Royal Free Hospital for the initial 6 months whilst the trial was set up at a 117 new second site, Barnet General Hospital. The trial recruitment period was therefore extended 118 for a further 6 months, and recruitment was completed within the revised timeline. The results 119 are reported using Consolidated Standards of Reporting Trials (CONSORT) guidelines.

120

# 121 Patient population

122 Patients (>16 years) admitted to hospital as an emergency with a diagnosis of acute 123 pancreatitis confirmed by the international consensus criteria were eligible for this study (21). 124 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 125 126 three times greater than the upper limit of normal; and 3. Characteristic findings of acute 127 pancreatitis on contrast-enhanced computed tomography (CT) and less commonly magnetic 128 resonance imaging (MRI) or transabdominal ultrasound (US). Exclusion criteria were tertiary 129 referrals of patients transferred from another hospital for the management of complications of 130 acute pancreatitis, those requiring immediate admission to the ICU, known chronic pancreatitis in whom an acute exacerbation cannot be confirmed, a history of cardiac failurein the past three months and those unable to provide fully informed consent.

133

# 134 Recruitment, Randomisation & Blinding

135 Patients with suspected or confirmed acute pancreatitis were screened by the emergency 136 department (ED) physicians, general surgical team on-call or trial research nurses, and 137 screening information was recorded in a recruitment log. Diagnosis of acute pancreatitis was 138 confirmed by the general surgical registrar on call. Eligible patients were provided with both 139 an abbreviated and an in-depth patient information sheet (PIS). Those wishing to be included 140 in the GAP trial were consented by a member of the clinical or research team trained in Good 141 Clinical Practice (GCP) (22). The trial nursing staff were contacted through a GAP trial 142 telephone hotline, set up in each site, within four hours of diagnosis. Consenting patients were 143 randomised on a 1:1 basis stratified by site of admission using the 'Sealed Envelope' 144 (www.sealedenvolpe.com) internet-based randomisation system by trial nursing staff. 145 Following admission to the ward trial participants received either GDFT or Standard of Care 146 (SC) which was commenced within six hours of the diagnosis and was continued for the next 147 48-hours of inpatient stay. It was not possible to blind the research nurses delivering GDFT or 148 the treating clinicians to the treatment group. However, the participants, outcome assessors 149 of health-related quality of life, health economics and statisticians were blinded to the 150 treatment groups. Patient blinding was aided by cardiac output monitoring of both intervention 151 and control groups at the same time points but performing GDFT in the intervention group 152 alone. Cardiac output data from the SC group were not available to the treating clinicians but 153 was included in the outcome analysis.

154

# 155 Intervention (GDFT)

GDFT was carried out for the initial 48-hours of admission. A ward-based stroke volume (SV)
optimisation algorithm was designed (figure 1) using a non-invasive cardiac output measuring
device (NICOM). The Cheetah NICOM<sup>™</sup> 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 hours for 48-hours cardiac output studies were performed, and the SV optimised as follows:

165 After randomisation SV was recorded and an initial bolus of 250 ml of IV balanced crystalloid was administered over 5 to 10 minutes. A sustained rise in SV of greater 166 167 than 10% for 15 minutes or more was taken to indicate fluid responsiveness and a 168 repeat 250 ml bolus was administered. If SV did not rise greater than 10% then the 169 patient was deemed fluid unresponsive and no further fluid boluses were administered. 170 SV was monitored four hourly and a drop in SV by more than 10% from the previous 171 reading initiated a further fluid bolus. All fluid boluses in the GDFT group were balanced 172 crystalloid solution (figure 1).

173

174 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<sup>™</sup> every 4 hours by trial nursing staff, however the readings were not made available to the clinical team.

179

180 Primary outcome measures

181 The primary outcome of the trial was an assessment of feasibility. In the trial protocol we 182 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 hours of admission;

e) completion rate of 48-hours of GDFT;

190 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 controlgroup at 90 days was decided as a measure of safety of the intervention.

193

# 194 Secondary outcome measures

195 Total IV fluid administration volumes (crystalloids, colloids and others including blood 196 products), vital signs (temperature, heart rate, blood pressure, respiratory rate and oxygen 197 saturation) and haemodynamic monitoring (CO and SV) during the intervention period were 198 recorded. Severity of pancreatitis was assessed by serum C-reactive protein (CRP), modified 199 Glasgow score and modified Marshall score for assessment of organ failure. Modified 200 Glasgow score is a composite score for predicting severity of acute pancreatitis which is 201 performed on admission and repeated at 48 hours (23). The parameters include PaO2 202 <7.9kPa, age >55 years, white cell count >15 x 10<sup>9</sup>/L, calcium <2 mmol/L, urea >16 mmol/L, 203 lactate dehydrogenase >600 IU/L, serum albumin <32 g/L, and blood glucose blood glucose 204 >10 mmol/L. A score of 3 or above is considered as high risk (>20%) for severe pancreatitis 205 with a positive predictive value of 79% (23).

