

2021-12-15

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

Froghi, F

<http://hdl.handle.net/10026.1/19513>

10.1016/j.jjsu.2022.106737

BRITISH JOURNAL OF SURGERY

Oxford University Press

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

1 **Abstract**

2
3 **Background:** Goal-directed fluid therapy (GDFT) reduces complications in patients
4 undergoing major general surgery. There are no reports of cardiac output evaluation being
5 used to optimise the fluid administration for patients with acute pancreatitis (AP) in a general
6 surgery ward.

7
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
23 **Conclusion:** Ward-based GDFT is feasible and shows a signal of possible efficacy in AP in
24 this early-stage study. A larger multi-site RCT is required to confirm clinical and cost
25 effectiveness.

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

28
29 **Ethical approval:** London Central Research Ethics Committee (REC ref: 17/LO/1235, project
30 ID: 221872)

31
32 **Funding:** National Institute for Health Research (NIHR) Research for Patient Benefit
33 Programme (RfPB) (Grant Reference Number PB-PG-0815-20002).

34
35 **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

83 With the development of non-invasive cardiac output monitors, it is now possible to measure
84 cardiac output as a guide for intravascular volume replacement in a ward setting (17). Ward-
85 based GDFT has the potential to correct the organ hypoperfusion resulting from inflammation
86 and tissue damage which may result in decreased morbidity, improved health-related quality
87 of life (HRQoL) and increased survival associated with AP. Reduced acute organ injury may
88 also lead to a reduced need for ICU admission and overall hospital length of stay with a
89 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.
125 Abdominal pain consistent with acute pancreatitis; 2. Serum amylase or lipase activity at least
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

131 pancreatitis in whom an acute exacerbation cannot be confirmed, a history of cardiac failure
132 in 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.sealedenvelope.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)*

156 GDFT was carried out for the initial 48-hours of admission. A ward-based stroke volume (SV)
157 optimisation algorithm was designed (figure 1) using a non-invasive cardiac output measuring
158 device (NICOM). The Cheetah NICOM™ device (Cheetah Medical Ltd, Maidenhead,

159 Berkshire, UK) was used on the ward for guiding GDFT by the GAP trial research nurses. Trial
160 nursing staff were experienced ICU nurses who had received training in Cheetah NICOM
161 measurements and delivering the intervention. The IV fluid administration regimen in the
162 GDFT group consisted of maintenance IV fluid (balanced crystalloid solution) at a rate of 1.5
163 ml/kg/hr. Every 4 hours for 48-hours cardiac output studies were performed, and the SV
164 optimised as follows:

165 After randomisation SV was recorded and an initial bolus of 250 ml of IV balanced
166 crystalloid was administered over 5 to 10 minutes. A sustained rise in SV of greater
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)*

175 In the SC group, IV fluid therapy (rate, volume and type) was at the discretion of the clinical
176 team caring for the patient. Patients in SC group had haemodynamic monitoring using the
177 Cheetah NICOM™ every 4 hours by trial nursing staff, however the readings were not made
178 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:

- 183 a) the ability to identify and recruit 50 patients at the selected sites to a study of acute
184 pancreatitis over the 17-month study period;
- 185 b) a recruitment target of 30% of eligible patients;

- 186 c) availability of the study team to recruit into this study for a condition presenting as an
187 emergency 24/7;
- 188 d) ability to randomise and commence ward GDFT within 6 hours of admission;
- 189 e) completion rate of 48-hours of GDFT;
- 190 f) withdrawal rate from GDFT protocol (aim was <20%).

