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Multicentre Observational Cohort Study of NSAIDs as Risk Factors for Post-Operative Adverse Events in Gastrointestinal Surgery: Study Protocol

STARSurg Research Collaborative*

*collaborating members are shown below

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Abstract

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as post-operative analgesia by the Enhanced Recovery After Surgery Society. Recent studies have raised concerns that NSAID administration following colorectal anastomosis may be associated with increased risk of anastomotic leak. This multicentre study aims to determine NSAIDs' safety profile following gastrointestinal resection.

Methods and Analysis

This prospective, multicentre cohort study will be performed over a two-week period utilising a collaborative methodology. Consecutive adults undergoing open or laparoscopic, elective or emergency gastrointestinal resection will be included. The primary endpoint will be 30-day morbidity, assessed using the Clavien-Dindo classification. This study will be disseminated through medical student networks, with an anticipated recruitment of at least 900 patients. The study will be powered to detect a 10% increase in complication rates with NSAID use.

Ethics and Dissemination

Following Research Ethics Committee Chairperson review, a formal waiver was received. This study will be registered as clinical audit or service evaluation at each participating hospital. Dissemination will take place through previously described novel research collaborative networks.

Discussion

This study will be the first large prospective series providing evidence on the over-all safety of NSAIDs following bowel resection. This data will inform any future powering of a randomised controlled trial to provide the highest quality evidence on this topic.

Background

The Enhanced Recovery After Surgery Society recommends use of non-steroidal anti-inflammatory drugs (NSAIDs) as part of post-operative analgesia protocols[1]. The routine use of NSAIDs is also endorsed by the World Health Organisation's Pain Relief Ladder. NSAIDs have been shown to be generally effective and safe as post-operative analgesia, with an opioid-sparing effect[2-3].

Recent evidence has questioned the safety of NSAIDs following major gastrointestinal surgery. Two retrospective analyses of different prospective databases of patients undergoing primary colorectal anastomosis found that specific NSAIDs may increase risk of anastomotic leak. The first showed that amongst 2800 patients post-operative diclofenac use was independently associated with increased risk[4]. The second studied 500 patients, finding that the introduction of protocolised use of celecoxib brought a significant increase in the anastomotic leak rate from around 3% to 15%[5]. A further retrospective study of 800 patients also suggested that non-selective NSAIDs may increase anastomotic leak rates[6].

These clinical findings are supported by animal studies that have demonstrated that NSAID use following bowel anastomosis may be associated with decreased anastomotic strength and increased leak rates [7-8]. NSAIDs are implicated in reducing collagen synthesis and hydroxyproline deposition during the healing process. Down-regulation of prostaglandin expression may also increase microthrombus and microembolus formation, further contributing to post-operative adverse effects.

The need for further evidence

Concerns have been raised about the safety of NSAIDs following bowel anastomosis, however the majority of the evidence to-date is reliant upon secondary analyses or

retrospective series. Most studies concern colorectal surgery, with very little evidence available for oesophageal and gastric surgery. Furthermore, most studies focus on anastomotic leaks, providing no evidence on the broader side effect profiles of NSAIDs, which may include increased risk of gastrointestinal bleeding, cardiac ischaemia and renal failure.

Primary aim

The primary aim of this study is to determine the safety profile of post-operative NSAIDs after gastrointestinal resection in current practice across the United Kingdom (UK).

Hypothesis

The 30-day adverse event rate, following risk adjustment, should be equivalent in patients taking and not taking NSAIDs.

Methods

Study design

A national multicentre prospective cohort study disseminated through university medical school and student networks (Figure 1). The generic collaborative methodology has previously been described previously [9].

Study Setting

This study will take place in general surgical units in NHS hospitals. Any NHS hospitals performing elective or emergency gastrointestinal resection may participate. Each centre will contribute two weeks of consecutive patient data from up to two study periods.

Inclusion criteria

- Consecutive adult patients undergoing upper or lower gastrointestinal bowel resection.
- Patients undergoing either elective or emergency, and open, laparoscopic, laparoscopic-assisted or laparoscopic-converted procedures may be included.
- Bowel resection is defined as complete transection and removal of a segment of rectum, colon, small bowel, stomach or oesophagus.

Exclusion criteria

- Patients under 18 years of age.
- Appendicectomy for acute appendicitis. Patients who undergo incidental appendicectomy as part of another procedure may be included.
- Any procedure with bowel repair, but without resection.
- Wedge resection without complete bowel transaction.
- Trauma indication.
- Gynaecological primary indication.

- Urological primary indication.

Primary outcome measure

The primary outcome measure will be the 30-day adverse event rate, measured by the Clavien-Dindo classification. This is an internationally standardised and validated scoring system for post-operative complications (Table 1)[10].

Secondary outcomes

Secondary outcome measures will be anastomotic leak, wound infection and cardiovascular events (Table 2).

Explanatory variables

Administration of NSAIDs from day one (day of surgery) through to the third post-operative day is the main explanatory variable. Patients will be stratified in to high (recommended daily dose or above) or low (below recommended daily dose, including once only) NSAID dose groups. Aspirin will not be considered as a NSAID for this analysis, although data on its administration will be collected. The Revised Cardiac Risk Index will be calculated for each patient to adjust for pre-existing cardiovascular risk (Table 3)[11].

Quality assurance

Although many collaborators participating in the study will be medical students, each local team must include at least one qualified doctor to closely supervise students. The study will additionally be registered with a sponsoring consultant surgeon at each site.

A detailed protocol describing how to register the study and an in-depth description of data fields and how to collect them will be made available to collaborators. This protocol will be

interactively presented and explained in detail at a national collaborator meeting. Regional leads for the study will also be encouraged to hold meetings with local collaborating teams to debrief them on the protocol. Feedback from these meetings will be used to clarify any ambiguities in the protocol.

