

# BMJ Open Prospective multicentre randomised controlled trial of the effect of Braun Enteroenterostomy in the Reconstruction after Pancreaticoduodenectomy on delayed gastric emptying (DGE): protocol for the BERP study

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## ABSTRACT

**Introduction** Despite advances in achieving low mortality rates with pancreaticoduodenectomy (PD), morbidity remains high. A key contributor to this morbidity is delayed gastric emptying (DGE) occurring with an incidence of up to 30%. The utility of a Braun enteroenterostomy (BE) appears promising to reducing the incidence of DGE, but current research is not definitive.

**Methods and analysis** This project will be designed as a prospective multicentre randomised controlled blinded study to assess how BE effects the rate of DGE after PD in the setting of malignancy, within Australia—with blinding of patients, outcome assessors and data analysts. Patients will be randomly assigned to PD with Billroth II reconstruction with BE versus PD with Billroth II reconstruction without BE. The primary outcome is the incidence of DGE as defined by the International Study Group of Pancreatic Surgery. Secondary outcomes will include length of hospital stay, postoperative pancreatic fistula incidence, development of major complications (Clavien-Dindo $\geq$ 3 a), quality of life and 90-day mortality. The study will be powered at 80% to detect a reduction in DGE rate from 30% to 15%, requiring a total of 264 study participants. An interim analysis will be performed once a total of 104 study participants have been recruited at which point the study will be able to detect reduction in DGE from 30% to 10% with 80% power. Statistical analysis will be done with intention-to-treat principles. The proportion of patients suffering DGE will be compared between treatment arms using a  $\chi^2$  test, with p values used to represent statistical significance.

**Ethics and dissemination** The study has been ethically approved by the Hunter New England Human Research Ethics Committee (2021/ETH11939), with results disseminated through presentation and publication.

**Trial registration number** CTRN12622000048785.

## INTRODUCTION

Pancreaticoduodenectomy (PD) remains the only method to cure a patient who

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Multicentre prospective randomised controlled study.
- ⇒ Patients and outcome assessors will be blinded to surgical allocation.
- ⇒ Unable to blind surgical team.
- ⇒ Practices will vary between sites particularly regarding the use of neoadjuvant cancer therapies and perioperative procedures (eg, enhanced recovery after surgery) in accordance with relevant institutional guidelines, which cannot be controlled but are inherent to multicentre studies.

presents with a periampullary malignancy. With improvement in operative techniques, better patient selection and advances in perioperative management, the mortality rates for these resections has reduced to less than 5% in the modern era, particularly in high volume centres.<sup>1</sup> However, the morbidity from this procedure remains high, with a key contributor to this morbidity being delayed gastric emptying (DGE) occurring with an incidence of upto 30%.<sup>2</sup> DGE is a clinical scenario where the stomach fails to empty well into the small intestine and creates problems with abdominal fullness, nausea and vomiting, and inability establishing an oral diet. Although DGE is not usually life-threatening, it leads to a longer hospital stay with increased hospital costs, and can be extremely frustrating for patients, families and treating clinicians. Higher severity DGE has also been associated with reduced long-term survival, as delays in establishing oral nutrition can delay the commencement of adjuvant therapies.<sup>3</sup>



Much of the aetiology for DGE post PD relates to the development of post-operative complications, including postoperative pancreatic fistula (POPF), biliary leak, post-operative haemorrhage and intra-abdominal abscess.<sup>4-7</sup> As such, the most important steps in preventing DGE is the minimisation of these complications, including their early identification and treatment. However, even with these complications accounted for, there is an excess level of DGE that still occurs. Other factors thought to contribute to DGE after PD include reduced motilin secretion after duodenal resection, effects from devascularisation and denervation particularly with extensive lymph node resection in cancer surgery, and the type of resection/reconstruction performed.<sup>8,9</sup> Nevertheless, the development of DGE postoperatively should concern the clinician of the development of an intra-abdominal complication.

