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Approaches for the treatment of perforated peptic ulcers: a network meta-analysis of randomised controlled trials – study protocol

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ABSTRACT

Introduction Perforated peptic ulcers are a life-threatening complication associated with high morbidity and mortality. Several treatment approaches are available. The aim of this network meta-analysis (NMA) is to compare surgical and alternative approaches for the treatment of perforated peptic ulcers regarding mortality and other patient-relevant outcomes.

Methods and analysis A systematic literature search of PubMed/MEDLINE, Cochrane Library, Embase, CINAHL, ClinicalTrials.gov trial registry and ICTRP will be conducted with predefined search terms.

To address the question of the most effective treatment approach, an NMA will be performed for each of the outcomes mentioned above. A closed network of interventions is expected. The standardised mean difference with its 95% CI will be used as the effect measure for the continuous outcomes, and the ORs with 95% CI will be calculated for the binary outcomes.

Ethics and dissemination In accordance with the nature of the data used in this meta-analysis, which involves aggregate information from previously published studies ethical approval is deemed unnecessary. Results will be disseminated directly to decision-makers (eg, surgeons, gastroenterologists) through publication in peer-reviewed journals and presentation at conferences.

PROSPERO registration number CRD42023482932.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This comprehensive network meta-analysis (NMA) will incorporate all accessible evidence regarding various treatment approaches for perforated peptic ulcers in terms of overall survival.
⇒ The findings will be evaluated and deliberated on with representatives of patients.
⇒ Transitivity assumption: This NMA relies on the assumption of transitivity. Should this assumption be compromised, it could introduce bias into the analysis results.
⇒ Heterogeneity: In this NMA, data from numerous studies will be combined, each potentially employing different methodologies, involving diverse patient populations and exhibiting varying effect sizes. Such diversity can result in heterogeneity within the network, potentially impacting the validity and comprehensibility of the findings.

INTRODUCTION

Peptic ulcers are common, with a lifetime prevalence of 5%–10% and an incidence of 0.1%–0.3% per year.[1] They result from a damaging effect of acid and digestive enzymes on the mucosa of the stomach and duodenum.[2] Despite the decrease in hospitalisation and mortality rates over the past 30 years, complications (such as perforations and bleeding) occur in 10%–20% of patients.[3]

Although perforations occur less frequently than bleeding, they are the most common indication for emergency surgery.[4] Perforated peptic ulcers (PPU) are a life-threatening complication, which is associated with high morbidity and mortality and must be treated immediately.[5] Open surgical, laparoscopic, combined endoscopic and interventional radiological, combined endoscopic and laparoscopic, conservative approaches exist for the treatment of PPU.

The open surgical treatment of PPU is currently the standard treatment. The most important techniques are the repair with a free (Graham) or pedicled omentum patch (Cellan-Jones). Small-uncomplicated perforations can be treated with a simple repair. In the emergency situation of an acutely bleeding PPU, measures such as ulcer resection or vascular ligations are used.[6]

In 1946, a case series of 28 patients with PPU was described for the first time, with a mortality rate of 14%, who were treated conservatively.[7] Conservative therapy consists of H2-blockers, proton pump inhibitors, antibiotics, intravenous fluid resuscitation, placement of a nasogastric tube, close monitoring

and percutaneous drainage.[6 8–10] Intensive medical monitoring is obligatory.

Currently, laparoscopy represents the gold standard for elective procedures such as laparoscopic cholecystectomy and in colorectal surgery.[11] Nevertheless, laparoscopy seems to be limited in emergency medicine such as PPU. Therefore, the literature discusses whether the laparoscopic treatment approach offers an advantage over the open surgical method in PPU.[12–17] Endoscopic interventions are the basis in the diagnosis of PPU and may provide a middle ground between surgical and alternative treatment approaches. Endoscopic techniques for the treatment of PPU include over-the-scope or standard clips, endoscopic sutures and metal stents.[18] Additionally, there is a combined endoscopic and interventional radiological approach available, which can be executed without the need for general anaesthesia.[18]

