TRIAL PROTOCOL

Timing Of Nutrition In emergenCy laparotomy

TONIC

A randomised trial comparing early parenteral nutrition vs standard nutritional care in adults undergoing emergency laparotomy.

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2025)

Version Number: 1.0

Version Date: 13-NOV-2025

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

Funding and support in kind

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The funder of the trial will have no role in the trial design, data collection, data analysis or data interpretation, or in the writing of the final report; and the decision to submit the report for publication.

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as stated in this and any subsequent approved protocol will be explained.

Trial name:	TONIC Trial
Protocol version number:	Version: 1 0
Protocol version date:	13-NOV-2025
CI name:	Mr Matthew Lee
Signature and date:	_____ __ __/__ __ __/__ __ __ __

Sponsor statement

By signing the IRAS form for this trial, the University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the TONIC trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the TONIC trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031), Mental Capacity Act 2005; and subsequent amendments thereof.

Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name:	TONIC Trial
Protocol version number:	Version: 1.0
Protocol version date:	13-NOV-2025
PI name:	
Name of Site:	
Signature and date:	_____ __ __/__ __ __/__ __ __ __

ADMINISTRATIVE INFORMATION

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BCTU	Birmingham Clinical Trials Unit
BHP	Birmingham Health Partners
CACE	Complier-adjusted causal effect
CCI	Comprehensive Complication Index
CDC	Clavien Dindo Classification
CI	Chief Investigator
CRF	Case Report Form
CT	Computerised Tomography
CVC	Central Venous Catheter
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSA	Data Sharing Agreement
eCRF	electronic Case Report Forms
EDC	Electronic Data Capture
EQ-5D-5L	EuroQoL-5D-5L
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICU	Intensive Care Unit
IQR	Inter-quartile range
ISF	Investigator Site File

Abbreviation	Term
MUST	Malnutrition Universal Screening Tool
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NELA	National Emergency Laparotomy Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRS-2002	Nutrition Risk Screening
OR	Odds Ratio
PI	Principal Investigator
PICC	Peripherally Inserted Central Cannula
PIS	Participant Information Sheet
PN	Parenteral Nutrition
PPI	Patient and Public Involvement
PRO-diGI	Patient Reported Outcomes of GastroIntestinal recovery
PROMs	Patient-Reported Outcome Measures
QALY	Quality-Adjusted Life Year
QoR-15	Surgical Quality of Recovery-15
RAG	Red Amber Green
RCT	Randomised Controlled Trial
RDN	Research Delivery Network
REC	Research Ethics Committee
RGT	Research Governance Team
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoECAT	Schedule of Events Cost Attribution Template

Abbreviation	Term
SSI	Surgical Site Infection
TMF	Trial Master File
TMG	Trial Management Group
TPN	Total Parenteral Nutrition
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Birmingham
VAS	Visual Analog Scale

TRIAL SUMMARY

Title

Timing of Nutrition in Emergency Laparotomy (TONIC)

Objective

The primary clinical objective is to determine whether early parenteral nutrition (PN) in patients undergoing emergency laparotomy/laparoscopy reduces in hospital complications as compared to usual nutritional care.

Trial design

A multi-centre, two arm, parallel group, superiority, pragmatic randomised controlled clinical trial, with an internal pilot to assess feasibility and full economic evaluation to assess cost-effectiveness.

Participant population and sample size

Adult patients aged 18 years or older undergoing National Emergency Laparotomy Audit (NELA) eligible emergency laparotomy/laparoscopy. To detect a 6 point difference in the Comprehensive Complication Index (CCI) score of in hospital complications assessed at discharge, allowing a 5% attrition rate, a sample size of 898 participants (449 in each arm) are required to achieve 90% power.

Setting

Approximately 25 UK-wide NHS hospitals providing emergency surgical services, which have a nutritional support team.

Eligibility criteria

➢ Inclusion criteria

- Aged ≥18 years
- Scheduled for NELA eligible expedited, urgent or immediate emergency laparotomy or laparoscopy according to National Confidential Enquiry into Patient Outcome and Death (NCEPOD) criteria
- Able to give informed consent, with interpreters where necessary OR personal consultee/legal representative provides assent/consent if a patient temporarily lacks capacity

➢ Exclusion criteria

- Undergoing trauma-related laparotomy or laparoscopy
- Being treated with palliative/end of life intent
- Abdominal surgery in the preceding 30 days
- On long term PN prior to admission

Intervention and Comparator

The intervention is early PN started within 48 hours of emergency laparotomy or laparoscopy. The control arm is standard nutritional care which can include a combination of oral nutritional supplements, nasoenteric feed, or no additional nutritional support. PN is permitted in the control arm, but should not be started before five days after surgery, unless otherwise indicated, in line with NICE guidance.

Outcome measures

➢ Primary Outcome

- In-hospital complications assessed at point of hospital discharge, assessed using the Comprehensive Complication Index (CCI)

➢ Secondary outcomes

Clinical outcomes (all related to index surgery only)

- Number and severity of complications at 30 and 90 days post-operation, assessed using the CCI
- Number and severity of complications (respiratory, cardiovascular, surgical site infection (SSI), reoperation), including mortality measured using the Clavien Dindo Classification (CDC) System at 30 and 90 days
- Sit to stand test at discharge
- Number and severity of infectious complications (SSI, vascular line infection, hospital acquired pneumonia, urinary tract infection, all defined according to the CDC), assessed in hospital, prior to discharge
- Length of post-operative hospital stay (in nights following operation)
- Assess the impact of early PN on unplanned readmissions following discharge up to 90 days after operation
- Discharge destination (usual residence, residential, or nursing home)
- Use and duration of PN and total calories administered post-operatively, recorded for each arm at discharge

- Use of other nutritional interventions (Oral Nutritional Supplements), recorded for each arm prior to discharge
- Process metrics:
  - Time from randomisation to line insertion (hours)
  - Time from operation to starting PN (hours)
- Barthel index of function (including activities of daily living) completed at discharge, 30 and 90 days post-operation

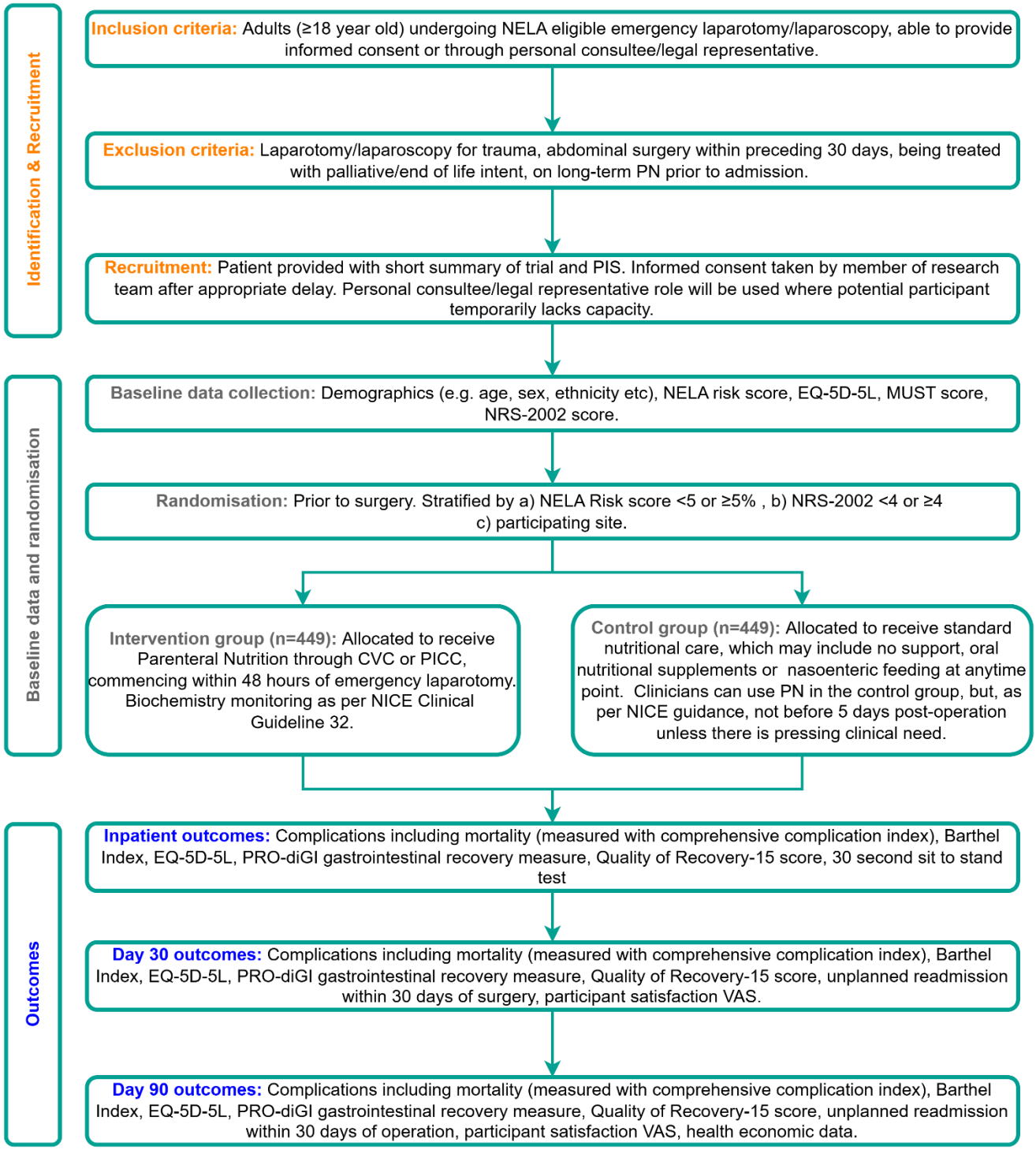
Patient reported outcomes

- Recovery using the Surgical Quality of Recovery-15 (QoR-15) on discharge, 30 and 90 days post-operation
- EuroQoL-5D-5L (EQ-5D-5L) on discharge, 30 and 90 days post-operation
- Gastrointestinal recovery (PRO-diGI) on discharge, 30 and 90 days post-operation
- Assessment of patient treatment satisfaction using a visual analogue scale 30 and 90 days post-operation

Health economic analysis

A cost-effectiveness analysis using individual patient data will be undertaken from the NHS and personal social service perspective, with a 90 day timeframe.

