RAPID-I

Randomised treatment of Acute Pancreatitis with Infliximab: Double-blind multi-centre trial

Phase IIb, randomised, double-blind, placebo-controlled, multi-centre trial of infliximab with transcriptomic biomarker and mechanism evaluation in patients with acute pancreatitis.

Protocol v3.0 28/06/2018

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UNIVERSITY OF LIVERPOOL

NHS The Royal Liverpool and Broadgreen University Hospitals NHS Trust

CTRC Clinical Trials Research Centre

MRC Medical Research Council

NHS National Institute for Health Research

PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator (CI):

Signature: _____ **Date:** 29/6/18

Professor, Robert Sutton
Professor of Surgery, Institute of Translational Medicine, University of Liverpool

Authorised on behalf of Sponsor:

Signature: _____ **Date:** 29 JUNE 18

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Authorised by the Lead Statistician:

Signature: _____ **Date:** 28/06/18

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General Information

This document describes the RAPID-I trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. This will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre, the Clinical Trials Research Centre (CTRC), to confirm they have the most up-to-date version. Clinical problems relating to this trial should be referred to the CI, Professor Robert Sutton, via the CTRC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements; waivers to authorise non-compliance are not permitted.

Protocol non-compliance, whether reported prospectively (e.g. where an investigation cannot be undertaken on a scheduled date because of a clinical contraindication) or retrospectively noted (e.g. as a result of central monitoring) is recorded as protocol deviation, the incidence of which is monitored and reported to trial oversight committees.

The template content structure is consistent with Standard Protocol Items: Recommendations for Interventional Trials 2013 (SPIRIT) and has regard for the Health Research Authority (HRA) guidance. Regulatory and ethical compliance information is located in section 10.6.

Relationship Statements

Roles and responsibilities are fully described in section 14.

The University of Liverpool is the sponsoring organisation and will formally delegate specific sponsoring roles to the CI and Clinical Trials Unit, but remains legally responsible for the trial. The clinical management and governance of all patients screened and/or entered into RAPID-I including identification of patients who lack capacity is the responsibility of each recruiting hospital NHS Trust.

Clinical Trials Unit (CTU): the CTRC at the University of Liverpool in collaboration with the CI, Professor Robert Sutton, will have overall management responsibility for the trial and will be responsible for the co-ordination of centres.

CTRC as part of the Liverpool Clinical Trials Collaborative has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as the Collaborative standards and systems were assessed by an international review panel as reaching the highest quality. The CTRC has a diverse trial portfolio underpinned by methodological rigour, a Good Clinical Practice (GCP) compliant data management system, and core standard operating procedures.

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The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File:

Committee/Group	**Document Title**
Trial Management Group (TMG) Trial Steering Committee (TSC) Independent Data and Safety Monitoring Committee (IDSMC)	RAPID-I Trial Oversight Committee Membership
Principal Investigators (PI)	RAPID-I Participating Centres

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Glossary

A&E	Accident and Emergency Department
ABPI	Association of the British Pharmaceutical Industry
ACD	Acid Citrate Dextrose
AE	Adverse Event
ANCOVA	Analysis of covariance
AP	Acute pancreatitis
AR	Adverse Reaction
AUC	Area under the curve
AUDIT	Alcohol Use Disorders Identification Test
BRU	Biomedical Research Unit
CECT	Contrast enhanced computerised tomography scan
CI	Chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRN	Clinical Research Network
CRP	C-reactive protein
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
CyTOF	Cytometry by time of flight
DNA	Deoxyribonucleic acid
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
eMC	Electronic Medicines Compendium
EQ	EuroQol
eQTL	Expression Quantitative Trait Loci
EU	European Union
EUDRACT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HRA	Health Research Authority
HRUQ	Health Resource Use questionnaire
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
ISRCTN	International Standard Registered Clinical Study Number
I.V.	Intravenous
M	Mean
MHRA	Medicines and Health Care Products Regulatory Agency
MRI	Magnetic resonance imaging
MSD	Merck, Sharp and Dohme Limited
N/A	Not applicable
NBC	NIHR National Biosample Centre

NCT	National Clinical Trial
N/D	Not determined
NHS	National Health Service
NICE	National Institute for Heath and Care Excellence
NIHR	National Institute for Health Research
NIMP	Non-Investigational Medicinal Product
NK	Not known
NR	Not recorded
NRLS	National Reporting and Learning System
NYHA	New York Heart Association
PBMC	Peripheral blood mononuclear cell
PI	Principal investigator
PISC	Patient Information Sheet and Consent Form
PLICS	Patient-level information and costing systems
QA	Quality assurance
QALY	Quality-Adjusted Life Years
QC	Quality control
qPCR	Quantitative polymerase chain reaction
RAC	Revised Atlanta Classification
R&D	Research and Development
RAPID-I	Randomised treatment of Acute Pancreatitis with Infliximab: Double-blind, placebo-controlled, multi-centre phase II trial
REC	Research Ethics Committee
RLBUHT	Royal Liverpool and Broadgreen University Hospitals NHS Trust
RN	Research Nurse (Registered)
RNA	Ribonucleic acid
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SEM	Standard error of the mean
SOFA	Serial Organ Failure Assessment
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPIRIT	Standard Protocol Item: Recommendations for Interventional Trials 2013
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Thymus
T.D.S.	Ter die sumendum (three times a day)
TMG	Trial Management Group
TNFα	Tumour Necrosis Factor alpha
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UK	United Kingdom

1 PROTOCOL SUMMARY

Full Title:	Phase IIb, randomised, double-blind, placebo-controlled, multi-centre trial of infliximab with transcriptomic biomarker and mechanism evaluation in patients with acute pancreatitis.
Short Title:	Randomised treatment of Acute Pancreatitis with Infliximab: Double- blind, placebo-controlled, multi-centre phase II trial.
Acronym:	RAPID-I
Phase:	IIb
Target Condition:	Acute pancreatitis (AP)
Sample size:	290 (provided that no treatment arms are dropped prematurely)
Trial Design:	Randomised, double-blind, placebo-controlled, multicentre trial, employing an adaptive trial design with two interim analyses.
Main Inclusion Criteria :	Adult patients attending Accident and Emergency (A&E) at or admitted to recruiting hospitals via a GP with a new diagnosis of AP established by two of: (1) typical continuous upper abdominal pain; (2) amylase and/or lipase three or more times the upper limit of normal; (3) characteristic findings on abdominal imaging (if undertaken urgently by CT or MRI); *and* in whom trial treatment can be started within 12 hours of recorded admission and allowing 120 min for Pharmacy to prepare trial medication; *and* from whom appropriate consent is obtained (from the patient or their legal representative).
Main Exclusion Criteria :	Age <18 or >85; patients with a bodyweight over 200 kilograms (kg); onset of abdominal pain over 24 h before admission; previous AP or chronic pancreatitis; multiple sclerosis, systemic vasculitis, Guillain-Barré syndrome or other demyelinating disorder; epilepsy; moderate to severe heart failure and/or coronary disease; on home oxygen or home mechanical ventilation; advanced liver disease; cancer for which chemotherapy and/or radiotherapy ongoing/completed in last 6 months; haematological malignancy; cancer with palliative care; infection prior to AP onset; history of tuberculosis, or household contact with those with tuberculosis or opportunistic infection; history of infective hepatitis; live vaccine, infectious agent or

	immunosuppressive therapy within one month; hypersensitivity to infliximab or to inactive components of REMICADE® or to any murine proteins; pregnancy or lactation at admission; females of childbearing potential who do not agree to use adequate contraception up to Day 90; participation in investigational medicinal product study within last three months.	
Study Centres and Distribution:	Multicentre trial across the UK. Initially six tertiary pancreatic centres will participate with the potential to increase the number of participating centres to 20.	
Patient Study Duration:	In-patient stay for treatment of AP with follow-up of 90 days.	
Overall Study duration:	27 months (recruitment for 24 months with follow up of 90 days)	
Agent/Intervention:	**Intervention:** Blinded single intravenous (i.v.) infusion of 5 mg/kg or 10 mg/kg infliximab (REMICADE®) in 250 ml (500 ml for patients weighing over 100 kg) 0.9% sodium chloride infused over 2 hours begun within 12 hours of admission to hospital. **Control:** Blinded single placebo i.v. infusion of 250 ml (500 ml for patients weighing over 100 kg) 0.9% sodium chloride.	
	Objectives	**Outcome Measures**
Primary:	To determine the efficacy of a single i.v. infusion of 5 mg/kg or 10 mg/kg infliximab in the treatment of AP.	C-reactive protein (CRP) on days 2, 4, 7 (+/- 1), 14 (+/- 2) and 28 (+/- 2), summated as area under the curve (AUC).
Secondary:	To evaluate the safety of a single i.v. infusion of 5 mg/kg or 10 mg/kg infliximab in AP. To develop a clinically meaningful outcome measure for AP that can be used for drug regulatory purposes. To develop national capacity in the National Institute for Health Research (NIHR) networks to undertake trials in pancreatitis.	Cumulative pain score, opiate requirements, nutritional deficit (number of days nil by mouth +/- specified nutritional support), decline in serum albumen (negative AUC) and haematocrit (negative AUC), rise in neutrophils (AUC), presence and duration of systemic inflammatory response syndrome, cumulative selective serial organ failure assessment (SOFA) score, local pancreatic injury on contrast-

		enhanced computerised tomography scan (CECT day 14 +/- 2 days), severity classification, infection, length of stay, mortality and patient reported outcome (EQ-5D-5L) on days 4, 14 (+/- 2 days), 28 (+/- 2 days) and 90 (+/- 3 days).

Schematic of Study Design:

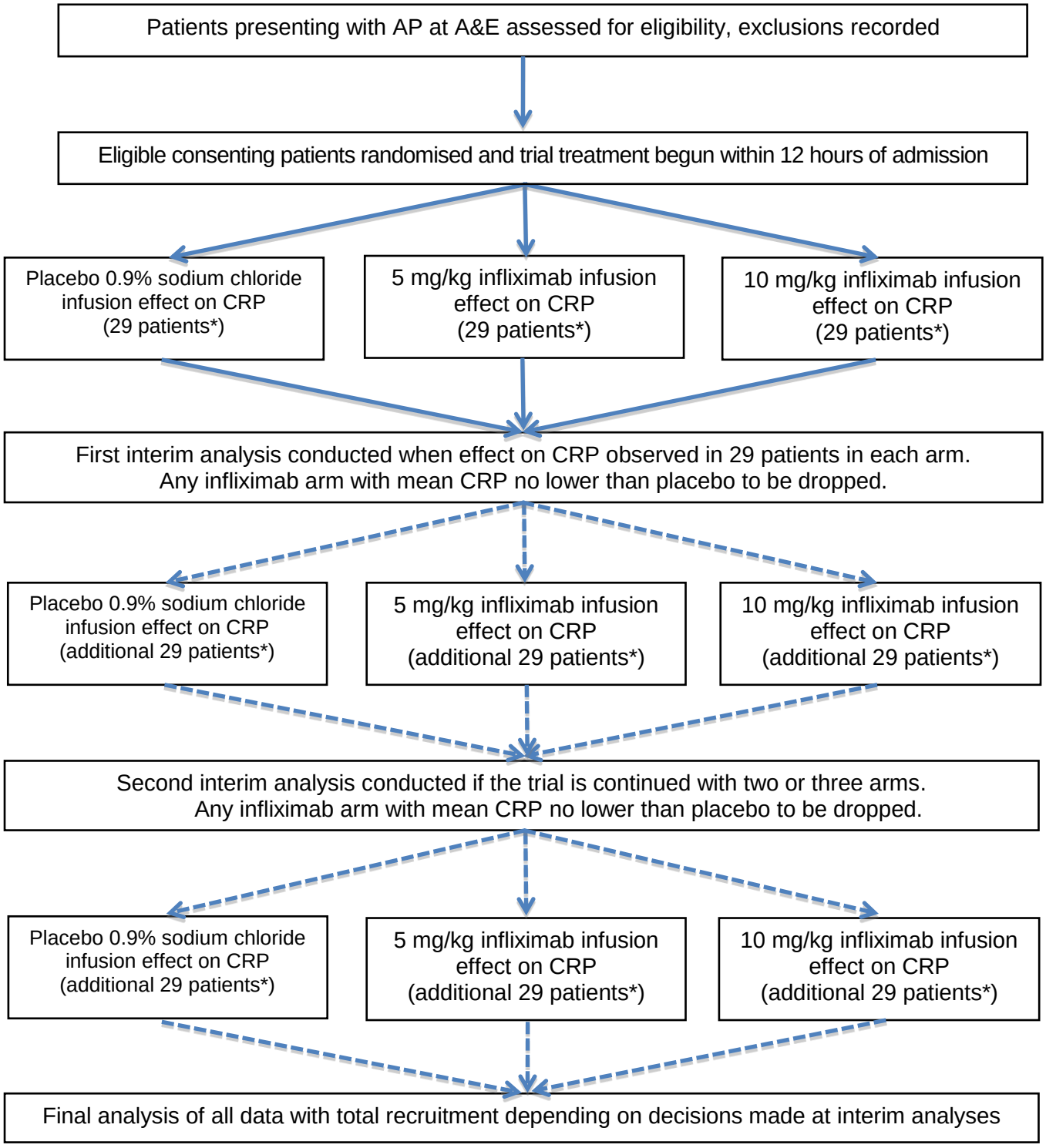


Figure 1: Flow diagram of RAPID-I.

*Number of patients where primary outcome has been observed, not number of patients recruited.

2 INTRODUCTION

2.1 Background

AP is an inflammatory disorder of the pancreas causing excruciating pain, gastrointestinal dysfunction and pronounced systemic inflammatory responses with circulatory and respiratory disturbances that can lead to organ failure and death[1]. AP is one of the commonest gastrointestinal causes of emergency admission to hospital and over the last five decades has increased in incidence in all countries surveyed[1,2]. Despite many randomised clinical trials and systematic reviews there are no accurate means to predict disease course on admission[3] and there is no licensed specific therapy that ameliorates, let alone aborts, the condition[4,5]. This failure is likely due to the choice of agent and speed of treatment delivery in randomised trials[5,6], coupled with a lack of focus on widely applicable outcome measures for all patients[5], not just those developing persistent organ failure (>48 hours). Trial randomisation has been within 72 to 120 hours of admission, very late in the treatment of a medical emergency, complicated by inaccurate prognostic indices to stratify severity. The failure of prognostication, precluding accurate stratification in trials, is in part due to an absence of studies using systems medicine approaches. The work proposed here will address these issues, testing a treatment with robust proof of principle, markedly reduced door-to-needle time and well-defined outcome measures with effective application of systems medicine.

Tumour necrosis factor alpha (TNFα) has a major role in the pathogenesis and severity of acute pancreatitis[7,8]; it is released by injured pancreatic acinar cells in response to toxins[9] (bile acids, ethanol metabolites) implicated in human AP[6] and in large amounts by leukocytes[10], orchestrating cascades in the local and systemic inflammatory responses that are so deleterious in AP[7,11-14]. Circulating TNFα levels rise early and remain elevated for days in human AP, proportional to severity[11-14,] presenting a suitable drug target to inhibit the amplified immune responses that further damage the pancreas and drive widespread organ dysfunction. Anti-TNF therapy for other indications dramatically reduces the incidence of AP to less than one tenth of that without (OR=0.04, 95% CI=0.01-0.16)[15], providing the foundation for the proposed trial of the intravenous (i.v.) anti-TNF agent infliximab in AP.