Moreover, a combined approach using laparoscopy and endoscopy can be employed for treating a PPU. In such instances, the perforation is closed endoscopically through stent placement, while lavage and drainage procedures are conducted laparoscopically.[19]

Despite various treatment options, postoperative complications such as sepsis, intra-abdominal abscess, wound dehiscence, incisional hernia, leakage, pneumonia and ileus occur in approximately 30% of the patients.[3 20] Peptic ulcers continue to be a significant health problem that can demand significant financial resources and involve multiple disciplines.[2] The aim of this study is to compare surgical and alternative approaches for the treatment of PPU in terms of mortality and other patient-relevant outcomes and to evaluate them using network meta-analysis (NMA).

METHODS AND ANALYSIS

Literature search and data analysis are performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[21] This study was preregistered in PROSPERO (ID: CRD42023482932).[22] The study commenced in November 2023 with the development of a protocol and is scheduled to conclude by December 2024.

Search strategy

An electronic literature search will be conducted identifying all published and unpublished randomised controlled trials (RCTs) in all languages. All non-English studies will be translated, and these will be comprehensively assessed and reviewed for possible inclusion in the NMA.

The following databases will be searched:

- PubMed (1966 until today).
- Cochrane Library (from the beginning until today).
- Embase (from the beginning until today).
- CINAHL (1982 until today).
- ClinicalTrials.gov.
- ICTRP.

The search strategies for each database are presented in online supplemental material 1.

Two reviewers will independently review the titles and abstracts. All potentially relevant studies will be coded as ‘accessible’ (eligible, potentially eligible or unclear) or ‘inaccessible’. The full texts of all potentially relevant studies will be screened and reviewed independently by the two reviewers. Studies will also be identified for shortlisting. Excluded studies will also be logged. In case of ambiguity or disagreement between the two reviewers, a third reviewer will be consulted to reach consensus. The selection process will be documented in detail and a PRISMA flow diagram and table of characteristics of included studies will then be produced.

Inclusion and exclusion criteria

Publications of RCTs comparing two therapies for patients with PPU will be considered. Reviews, clinical case reports or case series, scientific papers with fewer than 10 patients, commentaries and letters will not be considered. No restrictions on language will apply (table 1).

Data collection

A standardised data collection form will be used for study characteristics and outcome data. Two review authors will independently extract all relevant data from the selected studies. The collected data will be shared and reviewed again. Any discrepancies will be discussed and consensus will be reached or a third independent author will be consulted. Data collection will be finished by May 2024.

The following data will be extracted:

- Author name, publication year, country of study, language, study duration.
- Study design: inclusion/exclusion criteria, randomisation, risk of bias, study duration/follow-up period.
- Participant characteristics: intervention and comparison group size; age distribution; sex, body mass index (kg/m^2), concomitant diseases (patients), ASA (American Society of Anesthesiologists) score (1–5), drinking history (yes/no), smoking history (yes/no), ulcer history (yes/no), use of non-steroidal anti-inflammatory drugs (yes/no), APACHE (Acute Physiology And Chronic Health Evaluation) II-score (0–34 points); symptom duration (hour), previous upper abdominal surgery (patients).
- Characteristics of intervention: surgical (open surgical or laparoscopic), alternative treatment approach (combined endoscopic and radiological interventional, combined endoscopic and laparoscopic) or conservative therapy.
- Intraoperative findings: median size of perforation (mm), location of perforation (stomach (prepyloric, pyloric), duodenal), median blood loss (ml), success to close the perforation (yes/no), conversion to another treatment approach (yes/no).
- Mortality (in hospital, 30 days, 90 days).
- Morbidity (Clavien-Dindo classification).[23]
- Operation time (minutes).