TRIAL SCHEMA



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1. BACKGROUND AND RATIONALE

1.1 Background

Around 21,000 people undergo major emergency abdominal surgery each year in England and Wales[1]. Emergency laparotomy involves an incision in the centre of the abdomen to provide access to abdominal organs and is used to treat intra-abdominal sepsis, perforated viscus, obstruction, and ischaemia. These conditions have high morbidity (up to 47%[2]) and mortality (between 9-18%) rates[3]. Work by the National Emergency Laparotomy Audit (NELA) has improved outcomes in emergency laparotomy, through early commencement of antibiotics, early Computerised Tomography (CT) scanning for diagnosis, timely intervention with consultant input, and stratified use of intensive care beds. This has reduced 90 day mortality for the whole emergency population from 15% to 9.6%[1]. However, the 9.6% mortality rate represents a plateau, with no improvement since 2021, suggesting that current approaches may have reached their maximum benefit. Therefore, we need to change other aspects of the treatment pathway by introducing new interventions.

A good candidate intervention would be one that is widely available, with common processes to deliver, and a known risk profile. One such intervention is parenteral nutrition (PN), which is a method of delivering nutrition intravenously. This bypasses a non-functioning gut (common in emergency surgical conditions), to directly deliver nutrients via blood, and does not rely on patient appetite to ensure delivery of calories and nutrients[4]. PN is often delivered following emergency laparotomy[5, 6]; as patients struggle to meet nutritional requirements through enteral routes following surgery, with frequent interruptions[7]. Pilot work also shows that patients spend an average of seven days without enteral nutrition prior to emergency laparotomy[8]. This exacerbates malnutrition, which affects 30% of patients on admission to hospital [9], and 20-30% will see their nutritional status deteriorate during their admission[10]. Malnutrition causes impaired wound healing, poor immune function[11], and higher rates of complications and death after surgery[12].

Evidence for nutritional intervention in the hospital setting is varied. A large randomised controlled trial (RCT) which tailored enteral nutritional support to medical patients showed a significant reduction in adverse events (AE) ([Odds Ratio (OR)] 0·79 [95% Confidence Interval 0·64–0·97]) and 30-day mortality (OR 0·65 [0·47–0·91])[13]. This trial randomised 2088 patients to receive either standard nutritional care (regular hospital meals), or to receive tailored nutritional interventions. In 91% of cases in the intervention arm, patients received oral nutritional supplements; 12/1015 received PN. This RCT demonstrates two relevant findings. First, it is possible to deliver a pragmatic nutritional multi-centre study. Second, it is possible that acute nutritional intervention can change clinical outcomes in hospitalised patients.

Large randomised trials of early versus late PN in critical care populations have shown early intervention reduced days on ventilation and time in intensive care, but not length of stay[14]. These trials are largely mixed populations and lack clear subgroup reporting to understand the differential impact of nutrition on those with 'medical' or 'surgical' diseases. In addition, the outcomes focused on in these studies may not be patient-centred or directly attributable to PN as an intervention. For example, whilst important for the patient, hospital length of stay may be influenced by non-medical factors such as social care support, or cultural and financial attitudes to discharge. It is therefore a context sensitive process measure and should not inform clinical decisions. The TOP-UP pilot trial compared nasoenteral feeding with and without supplemental PN in the critical care population. Although a pilot trial, this showed a trend towards benefit for surgical patients in terms of mortality, function at intensive care unit (ICU) discharge, and improved quality of life, when supplemental PN was implemented[15]. Our interpretation of this is that existing trials suggest some benefit in early muscle function as evidenced through a reduction in the time ventilatory support was required. Early use of parenteral routes to maximise nutrition intake is feasible in ICU settings and may lead to measurable differences in outcomes at 7 days.

Outside critical care, there are few high-quality nutrition studies for the emergency surgical patient. Our systematic review identified 14 RCTs, of which 10 compared different PN formulations, one explored amino acid supplementation, and three investigated enteral nutrition[16]. These trials had several issues including non-standardised endpoints, single centre designs, and small sample sizes making them prone to type II errors. Comparators were typically between different forms of PN, rather than PN vs standard care or an enteral nutrition strategy, which means the trials provide only incremental gains in knowledge. Finally, we identified several methodological and bias related issues in the conduct of these studies. This indicates that while there is interest among surgeons in early PN for emergency patients, a well-designed RCT is needed.

Given this interest, it is not surprising that trials of peri-operative PN have been undertaken. The three key trials in this field are the Veterans 1991[17], Perineal 2016[18], and Gao 2022 studies[19]. The Veterans Trial randomised 395 patients undergoing elective cancer surgery to pre-operative PN or standard care. This found that infectious complications were reduced in the most severely malnourished group[17]. Perineal compared nasojejunal feed versus Total Parenteral Nutrition (TPN) following pancreaticoduodenectomy. Randomising 204 patients, they found that TPN reduced post-operative complications by 10% and delivered significantly more calories vs the parenteral route. Gao randomised 230 patients at high risk of malnutrition undergoing elective gastrointestinal cancer surgery to early supplemental PN (before day 3) vs delayed supplemental PN (starting on day 8). This reduced rates of nosocomial infection (8.7% vs 18.4%)[19]. These studies all address practice in the elective setting and cannot tell us about the impact of PN on outcomes following emergency laparotomy. Notably, these studies draw on a small sample size, and the fragility index[20] of the latter is 1, showing a non-robust effect in a

small sample size. Guidance on nutritional intervention for the acutely unwell surgical patient is vague; recommending tailoring to the patient, albeit with a recognition that earlier intervention may be beneficial[21, 22].

1.2 Trial rationale

This trial aims to explore the impact of early nutritional supplementation (<48 hours post laparotomy/laparoscopy) versus standard nutritional care following emergency laparotomy/laparoscopy. It is needed because outcomes following emergency laparotomy/laparoscopy have plateaued, necessitating the assessment of new interventions. Previously published studies have examined the impact of nutritional supplementation in acute medical populations[13], and elective surgical populations[15, 17, 18]. The James Lind Alliance has recognised the importance of addressing nutrition early in vulnerable groups[23], and also for interventions to improve outcomes around the time of emergency surgery[24]. Our patient and public involvement (PPI) engagement has highlighted how aware patients are around the lack of food following major emergency surgery, and its consequences such as weight loss, infection, and impaired recovery. Our PPI engagement demonstrates that patients would be willing to have lines placed to allow delivery of PN as a nutritional supplement. No similar trial focused on this patient group has been conducted.

A pragmatic control arm of standard care has been selected. This will include either no intervention, oral nutritional supplementation or nasoenteric feeding where tolerated, or PN delivered at five or more days after laparotomy/laparoscopy, in line with National Institute for Health and Care Excellence (NICE) clinical guideline 32[25, 26]. The trial team considered the use of a placebo intervention, but this was deemed potentially harmful as it could blind teams to volume and composition of fluids received, meaning that electrolyte and other abnormalities would be more common if this approach was used.

1.2.1 Justification for participant population

This trial will recruit adult patients undergoing major emergency abdominal surgery, closely reflecting the population who would receive the intervention in the real world, should a benefit be shown. It also reflects a pragmatic approach to sampling. We have considered issues around inclusivity and will provide translated materials for the two most common languages after English, which are spoken in our study centres. We will ensure ethically approved approaches to recruitment of patients with transient loss of capacity, through personal consultee routes.

1.2.2 Justification for design

A pragmatic RCT is the most appropriate study design to compare the effectiveness of two treatments in routine clinical practice. TONIC is a pragmatic, multi-centre, two-arm, parallel group RCT with an internal pilot to assess feasibility, and a full economic evaluation to assess cost-

effectiveness. The control arm describes standard care. Whilst variable, this is typically a reactive approach, with no interventions in the 48 hours after surgery[8], and often not until day 5 in keeping with NICE guidance[25].

1.2.3 Justification for choice of intervention

Following surgery, the gastrointestinal tract does not function normally, and this dysfunction can extend to seven days post-operatively. This means that nutrition cannot be delivered enterally. Therefore, delivering intravenously using PN is the feasible mode of delivery. This is a well-established intervention already used in this patient group. The timing of this intervention is being brought forward to within 48 hours of laparotomy/laparoscopy for this trial. There are several manufacturers of PN, and sites will have processes specific to each product. To be pragmatic, we are allowing sites to use their preferred product.

The control arm reflects standard nutritional care. This may be a period of starvation followed by resumption of gut function and feeding, early nasoenteric feeding, and/or oral nutritional supplements. These methods are used variably and reactively. Clinicians can also use PN in the control group, but, as per NICE guidance, not before 5 days post-operation, unless there is pressing clinical need e.g. emergency reintervention, unplanned escalation to intensive care, development of enterocutaneous fistula.

1.2.4 Justification of choice of primary outcome

The primary outcome was selected following focus groups with patients and clinicians, and a review of the literature[27]. The outcome most likely to be affected in the short term by the intervention is post-surgical complications, based upon clinical experience, supporting data from the national audit of small bowel obstruction[28], and the 2019 Schuetz trial[13]. This will be measured using the Comprehensive Complication Index (CCI)[29].

The CCI is based on the conventional Clavien-Dindo classification (CDC) which has been widely used in surgical research[29]. The CCI is the mathematical summation of complications graded using the conventional CDC and takes into account the number and severity of each complication to obtain a value from 0 (no complications) to 100 (death). As all post-operative complications are included, it is more sensitive than other surgical morbidity endpoints.

This score allows for repeated complications during an admission, and not simply the worst complication. This means that several minor complications can give a higher score than a single bad complication. The nuance afforded by this score increases the likelihood of detecting differences between groups.

The day of discharge has been selected as the time to assess for in-hospital complications (primary outcome). This is a plausible timepoint to assess the effect of the intervention, and will allow us to accurately collect data on complications. The common complications where we anticipate the effect of the intervention are in wound healing and infection, including both wound and respiratory infections. Complications occurring after discharge are temporally distant from the intervention and therefore less attributable to this. Ascertainment of complications at 30 and 90 days is also increasingly challenging, and so data might be unreliable.

2. AIMS AND OBJECTIVES

Aims

To investigate the clinical and cost effectiveness of early PN in the prevention of complications following emergency laparotomy or laparoscopy.