206

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 nonventilated ward patients, serial arterial partial pressures of oxygen (PaO<sub>2</sub>) and functional inspired oxygen (FiO<sub>2</sub>) ratios were derived from peripheral oxygen saturations (SpO<sub>2</sub>) / FiO<sub>2</sub> 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-hours (25). All predefined complications of pancreatitis were
 recorded up to discharge and at follow-up at 30- and 90-days post randomisation.

217

# 218 Sub-studies

219 A qualitative study was conducted to explore the reasons for participation and non-220 participation of eligible patients and patients' and clinicians' acceptability of the trial to assist 221 in optimisation of recruitment strategies employed for the definitive trial. Interviews with a 222 sample of eligible patients were held to explore patient perspectives of fluid therapy treatment, 223 their understanding of the two treatments, reasons for taking part or refusing the trial, and the 224 acceptability of randomisation between the procedures. Interviews with clinical staff were 225 conducted to explore their views about the trial, clinical equipoise, and their understanding of 226 the recruitment challenges. Semi-structured interviews informed by a topic guide were 227 developed in conjunction with the trial management group.

228

229 Health-related quality of life (HRQoL) was assessed using EQ5D-5L questionnaire (27) on 230 admission and subsequently on day 7, day 30 and day 90. Resource use data for health 231 economic analysis on length of hospital stay, length of ICU stay, and number of days 232 ventilated, time to return to pre-pancreatitis activities, number of work-days lost (in those who 233 work), and costs (NHS and personal social services (PSS) perspectives) were collected. The 234 additional costs for the intervention arm were accounted for in the form of device cost, 235 consumables and additional nurse time per fluid challenge. All clinical and HRQoL outcomes 236 were measured up to discharge and subsequently at 30 days and 90 days post randomisation 237 by face-to-face or telephone follow-up.

238

239 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

242 hosted at University College London (UCL) (28). The two groups were compared using 243 descriptive statistics to ensure they had similar baseline characteristics. As this was a 244 feasibility study, all analyses other than recruitment rate and withdrawal rates were considered 245 exploratory. For the primary outcome, the proportion of patients who consented to be 246 randomised and the rate of withdrawal from GDFT protocol were calculated. The median 247 number of complications in each group were presented. The secondary outcomes were 248 presented for each group using the mean and standard deviation (SD) or frequencies and 249 proportions as appropriate. Mean profile plots, by arm, were also used to graphically to 250 describe secondary outcomes. The mean difference in quality-of-life scores between the two 251 groups at 7 days is presented with a 95% CI. All other secondary outcomes collected over 252 time will be summarised for each group using mean profile plots. The frequency and nature of 253 adverse events were reported for each group.

- 254
- 255 **Results**

#### 256 Patient recruitment

257 Overall, 142 patients were screened for eligibility of which 26 patients (26/142, 18.3%) were 258 excluded. Reasons for exclusion were: not referred to trial team in the appropriate time (within 259 4 hours of diagnosis of AP) (n=19), unable to provide informed consent due to language barrier 260 (n=6), and not meeting inclusion criteria after further scrutiny (n=1). A total of 116 patients 261 were eligible of the 142 screened (116/142, 81.7%) of whom 50 patients were randomised to 262 either GDFT (n=25) or SC (n=25) during the study period from January 2018 to October 2019 263 between the two sites (Royal Free Hospital and Barnet Hospital) (figure 2). Hence, the 264 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 265 266 patients (n=66/116, 56.9%) were: no research staff availability (n=44), patient declined (n=21), 267 recruiting physician not trained in Good Clinical Practice (GCP) (n=1).