Table 1 Inclusion and exclusion criteria and outcomes

Category	Inclusion criteria	Exclusion criteria
Language	No language restrictions	
Study design	► Publications of RCTs that compare (at least) two treatment approaches for PPU	► Review papers ► Clinical case reports or case series ► Scientific work with less than 10 patients ► Comments ► Letters
Interventions	► Surgical treatment (open surgical treatment and laparoscopic treatment) ► Combined endoscopic and interventional radiologic treatment ► Combined endoscopic and laparoscopic treatment ► Conservative therapy	
Population	► Patients regardless of age, nationality, symptoms, medical history ► Preoperative clinical diagnosis and intraoperative confirmation of a PPU (gastric or duodenal ulcer) ► Treatment of the PPU with one of the treatment methods described (open surgery, laparoscopic, combined endoscopic and interventional radiological, combined endoscopic and laparoscopic, conservative) ► If necessary, formation of subgroups if sufficient studies have been selected	► Patients without diagnosis of PPU
Main outcome: mortality (in hospital, 30 days, 90 days)		
Additional outcomes: ► Morbidity (Clavien-Dindo classification)[23] ► Operation time (minutes) ► Postoperative length of hospital stay (days) ► Postoperative pain (predefined in each study) ► Leakage (all, postoperative blue dye test, contrast medium) ► Nasogastric tube duration (days) ► Time to resume to diet (days) ► Reoperation/reintervention (yes/no) ► Median size of perforation (mm) ► Location of perforation (stomach (prepyloric, pyloric), duodenal) ► Median blood loss (mL) ► Success to close the perforation (yes/no) ► Conversion to another treatment approach (yes/no) ► Perioperative analgesic requirement (number of patients) ► Decrease in CRP level and leucocyte count (before intervention to 4 days after intervention) ► Postoperative opiate use (days) ► Cosmetic outcome (VAS score for scar appearance) ► Total cost (Euro) ► Return to normal physical activity (days) ► Intravenous infusion administration (days)		

CRP, C-reactive protein; PPU, perforated peptic ulcer; RCTs, randomised controlled trials; VAS, Visual Analogue Scale.

- Postoperative length of hospital stay (days).
- Postoperative pain (predefined in each study).
- Leakage (all, blue dye test postoperative, contrast medium).
- Nasogastric tube duration (days).
- Time to resume to diet (days).
- Reoperation/reintervention (yes/no).
- Decrease in CRP level and leucocyte count (before intervention to 4 days after intervention).

- Perioperative analgesic requirement (number of patients).
- Postoperative opiate use (days).
- Cosmetic outcome (VAS score for scar appearance).
- Total cost (Euro).
- Return to normal physical activity (days).
- Intravenous infusion administration (days).

For each study, the risk of bias will be assessed using the Cochrane Handbook for Systematic Reviews of Interventions and version 2 of the Cochrane 'Risk of bias' tool (RoB2).[24 25]

The following characteristics will be reviewed:

- Bias due to the randomisation process.
- Bias due to deviations from the intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias due to selection of the reported outcome.

Potential bias is rated as 'high,' 'somewhat concerning,' or 'low.'

A citation from the study report and a justification for the rating will be provided in the 'bias risk' table. The presence of bias risk information based on unpublished data or due to correspondence with a study author will be noted in the 'bias risk' table. The overall risk of bias is determined with signal questions and using the algorithm provided by the RoB 2 tool.

RoB 2's overall judgement of treatment effects provides a basis for the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment.[25]

Statistical analysis

To address the question of the most effective treatment approach, an NMA will be performed for each of the outcomes mentioned above. A closed network of interventions, as shown in figure 1, is expected.

The standardised mean difference with its 95% CI is used as the effect measure for the continuous outcomes, and the OR with 95% CI will be calculated for the binary outcomes.

