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The current status of clinical trials in emergency gastrointestinal surgery. A systematic analysis of contemporary clinical trials

Amelia Milton[1], Thomas M. Drake MBChB, BMedSci[2,3], Matthew J. Lee MBChB, BSc[1,4]

[1]The Medical School, University of Sheffield, Sheffield, UK, aimilton1@sheffield.ac.uk

[2]Department of Clinical Surgery, University of Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, UK, t.drake@ed.ac.uk (do not publish)

[3]Institute for Cancer Sciences, University of Glasgow, Switchback Road, Bearsden, Glasgow, G61 1BD

[4]Department of General Surgery, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, m.j.lee@sheffield.ac.uk

Corresponding author: Mr Matthew Lee, Dept of General Surgery, Northern General Hospital, Sheffield, UK, S5 7AU

Twitter: @wannabehawkeye

Email: m.j.lee@sheffield.ac.uk

Telephone: (+44) 01142 434 343

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Declarations

Ethics: This study did not utilise patient data and therefore no ethical approval was required.

Consent for publication: This study did not utilise patient data and therefore did not require any consent from patients for publication.

Availability of data and material: Data is available on request to investigators and is presented in Table 1.

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Abstract

Background

Emergency gastrointestinal surgery (EGS) conditions represent a significant healthcare burden globally requiring emergency operations that are associated with mortality rates as high as 80%. EGS is currently focussed on quality improvement and internal audits, which occurs at a national or local level. An appreciation of what EGS trials are being conducted is important to reduce research wastage and develop coordinated research strategies in surgery. The primary aim of this study was to identify and quantify recent and active trials in emergency gastrointestinal surgery. The secondary aim was to identify conditions of interest, and which aspects of care were being modified.

Methods

A systematic search of WHO, UK, US, Australian and Canadian trials databases was undertaken using broad terms to identify studies addressing emergency abdominal surgery and specific high-risk diagnoses. Studies registered between 2013-2018 were eligible for inclusion. Data on study topic, design, and funding body were collected. Interventions were classified into 'peri-operative', 'procedural', 'post-operative', 'non-surgical' and 'other' categories.

Results

Searches identified 5603 registered trials. After removal of duplicates, 4492 studies remained and 42 were eligible for inclusion. Almost 50% of trials were located in Europe and 17% (n=7) in the USA. The most common condition addressed was acute appendicitis (n=11), with the most common intervention being procedure based (n=23). Hospital based funding was the most common funder (n=30).

Conclusion

There is large disparity in the number of surgical trials in emergency surgery, which are primarily focussed on high-volume conditions. More research is needed into high-mortality conditions.

Evidence level: 1a (oxford)

Keywords: Emergency surgery; randomised trials; research methodology

Background

Emergency general surgery (EGS) conditions represent a significant healthcare burden globally[1]. Many of these conditions require emergency operations, with associated mortality rates ranging from 1.1% at 24 hours to 8.6% at 30 days. Even in high income countries such as the UK where high risk emergency surgical procedures account for 12.5% of total operations, death rates are as high as 80% [1,2]. In addition, routine procedures in emergency surgery such as small bowel resection are associated with high morbidity rates which has further implications for patient recovery and healthcare costs [1-3].

EGS activity is currently focussed on quality improvement and audits at a local or national level. These include the National Emergency Laparotomy Audit (NELA) in the UK and the National Surgical Quality Improvement Partnership (NSQIP) in the US [2,4]. Quality improvement relies on a high-quality evidence base to guide efforts that are primarily designed to improve patient outcomes. It is recognised that EGS lacks a high quality evidence base [5] which may account for why many aspects of surgical practice are based upon dogma [6].

To generate high-quality evidence to improve patient outcomes, it is necessary to conduct randomised clinical trials. The conduct of a clinical trial can take many years as funding and governance approvals must be secured, along with delivery of the study and analysis of findings. This means that there can be a significant period between the registration of a trial and the publication of findings. Knowing which trials are in progress is important to reduce research wastage and develop coordinated research strategies in surgery. It is considered standard practice for clinical trials to be registered on a database. This helps to prevent duplication and may also protect against publication bias.

The primary aim of this study was to identify and quantify recent and active trials in EGS. The secondary aim was to categorise research according to geographic base, funding body, condition of interest and intervention being trialled to grasp a better idea of what evidence-based research in emergency surgery is currently being undertaken.

Methods

This study was conducted with reference to the Cochrane handbook and is reported with in line with the applicable fields of the PRISMA guidelines [7,8].

Search strategy

Information on emergency surgery trials was sourced from the UK Clinical Trials [9], UK Research and Innovation (UKRI)[10], US Clinical trials [11], Australian New Zealand Clinical Trials Registry (ANZCTR) [12], World Health Organisation International Clinical Trials Registry Platform (ICTRP) [13], and Canadian International Standard Registered Clinical sTudy Number (ISRCTN) [14], databases online.