2.2 Rationale

TNFα is released in AP by injured pancreatic acinar cells to initiate immune responses in which TNFα is pivotal[9], driving many deleterious inflammatory cascades[7-15]. The central role of TNFα has been shown in animal AP models, with marked amelioration from anti-TNF treatment[7]. TNFα rises in human AP for a week or more, proportional to disease severity[11-14], and anti-TNF treatment used for other indications dramatically reduces the incidence of AP to less than one tenth of that without anti-TNF treatment[15]. Anti-TNF therapy has been documented to abrogate human AP[16]. Also, TNFα expression-enhancing -1031C and -863A alleles significantly increase the risk of organ dysfunction in AP[8]. A pilot trial of pentoxyfylline, which has weak anti-TNF effects, has found this treatment associated with reduced admission to and length of intensive care, although no other parameter was affected[17], suggesting more powerful anti-TNF therapy is required. Infliximab has been selected as it is given via i.v., which will ensure rapid bioavailability to treat AP. This is different from other biologics, which are given subcutaneously.

This trial will determine the efficacy of early initiation of anti-TNF treatment in AP, setting new standards for trials in AP. Using a randomised, double-blind, placebo-controlled adaptive design[18,19] with two doses of a single i.v. infusion of infliximab at 5 mg/kg or 10 mg/kg, the trial will determine size of effect, safety and potential effectiveness. Proof of concept has been established from extensive

preclinical studies, clinical observational and pilot human trials[7-15]. The primary outcome measure of CRP is one of the most widely used measures of inflammatory disease severity[20] that has robust validity in AP[21], with representative clinical secondary outcome measures to substantiate efficacy.

High therapeutic response rates have been demonstrated in inflammatory bowel disease (IBD) using 5 mg/kg infliximab, the standard initial dose[22]. Severe IBD, however, presents a greater challenge, with higher TNFα production and faster consumption of infliximab by the reticuloendothelial system, as seen in pharmacokinetic analyses[23,24]. When an initial therapeutic response to 5 mg/kg is lost or in more severe IBD, 10 mg/kg has been shown to be more effective[25-28], as in rheumatoid arthiritis[29]. Similarly, higher dosing has been found more effective in preventing colectomy in severe IBD[30]. Effectiveness analyses have shown adequate trough levels to be an independent predictor of favourable outcome[25-28]. Although there is substantial experience in the use of infliximab, received by >2 million patients worldwide[31], dosing varies in different scenarios[22-30]. Using IBD as the paradigm but without data in AP to determine the size of the TNFα antigen sink[22] and confirm optimal dosing, the trial will test both doses, i.e. a single i.v. infusion of either 5 mg/kg or 10 mg/kg infliximab.

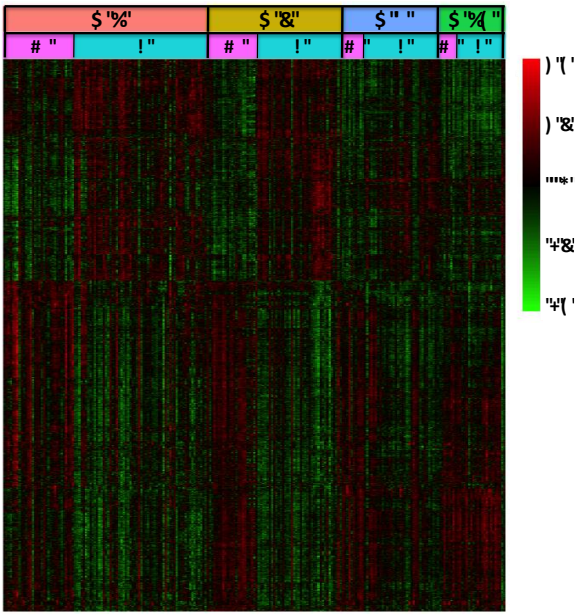


Figure 2. Heat map of differentially expressed genes (red +4 to green –4 on Affymetrix whole transcriptome microarrays) in blood from 92 patients with mild (M) versus severe (S, moderate and severe, RAC) AP on day one (D1, 1410 differentially expressed genes), two (1823), seven (395) and 14 (10 differentially expressed genes, but fewer samples available from later days). These data were used to derive the prognostic signature to be validated and define the 100 transcipts for exploratory efficacy and safety analyses of infliximab in AP, examining TNFα signalling, downstream effects, T cell function, and immune competence.

The trial provides a unique platform to undertake studies to validate a transcriptomic prognostic signature that predicts disease severity on admission more accurately than existing means[3], and add greatly to knowledge by evaluating the efficacy of infliximab in AP on TNFα signalling and downstream effectors. The National Institute for Health Research (NIHR) Liverpool Pancreas Biomedical Research Unit (BRU) identified a differential gene expression signature from blood taken on the day of admission for AP that predicts moderately severe and severe AP (Revised Atlanta Criteria, RAC[32]) with 91% sensitivity, 79% specificity and 87% accuracy. Previous measures applied on admission have at best 74% accuracy (CRP is accurate at 48 hours, but not on admission)[3]. This prognostic signature, identified from bioinformatic analyses of whole transcriptome Affymetrix arrays (see Figure 2) and confirmed by quantitative polymerase chain reaction (qPCR), has now been optimised with a core set of three genes (patenting in progress), to target appropriate resuscitation and supportive treatment in more severely affected patients. Three further genes may be added when a different classification (Determinants Based with mild, moderate, severe and critical categories[33]) is used. Functional analyses of the differentially expressed genes have shown TNFα signalling to be pivotal during the first week. There is pronounced suppression of thymus (T) cell function in severe disease, notably suppression of T regulatory cells, consistent with suppressive effects of high levels of TNFα on lymphocytes in AP[11-14], increasing the risk of infection[11,34,35]. Gene enrichment analysis suggests T cell apoptosis and necroptosis from ligation of tumour necrosis factor receptor 1; these major transcriptional changes will be used in the exploratory assessment of efficacy and safety of

infliximab treatment. If response to infliximab is most evident in severe AP, the prognostic signature may also be clinically useful in stratification for different doses; alternatively, response to infliximab may be predicted and/or monitored by a new transcriptomic signature.

Comprehensive data from the BRU AP cohort mirroring the anticipated trial recruitment confirm the validity of serum CRP levels (measured as area under the curve, AUC) as the primary outcome measure (see Figure 3).

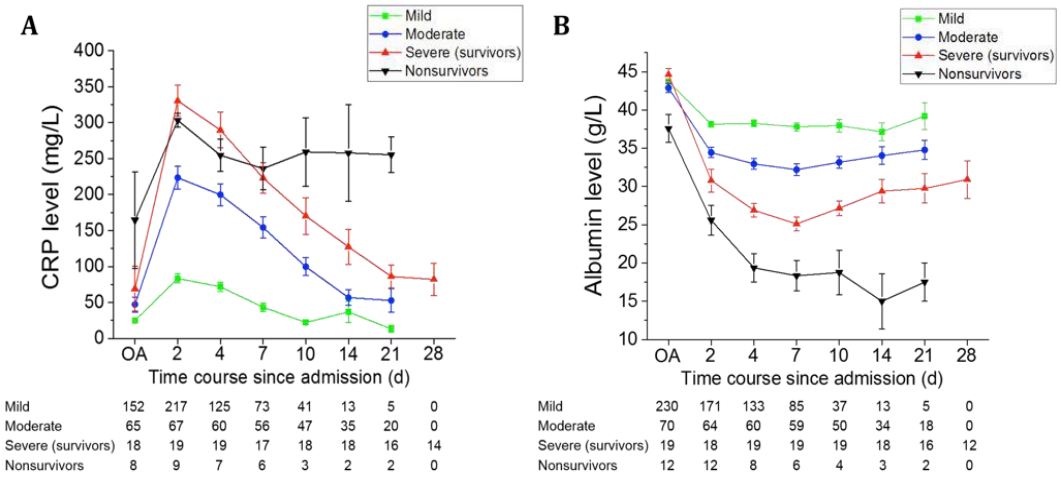


Figure 3. **Changes in serum (A) CRP and (B) albumin in 333 AP patients** with mild, moderate, severe or fatal (12 patients) AP (RAC) over four weeks from admission, showing the number of patients measured at each time point. Strong correlation is shown between these two parameters and the clinical impact of AP.

The data shown from a large patient cohort matching the inclusion and exclusion criteria of the trial confirm CRP rose in all patients to a level and for a period proportional to severity (normal <10 mg/L): in mild AP to 80 +/- 10 mg/L (mean +/- standard error of the mean, M +/-SEM), elevated for two weeks; moderate to 220 +/- 30 mg/L, elevated for four weeks; severe to 320 +/- 40 mg/L, elevated longer; in fatal AP as in severe AP, but remaining highly elevated.

CRP is widely used as a robust tool to determine clinical management in AP[1,3,21] and other inflammatory diseases[20], including composite scores in regulatory drug approval[36-38]; CRP falls in response to supportive intervention in AP[39]. Changes in CRP over time can be summarised by the AUC, which the BRU cohort shows to be directly proportional to disease outcome ($r=0.637$, $p<0.001$), notably the presence and duration of organ failure. AUC captures the whole clinical course far more comprehensively and accurately than a single measure, whether a maximum value or on a specific day. The validity of the secondary outcome measures has similarly been confirmed in this cohort, exemplified here by serum albumin levels (see Figure 2).

2.2.1 Risk and Benefits

AP accounts for over 50% of all admissions to hospital for pancreatic digestive disease, with an incidence of 30-50/100,000[1,2]. In ~70% of patients AP results in hospital stays of 6-7 days with pain and nutritional deficit requiring opiates and nutritional support, plus investigation and appropriate management of the commonest causes, these being gallstones (cholecystectomy +/- endoscopic sphincterotomy) or alcohol excess (counselling/abstinence/support), as well as hyperlipidaemia, hypercalcaemia or rarer causes[1,40]. After discharge patients typically require 3-6 weeks off work, plus further time dependent on cause. The outcome of such cases is considered mild in the 2013 RAC[32],

although severity is a continuum, and the total number of bed days occupied is greatest for patients with this severity level of AP. Ideally a treatment would abort/cure AP, preventing admission and permitting early return to work. Realistically the first effective treatment is likely to ameliorate not abort AP, yet will be a substantial improvement in reducing unmet need.

In ~20% of patients AP results in significant organ dysfunction or organ failure (<48 hours) and/or local pancreatic injury with acute fluid collections and/or necrosis that cause more prolonged pain, nutritional deficit and hospital stays over 2 weeks[1,32,40]. After discharge patients will typically require 6-12 weeks or more off work, dependent on cause and requisite management. Such cases are moderate in RAC[32].

In ~10% of patients AP results in persistent organ failure (>48 hours), likely with local injury causing more prolonged pain, prolonged nutritional deficit and hospital stays over 4 weeks[1,32,40]. Critical and/or high dependency care is required, often with intervention for pancreatic necrosis. Death is likely in up to half of this group, resulting in an overall likelihood of death in all cases of AP of 3-5% (mild, moderate and severe)[1,2]. After discharge surviving patients will typically have to take 12 or more weeks off, or may never return to work. Such cases are severe in RAC[32].

There is thus an urgent need for an effective treatment for AP. If the proposed trial demonstrates efficacy of infliximab in AP, a route will be established to a major improvement in the health of a major group of National Health Service (NHS) patients, reducing the human suffering from AP and permitting earlier return to normal life, reduced hospital stays and associated costs. In time there would be potential expansion of a range of therapeutic options. If the proposed trial does not demonstrate efficacy, there will nevertheless be development of national infrastructure to undertake trials in AP, refinement of measures and quality indicators for trials in AP, potential validation of a new prognostic in AP, and deeper understanding of the immune disorders in AP.

There is a risk to individual trial participants of infliximab-related i.v. infusion reactions, categorized as mild, moderate, severe, life-threatening or fatal[41,42]. These have been reported in 5-25% of patients on long-term infliximab, the majority of which occur after repeated administration and are mild, e.g. pruritus, flushing and myalgia, not requiring modification of the infusion[42]. Hydrocortisone and chlorphenamine will be given to all patients, with adrenaline, further chlorphenamine and paracetamol prescribed as required, prior to graded infusion with cautious initial dosing (protocol of standard care for other indications). Moderate reactions, e.g. chest tightness, urticaria, hypertension, would prompt infusion interruption, chlorphenamine and/or paracetamol and with favourable response, resumption of infusion[42]. Severe or worse reactions (<1% of patients) warrant immediate cessation of the infusion and emergency management with adrenaline, resuscitation and intensive support[42]. Delayed serum sickness-like reactions occur predominantly with repeated administration of infliximab and are usually self-limiting[42].

The other significant risk is an increased likelihood of infection, notably exacerbation or reactivation of tuberculosis, as well as potential reactivation of chronic viral infection and exacerbation of any bacterial infection consequent upon AP[43,44]. The risks of tuberculosis are predominantly associated with long-term administration of infliximab, as for inflammatory bowel disease or autoimmune arthritides (0.2-0.3 per 100 patient years[44]). Nevertheless exclusion criteria will include a history of tuberculosis, including that identified on chest x-ray, or chronic viral infection[44]. Tuberculin testing will take too long and interferon gamma release assays will be compromised by potential suppression of the adaptive immune response by AP. Since trial treatment is to be initiated within 12 h of admission (for a disease with an overall risk of organ failure of 20-30% and mortality off 3-5%), it is not feasible to undertake prior screening tests for chronic viral infection. The most significant viral risk is

reactivation of hepatitis B, addressed by combined hepatitis B surface antigen and core antibody testing after trial entry and monitoring of liver function tests during follow-up, with treatment in the unlikely event of reactivation[43]. Although routine prophylactic antibiotics against bacterial infection are not recommended in AP[40], the BRU found bacteraemia very early in some patients with AP and all patients in this trial will be prescribed piperacillin/tazobactam 4.5 g t.d.s for up to 7 days or until discharge, whichever is earlier (or the local centre's antibiotic(s) for intra-abdominal infection, e.g. in the case of penicillin allergy), starting at trial entry. To further ensure the safety of trial participants, there is a co-investigator at each NHS centre with extensive experience of anti-TNF treatment for IBD. The adaptive trial design with two interim analyses has safety as a critical consideration for the Independent Data and Safety Monitoring Committee (IDSMC) in determining whether to advise continuation.

2.3 Objectives

2.3.1 Primary Objective

The primary objective is to determine the efficacy of a single i.v. infusion of 5 mg/kg and 10 mg/kg infliximab in the treatment of AP.

2.3.2 Secondary Objectives

1. To evaluate the safety of a single i.v. infusion of 5 mg/kg or 10 mg/kg infliximab in AP.
2. To evaluate differential gene expression of 100 genes to:
    i. Validate an expression signature for accurate prediction of severe AP;
    ii. Undertake exploratory efficacy and safety analyses with representative transcriptomes of TNFα signaling and immune competence, including expression quantitative trait loci (eQTL);
    iii. To develop a gene expression signature to predict treatment response;
    iv. To increase knowledge of how infliximab is working in this patient group and develop stratified approaches, through mechanistic evaluation, complemented by cytokine and leukocyte subset analysis.
3. To validate a cumulative AP outcome score derived from the primary and secondary outcome measures of efficacy, in line with verbal and written advice obtained from the Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency and Food and Drug Administration to develop a clinically meaningful outcome measure that can be used for drug regulatory purposes[36-38].
4. To estimate the cost-effectiveness of infliximab expressed as the incremental cost per quality-adjusted life-year (QALY) gained, adopting a health and personal social service perspective
5. To develop national capacity in the NIHR networks to undertake trials in pancreatitis.

2.4 Outcome Measures/Endpoints

All measures have been widely used previously and confirmed in the BRU cohort to display abnormality that is proportional to severity, correlating strongly with major clinical outcomes.

2.4.1 Primary Outcome/Endpoint

The primary efficacy outcome measure will be the difference in mean serum CRP measured on days 2, 4, 7, 14 and 28 (summated as AUC) in the active arms (5 mg/kg or 10 mg/kg) versus the placebo arm. CRP assays will be undertaken centrally to ensure standardised measurement.