Recently, some surgeons have been incorporating a Braun enteroenterostomy (BE) in those who receive a Billroth II reconstruction in an attempt to reduce the DGE incidence. The BE requires the surgeon to take a segment of jejunum proximal (afferent) to the gastrojejunostomy (GJ) and perform a side-to-side anastomosis to a segment distal (efferent) to the GJ. Theoretically, oral intake that may pass into the afferent limb of the GJ does not need to return back to the stomach as the BE provides an alternative track for food to travel into the distal small intestine. Furthermore, the BE allows some biliary and pancreatic secretions to bypass the stomach, potentially reducing symptoms related to bile reflux. BE may also stabilise the afferent and efferent limbs of the GJ preventing angulation or twisting of the GJ. It can also reduce tension on the GJ. These ideas all contribute to the theory how BE could reduce the incidence of DGE after PD.

The literature looking at BE and its ability in reducing DGE incidence is of varied quality with small sample sizes.<sup>10</sup> Initial work was observational showing BE could reduce DGE, however, three randomised controlled trials (RCTs) that followed struggled to replicate these results.<sup>11-13</sup> These RCTs were powered to detect a larger than observed difference and with their small sizes and were likely underpowered as a result. More recently, Zhou *et al* performed a meta-analysis incorporating these RCTs as well as previous observational studies.<sup>14</sup> Although their pooled data reached statistical significance in the BE group being able to reduce DGE incidence (OR 0.32, 95% CI 0.24 to 0.43,  $p < 0.001$ ), of the 1604 study participants, only 158 came from RCTs. Considering this bias towards the non-RCTs in Zhou *et al*'s analysis, it is difficult to make recommendations for widespread BE use in the reconstruction in PD.

This paper outlines a protocol for a prospective randomised controlled trial with adequate power with the objective to determine whether introducing BE in the reconstruction after PD will reduce the rate of postoperative DGE in the setting of malignancy. We hope to provide useful data for surgeons so they are able to make better

informed decisions when introducing BE into their usual practice.

## METHODS AND ANALYSIS

This project will be designed as a multicentre randomised controlled patient blinded superiority trial with 1:1 allocation across high volume pancreatic surgery centres in Australia (defined as centres who do at least nine PDs per year).<sup>15</sup> Planned recruitment dates are from May 2022 to May 2025. It has been registered with the Australian New Zealand Clinical Trials Registry (Registration Number ACTRN12622000048785). The study will be conducted in consecutive adults undergoing planned Whipple PD with antecolic Billroth II reconstruction in the setting of malignancy involving the stomach, duodenum, pancreas or bile duct. Patients will be randomised to:

- ▶ Whipple PD with antecolic Billroth II reconstruction with BE (interventional group).
- ▶ Whipple PD with antecolic Billroth II reconstruction without BE (control group).

Participants will be identified through the multidisciplinary team meeting, outpatient clinic or acutely through emergency/inpatients. Patients who fulfil the inclusion and exclusion criteria for the study will then be offered to participate, at which point written informed consent will be taken by one of the study investigators. Baseline characteristics will be taken if the participant wishes to join the study. Patients will be randomised to having BE or not intraoperatively once the surgeon is able to confirm that the patient has resectable disease. Patients will be randomly assigned to either control or interventional group with a 1:1 allocation using a stratified (by site) permuted computer-generated block randomisation schedule through the Hunter Medical Research Institute. Allocation concealment will be ensured as the computer generated randomisation will not be performed until resectability is confirmed intraoperatively for consented study participants. Patients will be blinded to the allocation received, however the surgical team providing postoperative care will be aware of the procedure allocation. Patients will be recruited at centres within Australia, with stratification done by site to minimise confounders between variations in perioperative protocols in different sites.