To ensure collaborators understand the inclusion criteria and application of the Clavien-Dindo classification they will be asked to complete a case-based online e-learning module prior to starting data collection.

In order to overcome a learning curve in identifying patients and relevant data, all participating centres will be asked to pilot completing patient identification and the initial stages of the data collection form for one day in the week leading up to the main study starting date.

Throughout the data collection period the trial management group will hold weekly Twitter question and answer sessions (www.twitter.com/STARSurgUK), giving the opportunity for collaborators to clarify any uncertainties regarding the protocol. A summary of frequently asked questions will be distributed to all collaborators following each Twitter session, providing real-time feedback to collaborators.

Validation

Following data collection only data sets with >95% data completeness will be accepted for pooled national analysis. An independent assessor will validate 5% of all data points, with a target of >98% accuracy.

Data management

A standardised Microsoft Excel spreadsheet (Excel 2010; Microsoft, Redmond, WA, USA) with pre-set fields will be used to collect data at each centre. Data protection regulations at each centre will be complied with. Patient identifiable data will not be transmitted to the trial management group.

Anticipated minimum recruitment

It is estimated that an average centre performs approximately 15 gastrointestinal resections in a 14-day period. A minimum of 60 centres will be recruited, with at least two centres participating at each of 30 medical schools. Overall we anticipate recruiting at least 900 patients.

Power calculation

The study will have at least 80% power to detect an increase in the 30-day adverse event rate from 15% to 25% with NSAID use. It is anticipated that a third of patients will receive NSAIDS [4]. Based on recruiting 300 patients receiving NSAIDs and 600 control patients, this study will have 93.5% power to detect an increase in the complication rate from 15% to 25% (α=0.05).

Statistical analysis

Differences between demographic groups will be tested with the χ^2 test. Multivariable binary logistic regression will be used to test the influence of clinically plausible variables on the outcome measures, to produce adjusted odds ratios (OR) and bootstrapped 95% confidence intervals (95% CI). This will be performed firstly the whole dataset and then a matched group of 2:1 control:experimental (NSAID administration), using propensity scoring. Data handling will be performed in SPSS version 21.0 and statistical modelling in the R Foundation Statistical Programme 3.0.0.

Ethics and Dissemination

Research Ethics Approval

Following Research Ethics Committee Chairperson review, a formal waiver was received. The study will be undertaken as a clinical audit. This was further supported by written advice from a University NHS Trust Research & Development Office Director and the National Research Ethics Service (NRES). This study will be registered as clinical audit or service evaluation at each participating hospital.

Protocol dissemination

The generic collaborative methodology underlying protocol dissemination and collaborator recruitment has been described previously [9]. The protocol will be disseminated primarily through medical student networks, including student surgical and medical societies. The Association of Surgeons in Training (www.asit.org) will also disseminate the protocol to its members. A student local lead will be designated at each medical school to facilitate local dissemination. The protocol document will be made available online and will also be disseminated through social media, including Twitter (https://twitter.com/STARSurgUK) and Facebook (https://www.facebook.com/STARSurgUK).

Discussion

This paper describes the protocol to a novel study, addressing an important clinical question using rapid-delivery, snap-shot methodology. The development of the national network, formed by the natural geographical locations of medical schools within the United Kingdom, is also novel. The observational nature of this study means it is classified as audit. Within the confines of this, a detailed and protocolised approach is warranted to ensure maximum quality.

The multi-centre nature of this study means that the approaches taken to its design are pragmatic. In particular, the definitions used and the number of data-points are designed to aid local investigators to ensure simplicity of delivery, whilst containing enough detail to answer the relevant clinical question.

A randomised controlled trial would provide the highest level of evidence to guide patients and clinicians towards optimal post-operative analgesic regimes. In order to power these trials, and to justify funding applications, a multicentre observational study is required.

Tables

Table 1: The Clavien-Dindo classification of post-operative complications

Grade	Definition (Examples listed in italics)
I	Any deviation from the normal postoperative course without the need for pharmacological treatment other than the "allowed therapeutic regimens", or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics and electrolytes. This grade also includes physiotherapy and wound infections opened at the bedside but **not** treated with antibiotics. *Examples: Ileus, thrombophlebitis*
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. *Examples: Surgical site infection treated with antibiotics, myocardial infarction treated medically, deep venous thrombosis treated with low molecular weight heparin, pneumonia or urinary tract infection treated with antibiotics*
III	Requiring surgical, endoscopic or radiological intervention. *Examples: Return to theatre for any reason, endoscopic therapy, interventional radiology*
IV	Life-threatening complication requiring critical care management; CNS complications including brain haemorrhage and ischemic stroke (excluding TIA), sub-arrachnoidal bleeding. *Examples: Single or multi-organ dysfunction requiring critical care management, e.g. pneumonia with ventilator support, renal failure with filtration*
V	Death of a patient

Table 2: Secondary outcome measures

Outcome measure	Definition
Length of stay	Calculated counting day of admission counts as day 1, and the day of discharge as a whole day.
Anastomotic leak	Anastomotic leak detected clinically/symptomatically, radiologically, and/or intra-operatively.
Intra-abdominal/ intra-pelvic collection	Abscess/ collection leak detected clinically/symptomatically, radiologically, and/or intra-operatively.
Wound infection	Based on the Centre for Disease Control's definition of surgical site infection, which is any one of: (1) Purulent drainage from the incision (2) At least two of: pain or tenderness; localised swelling; redness; heat; fever; AND The incision is opened deliberately to manage infection or the clinician diagnoses a surgical site infection (3) Wound organisms AND pus cells from aspirate/ swab
Cardiac event	Includes myocardial infarction, unstable angina, sudden death from cardiac causes, ischaemic and haemorrhagic stroke, transient ischaemic attack, peripheral arterial thrombosis, peripheral venous thrombosis and pulmonary embolus.