2.4.2 Secondary Outcome/Endpoints

Secondary endpoints include:

Efficacy:

1. Cumulative pain scores (numerical rating scale from 0 to 10 daily for first 28 days).
2. Opiate requirements (morphine equivalents daily for first 28 days).
3. Nutritional deficit (number of days nil by mouth +/- specified nutritional support first 28 days).
4. Decline in serum albumen (negative AUC from admission value for first 28 days).
5. Decline in haematocrit (negative AUC from admission value for first 28 days).
6. Rise in neutrophils (AUC for first 28 days).
7. Presence and duration of systemic inflammatory response syndrome (for first 28 days).
8. Cumulative selective serial organ failure assessment[45] (SOFA for first 28 days) score.
9. Local pancreatic injury on CECT scan (Day 14).
10. Severity classification (RAC[32]).
11. Infective complications during first 90 days.
12. Length of hospital stay (up to 90 days).
13. Mortality (within first 90 days).
14. Patient reported outcome (EuroQol EQ-5D-5L[46] including the visual analogue scale EQ-VAS) at Day 4, Day 14, Day 28 and Day 90.

Safety:

15. Potential safety signals[47] will be adverse events related to infliximab including infusion reactions and delayed serum sickness reactions up to 90 days.
16. A further safety signal will be a significant increase in the incidence of infective complications associated with the use of infliximab over placebo.
17. Assay for antibodies to infliximab will be undertaken at Day 28.

Transcriptomics:

18. Absolute and/or relative expression of selected transcripts from samples taken on Days 2, 4, 7, 14 and 28.
19. Cytokine and leucocyte subsets profiles on Days 2, 4, 7, 14 and 28.

Outcome measures for AP trials:

20. Discriminant function (trial treatment versus placebo) of efficacy measures across domains: clinical, laboratory, critical care, local injury, infection, length of stay and patient reported outcome domains.

Health economics:

21. Incremental cost per QALY gained by trial treatment.

National AP trial capacity:

22. Time to recruitment of target sample size, this number depending on the adaptive design.

3 TRIAL DESIGN

RAPID-I is a randomised, placebo-controlled, double-blind, multi-centre, three-arm, phase IIb efficacy trial of infliximab in patients with AP. Patients will be randomised (1:1:1 allocation ratio) to receive an i.v. infusion of either 5 mg/kg or 10 mg/kg infliximab or placebo, initiated within 12 hours of admission to A&E. A delegated member of the research team will randomise online. Treatment allocation will only be revealed to Pharmacy to ensure the research team administering the treatment remain blinded. The feasibility of this design is predicated on experience from the NIHR Pancreas BRU rate of recruitment of patients with AP on the day of admission to observational studies, as well as responses to the feasibility questionnaires sent to six sites (see section 4). SPIRIT[48] and Consolidated Standards of Reporting Trials (CONSORT)[49] guidelines will be followed throughout.

Up to three analyses of the efficacy data (two interim analyses and a final analysis) are planned, as a smaller expected sample size can be achieved by using interim analyses. Recruitment will continue while both interim analyses are taking place. The first will take place after the primary outcome has been observed for 29 patients in each arm. At this point any treatment arm with a mean CRP AUC value larger or equal to the placebo group will be dropped. Should both treatment arms be dropped, the study will stop. A second interim analysis will take place after the primary outcome has been observed for an additional 29 patients in each of the remaining arms. The stopping rules will be as for the first interim analysis.

At the final analysis comparative t-statistics will be computed using an analysis of covariance (ANCOVA) model. If the resulting test statistic for either dose falls below a critical value of -2.196, the corresponding null hypothesis of no difference between the active group and placebo can be rejected and superiority of the active dose can be claimed. Note that it is possible to claim superiority of both doses over placebo.

The design has an overall (family-wise) error rate of 2.5% and 90% power (see 10.3 for details of the sample size calculations) and has been specified such that any treatment worse than placebo at interim analysis will be dropped. To account for (potentially) dropping a dose for other reasons, the conditional error principle will be used to adjust the design[19]. This will ensure that the overall type I error rate of the study is still controlled and result in an increased power compared to not accounting for this unplanned modification.

4 STUDY SETTING AND SELECTION OF CENTRES/CLINICIANS

4.1 Selection of Centres/Clinicians

The criteria for the selection of centres recruiting patients for the RAPID-I trial are:

1. An NHS Hospital providing tertiary Pancreatology, Gastroenterology and A&E services.
2. Gastroenterology services with expertise in biologic therapies.
3. Three Investigators at each site comprised of an emergency medicine physician, gastroenterologist with expertise in biologics and pancreatic surgeon or physician responsible for the management of patients with acute pancreatitis, the last normally to be the Principal Investigator at the centre.
4. Sufficient research capacity comprised of staff, time and facilities to undertake the trial, including patient screening and recruitment, randomisation, collection, centrifugation (clotted blood) and forwarding to the NIHR National Biosample Centre of all samples, preparation and administration of trial treatment by infusion pump initiated within 12 hours of admission, daily inpatient and scheduled outpatient assessments including CECT on Day 14 +/- 2 days, collection of blood samples at weekends, collection and provision to the CTRC of all required data, identification and management of adverse events including notification to CTRC within protocol defined timeframes, identification and provision of information to the CTRC of all protocol breaches.
5. Pharmacy with capacity and capability for aseptic preparation of trial medication within 120 min of request immediately following consenting of patient, or within a period that will allow administration of trial medication to the patient within 12 hours of admission.
6. Capacity to transfer blood samples to the NIHR National Biosample Centre within protocol defined timeframes.
7. All staff contributing to the trial must have valid certified GCP training throughout the conduct of the trial. Requirements of the Sponsor are that renewal of GCP must occur every 3 years and the certificate should be provided to CTRC.
8. The Centre works to the International Association of Pancreatology/American Pancreatic Association evidence-based guidelines for the management of AP[39].

Centres fulfilling the criteria will be selected to be recruitment centres. Following obtention by the CTRC of all necessary global approvals (Health Research Authority, HRA; Research Ethics Committee, REC; MHRA), centres will be opened to recruitment once local approval has been issued ("Capacity and Capability" confirmation/Research and Development (R&D) Approval), and once study-specific conditions (e.g. site personnel training requirements) and all necessary documents have been returned to CTRC as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the 'RAPID-I Participating Centres' log, maintained separately to the protocol within the Trial Master File.

5 STUDY POPULATION

5.1 Inclusion Criteria

1) Adult patients attending A&E at or admitted to recruiting hospitals via a General Practitioner with a new diagnosis of AP established by two of:
    i. typical continuous upper abdominal pain;
    ii. amylase and/or lipase three or more times the upper limit of normal;
    iii. characteristic findings on abdominal imaging (if undertaken urgently by CT or magnetic resonance imaging, MRI);

and

2) Patients in whom trial treatment can be started within 12 hours of recorded admission and allowing 120 min for Pharmacy to prepare trial medication;

and

3) Patients from whom appropriate consent is obtained (consent to be given by the patient or their legal representative).

NB Please note all severity levels of AP are to be included in the trial.

5.2 Exclusion Criteria

1) Age <18 or >85.
2) Patients with a bodyweight of over 200 kilograms.
3) Onset of abdominal pain more than 24 hours before admission to hospital.
4) Known previous AP or chronic pancreatitis.
5) Known multiple sclerosis, systemic vasculitis, Guillain-Barré syndrome or other demyelinating disorder.
6) Known epilepsy.
7) Moderate to severe heart failure and/or coronary heart disease (New York Heart Association* (NYHA) Functional Class III/IV).
8) On home oxygen or home mechanical ventilation.
9) Known advanced liver disease, on waiting list for liver transplantation or considered unsuitable for transplantation.
10) Known cancer for which chemotherapy and/or radiotherapy is ongoing or was completed within less than 6 months from admission.
11) Known haematological malignancy.
12) Known cancer that is end-stage with ongoing palliative care or for which palliative care is appropriate.
13) Known established infection prior to AP onset.
14) Known history of (including that identified on chest x-ray) or household contact with individuals who have tuberculosis or opportunistic infection.
15) Known history of infective hepatitis.
16) Known immunosuppressive or biologic therapy within one month of admission.
17) Known live vaccines or therapeutic infectious agents within one month of admission.

18) Known hypersensitivity to infliximab or to inactive components of REMICADE® or to any murine proteins.
19) Known pregnancy or lactation at the time of admission.
20) Women of childbearing potential who do not agree to use adequate contraception up to Day 90.
21) Known to be currently participating in a trial testing any investigational medicinal product or participation in a clinical study involving a medicinal product in the last three months.

*** Table 2. New York Heart Association (NYHA) Classes**

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea or angina.
IV	Unable to carry out any physical activity without discomfort. Symptoms of heart failure or angina at rest. If any physical activity is undertaken, discomfort increases.

5.3 Co-enrolment Guidelines

Individuals who have participated in a trial testing any investigational medicinal product in the three months preceding screening will be ineligible for the RAPID-I trial. Where recruitment into another trial that does not involve an investigational medicinal product (e.g. observational study) is considered to be appropriate and without having any detrimental effect on the RAPID-I trial this must first be discussed with the CTRC who will contact the Chief Investigator (CI, Professor Robert Sutton).

6 RECRUITMENT AND RANDOMISATION

6.1 Participant Identification and Screening

A screening log will be maintained of all the patients who undergo screening, regardless of whether they decide to participate in or are deemed eligible for the trial, to provide important information for monitoring purposes. Reasons for not being eligible and timelines for providing information and approaching the patient for consent will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that patients or their legal representatives do not have to provide a reason unless happy to do so. Copies of the completed screening log should be sent to CTRC at the end of each month.

Patients will be reviewed upon their arrival in the A&E Department. As part of standard care, full medical history and concomitant medications will be obtained, a physical examination will be completed, blood and urine tests will be performed (full blood count, urea, creatinine, electrolytes, liver function tests, calcium, glucose, amylase and/or lipase, arterial blood gases and urine pregnancy test in women of childbearing age; one or two tests may be undertaken after the diagnosis of AP is made e.g. arterial blood gas), an electrocardiogram (ECG) and chest x-ray will be carried out. Those patients who meet the criteria for the diagnosis of AP and who are suitable for inclusion (see 5.1 and 5.2) will be provided with information about the trial (both verbal and written) to consider participation. At this point Pharmacy will be informed about potential recruitment of a patient into RAPID-I.

Only a doctor authorised on the site Delegation Log can confirm full eligibility of any patient; a record of this confirmation must be made in the patient's medical notes on the date of screening.

6.2 Informed Consent

Upon diagnosis of AP and following screening, suitable patients will be provided with verbal and written information about the trial and asked to provide written informed consent. As AP is an acute, life threatening condition that may inhibit higher brain function and the trial is set in an emergency setting, it is possible that a number of patients will be lacking capacity. In this case, if a Personal Legal Representative (as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) is available, they must be asked for a proxy decision, and if not available, a Professional Legal Representative (as defined by the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) will be asked for a proxy decision on the patient's behalf (see section 6.2.2).

The following consent forms will be signed as appropriate depending on the capacity of the patient:

- RAPID-I Patient Information Sheet and Consent form (Patient with Capacity)
- RAPID-I Personal Legal Representative Information Sheet and Consent form (Patients Lacking Capacity)
- RAPID-I Professional Legal Representative Information Sheet and Consent form (Patients Lacking Capacity)
- RAPID-I Patient that Regains Capacity Information Sheet and Consent Form (Patient Regaining Capacity)

6.2.1 Obtaining Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients

participating in CTRC coordinated trials. In obtaining and documenting informed consent, site staff should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Site staff delegated by the Principal Investigator (PI) and appropriately trained with experience in obtaining informed consent will conduct an interview with the patient (or their Legal Representative in the case of patients lacking capacity). The appropriate ethically approved Patient Information Sheet and Consent form (PISC) will also be provided, describing in detail the trial interventions/products, trial procedures and risks. The patient (or his/her Legal Representative) will be asked to read and review this document. Upon reviewing the document, the site staff will explain the research study to the patient (or his/her Legal Representative), including a discussion of the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. A contact point where further information about the trial may be obtained will be provided.

All patients (or their Legal Representatives) will be given the opportunity to ask any questions that may arise, the opportunity to discuss the study with their relatives, carers and/or associates and time to consider the information prior to agreeing to participate. As the approach for consent will take place in emergency settings, a fixed period cannot be prescribed over which the decision to participate should be considered. The amount of time to consider participation in RAPID-I before consent will differ on a case-by-case basis but in every case it should allow for sufficient time to confirm full eligibility, to carry out randomisation and to commence treatment within 12 hours from admission.

Consenting patients (or their Legal Representative in the case of patients lacking capacity) will then sign and date the informed consent document. Both the person obtaining consent and the patient (or their legal Representative) must personally sign and date the form. The original signed copy of the consent form must be filed in the Investigator Site File, and three copies must be made. One copy will be given to the participant or their Legal Representative for their records, another copy will be kept in the participant's medical notes (if the site has electronic notes the consent form will be scanned) and a copy should be sent to the CTRC. Consent forms should be submitted to the CTRC within 7 days of consent being obtained. The process of informed consent will also be detailed in the patient's medical notes.

Consent from the patient (or his/her Legal Representative in case of a patient lacking capacity) must be obtained prior to any trial-specific procedures or assessments and prior to randomisation, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment.

A patient may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking their informed consent (similarly a Legal Representative may withdraw the patient under the same conditions). It will be emphasized to all patients (and their Legal Representatives) that their welfare rights (or those of the patient) will be protected and the quality of their medical care will not be adversely affected if they decline to participate in this study, or decide to withdraw consent at a later time. The right of the patient (or his/her Legal Representative) to refuse to consent, or to withdraw without giving any reason, must be respected.

After the patient has entered the trial, the clinician is free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the patient. Nevertheless the

reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated.

6.2.2 Patients Lacking Capacity

As AP is an acute, life threatening condition that may inhibit higher brain function and the trial is set in an emergency setting, it is possible that a number of patients will be lacking capacity. Considering that the benefits of inclusion of patients lacking capacity outweigh the risks (there are no data to indicate that more adverse events (AEs) due to the study interventions would arise in such patients), that the odds for randomisation to the active treatment are 2:1 and that these patients could potentially benefit the most from receiving the trial intervention due to the severity of their condition, such patients will be included if eligible.

All patients must be assumed to have capacity unless it is established that they do not. The site research team will assess patient capacity in accordance with their local practices.

Please see table below for the hierarchy of informed consent from Legal Representatives if a patient is assessed to be lacking capacity.

Table 1 – Hierarchy of informed consent for an incapacitated adult

England, Wales and Northern Ireland	***Scotland***
1. Personal Legal Representative A person not connected with the conduct of the trial who is: a) suitable to act as the legal representative by virtue of their relationship with the adult, *and* b) available and willing to do so.	*1. Personal Legal Representative* 1A. Any guardian or welfare attorney who has power to consent to the adult's participation in research as defined in the Adults with Incapacity (Scotland) Act 2000. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.
2. Professional Legal Representative A person not connected with the conduct of the trial who is: a) the doctor primarily responsible for the adult's medical treatment, *or* b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board). A Professional Legal Representative may only be approached if no suitable Personal Legal Representative is available.	*2. Professional Legal Representative* A person not connected with the conduct of the trial who is: a) the doctor primarily responsible for the adult's medical treatment, *or* b) a person nominated by the relevant health care provider. A Professional Legal Representative may only be approached if it is not reasonably practicable to contact either 1A or 1B before the decision to enter the adult into the trial is made.

In those with impaired capacity if a Personal Legal Representative is available, they will be approached to consider participation in the trial and will be asked for a proxy decision on behalf of the patient. If not available, a Professional Legal Representative will be approached and asked for a proxy decision. Every effort will be made to identify a suitable Personal Legal Representative, prior to approaching a Professional Legal Representative.

If the patient regains capacity (which will be the case for the majority of patients), they will be informed about the trial and invited to continue with trial participation. They will be asked to sign the Patient that Regains Capacity Information Sheet and Consent form. They may choose to withdraw their involvement (patient follow-up) or they may choose to withdraw the use of their data (patient data).