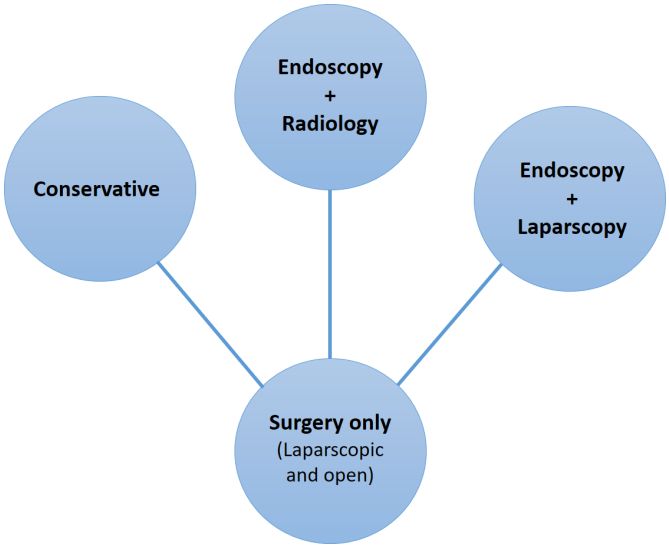

Figure 1 Network graph of direct evidence between interventions expected to be identified through the systematic review.

Frequentist NMA models will be calculated to synthesise the available evidence, as proposed by Rücker.[26] Studies with more than two arms will be included in the NMA considering within-study correlation.[27] To assess heterogeneity between studies, the between-study variance τ^2 and I^2 statistics will be estimated. The assumption of transitivity is statistically tested using the comparison between direct and indirect evidence.[28] Treatment approaches will be ranked in terms of efficacy using the P score, allowing an indication of the most effective treatment.[29]

Results will be presented using forest plots. Possible publication bias will be investigated using a comparison-adjusted funnel plot.[30]

All analyses will be performed using the software 'R' and the extension 'netmeta'.

The literature search on the databases will start in December 2023. The NMA will be completed in December 2024.

A 'summary of findings' table will be prepared for the NMA, which includes both relative and absolute effect measures. Here, the GRADE criteria (study limitations, consistency of effect, imprecision, indirectness, publication bias) will be used to determine the quality of the evidence. In regard to this, a classification will distinguish between high, moderate, low, very low. The methods and recommendations described in the Cochrane Handbook are applied.

The following outcomes will be included in the summary of findings table:

- Mortality (in hospital, 30 days, 90 days).
- Morbidity (Clavien-Dindo classification).[23]
- Operation time (minutes).
- Postoperative length of hospital stay (days).
- Postoperative pain ((predefined in each study).
- Leakage (all, postoperative blue dye test, contrast medium).
- Nasogastric tube duration (days).
- Time to resume to diet (days).
- Reoperation/reintervention (yes/no).
- Median size of perforation (mm).
- Location of perforation (stomach (prepyloric, pyloric), duodenal).
- Median blood loss (mL).
- Success to close the perforation (yes/no).
- Conversion to another treatment approach (yes/no).
- Perioperative analgesic requirement (number of patients).
- Decrease in CRP (C-reactive protein) level and leucocyte count (before intervention to 4 days after intervention).
- Postoperative opiate use (days).
- Cosmetic outcome (VAS (Visual Analogue Scale) score for scar appearance).
- Total cost (Euro).
- Return to normal physical activity (days).
- Intravenous infusion administration (days).

DISCUSSION

By conducting this analysis, we aim to achieve a thorough evaluation of various treatment options, enhancing our comprehension of their relative effectiveness. Employing this approach enables us to amalgamate data from diverse studies, facilitating both direct and indirect comparisons among treatment modalities to derive well-informed conclusions. The findings of this study hold the potential to enrich clinical practice and enhance the management of patients with PPUs. Additionally, we will explore potential influencing factors such as the intervention's scope, age considerations and the potential association with *H. pylori* infection.

ETHICS AND DISSEMINATION

In accordance with the nature of the data used in this meta-analysis, which involves aggregate information from previously published studies and does not involve direct interaction with human subjects, ethical approval is deemed unnecessary as it falls outside the scope of human subjects research requiring such oversight.