Objectives

- An RCT powered to test the hypothesis that early PN can reduce in hospital complications measured using the CCI, by 6 points at hospital discharge when compared to usual nutritional care in patients undergoing emergency laparotomy/laparoscopy
- An economic evaluation alongside a clinical trial with cost effectiveness modelling of a lifetime horizon, including perspectives from the National Health Service (NHS) and society

2.1 Internal pilot objectives

The trial includes a 6 month internal pilot phase, which will inform any decision on the continuation of the trial to complete recruitment as planned. The aims of the internal pilot are to assess:

- Recruitment rate (number and rate of participants recruited based on open centres)
- Data completeness for the primary outcome
- Return rate for the 90 day questionnaires
- Intervention delivery within 48 hours
- Cross-over rates between arms

Section 8.1 details the criteria that will determine continuation of the trial beyond the pilot phase.

2.2 Main trial objectives

2.2.1 Clinical aims and objectives

Primary Objective

The primary clinical objective is to determine whether early PN in patients undergoing emergency laparotomy/laparoscopy reduces in hospital post-operative complications assessed at hospital discharge as compared to usual nutritional care when measured using the CCI.

Secondary Objectives

Secondary objectives are to:

- Assess the impact of early PN on post-operative complications up to 90 days post-operation
- Assess the impact of early PN on activities of daily living up to 90 days post-operation
- Assess the impact of early PN on muscle function with sit to stand test at hospital discharge
- Assess the impact of early PN on patient reported outcomes (gastrointestinal recovery (PRO-diGI), quality of recovery (QoR-15)) up to 90 days post-operation
- Assess the rate of SAE related to early PN up to 89 days post-operation
- Assess the impact of early PN on unplanned readmissions following discharge up to 90 days post-operation
- Assess the impact of early PN on hospital length of stay during index admission
- Assess the impact of early PN on discharge destination following index admission
- Assess the impact of early PN on participant satisfaction with treatment
- Report PN use in both arms, including duration and calories administered
- Report use of any nutritional intervention in either trial arm
- Report pathway metrics related to randomisation, line insertion, operation, and time to starting PN.

2.2.2 Economic aims and objectives

Primary Objective

An economic evaluation conducted alongside a clinical trial, assessing cost-effectiveness over a 90 day period from an NHS and personal social service cost perspective.

Secondary Objectives

- Cost-effectiveness over 90 days from an NHS, personal social service and societal cost perspective
- Extrapolation of trial outcomes to establish cost-effectiveness over a lifetime horizon from an NHS cost perspective
- Expected Value of Information analysis to quantify the maximum amount a decision-maker would be willing to pay for eliminating all uncertainty in the economic results.

3. TRIAL DESIGN AND SETTING

3.1 Trial design

The TONIC trial is a multi-centre, two-arm, parallel group, superiority, individual participant-RCT with 1:1 allocation to early PN or standard nutritional care with an internal pilot and a full economic evaluation. Patients undergoing NELA eligible emergency laparotomy or laparoscopy will be randomised to either early PN started within 48 hours of emergency laparotomy/laparoscopy or standard nutritional care.

3.2 Trial setting

The study will be conducted in approximately 25 NHS hospitals across the United Kingdom (UK) providing emergency surgical services, which have a nutritional support team.

3.3 Sub-studies

There are no planned sub-studies.

3.4 Assessment of risk

Participants in both arms will be undergoing emergency laparotomy/laparoscopy as part of their standard medical care. The trial intervention is PN with the main risks relating to changes in blood electrolytes, high blood sugar, liver function changes (cholestasis), and potential infection of the peripherally inserted central catheter (PICC) line. These risks are generally manageable and monitored closely by healthcare professionals to prevent any lasting impact. The risks of PN will be mitigated through regular monitoring and adjustments of blood electrolytes and blood sugar levels, careful management of liver function and strict infection control measures for the PICC line.

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation: No higher than the risk of standard medical care.

4. ELIGIBILITY

4.1 Inclusion criteria

- Adult patients aged 18 years and over
- Scheduled for NELA eligible expedited, urgent or immediate emergency laparotomy or laparoscopy according to National Confidential Enquiry into Patient Outcome and Death NCEPOD criteria (see Table 1)
- Able to give informed consent, with interpreters where necessary OR personal consultee (England & Wales)/legal representative (Scotland) provides declaration/consent if a patient temporarily lacks capacity.

Table 1: NCEPOD criteria for urgency of surgery[30]

Term	Definition
Immediate	Immediate life, limb or organ-saving intervention – resuscitation simultaneous with intervention. Normally within minutes of decision to operate. Life-saving Other e.g. limb or organ saving
Urgent	Intervention for acute onset or clinical deterioration of potentially life-threatening conditions, for those conditions that may threaten the survival of limb or organ, for fixation of many fractures and for relief of pain or other distressing symptoms. Normally within hours of decision to operate.
Expedited	Patient requiring early treatment where the condition is not an immediate threat to life, limb or organ survival. Normally within days of decision to operate.

4.2 Exclusion criteria

- Undergoing trauma-related laparotomy or laparoscopy
- Being treated with palliative/end of life intent
- Abdominal surgery in the preceding 30 days.
- On long term PN prior to admission

4.3 Co-enrolment

Co-enrolment is permitted to observational or biomarker studies (non-interventional studies). Co-enrolment in other interventional trials is NOT permitted.

5. CONSENT

The majority of patients undergoing emergency laparotomy or laparoscopy will be able to provide fully informed consent. There are, however, a proportion of patients who meet the inclusion criteria for the study who are either unable to provide full consent or are not able to consent at all due to a temporary impairment resulting from the indication for their emergency laparotomy or laparoscopy. Patients may be unconscious, critically unwell, distracted by pain or anxiety, or have received large doses of opiates for pain relief, potentially affecting their ability to process information. The methods of gaining consent for inclusion in the study are different for patients who are able to provide consent and those who are not. The law around recruitment of patients that lack capacity is governed under the Mental Capacity Act in England and Wales and by Adults with Incapacity (Scotland) Act in Scotland. The terminology within each Act is different and as a result Section 5.3 of this protocol will explain the process for including patients without capacity in England and Wales and Section 5.4 will cover patients in Scotland.

Due to the nature of emergency laparotomy or laparoscopy, the time from the patient being approached for participation in the study and recruitment may be limited. There is therefore no minimum time between the patient (or consultee/representative) being given the information sheet for the trial and consent being obtained. This has been subject to consultation with patient representatives and approved by UK NHS research ethics committees (REC).

5.1 Patients able to provide informed consent

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to performing any trial related procedures. This task can be delegated by the PI to other members of the local research team (e.g. consultants, registrars, associate PI, research nurse), if local practice allows and this responsibility has been documented in the TONIC Site Signature and Delegation Log. All those delegated to take consent must have undertaken Good Clinical Practice (GCP) training.

5.2 Consent procedure (For patients able to provide informed consent)

A Participant Information Sheet (PIS) will be provided to facilitate the consent process. This will be supported by a short animation which covers the information from the PIS. Both the PIS and animation will be available in multiple languages. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the participant. They will also explain that participation is voluntary and that the participant is free to decide to take part and may withdraw from the trial at any time without affecting their care.

The potential participant will be given appropriate time to read the PIS and to discuss their participation with others outside of the site research team. This is flexible as the window to consent is limited by clinical urgency. The median time from admission to surgery for those categorised as needing surgery within 2, 6, and 18 hours is 10, 17, and 34 hours respectively. A flexible approach to recruitment consideration windows has been utilised in other studies (SUNRRISE[31], LaCeS[32]).

The potential participant will be given the opportunity to ask questions before providing consent. If the participant then expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the Informed Consent Form (ICF). The PI or delegate will then sign and date the ICF.

A copy of the ICF will be given to the participant, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, the participant understands and acknowledges that, a copy of the signed ICF will be transferred to the trial team at BCTU for review.

Consent will be obtained to collect contact details and use the participant's preferred contact details, i.e., e-mail address, mobile number, and/or postal address for the purpose of sending participants either online links to complete the electronic questionnaires or hard paper copies depending on what is preferred by the participant.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

5.3 Patients unable to provide informed consent (England and Wales)

Some patients who are eligible for the trial will have a temporary impairment to their ability to provide consent. This impairment will result from the condition for which they require surgical intervention. Patients who have a long-term cognitive impairment that prevents fully informed consent will be excluded from the trial.

If the patient does not have capacity for fully informed consent due to temporary impairment, where possible the trial will be briefly discussed with them, and they will be given the Summary PIS. In accordance with guidelines from the Health Research Authority (HRA), the trial will also be

discussed with the patient's relative or carer (Personal Consultee). The Personal Consultee will be asked if the patient has expressed any prior wishes with regard to participating in research and if the patient has expressed a preference, then this will be adhered to. The relative is not asked to provide consent on behalf of the patient but rather provide an opinion on the views and feelings of the potential participant.

The patient's relative/carer (Personal Consultee) must be:

- Told that they are being asked to advise on the views and feelings they believe the adult would have towards participation in the study
- Told that they are free to decide whether they wish to provide this advice or not
- Given sufficient information, in an understandable form, about the study to ensure that they provide informed advice

A Consultee Information Sheet will be provided to facilitate the assent process. If the consultee agrees that the patient can be included in the trial, the consultee will initial, sign and date the latest version of the Consultee Declaration Form.

If no Personal Consultee is available, the patient will not be included in the trial.

It is imperative that when a Personal Consultee has been consulted, that as soon as the participant is able to provide informed consent, the trial is explained to them and their written informed consent is sought. The participant will be given the PIS for delayed consent and their consent will be documented through the initialling, signing and dating of the latest version of the ICF for delayed consent.

If, at any stage, the participant refuses consent for involvement in the trial or asks to be withdrawn from the trial, their wishes must be adhered to. If the participant does not wish to continue, they will be withdrawn from the trial. Any data collected up to the point of withdrawal will be retained and used in the trial.

For a small number of patients (<2%), it is anticipated that they will not regain consciousness/capacity within 30 days, as these patients will have already received the intervention and reached the primary outcome, their data will be retained for use in the final analysis. If these patients regain capacity after 30 days, where practical, the local research team will consent them for their involvement in the study. In the event that the patient never regains capacity or dies, then they will remain in the trial and their data will be included in the analysis.