269 The baseline characteristics are shown in Table 1. The mean age (SD) for the overall study 270 cohort was 50.4 (18.0) years. There two groups were similar in age, gender or ethnicity. None 271 of the patients recruited had a past medical history of heart failure and only 2 (4%) patients 272 (GDFT 1 vs SC 1) had a history of chronic renal failure. 30% (15/50) of patients had suffered 273 previous episodes of acute pancreatitis. Previously known gallstones disease was present in 274 7 GDFT (28%) and 8 SC (32%) patients. The cause of acute pancreatitis requiring hospital 275 admission was predominantly unknown across both groups (46%), followed by gallstones 276 (32%), alcohol (26%) and others (6%). GDFT had a higher proportion of patients with gallstone 277 related pancreatitis, whilst SC had more patients with alcohol as a cause (Table 1). Patients 278 in the GDFT group had a longer period between symptom onset and hospital admission delay 279 (GDFT 3.75 (4.9) vs SC 1.56 (1.53) days). Intravenous (IV) fluids were administered following 280 hospital admission but prior to randomisation in 87% (n=43) of participants. The volume of IV 281 fluids received prior to trial intervention in GDFT group was 1332 (993) ml versus 1167 (713) 282 ml in SC group.

283

# 284 Intervention period

Overall, 36 patients (72%) completed the 48-hour 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-hours (n=10). Other reasons included patient withdrawal from the study prior to 48hours (n=2), transferred to another hospital due to cerebrovascular accident (n=1), patient death (n=1).

292

# 293 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).

300

# 301 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-hours 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 figure 3 and figure 4 respectively.

307

# 308 Monitoring during intervention

The stroke volume (SV) readings in GDFT group appear approximately 10% higher than SC group (figure 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. Systolic blood pressure was similar between the two groups (figure 6). A lower respiratory rate and higher oxygen saturation was also observed in the GDFT group (figure 6).

314

# 315 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. (figure 7).

320

A Glasgow severity score was performed on 26 patients (52%) on admission and only 17 patients (34%) at 48-hours. 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%

325 of patients (n=49) on admission. For those who remained inpatient at 48-hours, there was 326 evidence of organ failure in four patients (GDFT 2 vs SC 2). In the GDFT group, the two 327 patients had a transient oxygen requirement due to bi-basal atelectasis and small pleural 328 effusions on chest x-ray which resolved in less than 48-hours. Organ failure was observed in 329 two patients in SC group; these were due to acute kidney injury and type 1 respiratory failure 330 as well as local complications of pancreatitis which persisted for more than 48-hours. Both 331 patients required admission to intensive care unit. Progression to severe acute pancreatitis 332 (as defined by the revised Atlanta criteria) was observed in two patients in SC (8%) and none 333 in GDFT group (Table 6 and Figure 7). The median (IQR) levels of CRP on admission were 334 10 (19.5) mg/l for GDFT and 6 (15.5) for SC group. At day 7 post randomisation, the median 335 (IQR) CRP levels GDFT group was 70 (39) mg/l and 289 (45) mg/l for SC group (Figure 8).

336

# 337 Complications and outcome

338 At least one pre-defined complication occurred during the hospital stay in five patients in the 339 GDFT group (23.8%) and eight in SC group (32%). The median (range) of complication per 340 patient was 0 (0-3) for GDFT vs 0 (0-7) for SC. None of the patients in GDFT group developed 341 persistent organ failure and progression to severe acute pancreatitis whilst this was observed 342 in 2 (8%) patients in SC group. Documented SIRS occurred in GDFT (n=2, 8.3%) compared 343 to SC (n=6, 24%). Four patients underwent ERCP (GDFT 3 (12.5%) vs SC 1 (4%)) with one 344 post-ERCP complication in the GDFT arm. At 30- and 90-day follow-up, patients experiencing 345 new complications related to pancreatitis were rare (Table 6). One patient in SC arm died after 346 15 days in ICU due to severe necrotising pancreatitis developing infected pancreatic necrosis, 347 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 348 349 points which would include any re-admissions (Table 6).

350

# 351 Health related quality of life

352 Complete QoL data were available for 47/50 at baseline, 37/50 at 7 days, 35/50 at 30 and 90 353 days. Complete case analysis was adopted to estimate incremental quality adjusted life year 354 (QALY) for each patient. This approach reduced the sample size to 16 and 10 patients in the 355 GDFT and SC group, respectively. A summary of utility estimates for the two arms over the 356 trial period is provided in Table 7. Differences between treatment arms were not significant at 357 a 95% confidence level. The mean (95% CI) incremental QALYs in the GDFT group was 358 marginally lower than the control group (GDFT 0.191 (0.17-0.21) versus SC 0.2 0.17-0.02)), 359 mean difference -0.0096).

360

# 361 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 £4,857.82, which was lower than the SC group (£5,312.92). 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.