Strategies for data sharing and dissemination of results

Aggregate data from single trials will be combined in a dedicated database. Data will be stored in a repository and on request made available for secondary analyses to other researchers. Results shall be disseminated directly to decision-makers by means of publication in peer-reviewed journals, presentations at national and international conferences as well as specific events. Results will be actively presented to the bodies in charge of national and international treatment guidelines. Because results are expected to have a direct and relevant impact on patients' decision-making, we will specifically communicate them to patients through patients' organisations and the public.

Patient involvement

To enhance the relevance of this meta-analysis, active patient involvement is sought. Patients will be invited to participate in data interpretation and dissemination phases, ensuring that their perspectives contribute to a more patient-centred and meaningful synthesis of evidence. Additionally, their input will be crucial in ranking the importance of the outcomes analysed, reflecting the diverse priorities and values of the patient community in shaping the study's conclusions.

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Contributors The study concept and design were collectively developed by all authors (EW, JF, MG, JV, SZ, JKleeff, JKlose, UR and AR). MG designed literature search strategy. EW, JF und AR will conduct article screening and data extraction. JV and SZ will perform data analysis. JKleeff, JKlose, UR and AR act as surgical experts. All authors drafted this manuscript, revised it for content and have provided the final approval of this version. AR, the corresponding author, is the guarantor of the review.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Main aspects

P

	perforated peptic ulcers	

I

	Treatment	

Search guide overview

1	P	
2	I	
3	Studies	If needed

Databases and platforms involved

- PubMed (via NCBI)
- EMBASE (via Elsevier)
- Cochrane Library (via Wiley)
- Cinahl (via Ebsco)
- ClinicalTrials.Gov (via www.clinicaltrials.gov)
- ICTRP (via https://trialsearch.who.int/Default.aspx)

PubMed

P

1	**"Peptic Ulcer Perforation"[Mesh] OR** (Peptic[tiab] AND Ulcer[tiab] AND Perforat*[tiab])

I

2	Omentum*[tiab] OR Omental*[tiab] OR graham*[tiab] OR "Cellan Jones"[tiab] OR Cellanjones[tiab] OR "Falciform Ligament*"[tiab] OR "Over the scope*"[tiab] OR "Metal stent*"[tiab] OR
	"General Surgery"[Mesh] OR **"Surgical Procedures, Operative"[Mesh] OR** **"surgery" [Subheading] OR** Operat*[tiab] OR Surg*[tiab] OR Excision*[tiab] OR Dissection*[tiab] OR resect*[tiab] OR removal*[tiab] OR ectomy[tiab] OR ectomies[tiab] OR Preoperat*[tiab] OR Postoperat*[tiab] OR Perioperat*[tiab] OR
	"Endoscopes"[Mesh:NoExp] OR **"Radiology, Interventional"[Mesh] OR** **"Laparoscopes"[Mesh] OR** **"Minimally Invasive Surgical Procedures"[Mesh] OR** "Interventional Radio*"[tiab] OR "Minimally invasive repair*"[tiab] OR "Minimal invasive repair*"[tiab] OR Laparoscop*[tiab] OR Endoscop*[tiab] OR Celioscop*[tiab] OR Peritoneoscop*[tiab]

Studies

3	randomized controlled trial[pt] OR "Randomized Controlled Trials as Topic"[Mesh] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR study[tiab] OR studies[tiab]

Strings

1	"Peptic Ulcer Perforation"[MeSH Terms] OR ("Peptic"[Title/Abstract] AND "Ulcer"[Title/Abstract] AND "perforat*"[Title/Abstract])
2	"omentum*"[Title/Abstract] OR "omental*"[Title/Abstract] OR "graham*"[Title/Abstract] OR "Cellan Jones"[Title/Abstract] OR "Cellanjones"[Title/Abstract] OR "falciform ligament*"[Title/Abstract] OR "over the scope*"[Title/Abstract] OR "metal stent*"[Title/Abstract] OR "General Surgery"[MeSH Terms] OR "surgical procedures, operative"[MeSH Terms] OR "surgery"[MeSH Subheading] OR "operat*"[Title/Abstract] OR "surg*"[Title/Abstract] OR "excision*"[Title/Abstract] OR