Table 3: The Revised Cardiac Risk Index

Revised Cardiac Risk Index
1. History of ischemic heart disease
2. History of congestive heart failure
3. History of cerebrovascular disease (stroke or transient ischemic attack)
4. History of diabetes requiring preoperative insulin use
5. Chronic kidney disease (creatinine > 177 mmol/L)
6. Undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery

Acknowledgments:

The Royal College of Surgeons of England (www.rcseng.ac.uk) is providing complimentary meeting facilities for the training day. A regional meeting grant has been received from the Association of Surgeons in Training (www.asit.org) towards the costs of the national collaborator training day.

Authors' information

Dmitri Nepogodiev, MBChB is an academic foundation year 2 at the Norfolk & Norwich University Hospital.

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collaborator training day. This research received no other specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors Contributions:

Dmitri Nepogodiev

Conception, design, writing and editing of protocol

Stephen Chapman

Design and writing of protocol

James Glasbey

Design and writing of protocol

Michael Kelly

Design and writing of protocol

Chetan Khatri

Design and writing of protocol

J. Edward Fitzgerald

Conception, design, writing and editing of protocol

Aneel Bhangu

Conception, design and writing of protocol. Statistical analysis. Guarantor.

All authors read and approved the final manuscript.

List of abbreviations

NSAID: Non-steroidal anti-inflammatory drug.

OR: Odds ratio.

LOS = Length of stay

SSI = Surgical site infection

Competing interests: None.

References

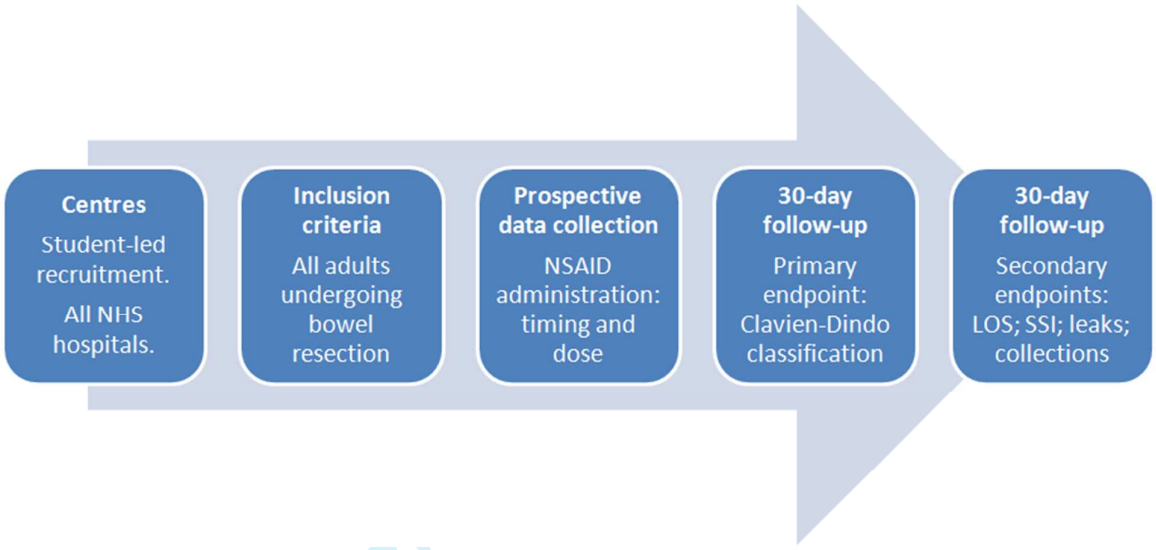
1. Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, Ljungqvist O, Soop M, Ramirez J: **Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations.** *Clinical nutrition* 2012, **31:**801-816.
2. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C, Morales O: **Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial.** *Anesthesiology* 2005, **103:**1225-1232.
3. Nauta M, Landsmeer ML, Koren G: **Codeine-acetaminophen versus nonsteroidal anti-inflammatory drugs in the treatment of post-abdominal surgery pain: a systematic review of randomized trials.** *American journal of surgery* 2009, **198:**256-261.
4. Klein M, Gogenur I, Rosenberg J: **Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data.** *Bmj* 2012, **345:**e6166.
5. Holte K, Andersen J, Jakobsen DH, Kehlet H: **Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery.** *The British journal of surgery* 2009, **96:**650-654.
6. Gorissen KJ, Benning D, Berghmans T, Snoeijs MG, Sosef MN, Hulsewe KW, Luyer MD: **Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery.** *The British journal of surgery* 2012, **99:**721-727.
7. Klein M, Krarup PM, Kongsbak MB, Agren MS, Gogenur I, Jorgensen LN, Rosenberg J: **Effect of postoperative diclofenac on anastomotic healing, skin wounds and subcutaneous collagen accumulation: a randomized, blinded, placebo-controlled, experimental study.** *European surgical research Europaische chirurgische Forschung Recherches chirurgicales europeennes* 2012, **48:**73-78.
8. Klein M: **Postoperative non-steroidal anti-inflammatory drugs and colorectal anastomotic leakage. NSAIDs and anastomotic leakage.** *Danish medical journal* 2012, **59:**B4420.

9. Bhangu A, Kolias AG, Pinkney T, Hall NJ, Fitzgerald JE: **Surgical research collaboratives in the UK.** *Lancet* 2013, **382:**1091-1092.

10. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C, et al: **The Clavien-Dindo classification of surgical complications: five-year experience.** *Annals of surgery* 2009, **250:**187-196.

11. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, et al: **Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.** *Circulation* 1999, **100:**1043-1049.

Figure 1: Flowchart of study design



LOS = Length of stay
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Abstract

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as post-operative analgesia by the Enhanced Recovery After Surgery Society. Recent studies have raised concerns that NSAID administration following colorectal anastomosis may be associated with increased risk of anastomotic leak. This multicentre study aims to determine NSAIDs' safety profile following gastrointestinal resection.

Methods and Analysis

This prospective, multicentre cohort study will be performed over a two-week period utilising a collaborative methodology. Consecutive adults undergoing open or laparoscopic, elective or emergency gastrointestinal resection will be included. The primary endpoint will be 30-day morbidity, assessed using the Clavien-Dindo classification. This study will be disseminated through medical student networks, with an anticipated recruitment of at least 900 patients. The study will be powered to detect a 10% increase in complication rates with NSAID use.

Ethics and Dissemination

Following Research Ethics Committee Chairperson review, a formal waiver was received. This study will be registered as clinical audit or service evaluation at each participating hospital. Dissemination will take place through previously described novel research collaborative networks.

Background

The Enhanced Recovery After Surgery Society recommends use of non-steroidal anti-inflammatory drugs (NSAIDs) as part of post-operative analgesia protocols[1]. The routine use of NSAIDs is also endorsed by the World Health Organisation's Pain Relief Ladder. NSAIDs have been shown to be generally effective and safe as post-operative analgesia, with an opioid-sparing effect[2 3].

Recent evidence has questioned the safety of NSAIDs following major gastrointestinal surgery. Two retrospective analyses of different prospective databases of patients undergoing primary colorectal anastomosis found that specific NSAIDs may increase risk of anastomotic leak. The first showed that amongst 2800 patients post-operative diclofenac use was independently associated with increased risk[4]. The second studied 500 patients, finding that the introduction of protocolised use of celecoxib brought a significant increase in the anastomotic leak rate from around 3% to 15%[5]. A further retrospective study of 800 patients also suggested that non-selective NSAIDs may increase anastomotic leak rates[6].

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The need for further evidence

Concerns have been raised about the safety of NSAIDs following bowel anastomosis, however the majority of the evidence to-date is reliant upon secondary analyses or

retrospective series. Most studies concern colorectal surgery, with very little evidence available for oesophageal and gastric surgery. Furthermore, most studies focus on anastomotic leaks, providing no evidence on the broader side effect profiles of NSAIDs, which may include increased risk of gastrointestinal bleeding, cardiac ischaemia and renal failure.

Primary aim

The primary aim of this study is to determine the safety profile of post-operative NSAIDs after gastrointestinal resection in current practice across the United Kingdom (UK).

Hypothesis

The 30-day adverse event rate, following risk adjustment, should be equivalent in patients taking and not taking NSAIDs.

Methods

Study design

We plan to undertaken a national multicentre prospective audit which will be disseminated through university medical school and student networks (Figure 1). The generic collaborative methodology has previously been described previously [9].

Study Setting

This study will take place in general surgical units in NHS hospitals. Any NHS hospitals performing elective or emergency gastrointestinal resection may participate. Each centre will contribute two weeks of consecutive patient data from up to two study periods.

Inclusion criteria

- Consecutive adult patients undergoing upper or lower gastrointestinal bowel resection.
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- Trauma indication.
- Gynaecological primary indication.

- Urological primary indication.

Primary outcome measure

The primary outcome measure will be the 30-day adverse event rate, measured by the Clavien-Dindo classification. This is an internationally standardised and validated scoring system for post-operative complications (Table 1)[10].

Secondary outcomes

Secondary outcome measures will be anastomotic leak, wound infection and cardiovascular events (Table 2).

Explanatory variables

Administration of NSAIDs from day one (day of surgery) through to the third post-operative day is the main explanatory variable. Patients will be stratified in to high (recommended daily dose or above) or low (below recommended daily dose, including once only) NSAID dose groups. Data will be collected on the specific NSAID administered in order to allow analysis by NSAID type. Aspirin will not be considered as a NSAID for this analysis, although data on its administration will be collected. The Revised Cardiac Risk Index will be calculated for each patient to adjust for pre-existing cardiovascular risk (Table 3)[11]. Data will be collected on the operation type (Colorectal or Upper GI/hepatobiliary) to facilitate analysis of homogenous operative groups.

Quality assurance

Although many collaborators participating in the study will be medical students, each local team must include at least one qualified doctor to closely supervise students. The study will additionally be registered with a sponsoring consultant surgeon at each site.

A detailed protocol describing how to register the study and an in-depth description of data fields and how to collect them will be made available to collaborators. This protocol will be interactively presented and explained in detail at a national collaborator meeting. Regional leads for the study will also be encouraged to hold meetings with local collaborating teams to debrief them on the protocol. Feedback from these meetings will be used to clarify any ambiguities in the protocol.

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Data management

A standardised Microsoft Excel spreadsheet (Excel 2010; Microsoft, Redmond, WA, USA) with pre-set fields will be used to collect data at each centre. Data protection regulations at each centre will be complied with. Patient identifiable data will not be transmitted to the trial management group. The required anonymous data fields are shown in table 4.

Anticipated minimum recruitment

It is estimated that an average centre performs approximately 15 gastrointestinal resections in a 14-day period. A minimum of 60 centres will be recruited, with at least two centres participating at each of 30 medical schools. Overall we anticipate recruiting at least 900 patients.