6.3 Eligibility Confirmation

Once a patient has been screened and has had all eligibility assessments performed (see sections 5 and 6.1) and Informed Consent has been obtained (see section 6.2), a doctor authorised on the site Delegation Log must confirm full eligibility of the patient. A record of this confirmation must be made in the patient's medical notes on the date of screening.

6.4 Baseline

Informed consent must be obtained before baseline as trial-specific data and blood samples are required as part of baseline assessment.

Once the patient (or their Legal Representative) has provided written informed consent and a doctor authorised on the trial site Delegation Log has confirmed full eligibility, the baseline assessments will be undertaken. The consented patient's weight will be determined using a bed-weighing scale to calculate trial treatment dosage. A doctor authorised on the trial site Delegation Log will complete a signed prescription for the trial intervention. Randomisation will be carried out by a member of the research team delegated the duty on the delegation log. Pharmacy will be made aware of the eligible patient so that they know to expect the treatment allocation email and can allocate time to prepare the trial treatment.

Further baseline assessments to be completed while trial medication is being prepared are:

1. A blood sample to determine Hepatitis B surface antigen and Hepatitis B core antibody status with results to be obtained after randomisation and administration of trial intervention;
2. Omics blood samples (2.5 ml in each of two PAXgene® tubes for ribonucleic acid, RNA; 5 ml clotted blood in serum tube (centrifuged) for cytokines; 6 ml in acid citrate dextrose (ACD) tube for peripheral blood mononuclear cells, PBMCs; 8.5 ml in PAXgene tube for deoxyribonucleic acid, DNA);
3. Abdominal pain (numerical rating scale of pain in stomach area and opiate morphine equivalents received over last 24 hours);
4. Time of last food and drink, history of vomiting;
5. Selective SOFA score (cardiology, respiratory and renal only);
6. Recording of ward area;
7. Concomitant medications (if any change from screening).

At any convenient point following administration of trial treatment the aetiology of AP should be recorded, including that informed by transabdominal ultrasound, alcohol history with use of the Alcohol Use Disorders Identification Tool (AUDIT) assessment tool, fasting serum lipids, serum calcium and endoscopic ultrasound.

6.5 Randomisation Procedures

Participants will be randomised by a delegated member of the research team to receive either arm A infusion of 5 mg/kg infliximab or arm B 10 mg/kg infliximab or arm C placebo (in a ratio of 1:1:1) once:

a. Eligibility criteria have been fulfilled;

b. Fully informed written consent has been obtained;
c. Full eligibility has been confirmed by an authorised doctor;
d. Baseline patient weight has been determined.
e. The prescription has been completed for the trial infusion and accompanying medications by an authorised doctor.

A delegated member of the research team will randomise participants by means of a secure, 24-hour web-based randomisation system stratified by centre using a programme controlled centrally by the CTRC. A personal login username and password, provided by the CTRC, will be required to access the randomisation system; designated research staff will be issued with their personal login and password upon completion of training in use of the system.

When patient consent and full eligibility are confirmed in the system, a unique study number (randomisation number) will be displayed on a secure webpage and an automated email confirmation providing the treatment allocation will be sent to the Pharmacy. The site's PI, CTRC Trial Coordinator and the research staff member responsible for randomisation will receive a separate email confirming that randomisation has taken place without revealing treatment allocation. Administration of the trial treatment must be begun within 12 hours of hospital admission. It is the responsibility of the PI or delegated research staff to inform the Pharmacy department at their centre prior to randomisation to ensure there is sufficient supply of the study treatments.

Randomisation: web access http://ctrc.liv.ac.uk/Randomisation/Rapid.One

If there are any problems with the randomisation systems, contact the coordinating CTRC on 0151 794 9774, or via email on rapid.one@liverpool.ac.uk

(Note that the coordinating CTRC is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Centres will be provided with emergency back-up randomisation envelopes to be used in the event of a failure outside CTRC office hours or if the problem cannot be resolved in a reasonable timeframe. These will be stored in the Pharmacy at each individual site. In the event that emergency back-up envelopes are required to be used, the Pharmacist will be contacted by the research team who will ask Pharmacy to randomise the patient. They will select the next sequentially numbered, opaque, pressure-sealed envelope that will give the randomised allocation. The envelope will be similar to those used for pay slips, which cannot be viewed without fully opening with a construction that is resistant to accidental damage or tampering. Page 1 of the randomisation envelope must be returned to the CTRC in a pre-paid envelope, and pages 2 and 3 of the randomisation envelope will be inserted into the Pharmacy Site File. Upon receipt at CTRC, there will be a check to ensure the envelopes have been used in sequence. The site should also email the Trial Coordinator within 24 hours to notify CTRC that it has been necessary to use a back-up envelope.

A member of the Pharmacy trial team will check to ensure that the correct number of randomisation envelopes are present, that they are intact and that the sequential numbering system is maintained. Any discrepancies should be immediately reported to the CTRC.

6.6 Who is Blinded to Allocations

The participants, CTRC staff (excluding statistical team members as appropriate and independent data management team who will process site accountability logs), and all members of the site research teams (including the delegated member randomising the patient but excluding Pharmacy staff) will be blinded to treatment allocations.

Once the delegated research team member performs randomisation and the Pharmacist is provided with the allocation to either Arm A, B or C, the Pharmacist will prepare the infusion, which will be covered by an opaque sleeve and labelled for blinding.

Piperacillin/tazobactam (or the local centre's antibiotic(s) of choice for intra-abdominal infections as defined in the recruiting centre's written antibiotic policy e.g. if the patient has penicillin allergy), hydrocortisone and chlorphenamine will be prescribed for all trial patients and given to ensure equipoise between trial arms and to maintain blinding. Adrenaline will also be prescribed for use as required to counter severe anaphylactic reactions/shock from the infusion, should this occur, and paracetamol to be used as required. Severe anaphylactic reactions/shock are to be managed according to the Resuscitation Council (United Kingdom, UK) guidelines.

The IDSMC (and the trial statistical team) will be the only body with access to unblinded comparative data, which it will monitor to advise the Trial Steering Committee (TSC) on continuation or cessation of the trial.

For unblinding procedures see section 8.5.

7 PARTICIPANT TIME LINE, PROCEDURES AND ASSESSMENTS

7.1 Schedule for Follow-up

The total duration of the study is 90 days from commencement of trial infusion, which must be administered as a single dose infusion starting within 12 hours of admission to hospital. Assessments will be conducted in line with the schedule in the table below. If patients are discharged before assessment time points are reached, they will be assessed as outpatients.

Table 3. Schedule of Assessments.

Procedures		Screening	Consent	Baseline / Randomisation	IMP Administration	As required from trial entry	Day 2 (12-36 h)	Day 4 (60-84 h)	Day 7 (+/- 1 day)	Day 14 (+/- 2 days)	Day 28 (+/- 2 days)	Day 90 (+/- 3 days)
Diagnostic blood tests (amylase, lipase)		X										
Assessment of diagnosis of acute pancreatitis		X										
Review of medical history		X										
Review of concomitant medications		X				X						
Physical exam	Complete	X										
	Symptom-directed (including vital signs)	X				X						
Blood tests (consent is mandatory before trial bloods at baseline, Days 2, 4, 7, 14, 28 and 90 can be taken)	Full blood count and differential	X				X	X	X	X	X	X	X
	Creatinine	X				X	X	X	X	X	X	X
	Liver function tests	X				X	X	X	X	X	X	X
	Calcium	X				X						
	Glucose	X				X						
	Arterial blood gases	X				X						
	Hep B surface antigen + core antibody assay			X								
	CRP[A] (for central lab)						X	X	X	X	X	
	Omics blood samples[B]			X			X	X	X	X	X	
	Measurement of infliximab levels								X		X	
	Detection of antibodies to infliximab										X	
Pregnancy test (urine)		X									X	
ECG		X										
Chest x-ray		X										

Procedures	Screening	Consent	Baseline / Randomisation	IMP Administration	As required from trial entry	Day 2 (12-36 h)	Day 4 (60-84 h)	Day 7 (+/- 1 day)	Day 14 (+/- 2 days)	Day 28 (+/- 2 days)	Day 90 (+/- 3 days)
Assessment of eligibility criteria	X										
Signed consent form		X									
Confirmation of full eligibility by an authorised doctor			X								
Patient weight			X								
Randomisation			X								
Prescription of piperacillin/tazobactam[C], hydrocortisone, chlorphenamine, adrenaline and trial infusion			X								
Pharmacy preparation of trial infusion			X								
Administration of piperacillin/tazobactam or alternative(s)[D]			X		X						
Administration of hydrocortisone and chlorphenamine			X								
Administration of trial infusion				X							
Assessment of Adverse Events				X	X						
Daily assessment of abdominal pain[E]			X		X						
Daily recording of nutrition and route[F]			X		X						
Daily selective SOFA score[G]			X		X						
Daily recording of ward area			X		X						
Imaging and interventions					X						
Aetiology[H]					X						
Contrast enhanced pancreatic CT scan									X		
EQ-5D-5L							X		X	X	X
HRUQ[I]										X	X
Data Collection	X	X	X	X	X	X	X	X	X	X	X

Assessments for Day 2 and Day 4 must take place 12-36 h and 60-84 h respectively, after commencement of trial infusion.

[A] 5 ml clotted blood in SST tube (centrifuged) for CRP

[B] 2.5 ml in x 2 PAXgene tubes for RNA; 5 ml in SST tube (centrifuged) for cytokines; at baseline: 8.5 ml in PAXgene tube for DNA; at baseline, Day 4 and 14: 6ml in ACD tube for PBMCs.

[C] Alternative antibiotics (e.g. if penicillin allergy) for intra-abdominal infection as defined in local written antibiotic policy.

[D] Administered for up to 7 days or until discharge, whichever time point is earlier; alternatives given in section 6.6.

[E] Daily numerical rating scale of abdominal pain and daily administration of opiates during inpatient stay for up to 28 days.

[F] For nutritional assessment see section 7.1.1, recorded during inpatient stay for up to 28 days.

[G] Cardiac, respiratory and renal only; if no lab test, most recent value from previous day to be used; up to 28 days as [E, F].

[H] Transabdominal ultrasound, alcohol (AUDIT) and drug history, fasting plasma lipids, calcium, +/- endoscopic ultrasound.

[I] Health Resource Use questionnaire (HRUQ, to be completed if patient has been discharged from index (trial) admission).

The following activities will occur at each of the time points with every effort made for these activities to be conducted on the day as specified and if not then within the time window specified.

7.1.1 Continuous Recordings

All patients administered a trial infusion are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Symptom directed physical examination, abdominal pain (daily numerical rating scale and administration of opiates), nutrition and route (no nutrition, reduced oral intake, normal oral intake, nutritional supplements, enteral via nasogastric or nasojejunal tube, parenteral, other) and selective SOFA score (cardiac, respiratory and renal only; if no lab test, using most recent value from previous day) will be recorded daily until Day 28 or discharge, whichever is soonest. Imaging and therapeutic interventions (e.g. mechanical ventilation, drainage, necrosectomy) and ward area (A&E, Level 3/General Ward, Level 2/High Dependency Unit, Level 1/Intensive Care Unit, other) will be recorded until Day 90 or discharge, whichever occurs soonest.

Piperacillin/tazobactam should be administered for up to 7 days or until discharge, whichever time point is earlier. Alternative antibiotics are given in section 6.6 and 8.9.1. Concomitant medications (drug and duration, see section 8.9.3 for required information) and adverse events will be collected from screening until Day 90 (during the in-patient stay and at subsequent out-patient visits).

All routine blood tests (e.g. full blood count, liver function tests) in the tabulated schedule (routine admission assessment and on Days 2, 4, 7, 14, 28 and 90) will be conducted by the clinical team and results used by the clinical team). The primary outcome measurement of CRP will be measured in samples taken on Days 2, 4, 7, 14 and 28, with the CRP assay undertaken centrally to ensure standardised measurement. The clinical team will not have access to the results of the centralised assay of CRP for clinical management, but may assay CRP locally at any time if considered clinically necessary.

Aetiology will be recorded when available either during the in-patient stay or follow-up period until Day 90; severity classification (RAC[32]) will also be made during this period.

7.1.2 Day 2 (12-36 h after commencement of trial infusion)

Full blood count, differential and liver function tests undertaken locally; CRP (centrifuged) and Omics blood samples will be taken at this time point for assessment at a central laboratory.

7.1.3 Day 4 (60-84 h after commencement of trial infusion)

Full blood count, differential and liver function tests undertaken locally; CRP (centrifuged) and Omics blood samples (including ACD for PBMCs) will be taken at this time point for assessment at a central laboratory. Patients will also be asked to complete the EQ-5D-5L questionnaire.

7.1.4 Day 7 (+/-1 day)

Full blood count, differential and liver function tests undertaken locally; CRP (centrifuged), Omics blood samples and bloods for infliximab levels will be taken at this time point for assessment at a central laboratory.

7.1.5 Day 14 (+/-2 days)

Full blood count, differential and liver function tests undertaken locally; CRP (centrifuged) and Omics blood samples (including ACD for PBMCs) will be taken at this time point for assessment at a central

laboratory. A CECT scan will also be performed to assess local pancreatic injury; these scans will be available to be read locally but will be assessed by a centralised panel as a secondary measure of trial outcome. Patients will also be asked to complete the EQ-5D-5L questionnaire.

7.1.6 Day 28 (+/-2 days)

Full blood count, differential and liver function tests undertaken locally; CRP (centrifuged), Omics, infliximab level and antibodies to infliximab blood samples will be taken at this time point for assessment at a central laboratory. Patients will also be asked to complete the EQ-5D-5L questionnaire and, if discharged from their index (trial) admission, a Health Resource Use questionnaire (HRUQ). Women of childbearing potential will have a urine pregnancy test.

7.1.7 Discharge

Date of discharge will be recorded.

7.1.8 Day 90 (+/-3 days)

Full blood count, differential and liver function tests will be undertaken locally. Patients will be asked to complete the EQ-5D-5L questionnaire and, if discharged from their index (trial) admission, a HRUQ. Date and length of in-patient stay of any readmission(s) during the first 90 days will be recorded as well as reason(s), intervention(s) and outcome. Women of childbearing potential will be asked if they have become pregnant since entering the trial.

7.1.9 Beyond Day 90

Data on the length of in-patient stay beyond 90 days during the index admission (at the start of which trial medication was given) will not be obtained as part of this protocol, but may be sought subsequently as well as reason(s), intervention(s) and outcome.

7.2 Efficacy

Efficacy will be determined by comparison of the cumulative CRP (AUC) between trial treatment arms. Further exploratory efficacy analyses will be comparison between trial treatment arms of the secondary outcome measures, all of which represent the disease and capture severity. Comparison of the time course of immune response gene expression and serum cytokines (including TNFα and Interleukin-6) will also be made between treatment arms.

Level of care, investigations, treatments, length of stay and resource use will be recorded in trial participants' Case Report Forms (CRFs) and via the Finance Departments of participating centres provision of patient-level information and costing system (PLICS) data. Unit costs will be obtained from standard sources. Quality-adjusted life years (QALYs) will be estimated as AUC, using data from the EQ-5D-5L questionnaire administered on Days 4, 14, 28 and 90.