Postoperative outcomes will be taken on postoperative day 1, as well as days 8, 15 and 22 as these three time points represent important stages relating to the classification of DGE severity, as defined by the International Study Group for Pancreatic Surgery (see below). A final review will be taken on postoperative day 90 to complete collection of all outcome measures at which point patients will be unblinded from their allocation. All required study outcomes will be taken by a blinded outcome assessor who is a member of the research team and is unaware of the whether the study participant received the BE or not. Outcome assessors will be unblinded once data collection is complete for the study participant on day 90. **Table 1**

**Table 1** Timeline of study participants

	MDT	Outpatient clinic	Emergency/inpatient	Day of surgery	POD 1	POD 8	POD 15	POD 22	POD 30	POD 90
Screening for eligibility	✓	✓	✓							
Informed Consent		✓	✓							
Baseline Characteristics		✓	✓							
Randomisation				✓						
Intraoperative variables				✓						
Postoperative outcomes					✓	✓	✓	✓		✓
Allocation unblinding										✓
Quality of Life score		✓		✓(done prior to surgery if not already done)					✓	✓

MDT, multidisciplinary team ; POD, postoperative day.

presents the timeline for study participants. All data will be entered electronically through password protected accounts on REDCap. All personal information will be kept confidential with REDCap through coded identification numbers, with physical participant information records kept in locked file cabinets. Data analysts will also be blinded to the surgical allocation.

### Patient and public involvement

Patients or the public were not involved in the design of this project.

### Inclusion criteria

Patients who will be included in this study will need to fulfil the below criteria.

- ▶ Any adult patient undergoing Whipple PD with planned antecolic Billroth II style reconstruction in the setting of malignancy.
- ▶ Planned open or minimally invasive approach.
- ▶ Participant able to provide informed consent to enter the study.

### Exclusion criteria

The following will be exclusion criteria for this study:

- ▶ Any procedure involving total pancreatectomy.
- ▶ Roux-en-Y reconstruction.
- ▶ Pancreatico-gastrostomy anastomosis.
- ▶ Age <18 years.
- ▶ Previous diagnosis of gastroparesis.
- ▶ Known preoperative glycated haemoglobin (HbA1C)>7.5%.
- ▶ Benign pathologies.
- ▶ Redo surgery.
- ▶ Those who have previously had major upper gastrointestinal procedures.
- ▶ Participants in another trial that might alter the outcome measures of this trial.
- ▶ Inability to provide informed consent or expected lack of compliance with postoperative regimen.

### Collected variables

Collected baseline variables will be age, sex at birth, body mass index (BMI), diabetic control via HbA1C, whether the patient had any neoadjuvant therapies, severity of gastric outlet obstruction for those who present in this manner (using the gastric outlet obstruction scoring system) and nutritional status assessed with the Controlling Nutritional Status (CONUT) score. Collected intraoperative variables include pancreatic gland texture (firm or soft), pancreatic duct diameter and intraoperative blood loss. Postoperatively, the final histopathology will be recorded along with the cancer stage using the conventional tumour-node-metastasis format. The surgeon who performed the procedure will also be recorded within our study database.

### Outcome measures

The primary outcome of this study will be incidence of DGE as defined by the International Study Group of Pancreatic Surgery (ISGPS).<sup>8</sup> DGE is defined with three different grades by the ISGPS.

- ▶ Grade A—Nasogastric intubation lasting more than three postoperative days, or the inability to tolerate a solid diet by postoperative day 7.
- ▶ Grade B—Nasogastric intubation lasting for 8–14 days, the need for reinsertion of the nasogastric tube (NGT) after 7 days, or the inability to tolerate a solid diet by postoperative day 14.
- ▶ Grade C—Nasogastric intubation lasting more than 14 days, the need for nasogastric reinsertion after 14 days, or the inability to tolerate a solid diet by postoperative day 21.

Secondary outcomes include:

- ▶ Time to first solid meal (days).
- ▶ Time until nasogastric removed (days).
- ▶ Time to first passage of wind (days).
- ▶ Presence of afferent loop syndrome (proportion).
- ▶ Use of parental nutrition (yes/no).