	"dissection*"[Title/Abstract] OR "resect*"[Title/Abstract] OR "removal*"[Title/Abstract] OR "ectomy"[Title/Abstract] OR "ectomies"[Title/Abstract] OR "preoperat*"[Title/Abstract] OR "postoperat*"[Title/Abstract] OR "perioperat*"[Title/Abstract] OR "Endoscopes"[MeSH Terms:noexp] OR "radiology, interventional"[MeSH Terms] OR "Laparoscopes"[MeSH Terms] OR "Minimally Invasive Surgical Procedures"[MeSH Terms] OR "interventional radio*"[Title/Abstract] OR "minimally invasive repair*"[Title/Abstract] OR "minimal invasive repair*"[Title/Abstract] OR "laparoscop*"[Title/Abstract] OR "endoscop*"[Title/Abstract] OR "celioscop*"[Title/Abstract] OR "peritoneoscop*"[Title/Abstract]
3	"randomized controlled trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH Terms] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract] OR "study"[Title/Abstract] OR "studies"[Title/Abstract]
4	#1 AND #2 AND #3

Embase

P

1	**'ulcer perforation'/exp OR** (Peptic NEAR/4 Ulcer NEAR/4 Perforat*):ti,ab,kw

I

2	Omentum*:ti,ab,kw OR Omental*:ti,ab,kw OR graham*:ti,ab,kw OR "Cellan Jones":ti,ab,kw OR Cellanjones:ti,ab,kw OR "Falciform Ligament*":ti,ab,kw OR "Over the scope*":ti,ab,kw OR "Metal stent*":ti,ab,kw OR
	'surgery'/exp OR Operat*:ti,ab,kw OR Surg*:ti,ab,kw OR Excision*:ti,ab,kw OR Dissection*:ti,ab,kw OR resect*:ti,ab,kw OR removal*:ti,ab,kw OR ectomy:ti,ab,kw OR ectomies:ti,ab,kw OR Preoperat*:ti,ab,kw OR Postoperat*:ti,ab,kw OR Perioperat*:ti,ab,kw OR
	'endoscope'/de OR **'interventional radiology'/exp OR** **'laparoscope'/exp OR** **'minimally invasive surgery'/exp OR** "Interventional Radio*":ti,ab,kw OR "Minimal* invasive repair*":ti,ab,kw OR Laparoscop*:ti,ab,kw OR Endoscop*:ti,ab,kw OR Celioscop*:ti,ab,kw OR Peritoneoscop*:ti,ab,kw

Studies

Box 3.e Cochrane Highly Sensitive Search Strategy for identifying controlled trials in Embase: (2020 revision); Embase.com format. S. 63-64. The search term "study" was added to make the search more sensitive
https://training.cochrane.org/handbook/current/chapter-04-technical-supplement-searching-and-selecting-studies

3	('randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab,tt OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab,tt OR (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt) OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR (open NEXT/1 label):ti,ab,tt OR ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt OR 'double blind procedure'/de OR (parallel NEXT/1 group*):ti,ab,tt OR (crossover:ti,ab,tt OR 'cross over':ti,ab,tt) OR ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients

	OR subject OR subjects OR participant OR participants)):ti,ab,tt OR (assigned:ti,ab,tt OR allocated:ti,ab,tt) OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR (volunteer:ti,ab,tt OR volunteers:ti,ab,tt) OR 'human experiment'/de OR trial:ti,tt) OR study:ti,ab,kw