Power calculation

The study will have at least 80% power to detect an increase in the 30-day adverse event rate from 15% to 25% with NSAID use. It is anticipated that a third of patients will receive NSAIDS [4]. A baseline complication rate of 15% was used to determine sample size, acting as a midpoint between high and low rates from various subgroups undergoing bowel resection. This rate was based on recent audit of emergency appendicectomy in the UK, a combination of elective and emergency surgery, and known morbidity profiling[10 12]. By recruiting 300 patients receiving NSAIDs and 600 control patients, this study will have 93.5% power to detect an increase in the complication rate from 15% to 25% (α=0.05).

Statistical analysis

Differences between demographic groups will be tested with the χ^2 test. Multivariable binary logistic regression will be used to test the influence of clinically plausible variables on the outcome measures, to produce adjusted odds ratios (OR) and bootstrapped 95% confidence intervals (95% CI). This will be performed firstly the whole dataset and then a matched group of 2:1 control:experimental (NSAID administration), using propensity scoring. Data handling will be performed in SPSS version 21.0 and statistical modelling in the R Foundation Statistical Programme 3.0.0.

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LOS = Length of stay

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Competing interests: None.

Authors Contributions:

Dmitri Nepogodiev

Conception, design, writing and editing of protocol

Stephen Chapman

Design and writing of protocol

James Glasbey

Design and writing of protocol

Michael Kelly

Design and writing of protocol

Chetan Khatri

Design and writing of protocol

J. Edward Fitzgerald

Conception, design, writing and editing of protocol

Aneel Bhangu

Conception, design and writing of protocol. Statistical analysis. Guarantor.

All authors read and approved the final manuscript.

Funding statement:

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Authors' information

Dmitri Nepogodiev, MBChB is an academic foundation year 2 at the Norfolk & Norwich University Hospital.

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Tables

Table 1: The Clavien-Dindo classification of post-operative complications

Grade	Definition (Examples listed in italics)
I	Any deviation from the normal postoperative course without the need for pharmacological treatment other than the "allowed therapeutic regimens", or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics and electrolytes. This grade also includes physiotherapy and wound infections opened at the bedside but **not** treated with antibiotics. *Examples: Ileus, thrombophlebitis*
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. *Examples: Surgical site infection treated with antibiotics, myocardial infarction treated medically, deep venous thrombosis treated with low molecular weight heparin, pneumonia or urinary tract infection treated with antibiotics*
III	Requiring surgical, endoscopic or radiological intervention. *Examples: Return to theatre for any reason, endoscopic therapy, interventional radiology*
IV	Life-threatening complication requiring critical care management; CNS complications including brain haemorrhage and ischemic stroke (excluding TIA), sub-arrachnoidal bleeding. *Examples: Single or multi-organ dysfunction requiring critical care management, e.g. pneumonia with ventilator support, renal failure with filtration*
V	Death of a patient

Table 2: Secondary outcome measures

Outcome measure	Definition
Length of stay	Calculated counting day of admission counts as day 1, and the day of discharge as a whole day.
Anastomotic leak	Anastomotic leak detected clinically/symptomatically, radiologically, and/or intra-operatively.
Intra-abdominal/ intra-pelvic collection	Abscess/ collection leak detected clinically/symptomatically, radiologically, and/or intra-operatively.
Wound infection	Based on the Centre for Disease Control's definition of surgical site infection, which is any one of: (1) Purulent drainage from the incision (2) At least two of: pain or tenderness; localised swelling; redness; heat; fever; AND The incision is opened deliberately to manage infection or the clinician diagnoses a surgical site infection (3) Wound organisms AND pus cells from aspirate/ swab
Cardiac event	Includes myocardial infarction, unstable angina, sudden death from cardiac causes, ischaemic and haemorrhagic stroke, transient ischaemic attack, peripheral arterial thrombosis, peripheral venous thrombosis and pulmonary embolus.

Table 3: The Revised Cardiac Risk Index

Revised Cardiac Risk Index
1. History of ischemic heart disease
2. History of congestive heart failure
3. History of cerebrovascular disease (stroke or transient ischemic attack)
4. History of diabetes requiring preoperative insulin use
5. Chronic kidney disease (creatinine > 177 mmol/L)
6. Undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery

Table 4: Required data fields

1	Patient age (whole years)	Years
2	Patient gender	Male, Female
3	ASA score	I, II, III, IV, V
4	History of ischaemic heart disease	Yes, no
5	History of congestive heart failure	Yes, no
6	History of cerebrovascular disease (stroke or transient ischemic attack)	Yes, no
7	History of diabetes	No, diet, controlled, tablet controlled, insulin controlled
8	Chronic kidney disease (creatinine > 177 umol/L)	Yes, no
9	Was the patient taking regular aspirin?	Yes, and re-started in first 7 post-op days; yes, but not restarted first 7 post-op days; No
10	Was the patient taking a peri-operative statin?	Yes high dose (40mg +OD simvastatin or equivalent), Yes low dose (5-20mg OD simvastatin or equivalent), No
11	Date of operation	DD/MM/YY
12	Time of operation	24 hour clock
13	Operative approach	Laparoscopy, laparoscopy converted to open, open
14	Primary operation performed	Hartmanns, left hemicolectomy, right hemicolectomy, subtotal colectomy, panproctocolectomy, anterior resection, abdominoperineal resection, small bowel resection, complete gastrectomy, partial gastrectomy, oesophagectomy, Whipples, other (free text)
15	Elective or Emergency	Elective, emergency
16	Anastomosis performed	Handsewn, stapled, stoma
17	Stoma formation	Planned temporary, permanent, none
18	Underlying pathology/ indication	Diverticular disease, hernia, malignancy, polyp, ischaemic bowel, adhesional obstruction, faecal perforation, ulcerative colitis, Crohn's disease, post-operative complication, other
19	Highest post-operative glycaemic reading within 72 hours of surgery using finger prick, blood gas or laboratory value (mmol/L).	Value (mmol/L)
20	Post-operative critical care admission?	Planned from theatre, unplanned from theatre, unplanned from ward, none
21	Post-operative ERAS pathway used?	Yes, no
22	Was an NSAID used post-operatively?	Yes - Ibuprofen, Yes -diclofenac, Yes - naproxen, Yes - celecoxib, Yes - rofecoxib, Yes - other, No
23	What day was the first dose of NSAID given?	Day 1-7 (day 1 is day of surgery), none given
24	What dose of NSAID was given?	Low, high, none given
25	Total length of stay (days)	Days
26	30-day re-admission?	Yes, no
27	Surgical Complication Grade (Clavien-Dindo Classification, list most severe Grade I-V)	None, I, II, III, IV, V
28	Anastomotic leak	Yes, no
29	Wound infection	Yes, no
30	Intra-abdominal/pelvic abscess	Yes, no
31	Cardiovascular event	Yes, no