191 A complication rate in the intervention group not more than 10% higher than that of the control
192 group 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 10⁹/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

207 The modified Marshall score was used to assess organ dysfunction in three systems:
208 respiratory, renal and cardiovascular (24,25). Organ failure was defined as presence of
209 Marshall score of 2 or more in any given organ system. As the study was conducted in non-
210 ventilated ward patients, serial arterial partial pressures of oxygen (PaO₂) and functional
211 inspired oxygen (FiO₂) ratios were derived from peripheral oxygen saturations (SpO₂) / FiO₂
212 ratios to assess respiratory failure (26). Indication for ICU admission and critical care outreach
213 (CCOT) review were as per hospital policy for invasive monitoring or organ support. Severe

214 acute pancreatitis was defined as the presence of organ failure as per modified Marshall score
215 which persisted for more than 48-hours (25). All predefined complications of pancreatitis were
216 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*

240 A pragmatic sample size of 50 patients was chosen for this feasibility study. Data was recorded
241 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
265 recruitment was 2 patients per calendar month. Reasons for not being able to recruit eligible
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).

268

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*

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

292

293 *Withdrawal rate and completion of follow up*

294 The total number of patients with complete data at the end of 90 day follow up was 45/50
295 (90%). There was one death in SC and none in the GDFT group. The number of patients who
296 withdrew from the study before the end of follow up period was 4 (3 in GDFT group and 1 in

297 SC group). The overall withdrawal rate was 8.9%. The reasons for withdrawal were available
298 for three patients and reported as “concerned about fluids” (n=1), “does not want to be called
299 again” (n=1), “no reason given” (n=1).

300

301 *Fluid administration*

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

307

308 *Monitoring during intervention*

309 The stroke volume (SV) readings in GDFT group appear approximately 10% higher than SC
310 group (figure 5). This trend was not demonstrated in the cardiac output readings. GDFT group
311 also appeared to have a lower heart rate than the SC group over the intervention period.
312 Systolic blood pressure was similar between the two groups (figure 6). A lower respiratory rate
313 and higher oxygen saturation was also observed in the GDFT group (figure 6).

314

315 *Secondary outcomes*

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

320

321 A Glasgow severity score was performed on 26 patients (52%) on admission and only 17
322 patients (34%) at 48-hours. Of those who had a Glasgow score on admission, two patients
323 had a predicted severe score (3 or more) in SC and one in GDFT group (Table 4). The Marshall
324 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)
348 length of hospital stay was lower by one day in GDFT at discharge and at 30- and 90-day time
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*

362 The mean inpatient length of stay was lower in the GDFT group compared to SC group
363 although this was not statistically significant. Unit prices are available in the supplementary
364 material. The difference in resource use was not statistically significant at any time point. The
365 average cost of inpatient stay up to 90-day follow up for GDFT was £4,857.82, which was
366 lower than the SC group (£5,312.92). The estimated cost difference was £1,610, £159, £455
367 in favour of the GDFT group at discharge, 30 days and 90 days respectively (Table 8).
368 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

380 to contact the trial team in the appropriate time window. Doctor change-over contributed to
381 missing recruitment across all stages of the trial. The trial team found it is easier to screen
382 patients during office hours and to identify potential trial participants at the RFH (as the team
383 were based there).

384

385 Patient acceptance and participation in the trial was good with a common belief that the
386 intervention could benefit other patients with the same condition. Severe pain and feeling
387 unwell was identified as reasons for patients declining participation in the trial. All patients
388 interviewed felt the information provided during informed consent process was clear. In
389 relation to delivery of treatment during the trial, two patients complained about visits made by
390 staff at night for monitoring. They felt it was disruptive for patients who wanted to sleep when
391 in the main ward.

392

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

397

398 **Discussion**

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

401

402 The primary outcome of the trial was feasibility. We have demonstrated that it is feasible to
403 recruit patients with acute pancreatitis to a randomised study of ward-based fluid therapy
404 determined by cardiac output evaluation. As regards the feasibility end points, we defined
405 these in the published protocol. The trial recruitment target was >30% and this was achieved
406 with 43% of eligible patients being recruited over the trial period. The study team was also
407 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.