Strings

1	'ulcer perforation'/exp OR ((peptic NEAR/4 ulcer NEAR/4 perforat*):ti,ab,kw)
2	omentum*:ti,ab,kw OR omental*:ti,ab,kw OR graham*:ti,ab,kw OR 'cellan jones':ti,ab,kw OR cellanjones:ti,ab,kw OR 'falciform ligament*':ti,ab,kw OR 'over the scope*':ti,ab,kw OR 'metal stent*':ti,ab,kw OR 'surgery'/exp OR operat*:ti,ab,kw OR surg*:ti,ab,kw OR excision*:ti,ab,kw OR dissection*:ti,ab,kw OR resect*:ti,ab,kw OR removal*:ti,ab,kw OR ectomy:ti,ab,kw OR ectomies:ti,ab,kw OR preoperat*:ti,ab,kw OR postoperat*:ti,ab,kw OR perioperat*:ti,ab,kw OR 'endoscope'/de OR 'interventional radiology'/exp OR 'laparoscope'/exp OR 'minimally invasive surgery'/exp OR 'interventional radio*':ti,ab,kw OR 'minimally invasive repair*':ti,ab,kw OR 'minimal invasive repair*':ti,ab,kw OR laparoscop*:ti,ab,kw OR endoscop*:ti,ab,kw OR celioscop*:ti,ab,kw OR peritoneoscop*:ti,ab,kw
3	'randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab,tt OR 'randomization'/de OR 'intermethod comparison'/de OR placebo:ti,ab,tt OR compare:ti,tt OR compared:ti,tt OR comparison:ti,tt OR ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)) OR ((open NEXT/1 label):ti,ab,tt) OR (((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt) OR 'double blind procedure'/de OR ((parallel NEXT/1 group*):ti,ab,tt) OR crossover:ti,ab,tt OR 'cross over':ti,ab,tt OR (((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt) OR assigned:ti,ab,tt OR allocated:ti,ab,tt OR ((controlled NEAR/8 (study OR design OR trial)):ti,ab,tt) OR volunteer:ti,ab,tt OR volunteers:ti,ab,tt OR 'human experiment'/de OR trial:ti,tt OR study:ti,ab,kw
4	#1 AND #2 AND #3

To switch off PubMed

5	#4 NOT ([medline]/lim OR [pubmed-not-medline]/lim)

To exclude document types not of interest

6	#5 NOT ('Conference Abstract'/it OR 'Note'/it)

Cochrane Library

P

1	**[mh "Peptic Ulcer Perforation"] OR** Peptic NEAR/3 Ulcer NEAR/3 Perforat*:ti,ab,kw

I

2	Omentum*:ti,ab,kw OR Omental*:ti,ab,kw OR graham*:ti,ab,kw OR "Cellan Jones":ti,ab,kw OR Cellanjones:ti,ab,kw OR Falciform NEAR/3 Ligament*:ti,ab,kw OR Over NEAR/3 the NEAR/3 scope*:ti,ab,kw OR Metal NEAR/3 stent*:ti,ab,kw OR
	[mh "General Surgery"] OR **[mh "Surgical Procedures, Operative"] OR** Operat*:ti,ab,kw OR Surg*:ti,ab,kw OR Excision*:ti,ab,kw OR Dissection*:ti,ab,kw OR resect*:ti,ab,kw OR removal*:ti,ab,kw OR ectomy:ti,ab,kw OR ectomies:ti,ab,kw OR Preoperat*:ti,ab,kw OR Postoperat*:ti,ab,kw OR Perioperat*:ti,ab,kw OR
	[mh ^"Endoscopes"] OR **[mh "Radiology, Interventional"] OR** **[mh "Laparoscopes"] OR** **[mh "Minimally Invasive Surgical Procedures"] OR** Interventional NEAR/3 Radio*:ti,ab,kw OR Minimal* NEAR/3 invasive NEAR/3 repair*:ti,ab,kw OR Laparoscop*:ti,ab,kw OR Endoscop*:ti,ab,kw OR Celioscop*:ti,ab,kw OR Peritoneoscop*:ti,ab,kw

Strings

1-2 as in the tables above

3	#1 AND #2

CINAHL

P

1	**MH "Peptic Ulcer Perforation" OR** TX (Peptic N3 Ulcer N3 Perforat*)