The primary outcome measure is serum CRP (5 ml clotted blood in SST tube, centrifuged, for serum) measured at Days 2, 4, 7, 14 and 28 time points with measurement in a central laboratory. **Centrifugation is mandatory to ensure separation of serum from clotted cells by gel to prevent degradation of CRP.** CRP rises to a peak then falls slowly for a substantial period in all patients with AP (see Figure 3 in section 2.2); CRP is a clinically useful marker of disease outcome that is the most studied and robustly validated marker in AP[12,14,20,21]. CRP is used to decide when imaging or intervention is necessary and as a means to determine progression or resolution of AP; CRP levels

fall in response to successful intervention[39]. BRU prospective data on a 330 patient cohort matching the inclusion and exclusion criteria of RAPID-I confirm CRP rises in all patient groups to a level and for a period proportional to severity (classified according to the RAC): in mild AP to 80 +/- 10 mg/L (M +/-SEM), elevated for two weeks; moderate to 220 +/- 30 mg/L, elevated for four weeks; severe to 320 +/- 40 mg/L, elevated longer. Changes in CRP over time can be represented by the area under the curve (AUC), which the BRU cohort shows to be directly proportional to disease outcome (RAC severity; $r=0.637$, $p<0.001$), notably the presence and duration of organ failure.

The secondary outcome measures will be pain (cumulative numerical rating scale and opiate administration in morphine equivalents), nutritional deficit (cumulative deficient intake and nutritional support given), decline in haematocrit (negative AUC from admission value for first 28 days), rise in neutrophils (AUC for first 28 days), decline in serum albumen (negative AUC from admission value for first 28 days), presence and duration of systemic inflammatory response syndrome (up to Day 28), cumulative serial organ failure assessment (SOFA for first 28 days) score, local pancreatic injury on pancreas contrast-enhanced computerised tomography scan (CECT on Day 14), severity (RAC[32]), infective complications (first 90 days), length of hospital stay, mortality (first 90 days), patient reported outcome (EQ-5D-5L[47]) at, Days 4, 14, 28 and 90 and adverse events related to infliximab. Where possible cumulative measures will be used, as with serum CRP, to reflect the overall impact of disease outcome. A blinded panel of pancreatic radiologists at the Royal Liverpool University Hospital will assess the extent of injury seen on CECT on Day 14. EQ-5D-5L will be used to calculate the incremental cost per QALY gained through trial treatment (see section 7.4.1 below). The measures have been confirmed in the BRU cohort to display abnormality in all patient groups, proportional to severity and clinical outcomes.

7.3 Procedures for Assessing Safety

Each trial participant's baseline data will assist identification of any adverse event, whether or not related to infliximab administration, distinct from any adverse reaction where there may be a relationship with infliximab. There will be monitoring during the infliximab infusion, and a member of the trial team will review trial participant in-patients daily. If discharged, participants will be asked whether they have experienced any adverse events at return visits until study completion at the Day 90 time point. The needs of each patient will determine further referral (e.g. to Infectious Diseases Physician[43]) and standard follow-up for AP.

Exploratory safety analyses will be undertaken using transcripts selected to assess (1) innate immune responses; (2) changes in T cell subsets and their functions; (3) other changes contributing to immune competence, complemented by cytokine profiling.

7.3.1 Safety Assessment 1

Hepatitis B surface antigen and core antibody will be assayed after trial entry[43]; standard liver function tests (albumen, bilirubin, alanine aminotransferase / aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase) will be monitored at all sampling time points (Days 2, 7, 14, 28 and 90).

7.3.2 Safety Assessment 2

Adverse events related to infliximab including infusion reactions and delayed serum sickness reactions (that typically occur after a second or subsequent infliximab infusion that will not to be given in this trial, but the reaction may still occur) will be reviewed during and subsequent to trial treatment up to Day 90 days.

7.3.3 Safety Assessment 3

Antibodies to infliximab will be measured at Day 28.

7.3.4 Safety Assessment 4

The number of infective complications in participants receiving infliximab at either dose will be compared with the number of infective complications in participants receiving placebo. Data on the number of infective complications in each treatment arm will be presented at each IDSMC meeting during the conduct of the trial (made available by the Trial Statistician and seen only by the IDSMC, see section 10.4) and analysed when the trial is complete (see section 10.5).

7.3.5 Safety Assessment 5

Exploratory (discovery) safety analyses will be undertaken using transcripts selected to assess (1) innate immune responses; (2) changes in T cell subsets and their functions; (3) other changes contributing to immune competence, complemented by cytokine profiling.

7.3.6 Safety Assessment 6

Urine pregnancy tests at baseline and the Day 28 time point will be performed for all female participants of childbearing potential. Pregnancy of female partners of male trial participants will not be assessed or reported as part of the trial.

7.4 Other Assessments

7.4.1 Health Economics

A cost utility analysis will be conducted to estimate the incremental cost per quality-adjusted life year (QALY) gained with infliximab (optimal dose) versus placebo (standard care).

The direct costs of health care resources used by patients in the trial after discharge from their index (trial) admission will be calculated from data collected using an HRUQ (Health Resource Use questionnaire) and administered by the RN at Days 28 and 90 (if patient discharged from their index (trial) admission). The questionnaire includes items related to use of primary care services, A&E, inpatients stays and outpatient clinic visits. Patients' use of secondary care services while admitted will be recorded directly using the study CRFs. These will be supplemented with PLICS data, obtained subject to agreement from the Finance Departments of each participating centre. These datasets include Health Resource Groups which detail costs for patient stays and treatments. Responsibility for the data collection and anonymization will rest with the site RN who will supply their site Finance Departments with the necessary details to ensure only information on consented participating patients are provided. It is the responsibility of the site Finance Departments to provide the site RNs with the data in a timely fashion and should the site RN so request, to ensure all patient identifying data have been replaced with the patient RAPID-I trial number. Anonymised PLICS data will be transferred securely from each site RN to the CTRC, and then on to the Centre for Health Economics and Medicines Evaluation, Bangor University for analysis.

QALYs will be estimated from patients' responses to the EQ-5D-5L questionnaire, administered on Days 4 (only if the patient is conscious and able to), 14, 28 and 90. The five attributes of this questionnaire (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarised into a single preference-based utility score.

7.4.2 Special Assays or Procedures

Transcriptomic (2.5 ml blood x 2 in PAXgene tubes) and cytokine (5 ml clotted blood in SST tube (centrifuged) for serum, in addition to separate 5 ml clotted blood in SST tube (centrifuged) for the primary outcome measure CRP) samples will be taken at baseline and at Days 2, 4, 7, 14 and 28 time points. Additionally, 8.5 ml PAXgene tube blood sample for DNA will be taken at baseline only, and samples will be taken at baseline, Days 4 and 14 for PBMC profiling (6 ml in ACD).

Trial samples (including those for CRP at the specified time points) will be packaged into kits (supplied by NIHR National Biosample Centre) and when possible *sent on the same day* and if not then *as promptly as possible thereafter* to the NIHR National Biosample Centre (NIHR NBC, Units 2&3, Java Park, Bradbourne Drive, Tilbrook MK7 8AT, UK).

Subsequently NanoString technology will be used for quantitative transcriptomic analyses, with eQTL analysis from Illumina genome-wide association study of patient DNA, assessing a panel of 100 gene transcripts defined from the BRU whole transcriptome cohort study at the time points specified. The transcripts have been selected from all those differentially expressed between mild and severe disease, with 20 transcripts representing each of (1) the largest and most consistent differential expression between mild and severe disease, including a prognostic signature; (2) TNFα and downstream signaling; (3) innate immune responses, notably those of neutrophils typical of AP; (4) changes in T cell subsets and their functions; (5) other changes contributing to immune competence. This will be complemented by Luminex cytokine profiling of TNFα, interleukin 6 (IL6), IL2, total interferon alpha and gamma, and by peripheral blood mononuclear cell subset mass cytometry (Cytometry by time of flight, CyTOF) in all participants.

Participants will be asked if they are happy to consent to any remaining samples being kept for use in future research studies (this will be optional to patients). Samples will be stored at the National Biosample Sample Centre for future and exploratory measurements.

7.5 Patient Transfer

For participants moving from the area in which they were originally recruited to the trial, every effort should be made for them to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via the participant's GP.

A transfer case report form (CRF) will be completed by the current site and returned to CTRC. CTRC will then forward the transfer CRF on to the new site, the PI at the new site will be asked to sign this CRF and return to CTRC to confirm that they are taking over responsibility for the patient in the trial. The current site should provide a copy of the participant's full CRF to the new site.

7.6 Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. Participants (or their Legal Representatives) are free to withdraw consent at any time without providing a reason.

If voluntary premature discontinuation of treatment occurs, the participant (or Legal Representative) should be asked to allow continuation of scheduled evaluations and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.

Follow-up of these participants will be continued through the trial research nurses, the PI at each centre and, where these are unsuccessful, through the participant's General Practitioner (GP, via the site), unless the participant explicitly also withdraws consent for follow-up.

7.6.1 Premature Discontinuation of Trial Intervention

Participants may prematurely discontinue trial treatment for any of the following reasons:

a. Withdrawal of consent.
b. Unacceptable toxicity.
c. Intercurrent illness preventing further treatment.
d. Any change in the participant's condition that justifies the discontinuation of treatment in the attending clinician's opinion.

If a participant wishes to prematurely discontinue trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 7.6.2).

7.6.2 Withdrawal from Trial Completely

Those who wish to withdraw consent for the trial completely will have pseudonymised data collected up to the point of that withdrawal included in the analyses, however the participant will not contribute further data to the trial. The CTRC must be informed in writing and a withdrawal CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

7.7 Loss to Follow-up

The minimum follow-up will be until Day 90 from the time of recruitment of the last participant. If any of the trial participants are lost to follow-up, contact will initially be attempted through the local PI or delegated research staff at each site. Wherever possible, information on the reason for loss to follow-up will be recorded.

In the case of a missed assessment visit, the scheduled measurements at the next visit should be carried out as planned and the lost data due to the missed visit will be considered as missing values.

7.8 Trial Closure

The end of the trial is defined in 7.8.1. The TSC, however, may close the trial prematurely on the recommendation of the IDSMC.

7.8.1 Definition of End of Trial

The end of the trial is defined as the date on which data for all participants are frozen and data entry privileges are withdrawn from all trial databases.

8 TRIAL TREATMENT

8.1 Introduction

Infliximab is a prescription drug with marketing authorisation for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. In the RAPID-I trial infliximab will be used outside the manufacturer's indication for the treatment of AP, and it is classed as an investigational medicinal product (IMP).

Participants will be randomised equally (section 5.10) to infusion with 5 mg/kg infliximab (arm A, section 8.2), infusion with 10 mg/kg infliximab (arm B, section 8.3) or infusion of 0.9% sodium chloride (arm C placebo, section 8.4).

Compulsory administration of non-investigational medicinal products (NIMPs) before and after the IMP/placebo infusions is described in section 8.9.1.

Please refer to the current Summary of Product Characteristics (SPC) for REMICADE® 100mg powder for concentrate for solution for infusion, available on the Electronic Medicines Compendium (eMC) website: https://www.medicines.org.uk/emc/. Additional information is also available in the RAPID-I Pharmacy Manual.

8.2 Arm A - Infusion of 5 mg/kg Infliximab

8.2.1 Formulation, Packaging, Labelling, Storage and Stability

Generic name: Infliximab

Brand name: REMICADE®

Supply and distribution: Commercial vials of infliximab will be supplied by Merck Sharp and Dohme (MSD) to the contracted distributor for distribution to trial centres. Shipment requests will be authorised by the CTRC.

Packaging: Type 1 glass vial with rubber stopper and aluminium crimp protected by a plastic cap.

Formulation: Each vial contains infliximab 100 mg powder in the form of freeze-dried white pellet, for concentrate for solution for infusion.

Labelling: Infliximab will be labelled by the distributor in accordance with regulation 46 SI2004/1031 and the detailed guidance provided in annex 13 of the European Union (EU) Good Manufacturing Practice (GMP) guide. Each vial will be labelled and used for RAPID-I trial use only.

Storage: Infliximab should be stored in a refrigerator at 2 °C to 8 °C and can be stored for up to 3 years, or less as per expiry/re-test date. Upon removal from refrigerated storage, infliximab must not be returned to refrigerated storage. *N.B. Storage instructions are for infliximab before reconstitution.*

Stability: Once reconstituted, the infliximab solution should be used as soon as possible and within 3 hours of reconstitution and dilution. When reconstitution and dilution are performed under aseptic conditions, infliximab infusion solution can be used within 24 hours if stored at 2 °C to 8 °C. Do not store any unused portion of the infusion solution for re-use.

8.2.2 Dosage, Preparation and Administration of Study Treatment/s

Dosage: 5 mg/kg is 5 mg of infliximab per kg of body weight. Each REMICADE® vial contains 100mg infliximab. The participant's weight will be detailed on the prescription and the trial pharmacy staff will calculate the appropriate dose and number of vials needed for that participant. As anaphylactic shock is a possible infusion reaction of infliximab, emergency resuscitation equipment should be available in the ward area within which the administration of study treatment is conducted, including an artificial airway.

Preparation: Reconstitute and dilute in accordance with the current manufacturer's SPC, available on the eMC website (https://www.medicines.org.uk/emc/).

NB For patients who weigh under or equal to 100 kg, please make up into a total volume of 250 ml with 0.9% sodium chloride. For patients who weigh over 100 kg and up to 200 kg, please make up into a total volume of 500 ml with 0.9% sodium chloride. This will ensure the concentration of infliximab infusion will not exceed 4mg / ml, as per manufacturer's SPC.

Reconstitution: Please refer to the RAPID-I pharmacy manual for instruction.

Administration: Diluted infliximab in 0.9%Sodium Chloride:

1. Should be administered intravenously and initiated within 12 hours of admission. The infusion should be started as soon as possible once provided by Pharmacy (this must be within 3 hours of reconstitution and dilution, or with 24 hours if stored under refrigerated conditions 2°C - 8°C)
2. Over a 2 hour period.
3. Via an infusion pump, using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less).
4. Qualified healthcare professionals (authorised by the PI on the Delegation Log) trained to detect any infusion-related issues should administer the infusion.
5. All patients administered REMICADE® are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions.

8.2.3 Specific Restrictions

The effect of co-administration of infliximab with other agents is unknown. Do not infuse infliximab concomitantly in the same intravenous line with other agents.

8.2.4 Overdose

Overdose may occur if the wrong patient weight has been supplied to Pharmacy, an incorrect weight is used in the calculation or the calculation has been done incorrectly. As per REMICADE® 100mg powder for concentrate for solution for infusion SPC, single doses up to 20 mg/kg have been administered without toxic effects. Special care must be taken by all site team members to avoid overdosing, notably by the Pharmacist who is most likely to identify an overdose has been prepared. In the event of identification of an overdose, unblinding should occur, the patient will be closely observed for any AE and the site team should notify the CTRC of the event and examine the reasons for the event occurring to ensure that it does not happen again. The CTRC will log this event as a protocol deviation.

8.3 Arm B - Infusion of 10 mg/kg Infliximab

8.3.1 Formulation, Packaging, Labelling, Storage and Stability

See section 8.2.1.

8.3.2 Dosage, Preparation and Administration of Study Treatment/s

Dosage: 10 mg/kg is 10 mg of infliximab per kg of body weight. Each REMICADE® vial contains 100 mg infliximab. The participant's weight will be detailed on the prescription and the trial pharmacy staff will calculate the appropriate dose and number of vials needed for that participant.

Preparation and administration are as described in section 8.2.2.

8.3.3 Specific Restrictions

See section 8.2.3.

8.3.4 Overdose

See section 8.2.4.

8.4 Arm C - Placebo

250 mls (for patients weighing under or equal to 100 kg) or 500 mls (for patients weighing over 100 kg and up to 200 kg) commercial sodium chloride (0.9%) solution:

1. Should be administered intravenously and initiated within 12 hours from admission.
2. Over a 2 hour period.
3. Via an infusion pump, using an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less).

8.5 Dose Modifications/Interruption

If a mild reaction occurs to the administration of trial treatment (e.g. pruritus, flushing or myalgia) then the infusion does not need to be modified. If a moderate reaction occurs (e.g. chest tightness, urticaria or hypertension), the infusion should be interrupted and chlorphenamine i.v. (if not already administered, or a further dose of 10 mg if 10 mg has already been administered) and/or paracetamol should be administered. If there is a favourable response following this, then the infusion can be resumed. If there is a severe reaction then the infusion should be immediately stopped and emergency management should take place with adrenaline, resuscitation and intensive support.