5.4 Patients unable to provide informed consent (Scotland)

Some patients who are eligible for the trial will have a temporary impairment to their ability to provide consent. This impairment will result from the condition for which they require surgical intervention. Patients who have a long-term cognitive impairment that prevents fully informed consent will be excluded from the trial.

If the patient does not have capacity for fully informed consent due to temporary impairment, where possible the trial will be briefly discussed with them, and they will be given the Summary PIS. In accordance with guidelines from the HRA, the trial will also be discussed with the patient's Legal Representative. For the purposes of TONIC, a patient's Legal Representative will be their nearest relative (See Appendix 1 for a hierarchical list of nearest relatives). Patients with long-term incapacity are not included in this trial so patients that have appointed a Welfare Attorney or Guardian will not be eligible.

The Legal Representative must be:

- Told that they are being asked to give consent on behalf of the incapacitated adult
- Told that they are free to decide whether they wish to make this decision or not
- Told that they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision
- Given sufficient information, in an understandable form, about the trial to ensure that they can make an informed decision

A Legal Representative (Nearest Relative) Information Sheet will be provided to facilitate the consent process. If the legal representative consents for the patient to be included in the trial, the legal representative will initial, sign and date the latest version of the Legal Representative (Nearest Relative) Consent Form.

If no Legal Representative is available, the patient will not be included in the trial.

It is imperative that when a Legal Representative has been consulted, that as soon as the participant is able to provide informed consent, the trial is explained to them and their written informed consent is sought. The participant will be given the PIS for delayed consent and their consent will be documented through the initialling, signing and dating of the latest version of the ICF for delayed consent.

If, at any stage, the participant refuses consent for involvement in the trial or asks to be withdrawn from the trial, their wishes must be adhered to. If the participant does not wish to

continue, they will be withdrawn from the trial. Any data collected up to the point of withdrawal will be retained and used in the trial.

For a small number of patients (<2%), it is anticipated that they will not regain consciousness/capacity within 30 days, as these patients will have already received the intervention and reached the primary outcome, their data will be retained for use in the final analysis. If these patients regain capacity after 30 days, where practical, the local research team will consent them for their involvement in the study. In the event that the patient never regains capacity or dies, then they will remain in the trial and their data will be included in the analysis.

5.5 Ongoing consent

At each visit, the participant's willingness to continue in the trial will be ascertained (through the participant, personal consultee or legal representative as appropriate) and documented in the medical notes. Throughout the trial, the participant, personal consultee or legal representative will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participant, personal consultee or legal representative will be given time to consider this information and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

In the UK, if a participant loses capacity during the 90 day study period, the advice/consent of a Personal Consultee (England/Wales)/Legal Representative (Scotland) on whether the participant should remain in the study will be sought and a declaration/consent obtained as described in sections 5.3 and 5.4.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution.

With the participant's consent (or assent from personal consultee/legal representative), their General Practitioner (GP) will also be informed that they are taking part in the trial.

5.6 Additional consent

We will also add additional statements to the ICF for the participant/personal consultee/legal representative to acknowledge that they understand that the Trial Office might in the future, for other related research, collect participant data available in NHS routine clinical datasets, including primary care data (e.g., Clinical Practice Research Datalink, The Health Improvement Network, QResearch) and secondary care data (Hospital Episode Statistics) through NHS Digital and other

central UK NHS bodies. The participant/personal consultee/legal representative will acknowledge that they understand that the Trial Office might send their name, address, date of birth, sex, NHS number (CHI number, Scotland) and trial number to the relevant national registry, and then for the national registry to link this to their data and send the information back to the Trial Office. The acknowledgement by the participant (or personal consultee/legal representative) will also allow access to other new central UK NHS databases that will appear in the future. This will allow us (subject to receipt of additional funding via another grant application) to assess longer-term impact and health service usage data without needing further contact with the trial participants.

6. ENROLMENT, RANDOMISATION and BLINDING

6.1 Identification

Patients booked for an emergency laparotomy or laparoscopy who may be eligible for inclusion in the study will be identified by the on-call surgical team with responsibility for their clinical care. Identification is through clinical handover, clinical notes, or from theatre booking lists. The clinical team will inform the patient about the study and seek permission for a member of the research team to discuss the study with them. If the patient agrees and is happy to be approached this will all be documented in the patients' medical records and the patient will be approached by a GCP trained member of the research team. This member of the research team may be either a member of the clinical team or a research nurse. The consent process will be undertaken as detailed in Section 5.

6.2 Screening and enrolment

Details of all patients approached about the trial will be recorded on the TONIC Participant Screening/Enrolment Log which will be kept in the ISF, and should be available to be sent to the Trials Office upon request.

Eligibility must be confirmed by a suitably qualified medical practitioner who is delegated this task on the TONIC Site Signature and Delegation Log.

6.3 Randomisation process

Randomisation should be performed pre-operatively for all participants.

Randomisation will be provided by BCTU using a secure online Electronic Data Capture (EDC) system (available at https://bctu-redcap.bham.ac.uk/), thereby ensuring allocation concealment. Unique log-in usernames will be provided to those who wish to use the online EDC system and who have been delegated the role of randomising participants into the trial as detailed on the TONIC Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online EDC system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

In the rare instance of the online system being unavailable, the trial office should be contacted and are available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham (UoB) closed days.

Please note: to randomise a patient when the online system is unavailable, the TONIC Trial Office should be contacted directly via email or telephone using the contact details outlined at the front of the protocol.

6.4 Randomisation procedure

After eligibility has been confirmed and informed consent (or declaration for those who cannot provide informed consent) has been received, the participant can be randomised into the trial using the online EDC system. A worksheet replicating the electronic randomisation form and the eligibility and consent form may be used to collate the necessary information prior to randomisation. All questions and data items on the online Randomisation Form and the eligibility and consent form must be answered prior to a potential participant being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the local PI, person randomising and nominated site contacts. The confirmatory email will also be sent to the TONIC Trial mailbox.

The local research team should add the participant to the TONIC Participant Recruitment and Identification Log which links participants with their Trial Number. The PI must maintain this document securely and it must not be submitted to the Trial Office. The TONIC Participant Recruitment and Identification Log should be held in strict confidence.

6.5 Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either early administration of PN or standard care via a central secure web-based randomisation system available 24 hours/day at the BCTU. A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over the following variables:

- NELA risk (<5 OR ≥5%) [33]
- Nutrition Risk Score (<3 OR ≥3) [34]
- Recruiting site (hospital name).

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.6 Blinding

This is an unblinded trial. It is not possible to blind participants or clinicians due to the interventions being used. It is not possible to blind outcome assessors as some outcomes are related to the delivery of the intervention.

All statisticians will be blind until the first version of the Statistical Analysis Plan (SAP) is approved, and one statistician (Mike Bradburn) will remain blind until final analysis.

6.7 Informing the participant's GP and other parties

If the participant has agreed, the participant's GP should be notified that they are in the TONIC trial, using the TONIC GP Letter.

The trial specific GP Letter will be sent to the participant's GP directly from the site that randomised the patient into the trial.

7. TRIAL INTERVENTION

The trial intervention is the early administration of PN, compared to standard nutritional care.

7.1 Trial intervention(s)

Participants will be randomised to receive:

- Early PN through central venous catheter (CVC) or PICC, commencing within 48 hours of emergency laparotomy/laparoscopy, with biochemistry monitoring as per NICE Clinical Guideline 32[33]
- Standard nutritional care, which may include no support, oral nutritional supplements or nasoenteric feeding at anytime point. Clinicians can use PN in the control group, but, as per NICE guidance, not before 5 days post-surgery unless there is pressing clinical need.

7.2 Trial intervention: Parenteral Nutrition

The trial intervention is intentionally pragmatic. Patients randomised to the intervention arm will receive early PN which will be administered intravenously and should be delivered either through a dedicated lumen of a central line placed at operation, or through a PICC line. These lines are inserted by anaesthetists or by specialised vascular access services, depending on local service specifications. Line access may be secured at any point from randomisation to commencement of intervention. Placement of these lines will be confirmed with a plain radiograph of the chest and is undertaken as per local processes, using aseptic techniques. Blood tests are performed prior to commencement of PN to ensure sodium, potassium, magnesium, and phosphate are in the correct range

PN is available pre-formulated from multiple suppliers in the UK. The trial does not specify or mandate the use of any particular brand; participating sites should continue to use the PN formulation routinely employed in their standard clinical practice. Sites will already have familiarity with a particular brand and will use this for the trial. PN provides carbohydrates, lipids, amino acids, vitamins, trace elements, electrolytes and water. These amounts vary according to the supplied bag. An appropriate base PN bag is selected based upon the nutrients required, particularly calories. Additional electrolytes can be added, tailored to the patient's biochemistry. The administration of PN is defined in UK guidance from NICE[26], which provides guidance on calculating calorie requirements. Sites will calculate appropriate rates of PN to be administered prior to commencement. Out of hours, this may include administering a volume defined by local out-of-hours feeding protocols, rather than a dose tailored to exact calorie requirements. At the commencement of PN, dosing is at a reduced rate to avoid metabolic consequences. This is slowly increased with ongoing monitoring of blood tests for evidence of electrolyte disturbance (e.g. abnormal sodium, potassium, phosphate, or magnesium levels). Blood tests (biochemistry including renal and liver function) are required daily for the first week of administration and

remain daily until blood tests results are stable. Following this, they can be decreased in frequency as per local protocols. This is in line with NICE guidance. PN is prescribed on a 24-hour basis and would continue until the participant has recovered gastrointestinal function, sufficient to allow adequate enteral intake. This is determined by the nutrition team in collaboration with the surgical team.

Some people are at higher risk of complications such as refeeding syndrome. This is a condition characterised by low serum concentrations of potassium, magnesium and phosphate. The electrolyte imbalance may cause neurologic, pulmonary, cardiac, neuromuscular, and hematologic symptoms—many of which, if severe enough, may result in death. Testing of additional nutrients such as B12 and Zinc may also be performed to ensure they are within normal range. Thiamine and B12 may also be administered prior to starting PN according to local protocols. Depending on clinical team decisions, the patient may have oral intake as well as receiving PN.

7.3 Comparator: Standard care

Standard of care is variable but reflects a reactive approach to nutritional care. This may include no support, oral nutritional supplements or nasoenteric feeding at anytime point. Clinicians can use PN in the control group, but, as per NICE guidance, not before 5 days post-surgery unless there is pressing clinical need. They may receive interventions such as oral nutritional supplements following surgery, nasogastric feeding, or be permitted to eat, whether or not they have fully recovered gastrointestinal function.