434

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

438

439 The secondary end points of the study aimed to assess signals of efficacy and to identify
440 whether ward based GDFT in acute pancreatitis was a cause of harm or clinical benefit.
441 Feasibility studies are not powered to evaluate efficacy of the intervention and hence statistical
442 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

491 The cumulative LOS in hospital was on average one day less in GDFT group compared to SC
492 whilst the cumulative length of ICU stay was similar. In the context of this feasibility study, this
493 could be a signal of early recovery and hospital discharge for patients with AP treated with
494 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

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

525

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

533

534

535 **References**

- 536 1. Roberts SE, Akbari A, Thorne K, Atkinson M, Evans PA. The incidence of acute
537 pancreatitis: Impact of social deprivation, alcohol consumption, seasonal and
538 demographic factors. *Aliment Pharmacol Ther* [Internet]. 2013 Sep [cited 2018 Sep
539 5];38(5):539–48. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23859492>
- 540 2. Párniczky A, Kui B, Szentesi A, Balázs A, Szûcs Á, Mosztbacher D, et al. Prospective,
541 Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. *PLoS*
542 *One*. 2016;11(10):1–19.
- 543 3. Van Dijk SM, Hallensleben NDL, Van Santvoort HC, Fockens P, Van Goor H, Bruno
544 MJ, et al. Acute pancreatitis: Recent advances through randomised trials. *Gut*.
545 2017;66(11):2024–32.
- 546 4. Moggia E, Koti R, Belgaumkar AP, Fazio F, Pereira SP, Davidson BR, et al.
547 Pharmacological interventions for acute pancreatitis. Vol. 2017, *Cochrane Database*
548 *of Systematic Reviews*. 2017. p. 1–14.
- 549 5. Iqbal U, Anwar H, Scribani M. Ringer’s lactate versus normal saline in acute
550 pancreatitis: A systematic review and meta-analysis. *J Dig Dis* [Internet]. 2018
551 Jun;19(6):335–41. Available from: <http://doi.wiley.com/10.1111/1751-2980.12606>
- 552 6. IAP/APA evidence-based guidelines for the management of acute pancreatitis.
553 *Pancreatology*. 2013 Jul 1;13(4 SUPPL. 2):e1–15.
- 554 7. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, et al. Effect
555 of a Perioperative, Cardiac Output–Guided Hemodynamic Therapy Algorithm on
556 Outcomes Following Major Gastrointestinal Surgery. *JAMA* [Internet]. 2014 Jun 4
557 [cited 2018 Oct 11];311(21):2181. Available from:
558 <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2014.5305>
- 559 8. Hamilton MA, Cecconi M, Rhodes A. A Systematic Review and Meta-Analysis on the
560 Use of Preemptive Hemodynamic Intervention to Improve Postoperative Outcomes in
561 Moderate and High-Risk Surgical Patients. *Anesth Analg* [Internet]. 2011 Jun [cited
562 2016 Aug 27];112(6):1392–402. Available from:

- 563 <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=000005>
564 39-201106000-00027
- 565 9. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's
566 Solution Reduces Systemic Inflammation Compared With Saline in Patients With
567 Acute Pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9(8):710–7.
- 568 10. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the
569 critically ill patient. *Curr Opin Crit Care*. 2001;7(3):204–11.
- 570 11. Bortolotti P, Saulnier F, Colling D, Redheuil A, Preau S. New tools for optimizing fluid
571 resuscitation in acute pancreatitis. *World J Gastroenterol* [Internet]. 2014 Nov 21
572 [cited 2018 Oct 11];20(43):16113–22. Available from:
573 <http://www.ncbi.nlm.nih.gov/pubmed/25473163>
- 574 12. Bolado F, Buxbaum JL, Vaillo-Rocamora A, Cárdenas-Jaén K, Maisonneuve P, De-
575 Madaria E. Early Weight-Based Aggressive vs. Non-Aggressive Goal-Directed Fluid
576 Resuscitation in the Early Phase of Acute Pancreatitis: An Open-Label Multicenter
577 Randomized Controlled Trial (The WATERFALL Trial), Design, and Rationale. *Front*
578 *Med* [Internet]. 2020 Sep 2 [cited 2021 Jan 2];7:440. Available from:
579 </pmc/articles/PMC7492535/?report=abstract>
- 580 13. Wang MD, Ji Y, Xu J, Jiang DH, Luo L, Huang SW. Early goal-directed fluid therapy
581 with fresh frozen plasma reduces severe acute pancreatitis mortality in the intensive
582 care unit. *Chin Med J (Engl)*. 2013;126(10):1987–8.
- 583 14. Mao EQ, Fei J, Peng YB, Huang J, Tang YQ, Zhang SD. Rapid hemodilution is
584 associated with increased sepsis and mortality among patients with severe acute
585 pancreatitis. *Chin Med J (Engl)*. 2010;123(13):1639–44.
- 586 15. Mao EQ, Tang YQ, Fei J, Qin S, Wu J, Li L, et al. Fluid therapy for severe acute
587 pancreatitis in acute response stage. *Chin Med J (Engl)*. 2009;122(2):169–73.
- 588 16. Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwendigela D, et al. Early Aggressive
589 Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis. *Am J*
590 *Gastroenterol* [Internet]. 2017 May 1 [cited 2021 Jan 2];112(5):797–803. Available