- ▶ Proportion of clinically significant DGE (defined as the total of grade B DGE+grade C DGE).
- ▶ Length of stay (days) (including first day documented 'ready for rehab').
- ▶ Postoperative pancreatic fistula incidence (ISGPS definition).<sup>16</sup>
- ▶ Proportion of Major Complications defined Clavien-Dindo classification  $\geq 3$  a.
- ▶ Ninety-day mortality.
- ▶ Quality of Life Score using questionnaires from the European Organisation for Research and Treatment of Cancer. The questionnaires used are the Quality of Life Questionnaire for Cancer patients and the Pancreatic Supplement, both of which have been validated in the setting of pancreatic cancer and PD.<sup>17-19</sup> These questionnaires will be done preoperatively, at 30 days postoperative and 90 days postoperative.

### Adverse events

PD carries significant risks to the patient associated with anaesthesia and the operation itself. Adverse events will be defined in this study as an unintended and potentially harmful occurrence (physical or psychological) that occurs to the patient after being randomised within this study including. Adverse events will be recorded for both interventional and control groups being monitored by the data monitoring committee (DMC) (see below).

### Operative specifics

Certain operative specifics will be required for patient recruitment within the study.

- ▶ The stomach resection will include the pylorus and the gastric antrum.
- ▶ The GJ and BE can be stapled or hand sewn, but each anastomosis must be a minimum of 60 mm in diameter.
- ▶ Antecolic reconstruction is overwhelmingly preferred unless the small bowel does not physically reach the gastric remnant via this route.
- ▶ Small bowel length between stomach and BE to be 20–30 cm.
- ▶ Small bowel length between hepatojejunostomy and BE to be 40–60 cm.

We have created a video that describes in detail these relevant operative specifics for circulation between the pancreatic surgeons involved in this trial.

### Postoperative management

Postoperatively, erythromycin 250 mg three times per day intravenously will be instituted in all patients from the first postoperative day as this has been shown to reduce DGE.<sup>20</sup> It will be converted to oral dosing when the patient is tolerating solid diet. It will be ceased on discharge or by 2 weeks. The NGT will be removed routinely by day 1 for all patients if the output in the preceding 24 hours is less than 100 mL and patients will be commenced on clear fluids orally, unless there are concerns from the operating team that this is unsafe to do so. Pureed diet will

be defined as the start of solid diet, and will be advised to be commenced as soon as the treating team see fit. If the patient postoperatively is displaying signs of DGE, through vomiting or inability to tolerate any oral diet with discomfort from abdominal distension then an NGT will be inserted at the discretion of the treating team. The remainder of postoperative care will be in accordance to local protocols, including provision of intravenous therapy, methods of regional and postoperative anaesthesia, removal of urinary catheters, abdominal drains and provision of venous thromboembolism prophylaxis.

### Statistical analysis

The current baseline DGE incidence with standard Billroth II reconstruction is approximately 30%.<sup>21</sup> Literature suggests that BE could reduce DGE rates to somewhere between 10% and 15%.<sup>14</sup> Assuming a DGE incidence rate of 30% in the control group, a sample size of 120 per arm will power the study at 80% to detect a DGE incidence of 15% in the intervention group (using a one-sided alpha of 0.025). Allowing for a 10% drop-out, 132 patients in each group would need to be randomised. We have elected to use a one-sided test as repeated research has shown BE does not increase the incidence of DGE.

An interim analysis will be conducted after outcome data are available for 104 patients, which will power the study at 80% to detect a drop in incidence of DGE from 30% to 10% between the control and interventional groups (using one-sided alpha at 0.025). The purpose of the interim analyses will be to assess futility or superiority. The trial will be considered to stop for futility if the conditional power of rejecting the null hypotheses at the final analysis is less than 20%. The trial will be considered to stop for superiority if the one sided p-value testing the null hypothesis that the DGE incidence rates are the same in both groups using a chi-square test is less than 0.025.