To provide an accurate picture of current clinical trials underway in emergency surgery, search limitations were set to addressing any study registered or actively recruiting between January 2013 to January 2018. Searches were conducted of each database using a selection of terms with broad reference to EGS and specific high-risk diagnoses [15]. These include "Emergency Surgery" OR "Appendicitis" OR "Diverticulitis" OR "Bowel Obstruction" OR "Pancreatitis" OR "Cholecystitis" OR "Peritonitis" OR 'Laparotomy" OR "Acute abdomen" OR "Diverticulitis" without language restrictions.

Inclusion & Exclusion Criteria

Emergency general surgery trials were defined as randomised controlled trials investigating non-elective and unplanned surgery of the GI tract. These included procedures from the upper oesophageal sphincter to anus, abdominal wall disease and liver disease. Studies addressing vascular, neurological, gynaecological, thoracic surgical emergencies and pharmacological testing were excluded, as were those registered before 2013 or not currently active during the relevant period.

Study Selection

Searches were conducted by one researcher. The title and abstract of each remaining database results were independently assessed by both researchers to confirm eligibility. Where there was a disagreement over eligibility, the abstract was discussed by researchers to reach an agreement.

Data extraction

Information regarding trial name, start date, sponsor, funding body and location of study, was tabulated on an excel spreadsheet. Multicentre trials were localised according to their primary clinical unit (the location of the chief investigator). Interventions were assigned into one of five categories "Procedural" (i.e. focussing on a specific procedure or aspect of a procedure during surgery including comparing surgical interventions to medical interventions), "Non-surgical" (i.e. not testing a surgical intervention), "Perioperative" (i.e. those interventions taking place in theatre), "Postoperative" (i.e. those interventions taking place following surgery) and "Other" (none of the above). Categories of funding source were defined in line with internationally selected guidelines [16]. As this is a systematic analysis of trials concerned with overview of current activity, no quality or bias assessment was performed.

Results

Search results

The research identified 5603 trials from initial screening. Following removal of duplicates, 4492 unique records were identified (figure 1). These underwent dual screening and 48 records were identified. Those excluded did not meet the inclusion criteria, being identified from broad search terms. After full review of their registration, 6 were removed for the following reasons; Not active or registered within the selected time period, (SCARELESS, CReST and LEONARDO; n=3), Observational study (STELLA; n=1), preventative or diagnostic procedure, (Prophylaxis of post-ERCP pancreatitis using temporary pancreatic stent vs rectal nonsteroidal anti-inflammatory drug and the use of different sized USS guided needles in the diagnosis of acute appendicitis; n=2).

In total 42 trials were identified. Fourteen were identified from ICTRP, 11 from the US clinical trials database, 10 from UK clinical trials, three from the ANZCTR and ISRCTN respectively, and one from UKRI (see Table, Supplemental Digital Content 1, http://links.lww.com/TA/B231). These addressed Emergency surgery (n=9), Cholecystitis (n=6), Pancreatitis (n=3), Laparotomy (n=5), Appendicitis (n=11), Bowel Obstruction (n=2), Acute Abdomen (n=1) and Diverticulitis (n=5). A summary list of trials identified is presented in table 1.

Timing and Type of Intervention

Over 50% (n=23) studies were found to be investigating a procedure within the operating theatre, for example using different techniques or different equipment. Nine studies investigated non-surgical management, such as using antibiotics to treat appendicitis followed by a delayed appendicectomy or the use of gastrografin for bowel obstruction. Six

studies were focussed on addressing peri-operative factors, for example the use of IV fluids during operating to improve outcomes or the insertion of rectus sheath blocks at the end of surgery to improve post-operative pain intensity. Three of the studies were focussed on post-operative outcomes mainly looking at physiotherapy and quality improvement in post-operative care. Two studies were classified as "other" focussing on the use of telemedicine in the remote management of damage control surgery and the use of a smart phone in assessing surgical site infections. Graphical representation of intervention categories is highlighted in figure 2.

Funding source

Hospital based funding was the most common funding category accounting for 30 trials. The category named affiliated medical research bodies was the second most common funding category with eight trials. These included the NIHR (National institute of health research), the UK MRC (medical research council), Canadian forces medical services, Hungarian pancreatic study group and Southwest oncology group. Private sponsors (n=3) are individually named sponsors. Commercially based sponsors included Bupa, a private health insurance company.

