BMJ Open

Evidence Map of Pancreatic Surgery - Protocol for a Living Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032353
Article Type:	Protocol
Date Submitted by the Author:	14-Jun-2019
Complete List of Authors:	Probst, Pascal; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Hüttner, Felix; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Meydan, Ömer; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Kalkum, Eva; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Kretschmer, Rüdiger; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Jensen, Katrin; University of Heidelberg, Institute of Medical Biometry and Informatics Kenngott, Hannes; University of Heidelberg, Department of General, Visceral and Transplantation Surgery Mihaljevic, A; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Thilo, Hackert; University of Heidelberg, Department of General, Visceral and Transplantation Surgery Buechler, Markus W.; University of Heidelberg, Department of General, Visceral and Transplantation Surgery Diener, M. K.; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC)
Keywords:	Evidence map, evidence management, Pancreatic surgery < SURGERY, systematic review, meta-analysis, living review

Evidence Map of Pancreatic Surgery - Protocol for a Living Systematic Review and Meta-Analysis

Pascal Probst[1,2] (PP): pascal.probst@med.uni-heidelberg.de

Felix J. Hüttner[1,2] (FJH) : felix.huettner@med.uni-heidelberg.de

Ömer Meydan [1,2] (OM): meydan@stud.uni-heidelberg.de

Eva Kalkum[2] (EK): eva.kalkum@med.uni-heidelberg.de

Rüdiger Kretschmer[2] (RK): kretschmer@evidencemap.surgery

Katrin Jensen[3] (KJ): jensen@imbi.uni-heidelberg.de

Hannes G. Kenngott[1] (HGK): hannes.kenngott@med.uni-heidelberg.de

André Mihaljevic[1,2] (AM): andre.mihaljevic@med.uni-heidelberg.de

Thilo Hackert[1] (TH): thilo.hackert@med.uni-heidelberg.de

Markus W Büchler[1] (MWB): markus.buechler@med.uni-heidelberg.de

Markus K. Diener[1,2] (MKD): markus.diener@med.uni-heidelberg.de

[1]Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

[2]The Study Center of the German Surgical Society (SDGC), University of Heidelberg, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany

[2]Institute of Medical Biometry and Informatics, University of Heidelberg, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany

Corresponding author:

Pascal Probst, MD, MSc

Department of General, Visceral and Transplantation Surgery

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg

Germany

T: +496221 56 6110

E-Mail: pascal.probst@med.uni-heidelberg.de

Abstract

Introduction

Pancreatic surgery is a large and complex field of research. Several evidence gaps exist for specific diseases or surgical procedures. An overview on existing knowledge is needed to plan and prioritise future research. The aim of this project is to create a systematic and living evidence map of pancreatic surgery.

Methods and analysis

A systematic literature search in MEDLINE, Web of Science and CENTRAL will be performed searching for all randomised controlled trials (RCT) and systematic reviews (SR) on pancreatic surgery. RCT and SR will be grouped in research topics. Baseline and outcome data from RCT will be extracted, presented and effect sizes meta-analysed. Data from SR will be used to identify evidence gaps. A freely accessible web-based evidence map in the format of a mind map will be created. The evidence map and meta-analyses will be updated periodically.

Dissemination

www.evidencemap.surgery will provide a permanently updated evidence map of pancreatic surgery to patients, physicians, researchers and funding bodies. Its use will allow clinical decision making based on primary data and prioritisation of future research endeavours.

Systematic review registration: PROSPERO 2019 CRD42019133444

Keywords: Evidence map, evidence management, pancreatic surgery, systematic review, meta-analysis, living review

Strengths and limitations

- Through a comprehensive search and selection of high-quality articles the best available evidence for pancreatic surgery will be gathered.
- Contrary to medical databases the evidence map in the form of a mind map will present randomised-controlled trials and systematic reviews ordered by research topics in an intuitive fashion.
- The evidence map of pancreatic surgery will strengthen the visibility of primary research results in pancreatic surgery.

Background

Quantity and quality of randomised controlled trials (RCT) for pancreatic surgery is increasing, however, there are still blind spots regarding specific operations and diseases [1]. Socio-economic pressure demands for prioritisation of relevant research projects in the field of pancreatic surgery. Since pancreatic diseases are devastating for patients and highly impair their quality of life [2,3], there is an urgent need for the best treatment, which should be based on the best available evidence. Consequently, patients undergoing pancreatic surgery should be included in prospective trials whenever evidence is lacking. Therefore, pancreatic surgery research should be performed according to an objective priority setting.