References

1. Nygren J, Thacker J, Carli F, F et al. **Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations.** *Clin Nutr* 2012, **31:**801-816.
2. Cepeda MS, Carr DB, Miranda N, et al.**Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial.** *Anesthesiology* 2005, **103:**1225-1232.
3. Nauta M, Landsmeer ML, Koren G: **Codeine-acetaminophen versus nonsteroidal anti-inflammatory drugs in the treatment of post-abdominal surgery pain: a systematic review of randomized trials.** *Am J Surg* 2009, **198:**256-261.
4. Klein M, Gogenur I, Rosenberg J: **Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data.** *Brit Med J* 2012, **345:**e6166.
5. Holte K, Andersen J, Jakobsen DH, et al.**Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery.** *Brit J Surg* 2009, **96:**650-654.
6. Gorissen KJ, Benning D, Berghmans T, et al.**Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery.** *Brit J Surg* 2012, **99:**721-727.
7. Klein M, Krarup PM, Kongsbak MB, et al. **Effect of postoperative diclofenac on anastomotic healing, skin wounds and subcutaneous collagen accumulation: a randomized, blinded, placebo-controlled, experimental study.** *Eur Surg Res* 2012, **48:**73-78.
8. Klein M: **Postoperative non-steroidal anti-inflammatory drugs and colorectal anastomotic leakage. NSAIDs and anastomotic leakage.** *Dan Med J* 2012, **59:**B4420.
9. Bhangu A, Kolias AG, Pinkney T, et al. **Surgical research collaboratives in the UK.** *Lancet* 2013, **382:**1091-1092.
10. Clavien PA, Barkun J, de Oliveira ML, et al. **The Clavien-Dindo classification of surgical complications: five-year experience.** *Ann Surg* 2009, **250**:187-96.

11. Lee TH, Marcantonio ER, Mangione CM, et al. **Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.** *Circulation* 1999,**100**:1043-9.

12. National Surgical Research Collaborative. **Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy.** *Br J Surg* 2013, **100**:1240-52.

Multicentre Observational Cohort Study of NSAIDs as Risk Factors for Post-Operative Adverse Events in Gastrointestinal Surgery: Study Protocol

STARSurg Research Collaborative*

*collaborating members are shown below

The STARSurg Steering Committee prepared this protocol manuscript:

Dmitri Nepogodiev[1], Stephen Chapman[2], James Glasbey[3], Michael Kelly[4], Chetan Khatri[5], J. Edward Fitzgerald[6], Aneel Bhangu[7]

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Abstract

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as post-operative analgesia by the Enhanced Recovery After Surgery Society. Recent studies have raised concerns that NSAID administration following colorectal anastomosis may be associated with increased risk of anastomotic leak. This multicentre study aims to determine NSAIDs' safety profile following gastrointestinal resection.

Methods and Analysis

This prospective, multicentre cohort study will be performed over a two-week period utilising a collaborative methodology. Consecutive adults undergoing open or laparoscopic, elective or emergency gastrointestinal resection will be included. The primary endpoint will be 30-day morbidity, assessed using the Clavien-Dindo classification. This study will be disseminated through medical student networks, with an anticipated recruitment of at least 900 patients. The study will be powered to detect a 10% increase in complication rates with NSAID use.

Ethics and Dissemination

Following Research Ethics Committee Chairperson review, a formal waiver was received. This study will be registered as clinical audit or service evaluation at each participating hospital. Dissemination will take place through previously described novel research collaborative networks.

Discussion

This study will be the first large prospective series providing evidence on the over-all safety of NSAIDs following bowel resection. This data will inform any future powering of a randomised controlled trial to provide the highest quality evidence on this topic.

Background

The Enhanced Recovery After Surgery Society recommends use of non-steroidal anti-inflammatory drugs (NSAIDs) as part of post-operative analgesia protocols[1]. The routine use of NSAIDs is also endorsed by the World Health Organisation's Pain Relief Ladder. NSAIDs have been shown to be generally effective and safe as post-operative analgesia, with an opioid-sparing effect[2 3].

Recent evidence has questioned the safety of NSAIDs following major gastrointestinal surgery. Two retrospective analyses of different prospective databases of patients undergoing primary colorectal anastomosis found that specific NSAIDs may increase risk of anastomotic leak. The first showed that amongst 2800 patients post-operative diclofenac use was independently associated with increased risk[4]. The second studied 500 patients, finding that the introduction of protocolised use of celecoxib brought a significant increase in the anastomotic leak rate from around 3% to 15%[5]. A further retrospective study of 800 patients also suggested that non-selective NSAIDs may increase anastomotic leak rates[6].