7.4 Summary of key steps in the intervention and control arms

The table below summarises the key steps in the intervention and control arms within the TIDiER framework[35]. The intervention arm is the intervention plus standard care.

Table 2: Key Steps in the intervention and control arms

	Standard Care	Intervention (Early Parenteral Nutrition <48 hours post-operatively)
Why	Reflects current practice in the NHS; a broadly reactive approach to perioperative nutrition.	Early nutrition may reduce complications and improve clinical outcomes by preventing nutritional deterioration and its sequelae. The gastrointestinal tract is typically non-functional following surgery, so parenteral route is preferred initially
Materials	Management in line with local policies for emergency	Venous access with PICC/CVC

	laparotomy recovery and local nutrition policies.	TPN is required, along with local nutrition policies.
Procedures	All patients screened with Malnutrition Universal Screening Tool (MUST) or equivalent at admission, and then weekly. Scores of three or more should lead to dietitian review.	Line placed to facilitate feeding, and chest x-ray performed to confirm placement. Baseline blood tests reviewed prior to commencement and key electrolytes replaced prior to commencement of PN or added to PN bag. May also receive B12/Thiamine if high-risk of refeeding syndrome. Energy requirements (Basal metabolic rate plus additional energy needs) are estimated in line with local policies and NICE guidance[25]. Feed is initially commenced at a low rate/volume, building to full energy requirements over a few days, with daily monitoring of electrolytes for the first 7 days. Additional safety tests including liver function monitoring are also performed, as well as monitoring for line sepsis.
Who provides	Oral nutritional supplements can be prescribed at the direction of a nutrition team member, or a member of the surgical team.	Access is provided by a vascular access specialist (either nurse, anaesthetist, or vascular radiologist depending on local service set up). Assessment of nutritional needs and requirements is led by the nutrition team and prescribed in conjunction with the responsible surgical team.
How	Provided at an individual level and on a face to face basis.	Provided at an individual level and on a face to face basis.
Where	On ward or critical care	On ward or critical care
When and how much	Nutritional intervention may be provided never, or up to several times a day with oral nutritional supplements. PN may be used	PN will be provided every 24 hours as per local protocols, until gastrointestinal recovery (passage of flatus/tolerance of diet) and the

	at 5 days post-op if required (NICE Clinical Guideline 32)	participant is able to achieve adequate enteral intake.
Tailoring	Route of any nutrition may be adapted depending on the participants drive to eat or ability to reach adequate calorie intake.	PN dosing may be adjusted daily according to energy requirements and changes in biochemistry.
Planned fidelity assessment	We will record use of nutritional interventions, their type and frequency. We will note if PN is used, and if so, its date of commencement.	We will record use of PN, including number of bags/calories received. We will record other nutritional interventions, their type and frequency.

7.5 Interaction or contraindications

As PN is a form of nutrition, there are no interactions or contraindications.

7.5.1 Permitted medication(s)/intervention(s) (including rescue medication)

Patients may take regular or acute medications for any indication as per routine care.

7.5.2 Concomitant medication(s)/intervention(s)

No changes to any concomitant medications are required.

7.5.3 Prohibited medication(s)/intervention(s)

No medications are prohibited.

7.5.4 Clinical deterioration during the trial

Should a participant develop symptoms needing additional or incremental treatment (e.g., steroids or antibiotics) during the trial, they will be managed appropriately by their local team including whether to continue the trial intervention. Participants should still be followed up.

7.6 Intervention modification or discontinuation

Participants who develop complications from PN such as cholestasis, significant hyperglycaemia, line sepsis, line occlusion, pneumothorax, or line fracture, may have PN administration paused, reduced, or stopped, as judged by the treating clinical team. These complications are routinely monitored for as part of clinical care.

7.7 Continuation of intervention after the trial

We would expect participants to recover gastrointestinal function following surgery, allowing the intervention to be stopped as intended. A small number of people may develop type III (chronic) intestinal failure and require long term PN at home. Local healthcare contracting exists for this situation and would be outside the scope of this study.

7.8 Intervention supply and storage

Parenteral nutrition is standard NHS stock, and so will be supplied to sites and stored and managed at sites as per local and product requirements.

7.9 Adherence

We will assess adherence in the intervention arm by reporting the percentage of participants who receive PN within 48 hours post-operation. Commencement of the intervention within the 48 hour timeframe is considered adherent and will be monitored centrally.

We will also assess adherence to the control group allocation by monitoring for cross-over to early PN in the control arm. Any participant in the control arm who receives PN within 5 days post-operatively is considered non-adherent.

Adherence to randomised allocation will be assessed in both arms. Sites will be monitored for PN use, and duration of use to identify potential cross-over risks. For the intervention arm, we will record use of PN, including number of bags/calories received. This information will be taken from clinical notes by the research team. We will record other nutritional interventions, their type and frequency. For the control arm, we will record use of nutritional interventions, their type and frequency. If PN is used, we will note its date of commencement and reason for administration. Adherence to intervention relies on commencement of PN within 48 hours post-operation. Adherence to control means no PN used until day 5.

8. OUTCOME MEASURES

8.1 Internal pilot outcomes

The internal pilot will be conducted across six centres, and we are aiming to recruit 60 participants. At the end of the internal pilot phase, the Trial Management Group (TMG) and Trial Steering Committee (TSC) will review the pilot data against a set of pre-specified Red-Amber-Green (RAG) criteria (Table 3).

Table 3: Internal Pilot Progression criteria

Criterion	Red (Stop) (% complete)	Amber (Modify) (% complete)	Green (Go) (% complete)
Participant recruitment (number of open centres achieving their individual target recruitment rate of average 2 participants per month)	<60%	60-99%	100%
Data completeness for primary outcome (number of expected data points recorded for those randomised)	<90%	90-99%	100%
Return rate for 90-day questionnaire (EQ-5D-5L, Barthel Index & PRO-diGI gastrointestinal recovery measure)	<70%	70-99%	100%
Intervention delivery (nutritional supplementation to have started within 48 hours)	<70% in intervention arm; >30% in control arm	70-99% in intervention arm; 1-30% in control arm	100% in intervention arm; 0% in control arm
Cross over rates between arms	>10%	≤10%	0%

The following actions will be taken:

- If all criteria are **GREEN (Go)**: progress to main trial; following the pilot phase we would still review trial processes to assess whether any changes could/need to be implemented to improve the trial.

- If any of the criteria are **AMBER (Modify):** review the trial processes to identify implementable changes. This may include recruiting additional centres and/or retraining centres in trial pathways and procedures. We would discuss with the TSC and funder about the need for a second internal pilot phase to verify resolution of issues, then if progress is satisfactory continue to the main trial.
- If any of the criteria are **RED (Stop)**: abandon the trial if the TSC and Funder feel this the appropriate course of action.

8.2 Main trial outcomes

8.2.1 Primary outcome(s)

Primary outcome is complications experienced post-op until discharge measured using the CCI at discharge from hospital.

Comprehensive Complication Index

The CCI is based on the conventional CDC which has been widely used in surgical research[36, 37]. The CCI is the mathematical summation of complications graded using the conventional CDC and takes into account the number and severity of each complication to obtain a value from 0 (no complications) to 100 (death). As all post-operative complications are included it is more sensitive than other surgical morbidity endpoints[38]. There is an online tool available to calculate the CCI at CCI® Calculator (cci-calculator.com).

8.2.2 Secondary outcomes

8.2.2.1 Clinical (timepoints relative to Index operation)

- Number and severity of complications at 30 and 90 days post-operation, assessed using the CCI[29].
- Number of complications (respiratory, cardiovascular, SSI, reoperation), including mortality, recorded by clinical team during inpatient stay, and reported by the participant at 30 and 90 days post-operation, collected through hospital records and measured using the CDC system[36].
- Number of infectious complications (SSI, vascular access line infection, hospital acquired pneumonia, urinary tract infection, all defined according to the CDC definitions[39]) assessed in hospital, prior to discharge.
- Barthel index of function (including activities of daily living)[40], completed by the clinical team / site staff at discharge, 30 and 90 days post-operation.
- Sit to stand test[41], at point of discharge.

- Quality of recovery (QoR-15), to measure quality of recovery after surgery and analgesia, participant completed at discharge, 30 and 90 days[42] post-operation.
- Length of post-operative hospital stay from operation to day of discharge (in nights following operation), collected through hospital records.
- Unplanned hospital readmission at 30 and 90 days following discharge up to 90 days post-operation, collected through hospital records.
- Discharge destination (usual residence, residential, or nursing home), collected through hospital records.
- EuroQol-5D-5L[43] (EQ-5D-5L) Health status questionnaire used to derive quality adjusted life years (QALYs), quality of life, and is used in the cost effectiveness analysis, participant completed, at discharge, 30, and 90 days post-operation.
- Patient reported outcome measure of gastrointestinal recovery (PRO-diGI) at discharge, 30, and 90 days post-operation. Includes domains related to pain, nausea, and psychological wellbeing [44].
- Assessment of patient treatment satisfaction using a 0-100 visual analogue scale, patient completed at 30 and 90 days post-operation.
- Use and duration of PN, and total calories administered post-operatively, will be recorded for each arm at discharge.
- Use of other nutritional interventions (oral nutritional supplements) prior to discharge, will also be recorded for each arm.
- Process metrics: time from randomisation to line insertion, and time from operation to starting PN in hours.

8.2.2.2 Economic

- Incremental cost per QALY at 90 days post-operation from an NHS and societal cost perspective.
- Incremental cost per QALY over lifetime horizon from an NHS cost perspective.
- Expected Value of Perfect Information analysis over lifetime horizon.

9. TRIAL PROCEDURES

Screening

Potential participants will be identified by the clinical team and the study introduced. With their permission, potential participant's information will be passed to the research team. Once the patient has been identified they will be entered on the screening log. The clinical team will ensure the patient meets the eligibility criteria. If the patient meets the eligibility criteria, the identifying clinical team member will provide the PIS to the patient. If the patient lacks capacity, the trial will be briefly discussed with them, and they will be given the Summary PIS and the trial will be discussed with the patient's relative or carer (Personal Consultee or Legal Representative).