- 591 from: <http://journals.lww.com/00000434-201705000-00027>
- 592 17. Dunham CM, Chirichella TJ, Gruber BS, Ferrari JP, Martin JA, Luchs BA, et al.
593 Emergency department noninvasive (NICOM) cardiac outputs are associated with
594 trauma activation, patient injury severity and host conditions and mortality. *J Trauma*
595 *Acute Care Surg.* 2012;73(2):479–85.
- 596 18. Fisher JM, Gardner TB. The “Golden Hours” of Management in Acute Pancreatitis.
597 *Am J Gastroenterol* [Internet]. 2012 Aug 3 [cited 2018 Oct 11];107(8):1146–50.
598 Available from: <http://www.nature.com/articles/ajg201291>
- 599 19. Froghi F, Soggiu F, Ricciardi F, Gurusamy K, Martin DS, Singh J, et al. Ward-based
600 Goal-Directed Fluid Therapy (GDFT) in Acute Pancreatitis (GAP) trial: Study protocol
601 for a feasibility randomised controlled trial. *BMJ Open.* 2019;9(10).
- 602 20. Chan A-W, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT
603 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*
604 [Internet]. 2013 Jan 9 [cited 2016 Oct 25];346(jan08 15):e7586–e7586. Available
605 from: <http://www.ncbi.nlm.nih.gov/pubmed/23303884>
- 606 21. Tenner S, Baillie J, Dewitt J, Vege SS. American college of gastroenterology
607 guideline: Management of acute pancreatitis. *Am J Gastroenterol.* 2013;108(9):1400–
608 15.
- 609 22. Good Clinical Practice (GCP) [Internet]. [cited 2018 Sep 14]. Available from:
610 [https://www.nihr.ac.uk/our-faculty/clinical-research-staff/learning-and-](https://www.nihr.ac.uk/our-faculty/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/)
611 [development/national-directory/good-clinical-practice/](https://www.nihr.ac.uk/our-faculty/clinical-research-staff/learning-and-development/national-directory/good-clinical-practice/)
- 612 23. Blamey SL, Imrie CW, O ’neill J, Gilmour WH, Carter DC. Prognostic factors in acute
613 pancreatitis. *Gut* [Internet]. 1984 [cited 2018 Apr 12];25:1340–6. Available from:
614 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1420197/pdf/gut00397-0014.pdf>
- 615 24. Marshall JC, Cook DJ, Christou N V., Bernard GR, Sprung CL, Sibbald WJ. Multiple
616 organ dysfunction score: A reliable descriptor of a complex clinical outcome [Internet].
617 Vol. 23, *Critical Care Medicine.* *Crit Care Med;* 1995 [cited 2020 Dec 19]. p. 1638–52.
618 Available from: <https://pubmed.ncbi.nlm.nih.gov/7587228/>