These clinical findings are supported by animal studies that have demonstrated that NSAID use following bowel anastomosis may be associated with decreased anastomotic strength and increased leak rates [7 8]. NSAIDs are implicated in reducing collagen synthesis and hydroxyproline deposition during the healing process. Down-regulation of prostaglandin expression may also increase microthrombus and microembolus formation, further contributing to post-operative adverse effects.

The need for further evidence

Concerns have been raised about the safety of NSAIDs following bowel anastomosis, however the majority of the evidence to-date is reliant upon secondary analyses or

retrospective series. Most studies concern colorectal surgery, with very little evidence available for oesophageal and gastric surgery. Furthermore, most studies focus on anastomotic leaks, providing no evidence on the broader side effect profiles of NSAIDs, which may include increased risk of gastrointestinal bleeding, cardiac ischaemia and renal failure.

Primary aim

The primary aim of this study is to determine the safety profile of post-operative NSAIDs after gastrointestinal resection in current practice across the United Kingdom (UK).

Hypothesis

The 30-day adverse event rate, following risk adjustment, should be equivalent in patients taking and not taking NSAIDs.

Methods

Study design

We plan to undertaken ~~A~~a national multicentre prospective ~~cohort study~~ audit which will be disseminated through university medical school and student networks (Figure 1). The generic collaborative methodology has previously been described previously [9].

Study Setting

This study will take place in general surgical units in NHS hospitals. Any NHS hospitals performing elective or emergency gastrointestinal resection may participate. Each centre will contribute two weeks of consecutive patient data from up to two study periods.

Inclusion criteria

- Consecutive adult patients undergoing upper or lower gastrointestinal bowel resection.
- Patients undergoing either elective or emergency, and open, laparoscopic, laparoscopic-assisted or laparoscopic-converted procedures may be included.
- Bowel resection is defined as complete transection and removal of a segment of rectum, colon, small bowel, stomach or oesophagus.

Exclusion criteria

- Patients under 18 years of age.
- Appendicectomy for acute appendicitis. Patients who undergo incidental appendicectomy as part of another procedure may be included.
- Any procedure with bowel repair, but without resection.
- Wedge resection without complete bowel transaction.
- Trauma indication.
- Gynaecological primary indication.

- Urological primary indication.

Primary outcome measure

The primary outcome measure will be the 30-day adverse event rate, measured by the Clavien-Dindo classification. This is an internationally standardised and validated scoring system for post-operative complications (Table 1)[10].

Secondary outcomes

Secondary outcome measures will be anastomotic leak, wound infection and cardiovascular events (Table 2).

Explanatory variables

Administration of NSAIDs from day one (day of surgery) through to the third post-operative day is the main explanatory variable. Patients will be stratified in to high (recommended daily dose or above) or low (below recommended daily dose, including once only) NSAID dose groups. Data will be collected on the specific NSAID administered in order to allow analysis by NSAID type. Aspirin will not be considered as a NSAID for this analysis, although data on its administration will be collected. The Revised Cardiac Risk Index will be calculated for each patient to adjust for pre-existing cardiovascular risk (Table 3)[11]. Data will be collected on the operation type (Colorectal or Upper GI/hepatobiliary) to facilitate analysis of homogenous operative groups.

Quality assurance

Although many collaborators participating in the study will be medical students, each local team must include at least one qualified doctor to closely supervise students. The study will additionally be registered with a sponsoring consultant surgeon at each site.

A detailed protocol describing how to register the study and an in-depth description of data fields and how to collect them will be made available to collaborators. This protocol will be interactively presented and explained in detail at a national collaborator meeting. Regional leads for the study will also be encouraged to hold meetings with local collaborating teams to debrief them on the protocol. Feedback from these meetings will be used to clarify any ambiguities in the protocol.

To ensure collaborators understand the inclusion criteria and application of the Clavien-Dindo classification they will be asked to complete a case-based online e-learning module prior to starting data collection.

In order to overcome a learning curve in identifying patients and relevant data, all participating centres will be asked to pilot completing patient identification and the initial stages of the data collection form for one day in the week leading up to the main study starting date.

Throughout the data collection period the trial management group will hold weekly Twitter question and answer sessions (www.twitter.com/STARSurgUK), giving the opportunity for collaborators to clarify any uncertainties regarding the protocol. A summary of frequently asked questions will be distributed to all collaborators following each Twitter session, providing real-time feedback to collaborators.

Validation

Following data collection only data sets with >95% data completeness will be accepted for pooled national analysis. An independent assessor will validate 5% of all data points, with a target of >98% accuracy.

Data management

A standardised Microsoft Excel spreadsheet (Excel 2010; Microsoft, Redmond, WA, USA) with pre-set fields will be used to collect data at each centre. Data protection regulations at each centre will be complied with. Patient identifiable data will not be transmitted to the trial management group. The required anonymous data fields are shown in table 4.

Anticipated minimum recruitment

It is estimated that an average centre performs approximately 15 gastrointestinal resections in a 14-day period. A minimum of 60 centres will be recruited, with at least two centres participating at each of 30 medical schools. Overall we anticipate recruiting at least 900 patients.

Power calculation

The study will have at least 80% power to detect an increase in the 30-day adverse event rate from 15% to 25% with NSAID use. It is anticipated that a third of patients will receive NSAIDS [4]. A baseline complication rate of 15% was used to determine sample size, acting as a midpoint between high and low rates from various subgroups undergoing bowel resection. This rate was based on recent audit of emergency appendicectomy in the UK, a combination of elective and emergency surgery, and known morbidity profiling[10 12]. ~~Based on recruiting~~By recruiting 300 patients receiving NSAIDs and 600 control patients, this study will have 93.5% power to detect an increase in the complication rate from 15% to 25% (α=0.05).