8.6 Blinding and Unblinding

8.6.1 Blinding

Infusion bags for IMP/placebo treatment will be covered in an opaque sleeve, sealed and labelled by the Pharmacist for blinding, thus Pharmacy departments are not blinded to the treatment allocation. Any evidence of seal breakage or tampering observed by any member of the trial team should be recorded as accidental unblinding as per section 8.6.2.1.

8.6.2 Unblinding

N.B. Allocation must not be routinely revealed to CTRC personnel. Unblinding will generally be discouraged during treatment.

If simply ceasing trial treatment is a viable option for the participant's care, it should not be necessary for unblinding to occur.

Justification: Unblinding is done on a per case basis (i.e. single participant) when knowing the treatment allocation is needed to:

1. Enable treatment of severe adverse event/s, or
2. Enable administration of another therapy that is contraindicated by the trial treatment, or
3. Enable appropriate ongoing care upon cessation of allocated trial therapy.

Procedure:

During CTRC office hours (Monday-Friday 9 am-5 pm, excluding bank holidays):

1. Site personnel should call the Trial Coordinator at CTRC who will contact the Chief Investigator (Professor Robert Sutton), to obtain approval where possible.
2. Once approved, site personnel should then request the unblinding from the local site Pharmacy (N.B. The PI is responsible for ensuring that all research personnel are aware of contact details for obtaining details of treatment allocation).

Out of CTRC office hours:

Site personnel should request the unblinding from the local site Pharmacy (N.B. The PI is responsible for ensuring that all research personnel are aware of contact details for obtaining details of treatment allocation), if Pharmacy is open.

Out of site Pharmacy office hours:

1. Assume all patients are on infliximab and administer treatment accordingly.

In all instances of unblinding:

1. Do not disclose treatment allocation to site personnel unless knowledge is directly relevant to patient care.
2. Record and report in writing to the CTRC, by use of the unblinding CRF (including the identity of all recipients of the unblinding information).

Please note, should an emergency situation occur, unblinding may occur without approval being in place from the CI and CTRC to enable management/treatment of patient.

8.6.2.1 Accidental Unblinding

If accidental unblinding occurs, this must be reported to the CTRC by use of the unblinding CRF. When reporting include details about:

1. Date of unblinding;
2. Detailed explanation of circumstances;
3. Recipients of the unblinding information;
4. Action to prevent further occurrence.

8.6.2.2 Unblinding at Trial Closure

Upon trial closure the criteria for unblinding will remain in effect. Pharmacy departments **should not** disclose treatment allocations on an individual basis.

Incidents of immunogenicity to even single low doses of infliximab are not uncommon; this is of concern because future use of the drug might be rendered ineffective. For this reason, at trial closure, the CTRC will notify local investigators in writing of unblinding information for patients under their care. A copy of this notification should be placed in the medical records and a copy retained in the Investigator Site File. It is the responsibility of the local investigator to notify trial participants of their allocated treatment.

8.7 Accountability Procedures for Study Treatment

IMP stock must be received at recruiting centres by a designated member of the Pharmacy department and must be stored in accordance with IMP regulations. Records of all shipments must be kept in the drug accountability records.

If IMP stock received from the distributor is unexpected, wrong, damaged (e.g. packaging, labelling) or out of acceptable temperature range, the stock must be quarantined and CTRC contacted for further actions. Any IMP defects or possible defects will be reported by CTRC to MSD within one business day of first becoming aware of the issue.

If any stock expires at the trial site during the trial or any surplus stock remains at the trial site at trial closedown, this must be notified to the CTRC who will authorise destruction. Stock will be destroyed locally according to site policy and documented in the drug accountability records.

8.8 Assessment of Compliance with Study Treatment

In all three arms, the full volume (250 ml, or 500ml for all patients weighing over 100kg) of the treatment infusion should normally be administered over a period of 2 hours. The total volume administered should be calculated from the infusion rate and time over which the infusion has run, and recorded once administered. Any defect in the opaque sleeve over the infusion bag or evidence of seal breakage or tampering observed by any member of the trial team should be recorded as accidental unblinding as per section 8.6.2.1.

8.9 Concomitant Medications/Treatments

8.9.1 Non Investigational Medicinal Products (NIMPs)

As NIMPs do not fall within the definition of investigational medicinal products, Articles 13 and 14 of Directive 2001/20/EC are not directly applicable. Therefore, these NIMPs should be dispensed and destroyed in accordance with local legislations and requirements. All NIMPs to be administered will be sourced via usual hospital procurement arrangements and stored in accordance with local hospital practice and in compliance with manufacturer's instructions. All NIMPs prescribed to participants taking part in RAPID-I will be recorded on the "Concomitant Medications CRF".

The following NIMPs are to be administered to **all participants <u>before and continued after</u>** the IMP/placebo infusion:

- piperacillin/tazobactam 4.5 g i.v three times a day (t.d.s) for up to 7 days or until discharge, whichever is earlier.
- as an alternative, centres may use one of their own antibiotic regimens for intra-abdominal infection as defined in their written local antibiotic policy (e.g. because of penicillin allergy) for up to 7 days or until discharge, whichever is earlier, and recorded in the trial CRF accordingly.

NIMPs to be administered to **all participants <u>before</u>** the IMP/placebo infusion are:

- 100 mg hydrocortisone i.v. (compulsory prophylactic), and
- 10 mg chlorphenamine i.v. (compulsory prophylactic).

NIMPs to be administered to participants as required are:

- chlorphenamine (further dose of 10 mg i.v.)
- paracetamol, and
- adrenaline, to be prescribed in advance of administration of trial IMP and used in the event of severe anaphylaxis according to the Resuscitation Council (UK) guidelines.

8.9.2 Medications Not Permitted/ Precautions Required

In the absence of compatibility studies, this medicinal product must not be infused with other medicinal products. The SPC for REMICADE®, available on the eMC website (https://www.medicines.org.uk/emc/), must be followed in all patients who are entered into the RAPID-I trial during the 90 days of follow-up, avoiding concurrent administration of other biological therapeutics, live vaccines and therapeutic infectious agents.

8.9.3 Data on Concomitant Medication

Concomitant medications are to be collected from trial entry until study completion at Day 90 and recorded on the "Concomitant Medications CRF". The details to be recorded are all NIMPs administered, antibiotics prescribed outside of the protocol, the use of opiates and use of inotropes. The PI or delegated research team member should reassess concomitant medications at each Trial visit and record the required medicines on the CRF. A photocopy of the original Concomitant Medication CRF should be sent to the CTRC within 7 days of all updates. The original copy of the CRF should only be sent to the CTRC on completion of follow-up for each participant.

9 SAFETY REPORTING

Safety reporting in clinical trials aims to ensure both the safety of trial participants and the safety of current and future patients. Effective safety reporting facilitates an ongoing assessment of risk- benefit ratio. Emerging safety data allows the Sponsor to safely manage the trial by introducing amendments to the protocol, provide updated information to investigators and participants where necessary, and determine whether it is safe to continue to conduct the trial or make changes to the protocol.

9.1 Terms and Definitions

"Adverse Event (AE)"
An adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Therefore an AE is any unfavourable or unintended change in the function (symptoms), structure (signs) or chemistry (laboratory data) in a subject to whom an IMP has been administered, including occurrences which are not necessarily caused by or related to that product.

"Adverse Reaction (AR)"
An adverse reaction is any untoward and unintended response in a subject to an investigational medicinal product that is related to any dose administered to that subject.

Therefore an AR is any unfavourable or unintended change in the function (symptoms), structure (signs) or chemistry (laboratory data) in a subject that is related to any dose of an IMP administered to that subject.

"Unexpected Adverse Reaction (UAR)"
An unexpected adverse reaction is an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Investigator's Brochure (IB) or the SPC, which may be referenced where the IMP in question is a product with a marketing authorisation.

"Serious Adverse Event (SAE), "Serious Adverse Reaction, or Unexpected Serious Adverse Reaction"
An AE, AR or UAR respectively that:

- results in death;
- is life threatening (places the subject, in the view of the Investigator, at immediate risk of death from the experience as it occurred – this does not include an adverse experience that, had it occurred in a more severe form, might have caused death);
- requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation – hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE);
- results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);

- other important medical events (these may not result in death, be life-threatening, or require hospitalisation, but may be considered a serious adverse event or experience when, based upon appropriate medical judgment, they are considered to jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

"Suspected Serious Adverse Reaction (SSAR)"
An adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question, which in the case of a licensed product is set out in the SPC for that product, and in the case of any other investigational medicinal product is set out in the IB relating to the trial in question.

"Suspected Unexpected Serious Adverse Reaction (SUSAR)"
An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question, which in the case of a licensed product is set out in the SPC for that product, and in the case of any other investigational medicinal product is set out in the IB relating to the trial in question.

"Reference Safety Information (RSI)"
The information used for assessing whether an adverse reaction is expected. This is contained in either the IB or the SPC.

9.2 Notes on Adverse Event Inclusions and Exclusions

The below sections provide guidance on what should, and should not be considered as AEs for the purposes of the RAPID-I trial:

9.2.1 Include

- An exacerbation of a pre-existing illness.
- An increase in frequency or intensity of a pre-existing episodic event/condition.
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration.
- Continuous persistent disease or symptoms present at baseline that worsen following the administration of the trial treatment.
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention.
- Injury or accidents.

9.2.2 Do Not Include

- Medical or surgical procedures* – the condition which leads to the procedure is the adverse event.
- Pre-existing disease or conditions present before treatment that do not worsen.
- Situations where an untoward medical occurrence has occurred, e.g. cosmetic elective surgery.
- Overdose of medication without symptoms or signs**.
- Widely recognised and documented clinical features of acute pancreatitis that are defined outcome measures in this trial (see section 7.2).

* *Cosmetic elective surgery is cited here as example of an event that is not reportable as an AE.*
** See also section 8.2.4** Error! Reference source not found.**. *If overdose occurred with resulting symptoms and signs that met the protocol criteria for AE/AR/SAE/SAR then they should be reported accordingly. This bullet is to note that although overdose of medication without symptoms or signs may be excluded from AE reporting this may still require investigation to ensure the protocol and regulatory requirements are met, e.g. for IMP management and administration to ensure participant safety.*

9.2.3 Notification of Deaths

There is an overall likelihood of death in all cases of AP of 3-5%, the likelihood of which is proportional to severity (mild, moderate and severe, RAC)[1,2,32]. All deaths that occur during the protocol-specified AE reporting period (randomisation to Day 90 time point), regardless of relationship to study drug, must be recorded. All deaths should be reported on a "Serious Adverse Event CRF" and returned to the CTRC within 24 hours.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the appropriate CRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a participant with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the participant was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the appropriate CRF. If the cause of death subsequently becomes available (e.g. after autopsy), "unexplained death" should be replaced by the established cause of death.

9.2.4 Reporting of Pregnancy / Lactation

A urine pregnancy test will be performed at Baseline for all female participants of childbearing potential. This will be repeated at the Day 28 visit. Female participants of childbearing potential must agree to use adequate contraception for up to 90 days following administration of study treatment.

Any pregnancy identified in a female participant up to 28 days from the day of trial treatment administration, whether associated with an AE or not, must be reported to the CTRC within 24 hours of the local research team becoming aware, in accordance with the timelines and contact information for an SAE. PIs shall follow pregnancies to term to obtain the outcome of the pregnancy and this is to be reported to the CTRC, which will report directly to MSD.
Patients who are known to be lactating at the time of screening will be excluded from the trial. If it is later discovered that a patient was lactating at the time of receiving the trial infusion, then any occurrences of this must be reported to MSD by CTRC, in accordance with the timelines and contact information for an SAE.

9.3 Notes on Severity / Grading of Adverse Events

The investigator responsible for the care of the participant should assign the severity/grading of each adverse event using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities

Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 2, hence, a severe AE need not necessarily be a SAE.

9.4 Relationship to Trial Treatment

The local Investigator responsible for the care of the participant should assign the causality of each AE using the definitions in Table 4. An AE whose causal relationship to the study drug is assessed by the investigator as “possible”, “probable”, or “definite” is an AR.

If any doubt about the causality exists the local Investigator should inform the CTRC who will notify the CI. In the case of discrepant views on causality between the local Investigator and others, the MHRA will be informed of both points of view.

Table 4: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

9.5 Expectedness

The Reference Safety Information (RSI) in RAPID-I is sections 4.3 to 4.9 of the REMICADE® 100mg powder for concentrate for solution for infusion SPC.

It is not a regulatory requirement for a reporting physician to provide their opinion of expectedness. Therefore, the reporting physician at the local research site will not be asked to make an assessment of expectedness. The assessment of expectedness will be made by the CI (or their medically qualified delegate) using the trial’s current MHRA-approved RSI following receipt of the “Serious Adverse Event CRF” at CTRC.

All events graded as serious and judged by the local reporting Investigator to be possibly, probably, or almost certainly related to the IMP, and assessed as **unexpected** by the CI or their delegate, will

be reported as a SUSAR (see section 9.2 and Summary of Product Characteristics for the list of Expected Adverse Events).

9.6 Follow-up After Adverse Events

All adverse events (AEs/ARs/SAEs/SARs/SUSARs) should be followed until satisfactory resolution or until the local Investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.

When reporting serious adverse events (SAEs/SARs/SUSARs) the local Investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved;
- resolved with sequelae (specifying with additional narrative);
- not resolved/ongoing;
- on-going at final follow-up;
- fatal or unknown.

9.7 Time Period for Adverse Event Reporting

Investigators and delegated members of the local research teams will actively monitor participants for all adverse events from randomisation until the end of their trial follow-up period (i.e. Day 90 time point), and report these to the CTRC on the appropriate CRFs (see section 9.8).

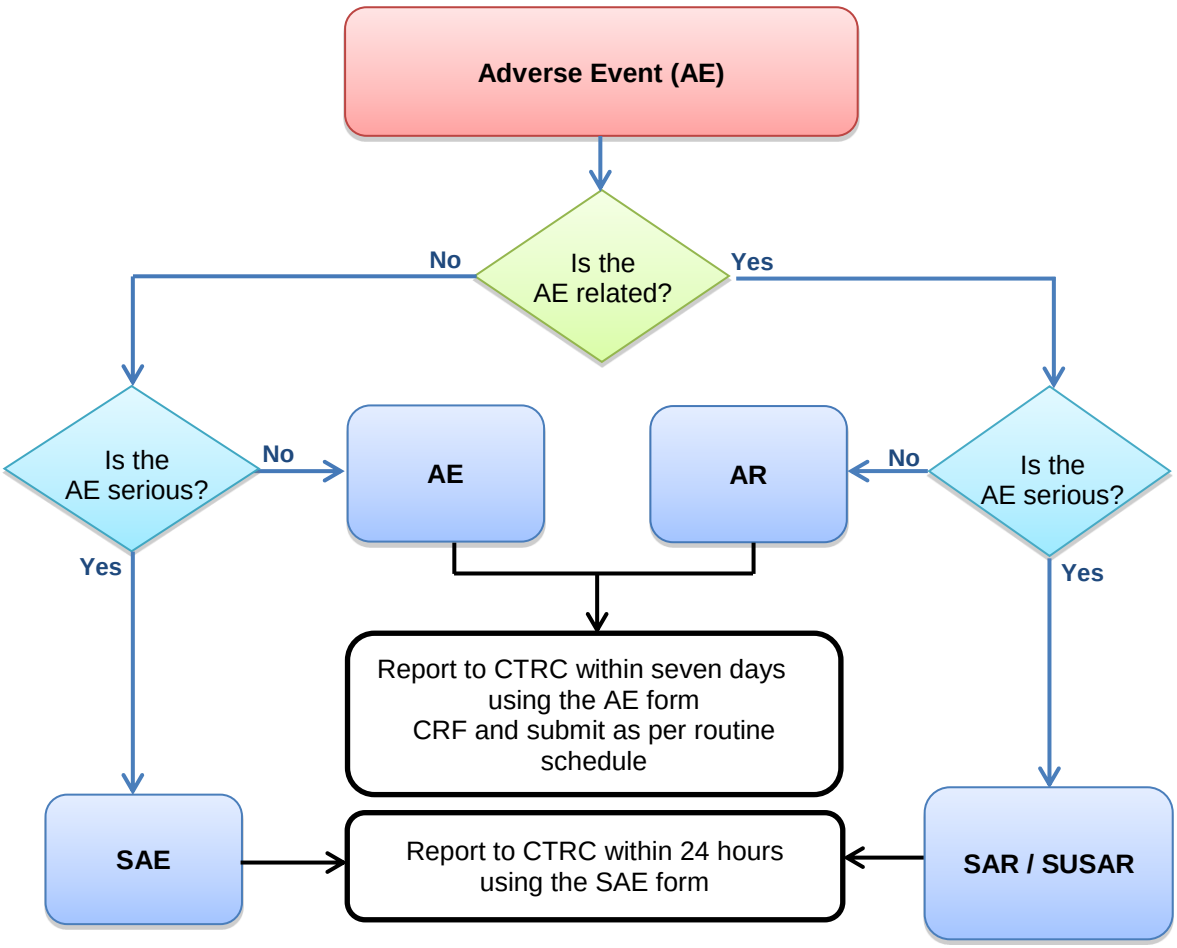
Outside of this period of active monitoring, should the Investigator (or other members of the local research team) become aware of adverse events that meet the definition of serious, these should also be reported to the CTRC. Any events assessed as serious, related and unexpected will be reported.