Emergency surgery

Nine studies addressed emergency surgery in general. Three of these trials focused on EGS procedures, such as laparoscopic versus open surgery (LaCeS), using nanotechnologies as a fixing method for prosthetic materials in emergency laparoscopic procedures and the role of endoluminal stenting in the acute management of obstructing colorectal cancer. Two trials were categorised as peri-operative management, investigating Fluid optimisation in

emergency laparotomy (FLO-ELA) and comparing direct and guide wire assisted techniques to artery cannulation in patients posted for emergency surgery and the association between oxygen saturations and post-operative cognitive dysfunction in the elderly undergoing EGS. The single post-operative trial investigated the outcomes of enhanced rehabilitation in patients following EGS. One trial was categorised as "other" investigating whether the use of a smart phone tool aided the earlier identification and management of surgical site infections in EGS patients. Four of the studies were carried out in the UK, one in China, France, India, Italy and Tasmania respectively. Five studies received hospital funding, three were funded by affiliated medical research bodies. The remaining study was privately funded.

Laparotomy

Five studies investigating laparotomy were identified. Two studies were categorised as procedural, investigating the outcomes of damage control surgery and comparing endoscopically assisted colostomy with Colopexy to Laparotomy (EACC). Two other trials were categorised as "peri-operative", one was based in the UK looking at interventions for quality improvement for patients undergoing emergency laparotomy (EPOCH) and the other was based in Dubai investigating the post-surgical use of rectal sheath blocks for pain management. One trial addressing laparotomy was categorised as "other", investigating the use of telemedicine to mentor surgeons in damage control surgery for critically injured trauma patients from afar. This trial took place in Canada and was funded by the Canadian armed forces. One trial (EPOCH) was funded by the National Institute of Health Research (NIHR), two trials were received hospital-based funding and one trial was privately funded in Dubai.

Appendicitis

Eleven trials addressing acute appendicitis were identified. Six trials were categorised as "non-surgical" and investigated the outcomes of antibiotics for the treatment of appendicitis when compared to surgery. Notably, four of these trials (CONTRACT; APPY; COMMA and CHINA), were focused exclusively on paediatric populations. Four trials investigated procedural techniques for appendicectomy. This included the use of Polymer clips versus endoloops (PECAS), Clips vs staples, the use of single versus multiple ports, and an interval appendicectomy post antibiotic therapy for acute appendicitis (CHINA). Four (36%) of the trials originated from the USA, three in the UK, one in Taiwan and the remaining three in Europe (see Figure, Supplemental Digital Content 2, http://links.lww.com/TA/B232). The majority (n=8) of trials identified from the search term appendicitis received hospital-based funding.

Cholecystitis

Six EGS trials addressed cholecystitis. Five (83%) of which focussed on EGS procedures, including intra-operative ERCP vs laparoscopic bile duct exploration for bile duct clearance in patients undergoing emergency cholecystitis, immediate vs delayed laparoscopic cholecystectomy in two trials, laparoscopic vs conservative treatment in acute cholecystitis, and intra-gallbladder or systemic Indocyanide green injection to facilitate cholecystectomy in patients with acute cholecystitis. One study investigated the use of extended antibiotic therapy post-operatively in reducing infections. Five (83%) of the studies were hospital funded, one was privately funded. All six of the trials were carried out in different countries including: Australia, Argentina, Finland, Japan, Taiwan and Saudi Arabia.

Bowel obstruction

Two studies addressing bowel obstruction were identified. The first study investigated the non-surgical use of water soluble contrast in addition to medical management for malignant bowel obstruction in adults. This study was performed in Australia and received hospital-based funding. The second procedure-based study compared outcomes associated with conservative or surgical management of malignant bowel obstruction. This was funded by Southwest Oncology Group and was carried out Canada.

Diverticulitis

Five studies addressing diverticulitis were identified. Four (80%) of the studies were procedure based EGS trials comparing laparoscopic lavage vs primary resection of an area of the colon in the treatment of acute diverticulitis. The remaining trial addressing diverticulitis was categorised as non-surgical investigating the rate of surgical site infection using vacuum assisted therapy in emergent contaminated abdominal surgery. One of the trials was being undertaken in the USA, the remaining three within Europe. All five (100%) of the trials were funded by hospital-based funding.

Acute pancreatitis

Three studies addressed pancreatitis. All three were categorised as 'procedural', one study investigated the use of stents for acute necrotizing pancreatitis, one compared the use of a stent vs no stent in acute pancreatitis and the other investigated the optimal time for cholecystectomy in acute biliary pancreatitis. One study was carried out in a US hospital where the funding originated. The second study took place in Hungary and was funded by the Hungarian pancreatic study group. The third study was undertaken in Egypt and was funded by the local hospital.

Acute Abdomen

One study addressing acute abdomen was identified (CLIPPER2). This trial compared the related morbidity rates of two different procedures; surgical versus endoscopic closure in patients with acute colonic perforations. The study took place in Germany and received local hospital-based funding.