Consent

If the identifying doctors/nurse/research team member are on the Site Signature and Delegation Log and have been delegated the task of taking consent, consent can be taken by them. If they are not on the delegation log as able to take consent, consent should be taken by a member of the site research team delegated this task.

Consent should be obtained from the patient, unless the patient lacks capacity, in which case, consent should be obtained from the patient's relative or carer (Personal Consultee or Legal Representative).

Baseline (Pre-randomisation)

Once informed consent has been obtained, patients will have key demographic data recorded. The research team will enter the data items needed to determine the Nutrition Risk Screening (NRS-2002) score on to the online EDC system, which will then calculate the score. Data collected as part of routine care includes the MUST, medical history, and the NELA mortality risk score. The patient will also complete an EQ-5D-5L questionnaire. The participant is to be guided to complete the questions on the EQ-5D-5L based on their health and wellbeing prior to the start of the episode that requires surgery. If the participant is not able to complete this then EQ-5D-5L will not be recorded.

Randomisation

Once consented and baseline assessments are completed, the patient can be randomised into the TONIC Trial. Details of both date and time of randomisation along with the randomised allocation will be recorded by the EDC system.

Interventions

Participants will be randomised to receive early PN (Intervention) or standard care. The intervention arm is the intervention plus standard care. See section 7 for full information on the trial interventions.

Intraoperative

Key routine operative data will be captured on surgical approach, principal diagnosis and key steps of procedure. This will be taken from the routine recording on the NELA database and/or clinical notes.

At discharge:

The complications experienced by the participant post-op up to discharge will be captured from clinical notes, and from consultation with the clinical team. The research team, in conjunction with the local PI will assign a Clavien Dindo classification to complications.

Process measures (time to line insertion) will be captured from clinical notes.

Nutrition outcomes will be captured from clinical records. Intended dosing of PN (total calorie requirement), and proportion of this administered, will be captured from clinical records.

The participant will undertake a 30 second sit to stand test. This should be performed on the day of discharge. However, when this is anticipated to occur over a weekend with no research staff available, this may occur up to two days prior to discharge. EQ-5D-5L, PRO-diGI, patient satisfaction visual analogue scale, and QOR-15 will be captured at this timepoint, with completion either directly by the patient or administered by a member of the research team. Barthel Index will be completed by a member of the research team. Discharge details will also include details of discharge destination (usual residence, residential, or nursing home).

Day 30 post-operation

The participant will be contacted by the research team. Complications will be captured from medical records, and from telephone discussion with the participant to identify those complications managed in the community. This includes unplanned readmissions if the patient has been discharged post-operation. Patient reported outcomes of PRO-diGI, QoR-15, EQ-5D-5L, and patient treatment satisfaction will be collected using an adaptive approach of telephone or electronic administration. Barthel Index will be completed by a member of the research team. These assessments should take place at day 30 +/- 3 days post-operation.

Day 90 post-operation

Complications will be captured from medical records, and from telephone discussion with the participant to identify complications managed in the community. This includes unplanned readmissions following discharge. Patient reported outcomes of PRO-diGI, QoR-15, and patient treatment satisfaction will be collected using an adaptive approach of telephone or electronic administration. Barthel Index will be completed by a member of the research team. These assessments should take place at day 90 +/- 7 days post-operation.

9.1 Schedule of assessments

Tabel 4: The timing of assessments is presented in the table below

Activity	Screening	Baseline	Surgery (Day 0)	During hospital stay for index surgery	At discharge	Day 30 ± 3 days	Day 90 ± 7 days
Eligibility check	✓						
Valid informed consent	✓						
Demographics (age, sex, ethnicity, diagnosis)		✓					
Relevant medical history taken		✓					
NELA risk score		✓					
MUST score		✓					
NRS-2002 score		✓					
Randomisation		✓					
Contact Details		✓					
Routine Bloods		✓					
Surgery			✓				

Activity	Screening	Baseline	Surgery (Day 0)	During hospital stay for index surgery	At discharge	Day 30 ± 3 days post-op	Day 90 ± 7 days post-op
PICC/CVC Line insertion/removal				✓			
Chest x-ray				✓			
PN (including date of commencement)				✓			
Use of nutritional interventions, including type and frequency.				✓			
Discharge details (destination and length of stay)					✓		
Complications (including infectious complications and mortality) - CCI					✓	✓	✓
Unplanned readmissions						✓	✓
30 second sit to stand					✓		
Barthel Index					✓	✓	✓
Patient reported measures							
EQ-5D-5L		✓			✓	✓	✓
PRO-diGI gastrointestinal recovery measure					✓	✓	✓

Activity	Screening	Baseline	Surgery (Day 0)	During hospital stay for index surgery	At discharge	Day 30 ± 3 days	Day 90 ± 7 days
Quality of recovery (QoR-15)					✓	✓	✓
Assessment of patient treatment satisfaction Visual Analog Scale (VAS)						✓	✓
Health Resource Use Questionnaire Form		✓				✓	✓
Safety and complications							
Side effects/adverse events			✓	✓	✓	✓	✓
Nutrition intervention related complications including metabolic and line-related			✓	✓	✓	✓	✓
Process measures							
Use and duration of PN/ other nutritional interventions					✓	✓	✓
Time to line insertion & time to commence PN				✓			

9.2 Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A participant may wish to cease to participate in a *particular* aspect of the trial.

Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

If a participant loses capacity during the study, data previously collected will be retained. Ongoing collection of patient reported outcome measures (PROMs) will not be carried out, but information from hospital documentation of unplanned readmission, complications, and mortality, will be collected and used in the analysis if the participants Personal Consultee

(England/Wales)/Legal Representative (Scotland) has provided a declaration/consent that the participant should remain in the study.

10. ADVERSE EVENT REPORTING

10.1 Definitions

Table 5: Definitions for Adverse Events

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities (including life threatening events and fatality).
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Consists of a congenital anomaly/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2 Adverse event recording – general

The recording and reporting of AEs will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the HRA. Definitions for AE reporting are listed in Table 5 in Section 10.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

10.3 Adverse event reporting period

The reporting period for AEs and Serious Adverse Events (SAEs) in TONIC will be:

- For PN related SAEs: from the day of PN until the end of the trial (90 days post-operation).
- For surgery related SAEs: from the day of surgery until the end of the trial (90 days post-operation).

The overall defined reporting period will end 90 days post-operation. After the participant has reached 90 days post-operation, sites will not be actively following up participants for SAEs.

10.4 Adverse events reporting in TONIC

Participants that meet the eligibility criteria for the TONIC Trial may experience numerous AEs. As these events are well characterised, it is highly unlikely that these AEs will reveal any new safety information relating to the trial intervention, PN. Due to this, events that meet the definition of an AE but not an SAE (see Table 5) will NOT be required to be reported to the trial team, these AEs should however be recorded as per local practice.

10.5 Serious Adverse Events reporting in TONIC

It is recognised that the frequency of SAEs in this participant population may be high. Many of these SAEs will be anticipated due to the potential of either the operation or PN undertaken by the participant. We have therefore outlined anticipated SAEs that do not require reporting and anticipated SAEs that do not require expedited reporting.

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but **not report** them to the trials office as per Section 10.5.1.

2. **Report SAEs to the trial office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 10.5.2.

3. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 10.5.3.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

10.5.1 Serious Adverse Events not requiring reporting to the Trial Office

Some events that meet the definition of an SAE will not require reporting to the Trials Unit on the trials dedicated SAE form or other CRFs. If any of the events outlined below in Table 6 occur during an individual's participation, from the date of surgery through to end of follow-up, reporting the event on a SAE form or on other CRFs is NOT required as these events are not considered to be critical to evaluations of the safety of the trial.

Table 6: SAEs that do not require reporting

Expected SAE	Process
Pre-planned hospitalisation	Document in medical notes only
SAEs related to pre-existing condition	
SAEs that are related to symptoms or progression of the participants disease	

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

10.5.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition), and the SAE, may be known. That is, such events are protocol-defined as "expected" (see Section 10.6.2 Assessment of expectedness of an SAE by the CI).

Such events should still be recorded by the trial team in the participant's medical notes and on the relevant Case Report Forms (CRFs), but do not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined.

10.5.2.1 All Participants

AEs are commonly encountered in patients undergoing an emergency laparotomy or laparoscopy. As part of the TONIC trial, we will also be collecting surgical complications (as detailed below), these will be collected for the trial related emergency laparotomy or laparoscopy (the index surgery), and will be recorded on trial specific CRFs:

Table 7: TONIC Trial SAEs requiring non-expedited reporting for all participants

Expected SAE	Process
Urinary tract infection	Report on the relevant trial specific CRFs
Acute kidney injury (not present at admission)	
Pneumonia	
Atrial fibrillation	
Myocardial infarction	
Cerebrovascular accident	
Deep vein thrombosis	
Pulmonary embolism	
Delirium	
Intra-abdominal collection	
Superficial surgical site infection	
Deep surgical site infection	

Superficial (skin) dehiscence	
Fascial (abdominal wall) dehiscence	
Anastomotic leak	
Unplanned ICU admission	

10.5.2.2 Participants randomised to PN

All participant randomised to PN should start PN within 48 hours of their operation. The safety of PN is well established and it's highly unlikely that the trial will reveal any new safety information relating to this intervention. Therefore, a strategy of targeted reporting of AEs will not affect the safety of participants. We will only collect specific AEs and side effects that have a high probability of being related to PN (as detailed below) and these will be recorded on trial specific CRFs.

Table 8: TONIC Trial SAEs requiring non-expedited reporting for participants allocated to PN

Expected SAE	Process
Hospital admissions lasting less than 24 hours	To be reported on trial-specific follow-up CRF
Surgical complications	To be reported on the relevant trial specific CRF
Hypoglycaemia	Report on the relevant trial specific CRFs
Hyperglycaemia	
Hypokalaemia	
Refeeding syndrome	
Cholestasis	
PICC/CVC complications: • Pneumothorax • Line infection • Line fracture • Line occlusion • Line thrombosis	

10.5.3 Serious Adverse Events requiring expedited reporting to the Trial Office

The SAEs listed in Table 9 require expedited reporting. These should be reported as outlined in table 9.