Patients will remain in their allocated arm (ie, intention to treat) as specified through randomisation for the purposes of statistical analysis. If a patient is randomised to receive a Billroth II reconstruction with BE (interventional group), but due to intraoperative circumstances BE is not done, these patients will remain in the BE group for the purposes of statistical analysis in accordance with intention-to-treat principles. Those patients who are randomised into the study, but intraoperatively the surgeon changes their mind and performs a reconstruction apart from Billroth II (eg, Roux-En-Y), will be excluded from the study as per the trial's Inclusion and Exclusion criteria. Reasons for changing the predetermined reconstruction will be noted, and reviewed throughout the study. If a patient is randomised into the study but is found to have unresectable disease and so does not receive a PD, then these patients will also be excluded as per the trial's Inclusion and Exclusion criteria. Those patients who were initially considered for the study, but do not end up having surgery (eg, due to disease progression) during neoadjuvant chemotherapy will not be randomised.

Characteristics of the groups at baseline will be summarised by treatment arm. The proportion of patients suffering DGE will be compared between treatment arms using a  $\chi^2$  test. Binary secondary outcomes will be compared between groups using the same method, continuous outcomes measured at a single time point will be compared between groups using an independent sample t-test, and those measured at multiple time points will be compared between groups at each time point using least square mean differences obtained from a linear mixed effects regression model (random intercept for each patient).

### Data monitoring

Analysis of adverse events that occur during the duration of the trial will require expert review via a DMC. The DMC will be independent of the study organisers and use the expertise of peers in the field. During the period of recruitment to the study, interim analyses will be supplied to the DMC. The DMC will advise the trial steering committee if:

- ▶ The active intervention has been proven, beyond reasonable doubt, to be different from the control for all or some types of participants.
- ▶ The evidence on outcomes is sufficient to guide decision from healthcare providers regarding recommendation of usage of BE with GJ in the setting of upper gastrointestinal malignancy.
- ▶ Patient recruitment is not sufficient and the trial period may need to be extended.
- ▶ The risk of continuing the trial is too great.

The trial steering committee can then decide on whether the study should continue, be terminated early or extended further.

Quality assurance of recorded data will be done by the Hunter Surgical Clinical Research Unit (HSCRU). Monitoring will include centralised review of electronic case report forms (eCRFs) and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include virtual monitoring with investigational sites for source data verification and review of the investigator's site file. The HSCRU will be given direct access to source documents, eCRFs and other study-related documents. The principal investigators will have access to all data through RedCAP for data analysis.

Participant retention will be a key focus for study investigators with periodic contact through phone-call and/or email. In the event these contact details change, participants will be contacted through their next of kin, general practitioners or other specialist healthcare providers. Participants may withdraw from the study at any time, and if so, participants will be asked if they would like all their data removed, or whether they allow data upto until their decision to withdraw to be included. Feedback will be requested from participants who have decided to withdraw to improve ongoing participant retention within this study.

### Ethics and dissemination

The study has been ethically approved the Hunter New England Human Research Ethics Committee (2021/ETH11939). Any modifications of the protocol which may impact on the conduct of the study including changes in study objectives, study design, sample size calculation, surgical procedures or significant administrative aspects will require formal amendment to the protocol with re-approval from the New England Human Research Ethics Committee. Once completed, the data will be analysed and disseminated through publication.

**Contributors** SG conducted the literature review, designed the protocol along with its formal write-up. SG is the corresponding author and the guarantor. KB, DB and MN conceptualised the research idea and provided expert guidance for the research protocol. NL and RC provided research support and assisted with requirements for ethics submission. All authors contributed to refinement of the study protocol and approved the final manuscript.

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**Disclaimer** The ultimate design of the study including its execution, analysis, interpretation of data or decision to submit results will be determined by the relevant authors, not by the funding source.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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