The two main surgically treated diseases of the pancreas are tumours and chronic pancreatitis [1]. For both entities, surgery remains the only chance of cure or long-term increase of quality of life, respectively [2,3]. Therefore, all patients bear the burden of a severe disease in need of major surgery, but also must carry the risk of postoperative morbidity which is as high as 73% [4]. Therefore, one of the major research interests is to find the most effective and safe way to operate patients. Since perioperative mortality in specialised centres is low nowadays [4], the focus lies on reduction of pancreas-specific complications like postoperative pancreatic fistula (POPF) [5], delayed gastric emptying (DGE) [6] or post-pancreatectomy haemorrhage (PPH) [7].

To systematically investigate the field of pancreatic surgery, two innovative methods of evidence-based medicine are combined: the living systematic review (SR) and evidence mapping.

Living SR follow the established methods of a SR. However, they overcome the difficulty that normal SR are soon outdated or redundant after their publication [8]. Living SR are assumed to achieve a greater validity with increased benefits for physicians and patients at lower spending of resources over time [9]. Some experts even think that living SR should become the flagship of synoptic evidence and the research community should have a strong interest to establish living SR in their fields [10].

Evidence mapping is also an emerging approach to systematic assessment of quantitative and qualitative aspects [11]. Although there is no universally applied definition of evidence mapping yet, its aim is usually to summarize evidence and identify gaps in the body of knowledge regarding a specific area of research. In times of scarcity of health system resources and overload of information, this approach may enable researchers and funding bodies to prioritise future research questions [12].

The combination of the methods of living SR and evidence mapping applied on pancreatic surgery will result in an intuitive and permanently up-to-date map of available evidence including living meta-analyses (MA). Through visualisation of available evidence, health-care professionals, patients and funding bodies gain direct access to highly relevant data.

Aim

The major problem of evidence management is that most research activities are not harmonised with clinical and political relevance. This results in production of waste-evidence, rather than needed evidence by prioritisation. The first step in priority setting would be an up-to-date characterisation of existing knowledge, lack of knowledge and research questions. Thus, the aim of this project is to create a systematic and living evidence map of pancreatic surgery.

Methods/ Design

The PRISMA-P guideline was followed [13]. Further, the living systematic review network guidelines on how living SR should be published [10], how living MA should be updated [14] and how living recommendations should be formed [15] will be followed wherever applicable. The project was prospectively registered (PROSPERO 2019 CRD42019133444) and for full transparency the protocol is herewith published open access.

Systematic literature search

A systematic literature search in all major electronic bibliographic databases with relevance for surgical literature will be searched [16]: MEDLINE (via PubMed), Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL). No restrictions will be applied regarding language or publication date. The full search strategy for MEDLINE (via PubMed) will be:

"((pancreas[MeSH terms] OR pancreas[tiab] OR pancreatic[tiab] OR pancreato*[tiab]) AND (resection* [tiab] OR removal [tiab] OR surger* [tiab] OR surgical [tiab] OR laparotom*[tiab] OR enucleation* [tiab] OR operation* [tiab] OR operated [tiab] OR "surgical procedures, operative"[MeSH terms] OR "general surgery"[MeSH terms])) OR (pancreaticoduodenectom*[tiab] OR pancreatoduodenectom*[tiab] OR pancreatoduodenectom*[tiab] OR duodenopancreatectom*[tiab] OR pancreatectom*[tiab] OR Whipple[tiab] OR Kausch-Whipple[tiab] OR ppWhipple[tiab] OR dpphr[tiab] OR PPPD[tiab] OR pancreaticoduodenectomy[MeSH] OR pancreatectomy[MeSH] OR "Pancreas/surgery"[Mesh] OR "Pancreatic Diseases/surgery"[Mesh] AND (randomized controlled trial [pt] OR random*[tw] OR RCT [tw] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [pt] OR systematic review [pt] OR meta-analysis [pt] OR re-view [pt] OR meta-analysis [tw] OR review [tw])".

The full search strategy for Web of Science and CENTRAL is displayed in appendix 1.

Study selection

Following the recommendations of the Cochrane Collaboration [17], titles, abstracts and full texts of identified articles will be screened independently by two reviewers.

Eligible study designs to be included will be RCT and SR with or without MA. SR will only be eligible if they meet minimal quality requirements i.e. SR must search at least two established literature databases and provide a critical appraisal with validated tools like the Cochrane Collaboration tool for assessing risk of bias [18] for RCT or like the ROBINS-I for non-randomised studies [19].