Table 9: SAE that require expedited reporting

Expected SAE	Process
Death	Report on SAE Form and provide to the TONIC Trial Office within 24 hours of becoming aware of the event.
Line infection – if it leads to systemic sepsis, requires escalation to HDU/ITU, or is considered medically significant by the investigator.	

Any other SAEs that are related and unexpected would require expedited reporting to the trial office.

10.6 SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the TONIC Trial Office.

To report an SAE to the TONIC Trial Office, the PI or delegate must complete, date and sign the SAE Form via the TONIC EDC Trial system using the information below within the timeline specified in sections 10.5.3. Any other relevant, appropriately anonymised, data should be submitted to the TONIC Trial Office using the TONIC Trial Mailbox (TONIC@trials.bham.ac.uk).

To report an SAE, the PI or delegate should:
Complete the SAE form via the TONIC trial EDC system
Please also Email TONIC@trials.bham.ac.uk to make the TONIC Trial Office aware that an SAE has been submitted, along with any other relevant anonymised documentation.

Where an SAE Form has been completed by someone other than the PI (or medically qualified delegate) initially, the original SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

On submission of an SAE form, a unique reference number will be assigned. The site and the TONIC Trial office should ensure that the SAE reference number is quoted on all

correspondence. The site should e-mail the trial mailbox to inform the TONIC Trial office that they have submitted an SAE.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE reference number within 1 working day of reporting, the site should contact the TONIC Trial Office.

Copies of the completed SAE form should be printed on resolution of the SAE and filed in the ISF.

10.6.1 Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 10: Categories of causality) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per Table 10, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention (i.e. early PN) or operation, will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 10: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	

Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will notify the Chief Investigator (CI) or delegate of the SAE including details of the unique reference number, who will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per Table 10: Categories of causality) with the intervention will be regarded as a related SAE. The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI, an independent clinical causality review will be performed.

10.6.2 Assessment of expectedness of an SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in Table 11: Categories of expectedness.

Table 11: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

10.6.3 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received, where significant new information is reported, the PI (or medically qualified delegate) should also consider review and update of relatedness and causality as applicable.

10.7 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The TONIC Trial Office will submit a progress report to the REC and Sponsor annually starting 12 months after the date of the favourable opinion was given. An electronic copy should be emailed to the REC within 30 days of the end of the reporting period.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and UoB RGT within 15 days of being notified.

Details of all Unexpected and Related SAEs, and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.8 Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

10.9 Follow-up of pregnancy outcomes for potential SAEs

Any participants that become pregnant from the date that PN (intervention) is started until 30 days after the last administration will be followed up to outcome of the pregnancy. The outcome of these pregnancies will be recorded via the pregnancy notification form and in the event of congenital anomalies or birth defects these should be reported as an SAE.

11. DATA HANDLING AND RECORD KEEPING

11.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Typically, the data provided on all eCRFs should routinely be recorded in the participant's medical notes, when this is not being conducted then data collected for the purpose of TONIC can be recorded on paper worksheets. Data should then be transcribed into the Trial EDC system and the data on paper worksheet will be considered the source data and should subsequently be filed in the ISF.

The data variables listed below (Table 12) will be collected as described in the source column. All other data will be collected into the patient record and transcribed into the eCRF. Where connectivity to the internet is an issue Worksheets will be provided to back up the eCRF within the EDC system.

Table 12: Source data in TONIC

Data	Source
Participant Reported Outcomes	The original record of questionnaire completion is the source data. Questionnaires can be completed by participants electronically or on paper. If completed electronically the electronic record will be the source data, held on BCTU servers as part of the electronically-enabled questionnaire completion. If completed on paper, the paper record will be the source data and will be entered onto the trial EDC system.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs.
Blood pressure	The routine clinic blood pressures at various time points will be available from the medical notes/electronic participant record system, which will be kept and maintained in line with normal

	local practice. The medical notes/electronic participant record system is the source and will be transcribed onto CRFs.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Health economics data	Data will be completed directly on to the CRF by the participant and this will constitute the source data. The CRF is source data.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the EDC system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.

11.2 Case Report Form (CRF) completion

eCRFs should be submitted directly into the TONIC trial system for each individual subject. Staff delegated to complete eCRFs will be trained to adhere to the eCRF completion guidelines. Worksheets will be provided to sites to aid with data collection only and will not form part of the eCRF.

The eCRFs will include (but will NOT be limited to) the forms detailed below.

Table 13: Case report forms in TONIC

Form Name	Schedule for submission
Screening Log	When a participant is being considered for approach to participate in the TONIC Trial.
Informed Consent	Prior to randomisation
Randomisation Form	At the point of randomisation
Baseline Data Form	As soon as possible after consent
Patient Contact Form	As soon as possible after consent
Index Surgery Form	Completed during hospital stay for index surgery

Follow-up CRFs including participant reported outcome measures	As soon as possible after each follow-up assessment time point
Serious Adverse Event Form	If expedited: within 24 hours of site research team becoming aware of event If non-expedited: in accordance with section 10.
Pregnancy Notification Form	As soon as possible after becoming aware of participant's pregnancy
Pregnancy Outcome Form	As soon as possible after outcome of pregnancy and/or birth of the child
Trial Exit/Change of status CRF	At the point of becoming aware of withdrawal/change of status or death

An eCRF should be completed for each individual participant.

In all cases, it remains the responsibility of the PI to ensure that the electronic CRF (eCRF) has been completed correctly and that the data is accurate. This will be evidenced by the electronic signature of the PI, or delegate(s). The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection. The delegated staff completing the eCRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the eCRF.

Data reported on each eCRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the TONIC trial specific working instructions on eCRF completion.

The following guidance applies to data and partial data:

- Time format – all times should be in accordance with the 24hr clock
- Rounding conventions – rounding should be to the nearest significant number according to the CRF: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied

- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

The eCRFs will be considered "complete" once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable.

11.3 Participant completed questionnaires

A list of all participant completed forms can be found in Table 14.

Table 14: A list of participant completed questionnaires

Name of questionnaires
EQ-5D-5L
Pro-DiGI gastrointestinal recovery measure
Quality of Recovery-15 questionnaire
Health Resource Usage questionnaire
Patient Satisfaction Visual Analogue Score

Participant completed questionnaires can be completed online or on paper. Questionnaires should generally be completed by the participant alone, however physical assistance in completing the form can be given by the research staff or the participant's friends and relatives where appropriate. In such circumstances, questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish to by selecting 'Prefer not to answer'.

11.4 Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan (DMP) and include the processes of data entry, data queries on trial data.

Data entry will be completed by the sites via a BCTU REDCap EDC system. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised via the trial EDC system, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

Trial EDC system access will be controlled by usernames and passwords, and any changes to data will require the user to be logged in using their username and password. Log-in details must not be shared with other individuals and under no circumstances should individual's access the system using another person's login details. Access within the system is restricted to the functionality and data that are appropriate for the individual's role in the trial.

11.5 Self-evident corrections

No self-evident corrections will be permitted.

11.6 Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial EDC System incorporates the following security countermeasures:

- **Physical security measures:** restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- **Logical measures for access control and privilege management:** including restricted accessibility, access controlled servers, separate controls of non-identifiable data.
- **Network security measures:** including site firewalls, antivirus software and separate secure network protected hosting.
- **System management:** the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team

- **System design:** the data collection system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- **Operational processes:** the data will be processed and stored within BCTU.
- **System audit:** The system will benefit from the following internal/external audit arrangements:
  - Internal audit of the system
  - Periodic IT risk assessment
- **Data Protection Registration:** UoB's Data Protection Registration number is Z6195856.

Data will be shared with the University of Sheffield to enable statistical and health economic analyses, where it will be held within an access restricted folder within the University of Sheffield's file store. All servers are virtual servers hosted within the University of Sheffield's virtual server estate. The system is hosted in data centres located in Sheffield, UK that are owned and operated by the University of Sheffield's IT Services department.

11.7 Archiving

All records created by following trial procedures and all documents listed in guidance relating to the conduct of the trial must be retained and archived for the specified period.

The TMF is normally composed of a sponsor file, held by the sponsor organisation, and an ISF, held by the site investigator. Documents are archived following regulatory requirements and local procedures.

Retained data should still be accurate, accessible and stored securely and confidentially.

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, ISFs, participants' hospital notes, copies of worksheets) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving. No documents will be destroyed without prior approval from the TONIC Trial Office.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a TONIC Site Signature and Delegation log between the PI and the Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a tele/video conference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The PI or delegate is required to keep the ISF up to date throughout the trial.

12.2 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1 On-site monitoring

All sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the TONIC trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff. Any issues noted will be followed up to resolution.

12.2.2 Central monitoring

The Trial Office will check received ICFs and eCRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the DMP. Sites will be sent queries raised via the trial EDC system requesting missing data or clarification of inconsistencies or discrepancies.

12.3 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trial Office of any relevant inspections or local audits.

12.4 Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the TONIC Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the TONIC Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of data queries. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the REC within 15 days of the end of trial. The Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1 Sample size

The CCI uses a combination of frequency and weighting to score complications along the CDC framework[36]. Previous literature has demonstrated the standard deviation of this measure to be ~27 for this population[18]. Perinel et al demonstrated an 8-point difference in CCI following early TPN in the elective setting, which corresponded to a 12% reduction in grade III-V complications[43]. Based on the increased acuity and complexity of this patient group, we believe a 6 point reduction in CCI to be a feasible and relevant effect size. A 6-point difference is equivalent to downgrading a class III complication to a class II complication[29]. Allowing for up to 5% attrition, 90% power, 5% two-sided significance threshold, a sample size of 449 participants in each arm is needed (total 898).

14.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. There are no planned interim analyses. A brief outline of the planned analyses is given below. The results of the analysis will be reported and presented according to CONSORT 2010 guidance[45].

The primary comparison groups will be composed of those randomised to early PN versus those randomised to standard nutritional care according to the intention to treat principle, i.e., all participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations.

The estimand framework will be used to clarify the interpretation of the treatment effect for the primary outcome[46]. The framework covers analyses' key points: analysis population, the treatments compared, primary endpoint, summary measure, and the handling of intercurrent events, and is covered in greater detail in the Statistical Analysis Plan.