- 619 25. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al.
620 Classification of acute pancreatitis - 2012: Revision of the Atlanta classification and
621 definitions by international consensus. *Gut* [Internet]. 2013 Jan 1 [cited 2020 Dec
622 19];62(1):102–11. Available from: <http://dx.doi.org/10.1136/gutjnl-2012-302779>
- 623 26. Öztekin Long, Nicole, M and Badre D. Pao₂ Fio₂ Derivation. *Bone* [Internet].
624 2008;23(1):1–7. Available from:
625 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf>
- 626 27. The EuroQol Group. EuroQol - a new facility for the measurement of health-related
627 quality of life. *Health Policy (New York)* [Internet]. 1990 [cited 2021 Jun 7];16(3):199–
628 208. Available from: <https://pubmed.ncbi.nlm.nih.gov/10109801/>
- 629 28. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap
630 consortium: Building an international community of software platform partners. Vol.
631 95, *Journal of Biomedical Informatics*. Academic Press Inc.; 2019. p. 103208.
- 632 29. Mounzer R, Langmead CJ, Wu BU, Evans AC, Bishehsari F, Muddana V, et al.
633 Comparison of Existing Clinical Scoring Systems to Predict Persistent Organ Failure
634 in Patients With Acute Pancreatitis. *Gastroenterology* [Internet]. 2012 Jun [cited 2018
635 Apr 12];142(7):1476–82. Available from:
636 <http://www.ncbi.nlm.nih.gov/pubmed/22425589>
- 637 30. Aggarwal A, Manrai M, Kochhar R. Fluid resuscitation in acute pancreatitis. *World J*
638 *Gastroenterol* [Internet]. 2014 Dec 28 [cited 2018 Sep 15];20(48):18092–103.
639 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25561779>
- 640 31. Myburgh JA, Mythen MG. Resuscitation Fluids. *N Engl J Med* [Internet]. 2013 Sep 26
641 [cited 2016 Dec 2];13369(26):1243–51. Available from:
642 <http://www.nejm.org/doi/abs/10.1056/NEJMra1208627>
- 643 32. Davies SJ, Minhas S, Wilson RJT, Yates D, Howell SJ. Comparison of stroke volume
644 and fluid responsiveness measurements in commonly used technologies for goal-
645 directed therapy. *J Clin Anesth*. 2013;25(6):466–74.
- 646 33. Neoptolemos JP, Raraty M, Finch M, Sutton R. Acute pancreatitis: The substantial

- 647 human and financial costs [Internet]. Vol. 42, Gut. 1998. p. 886–91. Available from:
648 <http://gut.bmj.com/>
- 649 34. Kahan BC, Rushton H, Morris TP, Daniel RM. A comparison of methods to adjust for
650 continuous covariates in the analysis of randomised trials. BMC Med Res Methodol
651 [Internet]. 2016 Apr 11 [cited 2021 Jul 12];16(1). Available from:
652 <https://pubmed.ncbi.nlm.nih.gov/27068456/>
- 653 35. Wadhwa V, Patwardhan S, Garg SK, Jobanputra Y, Lopez R, Sanaka MR. Health
654 care utilization and costs associated with acute pancreatitis. Pancreas [Internet]. 2017
655 Mar 1 [cited 2021 Jan 7];46(3):410–5. Available from:
656 <https://journals.lww.com/00006676-201703000-00019>
- 657 36. Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ, Camargo CA. Direct
658 Medical Costs of Acute Pancreatitis Hospitalizations in the United States. Pancreas
659 [Internet]. 2007 Nov [cited 2021 Jan 8];35(4):302–7. Available from:
660 <http://journals.lww.com/00006676-200711000-00002>
- 661 37. Andersson B, Appelgren B, Sjödin V, Ansari D, Nilsson J, Persson U, et al. Acute
662 pancreatitis - Costs for healthcare and loss of production. Scand J Gastroenterol
663 [Internet]. 2013 [cited 2021 Jan 8];48(12):1459–65. Available from:
664 <https://www.tandfonline.com/doi/abs/10.3109/00365521.2013.843201>
665
666

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 (SpO₂) 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.