369

# 370 Qualitative study

371 The qualitative study was conducted during the trial recruitment period and was able to identify 372 and mitigate factors that may hinder recruitment. An executive summary of the qualitative 373 study report is presented as supplementary material as the full qualitative evaluation has been 374 submitted for publication (Appendix 1). Problems were identified with cross-site working. The 375 need for additional research nurses to cover night and weekend cover at both sites were 376 highlighted. During initial trial set-up stages, issues with site initiation at the second site were 377 mainly due to lack of capacity within the hospital: space on wards, ward staff time, research 378 nurse time. Patient screening was identified as a difficult process as patients needed to be 379 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).

384

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

392

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-hours, 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.

397

# 398 Discussion

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

401

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 six hours of

408 diagnosis in patients presenting as an emergency 24/7 in both a district general hospital (BGH) 409 setting and a tertiary referral centre for management of pancreatic disorders (RFH). However, 410 there were important difficulties related to recruitment as identified by the contemporaneously 411 conducted qualitative study. The majority of the patients excluded from the trial were not 412 referred to the trial staff in the appropriate time for the intervention to commence. Screening 413 the ED presentations 24/7 for a time-based trial has been a challenge. Clinical teams in the 414 ED and on-call general surgical team played an essential role in identifying patients presenting 415 with suspected acute pancreatitis. A possible solution to increase recruitment in a subsequent 416 trial on efficacy would include a better education and engagement of the clinical teams 417 especially around the time when junior staff rotate from their placements. The referrals system 418 to the research trial staff can also be made simpler through electronic messaging systems and 419 remote consent processes. In hospitals with electronic medical records, this process can even 420 be automated to alert research staff of a biochemical diagnosis of pancreatitis (lipase or 421 amylase levels), or radiological results would alert the trial team of potential subjects with a 422 diagnosis of AP. As for the language barrier, the consent form and information leaflet could 423 be translated into the languages prevalent in the population that a specific hospital serves.

424

425 The withdrawal rate was low at 9% but many patients did not complete the planned 48-hour 426 duration of the intervention (28%). The main reason was patient discharge within 48-hours, 427 occurring in 14 patients (28%) which perhaps reflects that the majority of patients in the trial 428 had mild acute pancreatitis (76%) and had a rapid recovery and discharge. This issue could 429 be dealt with in a future trial either by increasing the recruitment to cover the trial dropout rate 430 or excluding those with mild disease. Increasing the trial size may be the better option as the 431 severity of pancreatitis may be difficult to determine at the time of admission (29) and there is 432 no certainty as to whether there will be more or less benefit of GDFT in those with mild, 433 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 compete follow up information in 90% of participants
at 90 days.

438

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.

443

444 Fluid therapy in the initial phase of hospitalisation remains the cornerstone of management in 445 AP. In our study, there was no evidence that GDFT altered the total volume of intravenous 446 fluids received during the 48-hour intervention. However, there were clear differences in the 447 timing of intravenous fluid administration. Patients in SC received more fluids in the first four 448 hours of intervention and less in the last eight hours whilst IV fluid administration was more 449 consistent in the GDFT group over the 48-hour intervention period. Although early aggressive 450 fluid administration has been advocated in AP (30) this is of unproven value and may be 451 associated with significant harms in some patient groups (14,15). This study raises the 452 possibility that a personalised strategy is required providing a targeted fluid volume only when 453 required (31). One patient in the GDFT group developed pleural effusion on chest x-ray 454 compared to three patients in the SC group. The relationship to fluid therapy in these patients 455 was not clear as they were not clinically overloaded and transient hypoxia and pleural effusion 456 is a recognised complication of acute pancreatitis. Overall, the rate of complication in the 457 GDFT was similar to that of SC group and the intervention was considered safe.

458

459 Possible benefits of improved fluid management in acute pancreatitis would be improved 460 haemodynamics, a reduction in organ injury, fewer complications, and reduced admissions to 461 the intensive care unit. Intervention fidelity was demonstrated by higher SV readings on an 462 average of 10% in the GDFT group which would suggest that the GDFT was achieving the

463 goal of improving systemic haemodynamics (32). This is supported by cardio-respiratory 464 parameters over the 48-hours in the GDFT group showing a lower heart rate, blood pressure, 465 respiratory rate and improved oxygen saturations. A major factor leading to cardio-respiratory 466 instability in acute pancreatitis is the development of SIRS (33). A further indication of efficacy 467 of the ward GDFT is the reduction of SIRS from 24% in controls to 8.3% in the GDFT group 468 as well as lower inpatient (7 days) CRP levels. Although, this could have been confounded by 469 the fact that patients in the GDFT group presented on average 1.5 days later than SC group 470 since the onset of symptoms. In a small sample size, this could simply be due to chance, 471 which can be adjusted for by using continuous covariates in a definitive trial (34). The delayed 472 presentation can potentially under-estimate the effect of GDFT, as the inflammatory processes 473 which would have been mitigated by the fluid therapy have already set in and the 'golden 474 period' for intervention has passed. Equally, the delayed presentation could mean patients in 475 the GDFT group had less acute presentation allowing patients to delay their hospital visit.