Table 15: Brief description of the TONIC Estimand

Estimand Attribute	Primary Analysis
Population	Patients aged 18 or over undergoing NELA eligible emergency laparotomy
Treatments	Early PN (defined for this study as commencement of PN within 48 hours of laparotomy) compared to standard nutritional care which can include a combination of oral nutritional

	supplements, nasoenteric feed, or no additional nutritional support.
Primary Endpoint	CCI Score of in hospital complications measured at point of hospital discharge
Summary Measure	Mean difference with 95% confidence interval
Handling of intercurrent events	• The analysis will be according to a 'treatment policy' estimand strategy, meaning treatment non-compliance or treatment switching will be ignored in the primary analysis and patients will be analysed as randomised. A secondary analysis with complier-adjusted causal effect (CACE) will be undertaken to estimate the maximal achievable benefit if received as planned (principal stratum strategy). This will be explored further in the Statistical Analysis Plan. • Death post-operation is reflected in the primary outcome (CCI) as a score of 100.

For all outcomes, appropriate summary statistics and differences between groups, (e.g., mean differences, ORs) will be presented, with 95% confidence intervals and p-values from two-sided tests also provided. Where possible intervention effects will be adjusted for the minimisation variables listed in Section 6. No adjustment for multiple comparisons will be made.

Continuous variables will be summarised by mean, median, minimum, and maximum value alongside the standard deviation and inter-quartile range (IQR). Categorical variables will be summaries by group with proportions and numbers, in each treatment arm and overall.

14.2.1 Primary outcome(s)

The Comprehensive Complication Index ranges from 0 (no complications) to 100 (death). Previous studies suggest a median CCI score of 21 (IQR 0-29)[8]. Data required to calculate this are all recorded complications, associated with a CDC. Full details of the CCI scoring will be given in the Statistical Analysis Plan (SAP).

The primary analysis will be conducted using linear regression with bootstrapped confidence intervals to account for the non-normal distribution, with covariates comprising randomised arm, site, plus minimisation factors. The treatment difference will be reported as a mean difference with 95% confidence interval. The p-value relating to the intervention group parameter as generated by the model will be presented. The primary analyses will be intention to treat.

As some treatment withdrawal or switchover is expected, the primary outcome will also be analysed using a CACE analysis, in order to estimate the maximal achievable benefit of nutritional supplementation if taken as planned. Further details including per-protocol definition of treatment adherence will be documented in the SAP.

14.2.2 Secondary outcomes

Secondary outcomes will be analysed for the intention to treat analysis population. Binary outcomes will be analysed using logistic regression with covariates of minimisation factors. The treatment difference will be reported as an OR with corresponding 95% confidence interval. Continuous secondary outcomes such as questionnaires and patient-reported outcome measures (PROMs) will be analysed analogously to the primary outcome using linear regression (95% confidence intervals will not be bootstrapped). Length of hospital stay will be log-transformed analysed using linear regression: summaries on mean fold difference and absolute difference will be presented.

For safety outcomes and adverse events, the following summaries will be presented: the number and percentages of patients reporting SAEs in each arm. In addition, the number of participants requiring further interventions or revisions will be summarised descriptively.

14.2.3 Planned subgroup analyses

Subgroup analyses will be performed on two variables used in the minimisation algorithm (NELA Risk (≥5%) and NRS ≥4 see Section 6 and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4 Missing data and sensitivity analyses

Since CCI at hospital discharge can be obtained from the patient's medical history and notes, there should be minimal missing data for the primary outcome. The sample size

calculation has incorporated a potential 5% attrition rate to allow for up to 5% missing data in the primary outcome. If the level of missing data is greater than 5%, then additional sensitivity analyses will be performed to investigate the impact of missing data. Full details of missing data and sensitivity analysis, including on secondary outcomes will be included in the Statistical Analysis Plan.

14.3 Planned final analyses

The primary analysis for the trial will occur once all participants have completed the final 90 day post-operative assessment and corresponding outcome data has been entered onto the EDC system and validated as being ready for analysis.

15. HEALTH ECONOMICS

A cost-effectiveness analysis using individual patient data will be undertaken from the NHS and personal social service perspective, with a 90-day timeframe. Secondary analyses will adopt a societal perspective and a lifetime horizon. All analyses will use QALYs, based on the EQ-5D-5L, as the measure of health outcome. Cost Effectiveness will be assessed probabilistically using the relevant funding thresholds recommended by NICE at the time of analysis. A value of information analysis will be undertaken using the results based on the lifetime horizon in order to identify the value of further research.

15.1 Within-trial economic evaluation

This will adopt recommended methods for economic evaluations that are undertaken alongside controlled trials. Resource use will cover length and type of hospital stay (as described by healthcare resource group); which will include adverse events (e.g. infections and further operations) but not details of PN. Days of PN will be recorded separately, for the purposes of the trial. After discharge, all other NHS and personal social service utilisation will be collected using a patient questionnaire, together with private expenditure and time off work for an analysis from a societal perspective. Unit costs will use mean national reference cost values, whilst the costs of PN will be based on a survey of consumable costs in the trial hospitals and estimates of staff time required for the initiation and cessation of PN. QALYS will be calculated based on EQ-5D-5L recorded at baseline, discharge, 30 days and 90 days. Utilities will be calculated using the method recommended by NICE at the time of analysis; whilst NICE currently recommends the use of a mapping approach, it is anticipated that an official tariff will be available in the near future. An incremental analysis will then be undertaken. A comprehensive one-way sensitivity analysis will be undertaken, together with a probabilistic sensitivity analysis with plots on the cost-effectiveness plane and the generation of cost-effectiveness curves and its associated frontier.

15.2 Model-based economic evaluation

A lifetime horizon will use the trial data, supplemented with a model that predicts complications, hospitalisations, health-related quality of life and mortality. Trial data will be supplemented with epidemiological data relating to life expectancy (e.g. life tables adjusted using appropriate standardised mortality ratios) and quality of life (e.g. EQ-5D-5L age and gender specific population norms). Costs and QALYs generated beyond 12 months will be discounted at 3.5% per annum. The process for developing the model will follow the guidelines for good research practice for health economic modelling from the International Society for Pharmacoeconomics and Outcomes Research. The modelling method will be determined following the within-trial analysis, with decision tree analysis or a lifetable model as potential options. The final health states will be supported by the trial data and face validity will be established from the extensive experience in clinical practice and

research of the clinician applicants. The same suite of sensitivity analyses and outputs as for the trial-based analysis will be used. In addition, a value of information analysis, the Expected Value of Perfect Information, will be undertaken in order to quantify the maximum amount a decision-maker would be willing to pay for eliminating all uncertainty in the economic findings. The main analysis will be based on observed mortality, utilities and complications, extrapolated over a patient's lifetime. Secondary analyses will estimate cost-effectiveness when the different combinations of mortality, health state utilities and complications are assumed to be equal across treatment arms after 90 days.

16. TRIAL ORGANISATIONAL STRUCTURE

16.1 Sponsor

The Sponsor for this trial is University of Birmingham (UoB).

16.2 Coordinating centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB. The centre responsible for statistical and health economic evaluation is the University of Sheffield.

16.3 Trial Management Group

The TMG comprises individuals responsible for the day-to-day management of the trial: the CIs, statisticians, trial management team leader, trial manager, data manager, health economist, nutrition experts, pharmacist, surgical experts and patient representative. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

16.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

16.5 Trial Steering Committee (TSC)

A TSC, comprising independent and non-independent members, will be established for the TONIC trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. The TSC will operate in accordance with a trial specific TSC Charter.

16.6 Data Monitoring Committee (DMC)

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC

during the trial. Reports will be supplied in confidence. No formal interim analyses are planned.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

16.7 Finance

The research costs of the trial are funded by National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) grant (NIHR155875), awarded to Mr Matthew Lee at the UoB. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Schedule of Events Cost Attribution Template (SoECAT). These costs should be met by accessing the Trust's Support for Science budget via the Research Delivery Network (RDN).

17. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018 and Mental Capacity Act 2005 and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. DATA PROTECTION AND CONFIDENTIALITY

Personal and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected and analysed include Name, NHS/CHI/H&C Number, gender, date of birth, telephone/mobile number, email and postal address, health information and medical history.

Participants will only be identified by their unique trial identification number, initials and partial date of birth on CRFs and on any correspondence with the Trial Office. Participants will acknowledge the transfer and storage of their ICF to the Trial Office, this will be conducted as part of the electronic consent process. This will be used to perform central monitoring of the consent process.

Participants will also acknowledge the transfer of their personal data for the purpose of medical research and analysis to the University of Birmingham, and University of Sheffield who will be processing data on behalf of the trial. This will be fully explained to the participant in the PIS and requires participants to acknowledge a specific statement on the ICF if they agree to this.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the TONIC trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

20. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

21. POST-TRIAL CARE

A small number of patients may have significant loss of intestinal length, leading to type III intestinal failure. This requires long-term PN. The need for long term home PN may be identified in either group at any time point. There are nationally commissioned pathways to provide this intervention outside of the trial.

22. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses. This will include staff at both UoB and the University of Sheffield.

Requests for data generated during this study will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

23. PUBLICATION PLAN

On completion of the trial, the data will be analysed, and a Final Study Report prepared. Results of this trial will be submitted for publication in a peer reviewed journal and the findings of the trial will be made public. This manuscript will be prepared by the CI and members of the TMG and submitted to the whole TMG in a timely fashion and in advance of being submitted for publication to allow time for review.

Outputs from this trial will be published under a corporate authorship group. Each publication will include a detailed description of the exact contributions of each person, following accepted guidelines for collaborative authorship models.

Any secondary publications and presentations prepared by investigators must be reviewed and approved the TMG. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues.

In all publications, authors must acknowledge that the trial was performed with the support of NIHR, University Hospitals Birmingham and the UoB (the Sponsor) and BCTU. Intellectual property rights will be addressed in the TONIC Clinical Trial Site Agreement between Sponsor and site.

Participants can request the published trial results from their PI once available.

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25. Appendix 1

Nearest relative is a special term used in the Mental Health Act 1983. Section 26 of the Mental Health Act 1983 sets out who will be your nearest relative.

The list is in strict order and the person who is highest on the list is your nearest relative.

List of nearest relative is:

1. Husband, wife or civil partner (including cohabitee for more than 6 months).
2. Son or daughter
3. Father or mother (an unmarried father must have parental responsibility in order to be nearest relative)
4. Brother or sister
5. Grandparent
6. Grandchild
7. Uncle or aunt
8. Nephew or niece