Upon becoming aware of a serious adverse event (SAE/SAR/SUSAR), the Investigator or other delegated member of the team must report this to the CTRC within 24 hours.

9.8 Reporting Procedures

Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTRC in the first instance. A flowchart is given below to aid in determining reporting requirements.

Figure 4. Flowchart for Reporting Requirements of Adverse Events (AE)



9.8.1 Non-serious Adverse Events (AEs/ARs)

All non-serious adverse events (i.e. AEs and ARs), whether expected or not, should be recorded on an "Adverse Event CRF", which should be transmitted to the CTRC within seven days of the local research team becoming aware of the event.

9.8.2 Serious Adverse Events (SAEs/SARs/SUSARs)

All serious adverse events (i.e. SAEs, SARs and SUSARs) must be reported to CTRC within 24 hours of the local site becoming aware of the event. The "Serious Adverse Event CRF" asks for the nature of the event, date of onset, severity, corrective therapies given, outcome and causality. The reporting local Investigator should assign the causality of the event. Additional information should be sent within 5 days if the event has not resolved at the time of initial reporting.

In line with MSD policies for the reporting of adverse events in connection with investigator-initiated studies supported by MSD, the CTRC will notify MSD of all serious adverse events (SAEs/SARs/SUSARs) that occur during the trial within two business days of becoming aware of the event. These reports will remain blinded.

All adverse events assessed as serious, related and unexpected (i.e. SUSARs) will be reported on to the MHRA and RAPID-I's Research Ethics Committee (REC) by the CTRC according to the following timelines; fatal and life-threatening SUSARs within 7 days of notification to CTRC and non-life

threatening SUSARs within 15 days. RAPID-I PIs will be notified of all SUSARs occurring throughout the trial by the CTRC. Local Investigators should report any SUSARs and/or SAEs as required locally.

9.9 Safety Reporting Responsibilities – Investigator

The Investigator is responsible for reporting all AEs regardless of their relationship to the trial intervention.

All serious adverse events (SAEs/SARs/SUSARs) must be reported to CTRC within 24 hours of the local research team becoming aware. All non-serious adverse events should be reported to CTRC within seven days of the local research team becoming aware.

Patient safety incidents that take place in the course of research should be reported to the National Reporting and Learning System (NRLS) by each participating NHS Trust in accordance with local reporting procedures.

Minimum information required for reporting serious adverse events (SAEs/SARs/SUSARs)

- Valid European Clinical Trials Database (EudraCT) number (if applicable)
- Sponsor trial number
- One identifiable coded subject (randomisation number)
- One identifiable reporter
- One SAE
- Suspect IMP (infliximab)
- A seriousness assessment
- A causality assessment

Process for reporting serious adverse events

i. The “Serious Adverse Event CRF” should be completed, signed and submitted to the CTRC by a local Investigator named on the trial’s ‘signature list and delegation of responsibilities log’ as responsible for reporting SAEs and making trial-related medical decisions. The Investigator should assess the SAE for the likelihood that it is a response to the trial intervention. In the absence of an authorised local Investigator, the CRF should be completed (excluding causality assessment) and signed by an alternative member of the local research team and submitted to the CTRC. As soon as possible thereafter, the responsible investigator should check the SAE form, make amendments as appropriate, provide a causality assessment, sign and re-send to the CTRC. Initial CRF reports shall be followed by detailed follow-up CRF reports as appropriate.

ii. When submitting a “Serious Adverse Event CRF” to the CTRC research sites should also telephone the appropriate Trial Co-ordinator or Data Manager on telephone number **0151 794 9774** to advise that an SAE report has been submitted.

iii. The “Serious Adverse Event CRF” must be submitted to the CTRC within 24 hours of the local research team becoming aware of the event; preferably this will be via fax:

Fax Number: 0151 795 8770

iv. The local reporting Investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. The participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up should continue after completion of protocol treatment as necessary.
vi. Follow-up information should be noted on another "Serious Adverse Event CRF" by ticking the box marked 'follow-up' and submitting to the CTRC as information becomes available. Extra, annotated information and/or anonymised copies of test results may be provided separately.
vii. The participant **must** be identified by trial randomisation number, date of birth and initials only. The participant's name **must not** be used on any correspondence.

9.9.1 Maintenance of Blinding at Sites

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for infliximab (irrespective of dose) and placebo. Unblinding will be done through the Pharmacy at each individual site. If unblinding needs to occur out of Pharmacy hours, it should be assumed that the participant is on infliximab and treatment should be administered accordingly. All instances of unblinding must be recorded and reported to the CTRC.

9.10 Safety Reporting Responsibilities – CTRC

The CTRC is undertaking duties delegated by the trial Sponsor and is responsible for the notification of serious adverse events to the CI (or appropriate delegate) for review and expectedness assessment, and onward expedited reporting of SUSARs and other SARs to the MHRA and REC. The CTRC will also notify trial PIs of all trial SUSARs.

Upon receipt of a "Serious Adverse Event CRF", CTRC will liaise with the trial CI (or appropriate delegate) who will evaluate the events reported for seriousness, expectedness and causality. These will be reviewed within 24 h and those that are identified as SUSARs will be reported to MHRA and REC by the CTRC. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

Timelines of onward reporting to MHRA and REC are as follows:

- SUSARs that are fatal or life-threatening must be reported not later than 7 days after the CTRC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTRC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- an increase in the rate of occurrence or a qualitative change of an expected SAR, which is judged to be clinically important;
- post-study SUSARs that occur after the patient has completed a clinical trial and are notified by a local Investigator to the CTRC.
- new events related to the conduct of the trial or the development of the IMP and likely to affect the safety of the participants, such as:

a. a SAE that could be associated with the trial procedures and which could modify the conduct of the trial;
b. a significant hazard to the participant population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
c. a major safety finding from a newly completed animal study (e.g. carcinogenicity);
d. any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- recommendations of the IDSMC, if any, where relevant for the safety of the participants.

9.10.1 Maintenance of Blinding at CTRC

Adverse events that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial treatments (i.e. SUSARs) will have to be unblinded at the CTRC prior to reporting to the MHRA and REC.

9.11 Safety Reports

Safety reports will be generated during the course of the trial that allow for monitoring of SAE and SAR reporting rates across sites, and reviewed at trial oversight committee meetings. The CTRC will send Developmental Safety Update Reports (DSURs) containing a list of all SAEs to the MHRA and REC annually. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTRC to carry out site visits if there is suspicion of unreported safety events in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

9.12 Urgent Safety Measures

An urgent safety measure is a procedure not defined by the protocol, which is put in place prior to authorisation by the MHRA and REC in order to protect clinical trial participants from any immediate hazard to their health and safety.

The CTRC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the urgent safety measure and the plan for further action. After discussion with the MHRA and REC, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

If the study is temporarily halted it may not recommence until authorised to do so by the MHRA and REC. If the study is permanently terminated before the date specified for its conclusion (in the original applications to MHRA and REC), the CTRC should notify the MHRA and REC within 15 days of the date of termination by submitting the formal End of Trial Notification.

9.13 Contact Details and Out-of-hours Medical Cover

Participants will be instructed to contact the local Investigator (their office number) during working hours. A patient card providing details of their participation in the RAPID-I trial will also be supplied. Outside working hours the normal local procedure should be followed. Ward and switchboard staff should be aware where they should direct calls in- and out-of-hours.

10 STATISTICAL CONSIDERATIONS

10.1 Introduction

Separate Statistical Analysis Plans (SAPs) will be developed prior to the interim and final analyses of the trial. The main features of these planned statistical analyses are included here in the protocol.

10.2 Method of Randomisation

Participants will be equally randomised to all treatment arms currently in the trial using a secure (24-hour) web-based randomisation programme controlled centrally by CTRC to ensure allocation concealment. Randomisation lists will be generated using block randomisation with random variable block length, stratified by site. The lists will be produced by an independent statistician (who is not otherwise involved in the RAPID-I trial) at CTRC.

10.3 Sample Size Calculation

An adaptive trial design[18] will be adopted and treatment arms may be dropped prematurely as outlined in section 10.4. The total planned sample size is 261, with each active treatment arm and the placebo arm having an equal number of patients (n=87). The study will seek to recruit a total of 290 patients to account for a 10% drop-out rate. The proposed sample size of 261 is based on a one-sided overall (family-wise) type I error of 2.5% and a power of 90% to detect a 25% smaller CRP AUC value than participants on placebo. This order of magnitude of drop is indicative of a meaningful impact on clinical outcomes in AP[39]. This specification of the effect of interest (reduction in CRP AUC) corresponds to a difference between the groups of 0.545s, where s is the standard deviation of CRP, and has the advantage that it is not necessary to pre-specify the standard deviation to obtain the required sample size.

10.4 Interim Monitoring and Analyses

Two planned interim analyses will occur during the 24-month recruitment period. Recruitment will continue while both interim analyses are taking place. The first will take place after the primary outcome has been observed for 29 patients in each arm. At this point any treatment arm with a mean CRP AUC value larger or equal to the control group will be dropped. Should both treatment arms be dropped, the study will stop.

A second interim analysis will take place after the primary outcome has been observed for a total of 58 patients in each of the remaining arms. The stopping rules will be as for the first interim analysis.

The design has been specified such that any treatment that is worse than placebo at the interim analysis has to be dropped. To account for (potentially) dropping of a dose for other reasons, the conditional error principle is to be used to adjust the design[19].

10.5 Analysis Plan

The IDSMC will review the results of the interim analyses and advise the TSC if any treatments are to be dropped on the basis of the pre-defined rule. The IDSMC will also be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up of recruited participants. Any such decision to discontinue recruitment, in all participants or in selected subgroups will be made only if

the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

The trial will be analysed using the International Conference on Harmonisation E9 Guidelines and reported using the 'Consolidation Standard of Reporting Trials' (CONSORT[47]) guidelines. Full analysis plans will be developed prior to the interim and final analyses of the trial. The main features of the statistical analysis are included here. The analysis of primary and secondary outcomes will use the principle of intention to treat, based on all randomised participants, as far as is practically possible.

For the final analysis of the primary outcome, comparative t-statistics will be computed using an analysis of covariance (ANCOVA) model. If the resulting test statistic for either dose falls below a critical value of -2.196, the corresponding null hypothesis of no difference between the active group and placebo can be rejected and superiority of the active dose can be claimed. Note that it is possible to claim superiority of both doses over placebo.

A last value carried forward strategy will be used to compute the CRP AUC for patients with missing CRP measurements. This strategy is conservative in that missing values lead to increased CRP AUCs and hence an increased drop-out rate will be penalized. If drop-out is similar between the arms then the effect of this strategy cancels out in the comparison and hence leads to robust conclusions.

To assess the sensitivity of this approach we will also conduct a complete case analysis; a longitudinal model will be used as a core secondary analysis. Sub-group analyses will examine outcome in mild AP using the Harmless Acute Pancreatitis Score[3] and in severe AP in those presenting with organ failure (SOFA scores; N.B. these tools cannot be used to stratify prior to trial treatment) as well as sub-group comparisons of the distribution of AP severities (RAC); if necessary, outcome will be analysed in a standardised period prior to cholecystectomy in mild AP.

For continuous secondary outcomes, data will be presented as means and standard deviations and analysed using two-sample tests (if data is skewed, medians and ranges will be presented and analysis will be by Mann Whitney U tests). For binary secondary outcomes, data will be reported in terms of relative risk and analysed using chi-squared or Fisher's exact tests as appropriate.

Bioinformatic analyses of transcriptomic, eQTL and complementary cytokine and leukocyte subset data will be undertaken and applied to differentially expressed genes, adopting an iterative approach informed by outcome, with sub-group efficacy and safety analyses of those positive or not for the differentially expressed predictive gene transcript signature.

10.6 Health Economic Analysis

The primary (cost utility) analysis will consider QALYs and costs from the perspective of the NHS. Unit cost data will be obtained from reference sources, including routine hospital data (NHS reference costs), the British National Formulary and nationally published data. Total costs will be calculated as the sum-product of resource use and unit cost for each patient.

The incremental analysis will be based on the mean costs and QALYs for each treatment group. The Health Economic Analysis Plan, agreed prior to the analysis, will define the analytic steps to be undertaken.

Sensitivity analyses will be conducted to test the robustness of findings. We will use such analyses based on the observed distributions of outcome and costs to test whether, and to what extent, the incremental cost-effectiveness ratios are sensitive to key assumptions in the analysis (e.g. unit prices, different utility estimates EQ-5D vs. EQ-VAS components of EQ-5D-5L).

The joint uncertainty in costs and QALYs will be addressed through application of bootstrapping and estimation of cost-effectiveness acceptability curves to allow for graphical representation of the probability of cost-effectiveness according to different thresholds of cost-effectiveness. The economic findings will be reported according to the consolidated health economic evaluation reporting standards (CHEERS) guideline[50].

11 REGULATORY AND ETHICAL APPROVALS

11.1 Statement of Compliance

This trial will be carried out in accordance with CTRC Standard Operating Procedures, the World Medical Association Declaration of Helsinki (1996), the principles of Good Clinical Practice (GCP) and all applicable legislation (data protection, clinical trials, human tissue).

11.2 Regulatory Approval

This trial will be registered with the MHRA and a Clinical Trial Authorisation (CTA) will be obtained prior to the trial commencing.

11.3 Ethical Considerations

This research protocol is designed scientifically with statistical plans of sufficient power to determine in a safe manner whether infliximab is an effective treatment for AP, something that is greatly needed.

Trial participants will be recruited in a fair way, representative of all patients with AP. Patients will be randomised into one of three arms, in one of which they will receive a placebo infusion (0.9% sodium chloride) and in the other two arms the infusion plus different doses of infliximab (5 mg/kg or 10 mg/kg). Although participants will not be able to choose their own treatment, the adaptive design of the study with two interim analyses will ensure that any treatment that is worse than placebo at interim analysis will be dropped. Furthermore, participants in all arms will receive required prophylactic medication comprised of 100 mg hydrocortisone and 10 mg chlorphenamine intravenously; piperacillin/tazobactam 4.5 g intravenously t.d.s, or alternative antibiotic(s) for up to 7 days or until discharge, whichever is earlier; and adrenaline will be prescribed so as to be immediately available if necessary. There will be thorough clinical supervision with joint management from Pancreatology and Gastroenterology specialists, the latter with substantial expertise in the use of infliximab.