Discussion

This study identified 42 EGS trials with activity in the last 5 years. We found that the majority of recent trials within emergency surgery are addressing low mortality conditions such as appendicitis (n=11), not those with high mortality rates such as emergency laparotomy (n=5) [17]. Although initial searches gathered nearly 4000 studies, on reviewal by the research team the majority of studies were not research in emergency surgery, merely being identified within the database because of the search term used. Across all settings funding was typically secured at a local level (n= 30), and eleven trials (26%) had cohorts less than 100 participants. Studies with smaller sample sizes, either due to a lack of funding or challenges in recruitment may hinder the progression of the EGS evidence base and perhaps only offering marginal gains [18].

In general, surgical trials are aimed at either improving long term outcomes, or perioperative morbidity in the elective setting, despite there being a lower risk of morbidity and mortality than seen in the EGS population. When comparing the population affected by emergency surgical conditions, and the evidence base to support interventions to the number affected and volume-based research within elective surgery there is a large disparity. Our evidence is supported by Morley et al [19] which identified between 2010 and 2012 only 39 out of 414 trials addressing surgery were aimed at emergency surgery. Their study showed that both

emergency and elective study trials had equal risks of being terminated early and were equally likely to be published once registered. This implies that EGS research has equal opportunities for success as that in elective settings, and more must to be done to bridge the gap in research. This study did not undertake formal comparison of the number of EGS trials to another clinical area as the research team could not select a suitable comparator population or condition.

Searches within each database showed that several EGS related studies were registered in the study period. Many did not meet the inclusion criteria because there were either observational studies or case series with very few participants [20]. Observational studies have an important role in informing surgical practice including describing epidemiology, outcomes and identifying potential areas for intervention. However, observational studies are poorly suited to attributing causation and testing solutions without considerable risk of selection bias. Trials in the emergency setting are challenging to conduct as emergency care is often delivered when time and resources are pressured [21]. There are potential challenges in identifying and recruiting patients, alongside implementing interventions in a timely and standardised manner. These practical issues require further research. Nevertheless, conducting surgical trials in this setting is possible, as is done routinely in intensive care medicine and in emergency medicine [22].

There are numerous challenges in the delivery of EGS trials. Firstly, the population of high-risk emergency surgical patients is highly heterogenous. These patients often have complex multi-system disease and uncertain diagnoses which may only be identified intraoperatively or even postoperatively. This represents a challenge in the recruitment and delivery of interventions. Secondly, this patient group is often critically unwell, and clinical delay due to

research may present barriers to recruitment. In addition, there is variation in practice and scope of EGS and constituent teams globally, which could contribute to the difficulty in enrolling patients in areas less well supported. There are however, some factors which should improve the feasibility of EGS trials. Emergency general surgery conditions are also common, meaning that a large population is available to participate in trial. Morbidity and mortality in this group are common, and often occur close to the index event of surgery [23] potentially meaning shorter-term follow-up are necessary to assess outcomes.

Our study identified very few EGS trials outside of high income settings with clinically significant sample sizes. Populations in low and middle-income settings have a higher requirement for emergency surgical services and poorer outcomes than high income populations [24]. However, in our study, the studies we identified within low-middle income countries had very few participants. Four out of the nine studies identified with fewer than 100 participants were carried out in low-middle income countries (EACC, Single-incision laparoscopic surgery in acute abdomen, Acute biliary pancreatitis - optimal time for cholecystectomy, and The onset time of rocuronium in emergency and elective surgery). These settings present unique challenges and may be where the greatest gains in outcome may be. Identifying interventions which are effective in improving outcomes from emergency surgery across the world would enable a far larger population to benefit. There are multiple reasons why surgical trials may not have been identified in these settings. First, these countries may not have requirements to register clinical trials prospectively and hence would not have been identified by our searches. This is unlikely as we searched multiple international databases and the requirement for prospective registration is common. Secondly, resource and ethical limitations may play a role. Clinicians in these settings are more stretched, dedicating most of their time to service provision, leaving very limited time

for participant recruitment or data collection. Moreover, they may lack the necessary resources to undertake research. International initiatives are aiming to change this, with capacity building networks being formed in surgery, such as the GlobalSurg collaborative [25], who have just launched a factorial randomised trial investigating skin preparation.

This study is not without limitations. Whilst it is expected that all trials are registered following the legislation implemented by the International Committee of medical Journal Editors in 2005 [26], it is possible that some may not be identified through the searches. We did not search for resulting publications and were unable to account for unpublished research, nor research that remains within the hospital or country where it was carried out, meaning it is available globally. This could be resolved by streamlining the regulation process, making all studies from the various databases available on one global database with unlimited international access. This would also make it simpler for authors to both recruit and register trials globally. However, a recent study suggests that 46% of EGS trials are published [19]. We recognise that the findings of our study may age, if significant changes are made to encourage future emergency surgery research, however it will provide a useful benchmark progress in this field. The strengths of this study include adherence to methodological principles, dual review of candidate studies, and interrogation of multiple databases using multiple search terms, meaning the majority of candidate studies should have been identified. This allows a robust estimate of international trial activity in EGS.