476

477 The number and severity of organ dysfunction is directly related to mortality in acute 478 pancreatitis (33). Whilst organ failure was observed equally in both groups, (GDFT 2 versus 479 SC 2), patients in SC group had organ failure which persisted more than 48-hours, requiring 480 organ support in ICU. Severe AP was therefore observed in two cases in SC (8%) and none 481 in the GDFT group who had transient organ failure. The lower rates of presentation with acute 482 pancreatitis is partly due to the small sample size of the study, and part due to the exclusion 483 of patients directly referred to ICU and inter-hospital transfers for tertiary care which are often 484 severe AP requiring intervention. Whilst adequately powered studies to confirm association is 485 required, this indicates that GDFT perhaps prevents the progression to severe disease by 486 correcting organ failure as it occurs. The two patients in SC group developed AKI and type 1 487 respiratory failure which are directly related to the rate and timing of IV fluid administration. 488 GDFT could therefore be beneficial in guiding fluid therapy in AP and further adequately 489 powered studies of effectiveness are indicated.

490

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.

495

496 Initial hospitalisation and subsequent complications of acute pancreatitis have been 497 associated with significant and rising healthcare costs over the last two decades (35). In the 498 United States, the estimated total cost of acute pancreatitis admission was \$2.2 billion at a 499 mean hospitalisation cost of \$9870 in 2003 (36). This estimate is mirrored in Europe, costing 500 €9,762 for treating AP per patient (37). In the trial a preliminary cost effectiveness evaluation 501 was performed and the healthcare costs for managing a patients with acute pancreatitis was 502 approximately £5000. This may be lower than previous costings as the majority of patients 503 had mild AP and the hospital stay was short. The reduction in hospital stay by on average 1 504 day in the GDFT group was the major factor in reducing the healthcare costs associated with 505 acute pancreatitis by approximately £500/patient in this study. Although these results may be 506 biased by the small sample size of this analysis and difficulty in obtaining QoL information in 507 sick patients. A further and more detailed study into cost-effectiveness would include staff 508 training in GDFT and time to deliver fluid optimisation.

509

510 In this feasibility study, we have demonstrated that recruiting into a trial of this novel 511 intervention was safe, feasible and acceptable by patients and clinicians. We have multiple 512 signals of possible efficacy which would strongly support a subsequent larger multi-centre 513 study of efficacy and cost effectiveness of ward based GDFT in acute pancreatitis.

514

515 **Competing interests:** The authors declare that they have no competing interests.

516

517 **Trial registration:** The GAP trial was registered on ISRCTN 36077283 (26-03-2018).

518

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525

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665

- 667 **Figure legends:** 668 669 Figure 1. SV optimisation protocol for GDFT 670 671 Figure 2. CONSORT diagram 672 673 Figure 3. Total intravenous fluids infusion trend during the intervention period 674 Mean (SE) total intravenous fluids infusion over 48 hours. 675 676 Figure 4. Urine output trend during the intervention period 677 Mean (SE) urine output over 48 hours. 678 679 Figure 5. Stroke volume and cardiac output during the intervention period 680 Mean (SE) profile plots of a) Stroke volume (SV, b) Cardiac output (CO) during the 48-hour intervention period. 681 682 Figure 6. Vital signs during the intervention period 683 Mean (SE) profile plots of a) Heart rate (HR), b) Systolic blood pressure (SBP), c) Respiratory rate (RR), d) 684 Oxygen saturation (SpO<sub>2</sub>) during the 48-hour intervention period. 685 686 Figure 7. Clinical grade of severity of acute pancreatitis 687 688 Clinical severity of acute pancreatitis as scored by the 2010 revised Atlanta criteria (25): Mild acute pancreatitis: 689 No organ failure and No local or systemic complications; Moderately severe acute pancreatitis: Organ failure that 690 resolves within 48 h (transient organ failure) and/or Local or systemic complications without persistent organ 691 failure; Severe acute pancreatitis: Persistent organ failure (>48 h) - Single or multiple organ failure. 692 693 Figure 8. C-reactive protein (CRP) levels (mg/l)
- 694 Mean (SE) CRP levels over 7 days.