Recruitment of patients will be upon admission to A&E following the diagnosis of AP. Due to the nature of the study (emergency care setting and trial treatments must be initiated within 12 hours) only limited time will be available to consider participation. However, in compliance with GCP, patients will be (i) accurately informed of the trial, risks, benefits, and alternatives, (ii) asked to ensure they understand how it relates to them, and (iii) make a voluntary decision about participation. They will have an opportunity to ask questions.

Moreover, as AP is an acute, life-threatening condition and the trial may produce benefit in individuals lacking capacity, such patients will be included if eligible. If patients are unable to give consent, a close relative, carer (Personal Legal Representative) or if unavailable an independent doctor or staff member (Professional Legal Representative) will be asked for a proxy decision using local standard operating procedures. The participant will be informed about the trial as soon as it is possible (once capacity has been regained) and asked to consent for continuation of any trial procedures and data collection.

Patient autonomy, privacy and welfare will be paramount and override continued pursuit of the research. Participants will be kept abreast of findings that might cause them to withdraw participation, without detriment.

As indicated in section 2.2.1, there are risks of infliximab-related i.v. infusion reactions and an increased risk of infection from infliximab, notably exacerbation or reactivation of tuberculosis, reactivation of chronic viral infection and/or exacerbation of any bacterial infection consequent upon AP. Care has been taken to minimise these risks at the screening phase with eligibility criteria excluding patients with any history of tuberculosis, opportunistic infections or chronic viral infections, as well as through the administration of prophylactic antibiotics to all trial participants to protect against bacterial infection.

Independent ethical review and all other regulatory approvals will be sought. To minimize potential conflicts of interest, the IDMSC will ensure independent oversight, advising the TSC on continuation or not of the trial, designed to minimize bias.

11.4 Ethical and Local Governance Approval

Prior to the trial being initiated at CTRC, a favourable ethical opinion will be obtained from a REC and global governance approval from the HRA. Prior to opening a centre to recruitment, CTRC will ensure that local governance approval has been obtained: for sites in England, this will be “Capacity & Capability” Confirmation; for sites in devolved nations, this will be R&D Approval.

11.5 Protocol Deviation and Serious Breaches

A breach of the protocol or GCP is ‘serious’ if it meets the regulatory definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. All confirmed serious breaches of GCP or protocol will be reported to the MHRA and REC in an expedited manner by the sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the CTRC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach of GCP or protocol and therefore requires expedited reporting to the MHRA and REC.

In determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants, the Sponsor may seek advice from medical expert members of the Trial Management Group (TMG) and/or of the independent oversight committees (IDSMC and TSC). In determining whether or not the breach is likely to significantly affect the scientific value of the trial, the Sponsor may seek advice from the Trial Statistician. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as ‘serious’ will be reported to the MHRA and REC within 7 days by the sponsor and notified to the TMG, IDSMC and TSC at their next meetings.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, REC or MHRA will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Other incidences of protocol non-compliance will be recorded as protocol deviations, the frequency of which will be monitored and reported to the trial oversight committees.

12 DATA MANAGEMENT AND TRIAL MONITORING

Details of the monitoring to be carried out for the RAPID-I study are included in the RAPID-I Trial Monitoring Plan, maintained separately to this protocol.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 14.4.

12.1 Source Documents

In order to resolve possible discrepancies between information appearing in the case report form (CRF) and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF.

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. Source data are contained in source documents (original records or certified copies).” (ICH E6, 1.51).

Source documents are defined as: “Original documents, data, paper and electronic records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).” (ICH E6, 1.52).

The CRF will be considered the source document for data where no prior record exists and which is recorded directly in the CRF. A RAPID-I source document list will be produced for each site.

Date(s) of conducting the informed consent process including date of provision of patient information, confirmation of full eligibility, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient’s medical record chronologically.

12.2 Data Capture Methods

The trial paper CRFs are the primary data collection instrument. All data requested on the CRF must be recorded. All missing data must be explained as follows:

- if a space on the CRF is left blank because the procedure was not done or the question was not asked, “N/D” should be recorded on the CRF;
- if the item is not applicable to the individual case, “N/A” should be recorded;
- if the data item is un-known, “NK” should be recorded;
- if a data item has not been recorded on source data, ‘NR’ should be recorded.

All changes to original CRF entries (e.g. correction of errors) must be initialled and dated in accordance with GCP.

Participant questionnaires such as EQ-5D-5L, Health Resource Use and pain numerical rating scales are source documents and **sites should photocopy them** in order to retain a copy at site before mailing originals to CTRC. Local research teams will ensure CRFs and questionnaires are sent to CTRC separately to the consent form as the consent form has patient identifiable data on it.

The CTRC will distribute CRFs to sites on an on-going basis. Completed CRFs should be returned to CTRC within 3 weeks of the visit date.

12.3 Monitoring

12.3.1 Central Monitoring

Data received at CTRC will be checked for missing or unusual values (range checks) and checked for consistency over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTRC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTRC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTRC to ensure reliability and validity of the trial data, to be detailed in the Trial Monitoring Plan.

Central checks of consent will be completed for each participant to ensure the completeness of consent and that the timing of consent is in line with the protocol.

Central monitoring will be performed in a proportionate manner as informed by the Trial Risk Assessment and Monitoring Plans.

12.3.2 Clinical Site Monitoring

In order to perform their role effectively, the Trial Coordinator (or Monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Participant Information Sheet and Informed Consent form (PISC).

12.4 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. All persons involved in the trial have a duty to preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Verification that appropriate informed consent has been obtained will be confirmed by the supply of copies of participants' signed informed consent forms to the CTRC by recruiting centres, therefore participants' names data will be transferred to the CTRC. This requirement will be explicitly stated in the PISC.

CRFs will be pseudonymised, will not contain details of participant names and will be labelled with the unique trial randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The CTRC will be undertaking activities requiring the transfer of identifiable data. The transfer of these data is disclosed in the PISC.

12.5 Quality Assurance (QA) and Quality Control (QC)

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented, recorded and reported in compliance with applicable regulatory, ethical and governance requirements. QC includes the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled: e.g. state what clinical site monitoring (and audit) is planned, if any. In accordance with the monitoring plan, site visits will or will not be conducted and source verification performed, if central monitoring processes indicate these are required. Monitoring activities could include, but are not limited to the following:

- The Trial Coordinator at the CTRC will verify that appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training.
- Greenlight checklists will be completed to confirm that all approvals are in place prior to trial initiation at CTRC and the individual site.
- The TMG will determine the minimum key staff required to be recorded on the site delegation log in order for the site to be initiated.
- Data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- Types and mechanisms of training of staff for the study will be specified.
- The PI and other key staff from each centre will attend site initiation training, coordinated by the CTRC, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will monitor screening, randomisation and consent rates between centres.
- The process for consent, recruitment and randomisation will be evaluated for compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan, maintained separately to this protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.

12.6 Records Retention

All trial documents will be retained for a maximum period of 25 years from the End of Trial.

The PI is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The PI at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial, ICH E6, Guideline for GCP) including the Investigator Site File and Pharmacy Site File, until the CTRC informs him/her that the documents are no longer to be retained. The PI is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of the required storage period. Delegation must be documented in writing.

The CTRC undertakes to store the sections of the Trial Master File relevant to their delegated duties, and originally completed CRFs, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. All electronic CRFs and trial data will be archived onto appropriate media for long-term accessible storage. Hard copies of data will be boxed

and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, IMP distributors, etc.).

13 INDEMNITY

RAPID-I is sponsored by the University of Liverpool (UoL) and co-ordinated by the CTRC. The University of Liverpool has vicarious liability for the actions of its staff, when through the course of their employment they are involved in the design and initiation of clinical research, including but not limited to the authorship of the Protocol. The University of Liverpool has appropriate insurance in place to cover this liability.

As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

14 ROLES AND RESPONSIBILITIES

14.1 Role of Study Sponsor and Study Funder

The Sponsor of this trial is the University of Liverpool. The Sponsor will ensure that clear agreements are reached, documented and carried out, respecting the dignity, rights, safety and wellbeing of participants and the relationship with healthcare professionals. This will provide for proper design, management, initiation, conduct, monitoring, data collection, data analysis, data protection, financing and reporting of this trial meeting appropriate scientific, legal and regulatory standards. The responsibility for design, conduct, management, data analysis, data interpretation, manuscript writing and dissemination of results is delegated to the Trial Management Group.

The funders of this study are the Medical Research Council and National Institute for Health Research who are providing financial funding through the Efficacy and Mechanism Evaluation Programme. The funders will ensure there is proper use of the funds they have allocated to provide value for money. The funders assure the quality of the study, taking the lead in establishing that the research proposal is worthwhile, of high scientific quality, has an appropriate research infrastructure with expert clinical trial management, has the capacity to comply with the principles of GCP and represents good value for money.

Merck, Sharp and Dohme (MSD) are supplying the IMP infliximab (REMICADE®) to be administered as trial medication in this study (MSD MISP Database number 53626) through an Investigator Initiated Clinical Trial Research Agreement between MSD and the Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT). MSD are not providing any financial funding in connection with this Agreement.

14.2 Funding and Support in Kind

Funder(s)	**Financial and Non-financial Support Given**
Medical Research Council and National Institute for Health Research	Financial funding (£1,595,142.70)
MSD (MERCK SHARP & DOHME LIMITED, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU)	Supply of infliximab (REMICADE®) (value of the medication calculated at £450,000)

14.3 Protocol Contributors

The individuals who contributed substantively to protocol development and drafting are listed below:

Name	Affiliations	Contribution to protocol
Robert Sutton	Institute of Translational Medicine (ITM), University of Liverpool	Led the writing of this protocol, clinical and scientific arrangements, trial design and conduct
Sreedhar Subramnian	RLBUHT	Clinical arrangements
Thomas Jaki	Department of Mathematics and Statistics, University of Lancaster	Statistical arrangements, trial design and conduct
Helen Hickey	CTRC, University of Liverpool	Protocol development, governance arrangements and trial conduct
Catherine Spowart	CTRC, University of Liverpool	Protocol development, governance arrangements and trial conduct
Michaela Brown	CTRC, University of Liverpool	Statistical arrangements, trial design and conduct
Paula Williamson	CTRC, University of Liverpool	Trial design and conduct
Dyfrig Hughes	Centre for Health Economics and Medicines Evaluation, Bangor University	Health Economics aspects
Catrin Plumpton	Centre for Health Economics and Medicines Evaluation, Bangor University	Health Economics aspects
Shakeel Herwitker	RLBUHT	IMP arrangements
Hannah Allsop	RLBUHT	IMP arrangements
Diane Latawiec	ITM, University of Liverpool	Laboratory arrangements.
Katie Neville	CTRC, University of Liverpool	Quality Assurance review

Advice was received from Co-Applicants to the EME Funding Programme and the BRU (subsequently RLBUHT Pancreas) Patient Advisory Group.

The design, conduct, data analysis, data interpretation, manuscript writing and dissemination of results are the responsibility of the TMG, subject to the approval of the University of Liverpool as Sponsor, the Medical Research Council and National Institute for Health as Funders and MSD supplying the IMP.

14.4 Trial Committees

14.4.1 Trial Management Group (TMG)

A TMG will be formed comprising the CI, other lead investigators (clinical and non-clinical), members of the CTRC and a lay member. A Sponsor representative will be invited to attend TMG meetings. The TMG will be responsible for the day-to-day running and management of the trial. Refer to the TMG terms of reference and trial oversight committee membership document for further details. Meetings will be in Liverpool with teleconferencing. The TMG will report to the TSC.

14.4.2 Trial Steering Committee (TSC)

The TSC will consist of an independent medical expert chairperson, an independent biostatistician and two independent lay members. TMG representatives will be given the opportunity to contribute as non-independent and non-voting TSC members. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

The TSC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Refer to the TSC terms of reference and trial oversight committee membership document for further details.

14.4.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC consists of an independent clinical trialist chairperson, an independent expert in Pancreatology and an independent expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analyses and monitoring are provided in section 10.4.

The IDSMC will provide a recommendation to the TSC concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

15 PUBLICATION AND DISSEMINATION

15.1 Publication Policy

The results from different centres will be analysed together and published as soon as possible. The design, conduct, data analysis, data interpretation, manuscript writing, and dissemination of results are the responsibility of the TMG on behalf of the University of Liverpool as Sponsor, the Medical Research Council and National Institute for Health as Funders and MSD supplying the IMP.

The TMG will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. The National Clinical Trial (NCT) identifier allocated to this trial will be attached to any publications resulting from this trial.

The members of the TSC and IDSMC will be listed with their affiliations in the Acknowledgements / Appendix of the main publication.

15.1.1 Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a byline as members of the Great Britain and Ireland Pancreatitis Study Group. It is expected that those contributors who fulfil all four of the above criteria and are listed in the byline will be identified in MEDLINE as authors, in accordance with the policy of the International Committee of Medical Journal Editors.

15.2 Dissemination to Key Stakeholders

The International Pancreatitis Study Group (founding members include Professor Sutton, Liverpool, now with representation in UK, United States, Spain, Hungary, New Zealand and China) will promote this trial in the national and international Pancreatic Societies including the Pancreatic Society of Great Britain and Ireland, European Pancreatic Club, American Pancreatic Association and International Association of Pancreatology, with encouragement of presentations, lectures and symposia. The RLBUHT Pancreas Patient Advisory Group will promote the study nationally with a long-term aim of international networking. Communication via the Clinical Research Networks, major NHS Trusts and pancreatic and gastrointestinal services will highlight the work, taking opportunities to discuss via various media.

Once findings concerning efficacy, safety, immune mechanisms in AP, validity of the predictive differential gene expression signature, development of a treatment response signature, a Cumulative AP Outcome Score and quality indicators have been made, the organisations outlined above as well as others will be used by those contributing to the study, including patients and the public, to present the findings and to carry forward work arising from the implications of the findings.

Publication of all original work and associated reviews is likely to lead to one or more high impact publications and potential future work. These findings may lead to several shifts in approach, including further AP trials as well as standard clinical management of the diagnosis and treatment in AP. If RAPID-I shows infliximab to be an effective treatment for AP, a pivotal phase III trial (RAPID-II) will

be pursued. Furthermore should the transcriptomic signatures be validated, commercialisation will be encouraged, to lead to market application.

The results of RAPID-I will be disseminated regardless of the magnitude or direction of effect.

15.3 Data Sharing

Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG. All publications shall include a list of participating PIs and collaborators.

16 CHRONOLOGY OF PROTOCOL AMENDMENTS

16.1 Version 1.0 (31/08/2017)

Please note version 1.0 (31/08/17) was not submitted to HRA, Ethics or MHRA for approval.

16.2 Version 2.0 (20/04/2018)

Please note version 2.0 (20/04/2018) was submitted to HRA and Ethics for approval. After receiving ethical provisional opinion, the following amendments were incorporated prior to resubmission:

- Exclusion criterion added; patients with a body weight of over 200 kilograms (Section 5.2, Page 24)
- Randomisation issues contact number updated (Section 6.5, Page 31 and Section 9.9, Page 53).
- New treatment instructions, as per SmPC update (30/05/2018); all patients, regardless of treatment arm, weighing over 100kg must receive 500 ml trial infusion rather than 250 ml, to ensure concentration of infliximab does not exceed 4 mg/ml (Section 8.2.2, Page 49, Section 8.4, Page 50 and Section 8.8, Page 52).
- AUDIT questionnaire removed from appendix.

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18 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents accompanying the protocol, separately updated and version controlled are:

Participant information sheets and consent form
GP Letter
Questionnaires