For elective surgery, time for preoperative optimisation and careful planning provide a controlled environment to undertake research aimed at improving surgical and perioperative outcomes. This is not a luxury afforded to research in the emergency setting. Nevertheless, this study highlights that there is a large disparity in the number of randomised trials in

elective versus emergency surgery that are currently being performed. It is imperative that this gap is addressed to improve both the quantity and quality of the literature in this field, which is key for improving EGS outcomes. Future studies should focus on high-risk groups (i.e. emergency laparotomy), in addition to high-volume groups (i.e. appendicitis) for maximal benefit. Researcher teams should include the wider surgical team, anaesthetists, intensivist, emergency physicians and methodologists. Teams should work to optimise trial designs in order to answer important research questions robustly, while adequately addressing the complex challenges to research in the emergency setting [27].

One way to improve outcomes in emergency surgeries, is by making funding more accessible. It was notable in this review that many of the studies were supported by local hospital funds, rather than national level funders such as the National Institute for Health Research (NIHR) in the UK, or the National Institute for Health (NIH) in the use. These strategic funding bodies could consider commissioned calls for EGS projects, and incentivisation of units to deliver emergency surgery research. This may help to increase the number of trials that are addressing high morbidity conditions such as laparotomy and bowel obstruction.

There is large disparity in the number of surgical trials in emergency surgery, which are primarily focussed on high-volume conditions. More research is needed into high-mortality conditions. Future efforts should focus on improving both the quantity and quality of research in these patients and ensuring findings are generalisable for patients across the world.

Author Contributorship

All authors were involved in the conception, design, analysis, manuscript drafting and critical revision of this work. All authors meet the ICMJE criteria for authorship.

References

1. GlobalSurg Collaborative. Mortality of emergency abdominal surgery in high-,middle- and low-income countries. *Br J Surg*. 2016;103(8):632–632.
2. NELA Project Team. The third Patient Report of the National Emergency Laparotomy Audit (NELA). 2017.
3. Scott J, Olubode O, Gabriel B. Use of National Burden to Define Operative Emergency General Surgery. *JAMA Surg*. 2016;151(6):e160480.
4. American College of Surgeons. ACS National Surgical Quality Improvement Program. ACS. 2017.
5. EMSurg Collaborators. Methodological overview of systematic reviews to establish the evidence base for emergency general surgery. *Br J Surg*. 2017;104(5):513–24.
6. Jenkins T. It's time to challenge surgical dogma with evidence-based data. *Am J Obstet Gynecol*. 2003;189(2):423–7.
7. Moher D, Liberati A, Tetzlaff J, Liberati A, Tetzlaff J, Altman D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Med*. 2009;6(7).
8. The Cochrane Collaboration. Part 2: General methods for Cochrane reviews. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Verson 5.1. 2011.
9. UKCTG. UK Clinical trials Gateway [Internet]. Date last accessed: 01/08/2018. Available from: https://www.ukctg.nihr.ac.uk/
10. UKRI Gateway. UK Research and Innovation.
11. NIH. Clinical Trials.gov [Internet]. Date last accessed: 01/08/2018. Available from: https://clinicaltrials.gov/

12. ANZCTR. Australian New Zealand Clinical Trials Registry.

13. WHO. WHO International Clinical Trials Registry Platform.

14. ISRCTN. Canadian International Standard Registered Clinical sTudy Number Registry [Internet]. Date last accessed: 01/08/2018. Available from: http://www.isrctn.com/

15. Symons N, Moorthy K, Almoudaris A, Bottle A, Aylin P, Vincent C, Faiz OD. Mortality in high-risk emergency general surgical admissions. *Br J Surg*. 2013;100(10):1318–25.

16. Ravinetto R, Nys K, Boelaert M, Diro E, Meintjes G, Adoke Y, Tagbor H, Casteels M. Sponsorship in non-commercial clinical trials: definitions, challenges and the tole of Good Clinical Practice guidelines. *BioMed Cent Int Heal Hum Rights*. 2015;15(34).

17. Boney O, Bell M, Conquest A, Cumbers M, Drake S, Galsworthy M, Gath J, Grocott MPW, Harris E, Howell S et al.. Identifying research priorities in anaesthesia and perioperative care:final report of the joint National Institue of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partneship. *BMJ Open*. 2015;5(12).