I

2	**(MH "Surgery, Operative+" OR** **MH "Endoscopes" OR** **MH "Laparoscopy" OR** (TX (Omentum* OR Omental* OR graham* OR "Cellan Jones" OR Cellanjones OR Falciform N3 Ligament* OR Over N3 the N3 scope* OR Metal N3 stent* OR
	Operat* OR Surg* OR Excision* OR Dissection* OR resect* OR removal* OR ectomy OR ectomies OR Preoperat* OR Postoperat* OR Perioperat* OR
	Interventional N3 Radio* OR Minimal* N3 invasive N3 repair* OR Laparoscop* OR Endoscop* OR Celioscop* OR Peritoneoscop*)))

Strings (due to the few hits the aspect studies is not involved)

1	MH "Peptic Ulcer Perforation" OR TX (Peptic N3 Ulcer N3 Perforat*)
2	(MH "Surgery, Operative+" OR MH "Endoscopes" OR MH "Laparoscopy" OR (TX (Omentum* OR Omental* OR graham* OR "Cellan Jones" OR Cellanjones OR Falciform N3 Ligament* OR Over N3 the N3 scope* OR Metal N3 stent* OR Operat* OR Surg* OR Excision* OR Dissection* OR resect* OR removal* OR ectomy OR ectomies OR Preoperat* OR Postoperat* OR Perioperat* OR Interventional N3 Radio* OR Minimal* N3 invasive N3 repair* OR Laparoscop* OR Endoscop* OR Celioscop* OR Peritoneoscop*)))
3	#1 AND #2

ClinicalTrial.gov
http://www.clinicaltrials.gov/

P

1	"Peptic Ulcer Perforation" OR "Peptic Ulcer Perforations"

I

2	Omentum OR Omental OR graham OR "Cellan Jones" OR Cellanjones OR "Falciform Ligament" OR "Over the scope" OR "Metal stent" OR
	Operation OR Surgery OR Excision OR Dissection OR resection OR removal OR ectomy OR ectomies OR Preoperation OR Postoperation OR Perioperation OR
	"Interventional Radio" OR "Minimally invasive repair" OR "Minimal invasive repair" OR Laparoscopy OR Endoscopy OR Celioscopy OR Peritoneoscopy

Strings

1	(EXPAND[Concept] ("Peptic Ulcer Perforation" OR "Peptic Ulcer Perforations"))
2	AND (Omentum OR Omental OR graham OR EXPAND[Concept] "Cellan Jones" OR Cellanjones OR EXPAND[Concept] "Falciform Ligament" OR EXPAND[Concept] "Over the scope" OR EXPAND[Concept] "Metal stent" OR Operation OR Surgery OR Excision OR Dissection OR resection OR removal OR ectomy OR ectomies OR Preoperation OR Postoperation OR Perioperation OR EXPAND[Concept] "Interventional Radio" OR EXPAND[Concept] "Minimally invasive repair" OR EXPAND[Concept] "Minimal invasive repair" OR Laparoscopy OR Endoscopy OR Celioscopy OR Peritoneoscopy)

3	1 AND 2

International Clinical Trials Registry Platform ICTRP (WHO Trials)
https://trialsearch.who.int/ (simple)
https://trialsearch.who.int/AdvSearch.aspx (advanced)

P

1	Peptic Ulcer Perforation

I

2	Omentum OR Omental OR graham OR Cellan Jones OR Cellanjones OR Falciform Ligament OR Over the scope OR Metal stent OR
	Surgery OR Interventional Radio OR Minimally invasive repair OR Minimal invasive repair OR Laparoscopy OR Endoscopy OR Celioscopy OR Peritoneoscopy

Strings (in advanced mode)

Fields	**String**
1 (Condition)	Peptic Ulcer Perforation
2 (Intervention)	Omentum OR Omental OR graham OR Cellan Jones OR Cellanjones OR Falciform Ligament OR Over the scope OR Metal stent OR Surgery OR Interventional Radio OR Minimally invasive repair OR Minimal invasive repair OR Laparoscopy OR Endoscopy OR Celioscopy OR Peritoneoscopy

3	1 AND 2

Strings (in simple mode)

1	Peptic Ulcer Perforation AND surgery