Statistical analysis

Differences between demographic groups will be tested with the χ^2 test. Multivariable binary logistic regression will be used to test the influence of clinically plausible variables on the outcome measures, to produce adjusted odds ratios (OR) and bootstrapped 95% confidence intervals (95% CI). This will be performed firstly the whole dataset and then a matched group of 2:1 control:experimental (NSAID administration), using propensity scoring. Data handling will be performed in SPSS version 21.0 and statistical modelling in the R Foundation Statistical Programme 3.0.0.

Ethics and Dissemination

Research Ethics Approval

Following Research Ethics Committee Chairperson review, a formal waiver was received. The study will be undertaken as a clinical audit. This was further supported by written advice from a University NHS Trust Research & Development Office Director and the National Research Ethics Service (NRES). This study will be registered as clinical audit or service evaluation at each participating hospital.

Protocol dissemination

The generic collaborative methodology underlying protocol dissemination and collaborator recruitment has been described previously [9]. The protocol will be disseminated primarily through medical student networks, including student surgical and medical societies. The Association of Surgeons in Training (www.asit.org) will also disseminate the protocol to its members. A student local lead will be designated at each medical school to facilitate local dissemination. The protocol document will be made available online and will also be

disseminated through social media, including Twitter (https://twitter.com/STARSurgUK) and Facebook (https://www.facebook.com/STARSurgUK).

Discussion

This paper describes the protocol to a novel study, addressing an important clinical question using rapid-delivery, snap-shot methodology. The development of the national network, formed by the natural geographical locations of medical schools within the United Kingdom, is also novel. The observational nature of this study means it is classified as audit. Within the confines of this, a detailed and protocolised approach is warranted to ensure maximum quality.

The multi-centre nature of this study means that the approaches taken to its design are pragmatic. In particular, the definitions used and the number of data-points are designed to aid local investigators to ensure simplicity of delivery, whilst containing enough detail to answer the relevant clinical question.

A randomised controlled trial would provide the highest level of evidence to guide patients and clinicians towards optimal post-operative analgesic regimes. In order to power these trials, and to justify funding applications, a multicentre observational study is required.

List of abbreviations

NSAID: Non-steroidal anti-inflammatory drug.

OR: Odds ratio.

LOS = Length of stay

SSI = Surgical site infection

Competing interests: None.

Authors Contributions:

Dmitri Nepogodiev

Conception, design, writing and editing of protocol

Stephen Chapman

Design and writing of protocol

James Glasbey

Design and writing of protocol

Michael Kelly

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Table 3: The Revised Cardiac Risk Index

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1. History of ischemic heart disease
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Table 4: Required data fields

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9	Was the patient taking regular aspirin?	Yes, and re-started in first 7 post-op days; yes, but not restarted first 7 post-op days; No
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19	Highest post-operative glycaemic reading within 72 hours of surgery using finger prick, blood gas or laboratory value (mmol/L).	Value (mmol/L)
20	Post-operative critical care admission?	Planned from theatre, unplanned from theatre, unplanned from ward, none
21	Post-operative ERAS pathway used?	Yes, no
22	Was an NSAID used post-operatively?	Yes - Ibuprofen, Yes -diclofenac, Yes - naproxen, Yes - celecoxib, Yes - rofecoxib, Yes - other, No
23	What day was the first dose of NSAID given?	Day 1-7 (day 1 is day of surgery), none given
24	What dose of NSAID was given?	Low, high, none given
25	Total length of stay (days)	Days
26	30-day re-admission?	Yes, no
27	Surgical Complication Grade (Clavien-Dindo Classification, list most severe Grade I-V)	None, I, II, III, IV, V
28	Anastomotic leak	Yes, no
29	Wound infection	Yes, no
30	Intra-abdominal/pelvic abscess	Yes, no
31	Cardiovascular event	Yes, no

References

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2. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C, Morales O: **Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial.** *Anesthesiology* 2005, **103:**1225-1232.
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9. Bhangu A, Kolias AG, Pinkney T, Hall NJ, Fitzgerald JE: **Surgical research collaboratives in the UK.** *Lancet* 2013, **382:**1091-1092.

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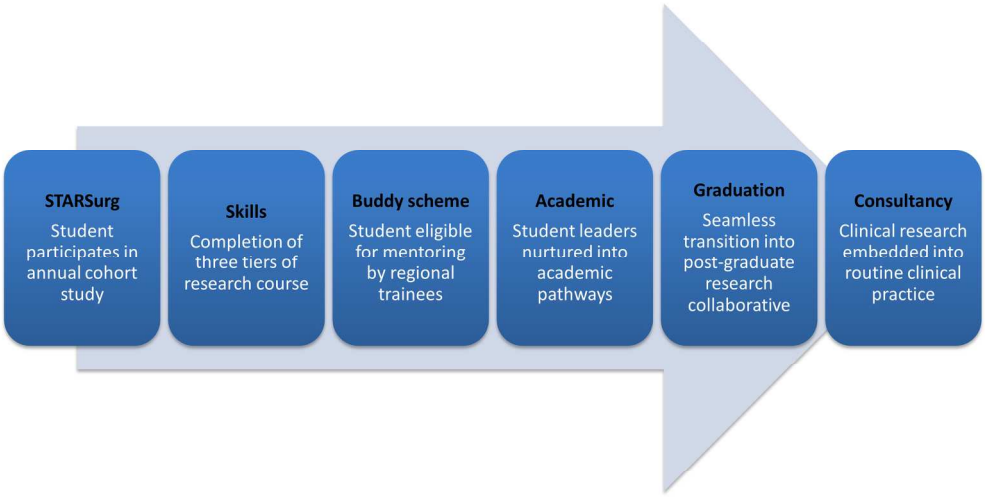

Figure 1
190x142mm (300 x 300 DPI)