18. Sakpal T. Sample Size Estimation in Clinical Trial. *Perspect Clin Res*. 2010;1(2):67–9.

19. Morley R, Edmondson M, Rowlands C, Blazeby J, Hinchliffe R. Registration and publication of emergency and elective randomised controlled trials in surgery: a cohort study from trial registries. *BMJ Open*. 2018;8(7).

20. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet*. 1996;13(347):984–5.

21. Good, A., Driscoll P. Clinical research in emergency medicine: putting it together. *BMJ Open*. 19(3):242–6.

22. Patterson T, Perkins A, Perkins G, Clayton T, Evans R, Nguyen H, Wilson K, Whitbread M, Hughes J, Fothergill RT et al.. Rationale and design of: A Randomized

trial of Expedited transfer to a cardiac arrest center for non-ST elevation out-of-hospital cardiac arrest: The ARREST randomized controlled trial. *Am Hear Jounral*. 2018;6(204):92–101.

23. Tengberg LT, Cihoric M, Foss NB, Bay-Nielsen M, Gögenur I, Henriksen R, Jensen TK, Tolstrup MB, Nielsen LB. Complications after emergency laparotomy beyond the immediate postoperative period – a retrospective, observational cohort study of 1139 patients. *Anaesthesia*. 2017;72(3):309–16.
24. Meara J, Leather A, Hagander L, Alkire B, Alonso N, Ameh E, Bickler SW, Conteh L, Dare AJ, Davies J et al.. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet Comm*. 2015;386(9993):569–624.
25. GlobalSurg Collaborative. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. *Lancet Infect Dis*. 2018;18(5):516–25.
26. What is the ICMJE definition of a clinical trial. ICMJE. 2018.
27. The G4 Alliance. Global Surgery & Anaesthesia Statistics The Importance of Data Collection.

Figure legends

Figure 1: PRISMA Flow Diagram

Figure 2: Intervention categories in EGS trials

Figure 1

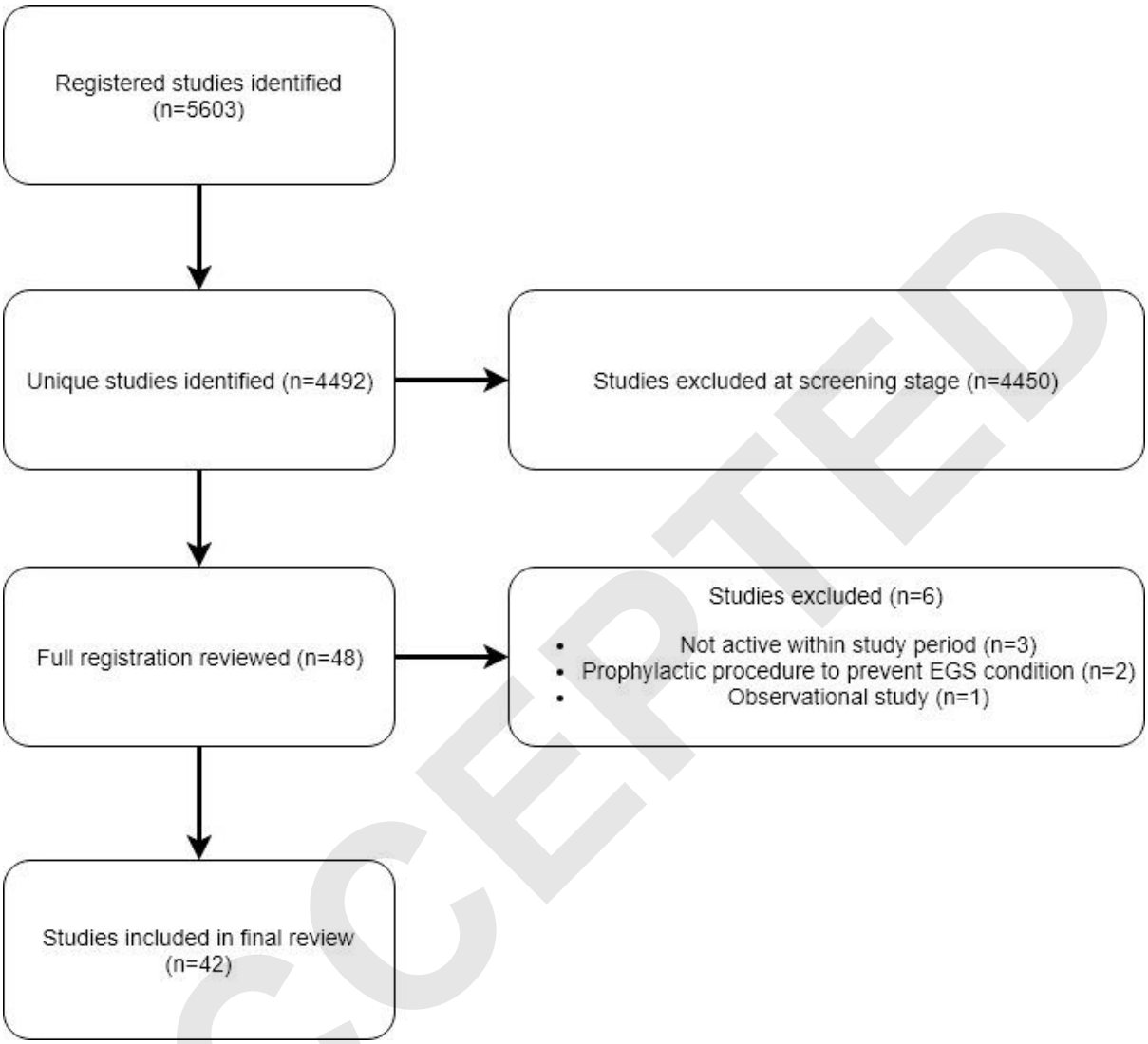
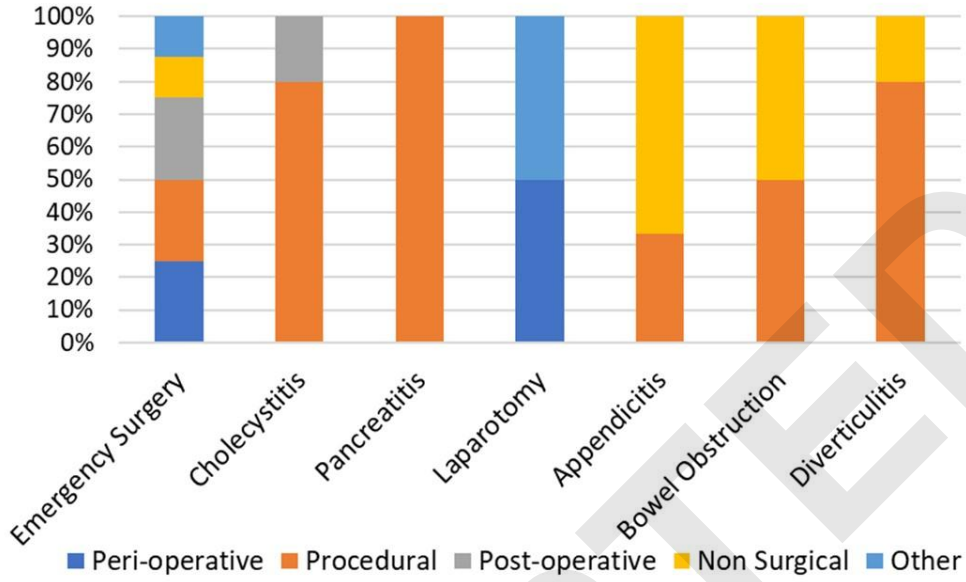


Figure 2



Tables

Table 1: Summary of included studies

Search Term	Acronym	Summary of trial details	Timing/ Type of intervention	Primary Outcomes
Emergency Surgery	FLO-ELA	The use of intravenous fluids post-operatively to improve recovery	Peri-operative	Recovery time
	LACES	Laparoscopic vs open surgery	Procedure based	30 day mortality rates
	ICE AGE	Complication rates following emergency abdominal surgery	Post-operative	Complication rates
	NA*	Reducing wound infections after emergency surgery in low-middle income countries LMIS's	Post-operative	Time until wound infection
	NA*	Colonic Stenting in Elective Surgery Versus Emergency Surgery in the Management of Acute Malignant Colonic Obstruction	Peri-operative	Rates of primary colorectal anastomosis
	TWIST	The use of a smartphone to assess surgical site infections.	Non-operative	Time from surgery to treatment for surgical site infection Outcome assessed at 30 day follow-up
	NA*	Nanotechnologies Applied to General Surgery and Emergency Surgery: Buckypaper as a New Fixing Method for Prosthetic Materials	Procedural	Time of durability without side effects of surgical device

	NA*	Direct or guide-wire assisted techniques of radial artery cannulation in patients posted for emergency surgery.	Procedure	To compare success rate of cannulation on first attempt between the two techniques
	NA*	The Association Between Variation in Oxygen Saturation (ScO2) and Incidence of Postoperative Cognitive Dysfunction (POCD) in a Population of Elderly Patients Admitted for Emergency Surgery.	Post-operative	Occurrence of POCD
Cholecystitis	NA*	Endoscopic Retrogradepancreatography versus laparoscopic common bile duct exploration for emergency cholecystitis	Procedure	Time of procedure
	NA*	Extended Antibiotic Therapy in Postoperative of Laparoscopic Cholecystectomy in Acute Cholecystitis	Post-operative	Incidence of infectious postoperative complications
	NA*	Acute Cholecystitis: Early Versus Delayed Laparoscopic Cholecystectomy	Peri-operative	Operative time
	NA*	Laparoscopic Cholecystectomy or Conservative Treatment in the Acute Cholecystitis of Elderly Patients	Post-operative	Specific Morbidity Index Scores
	NA*	Early versus early interval laparoscopic cholecystectomy for acute cholecystitis	Procedure	Operation time
	NA*	Intra-gallbladder or Systemic Indocyanide Green Injection Facilitate Cholecystectomy	Post-operative	CBD identification (white light and infrared fluroscence image)
Pancreatitis	NA*	Stent vs no stent in necrotising pancreatitis preventing walled off necrosis	Procedure	Mortality rates
	NA*	Early cholecystectomy was	Procedure	Gallstone

		done within 48 after admission vs delayed done after 30 days after randomization		related complications
	NA*	Preventive pancreatic stents in the management of acute biliary pancreatitis	Procedure	Mortality and morbidity at 30 days
Laparotomy	NA*	The use of telemedicine in off site management of emergency surgery	Perioperative	Safety and Feasibility of telemedicine
	NA*	Incomplete vs complete closure in emergency laparotomy	Procedure	major abdominal complications and mortality rates
	EACC	Endoscopically Assisted Colostomy With Colopexy for Critically Ill Patients Without General Anesthesia or Laparotomy (EACC)	Procedure	Safety and Tolerability of the procedure
	NA*	Ultrasound guided rectus sheath block by the end of the surgery vs multiholed catheter for pain management	Peri-operative	Self reported pain intensity
	EPOCH	Quality improvement intervention for patients undergoing emergency laparotomy	Post-operative	All cause mortality at 90 days following surgery
Appendicitis	CONTRACT	Interval appendicectomy outcomes in children compared to normal appendicectomy	Procedure	Complication rates
	CHINA	The childrens interval appendicetomy study	Per-operative	Complication rates
	COMMA	Polymer clips vs endoloops for closure of the appendiceal stump during emergency laparoscopic appendicectomy	Procedure	Time until next surgery
	PECAS	Polymer Clips Versus Endoloops for Closure of the Appendiceal Stump During Emergency Laparoscopic Appendicectomy	Procedure	Complication rates
	APPY	Appendectomy Versus Non-Operative Treatment For Acute Non-Perforated Appendicitis in Children	Non surgical	Complication rates

	APPAC	Open Appendicectomy Versus Antibiotic Treatment (Ertapenem) in the Treatment of Acute Uncomplicated Appendicitis	Non surgical	Recurrence rates
	NA*	Quality improvement intervention for patients undergoing emergency laparotomy	Non surgical	Quality improvement
	NA*	Comparative Study of Polymetric Clips (Hem-o-Lok) Versus Historical Endoscopic Staplers for Laparoscopic Appendectomy	Procedure	Time for procedure
	NA*	Single port vs multiport	Procedural	Post-operative pain
	NA*	Patient anxiety levels on the onset time of rocuronium in terms of anxiety scores	Peri-operative	Anxiety score
	NA*	Comparison of Medical and Surgical Treatment of Uncomplicated Acute Appendicitis in Children	Non surgical	Complication rates
Bowel Obstruction	NA*	The use of gastrografin in the treatment of bowel obstruction in addition to conservative management	Non-operative	Mortality rates
	NA*	Comparative Effectiveness Trial for Malignant Bowel Obstruction, surgery vs non surgery	Procedure	Number of days alive and outside the hospital
Diverticulitis	SCANDIV	Laparoscopic Peritoneal Lavage or Resection for Generalised Peritonitis for Perforated Diverticulitis	Procedure	Time until re-admission
	NA*	Vacuum Assisted Therapy in Emergent Contaminated Abdominal Surgeries	Procedure	Post-operative complication rates
	DILALA	Diverticulitis - laparoscopic lavage versus resection (Hartman procedure) for acute diverticulitis with peritonitis	Procedure	Post-operative complications
	LADIES	Laparoscopic lavage vs primary	Procedure	Post-

		resection in management of acute diverticulitis		operative complications
	LapLAV	Laparoscopic lavage vs sigmoid resection in management of acute diverticulitis	Procedure	Post-operative complications
Acute Abdomen	CLIPPER2	Endoscopic versus surgical closure of acute colonic perforations	Procedure	Closure-related morbidity, within 30 days after the closure procedure

NA*= not applicable

Table 1: Number of trials by database

Database	Number of Trials
ICTRP	13
UK Clinical Trials	10
US Clinical Trial	4
ANZCTR	3
ISRCTN	2
Gateway to Research UK	1