All interventions in pancreatic surgery will be included irrespective of the type of operation or disease. By intervention all kind of treatments are considered as long as they are aimed to affect the surgical outcome i.e. medical devices (e.g. stapler versus scalpel resection in distal pancreatectomy), perioperative management (e.g. prehabilitation of patients, or intraoperative fluid management), surgical strategy (e.g. open versus laparoscopic access to the abdominal cavity), drug (e.g. somatostatin analogues to influence POPF) and nutrition (e.g. immunonutrition to avoid complications). Interventions like endoscopic retrograde cholangiopancreatography, radiologically guided punctures or similar interventions are not considered pancreatic surgery. However, if these kinds of interventions are compared to a pancreatic operation, articles are eligible for inclusion. Moreover, studies on neo-/adjuvant treatment, or pancreatic transplantation will be excluded.

Data extraction

All stages of data extraction and quality assessment will be carried out independently by two reviewers using a predefined extraction sheet. Any disagreement will be resolved by consensus, or by consultation with a third reviewer. All extracted items for RCT and SR are shown in appendix 2.

Further, the methodological quality of included RCT will be assessed using the newly suggested Cochrane Collaboration tool for assessing risk of bias 2.0 [20]. The tool includes five standard domains of bias: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selecting of the reported result. These domains will be rated as ‘high risk’, ‘low risk’ of bias, or some concerns.

Finally, an overall risk of bias judgement will be made. As recently recommended for surgical trials, detailed information on blinding will be recorded and reported [21]. Furthermore, industrial funding will be considered as another potential threat to validity [22].

A database tailored for this project is created to save resources during data extraction and making data usable for presentation on the evidence map and for statistical analysis. The database (Microsoft SQL Server 2017 Express) will have a user interface (Microsoft .NET framework, Windows Forms) with automated plausibility checks of extracted data. After validation of the extracted data, the relational database will be able to export the extracted data in the exact form needed for presentation on the evidence map. Further, the database will have an interface to the statistical program to export data needed for the meta-analyses.

Data synthesis for creation of the evidence map

All included RCT and SR will be clustered according to the type of operation, the type of disease and the type of interventions. Consequently, studies on the same research topics will be grouped e.g. pylorus-resecting versus pylorus-preserving (intervention: surgical strategy) in partial pancreatoduodenectomy (operation) for tumours or chronic pancreatitis (disease).

Information on existing SR will be shown within the evidence map and will be used for identification of evidence gaps in the research topics i.e. missing RCT. Including SR in the evidence map is preferred to the inclusion of all other primary study types like non-randomised prospective trials or retrospective studies.

Information on existing RCT will also be shown within the evidence map and the extracted data will be used for pooling in meta-analyses. For each research topic the following set of outcomes will be reported in the meta-analyses: mortality, postoperative pancreatic fistula (graded as biochemical leak, B, C if the International Study Group of Pancreatic Surgery (ISGPS) definition [5] is used), delayed gastric emptying (graded as A, B, C if the ISGPS definition [6] is used), post-pancreatectomy haemorrhage (graded as A, B, C if the ISGPS definition [7] is used), bile leak (graded as A, B, C if the International Study Group of Liver Surgery definition [23] is used), chyle leak (graded as A, B, C if the ISGPS definition [24] is used), intraabdominal fluid collection/abscess, overall morbidity (if available according to the Clavien-Dindo classification [25]), Overall survival (as 1, 2, 3, 4 and 5 year survival rate and median overall survival), length of hospital stay and operation time.

Furthermore, for each outcome the certainty of the evidence will be rated using the GRADE system [26,27]. This includes limitations in the design from the risk of bias assessment (see above), indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and publication bias. Thus, the certainty of the evidence will be rated to be very low, low, moderate or high for each outcome.

Statistical analysis

If more than 3 RCT investigate the same research topic e.g. pylorus-resection vs. pylorus-preservation in pancreaticoduodenectomy, the above-mentioned outcomes of these RCT will be pooled in living meta-analyses.

Statistical analyses will be performed with R [28]. Dichotomous data (mortality, postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy hemorrhage, bile leak, chyle leak, intraabdominal fluid collection/ abscess, overall morbidity, survival rate) will be pooled in a Mantel–Haenszel model to estimate odds ratios and associated 95% confidence intervals. For continuous data (mean overall survival, length of hospital stay, operation time) mean differences and associated 95% confidence intervals will be calculated using an inverse-variance model. A two-sided level of significance below 5 per cent will be considered statistically significant. Continuous values reported as median with range will be converted to mean and sd [29]. For dichotomous and continuous data, a prediction interval will be calculated. Statistical heterogeneity among trials will be evaluated by means of the I^2 statistic. We will consider I^2 < 25% to indicate low statistical heterogeneity and I^2 > 75% to indicate high statistical heterogeneity. A random-effects rather than a fixed-effects model will be used for meta-analysis when clinical heterogeneity is assumed and at least 5 RCT are available.

If more than two interventions are compared within a research topic, a state-of-the art Bayesian network meta-analysis will be performed. Either linear or logistic random effects models will be applied. Pooled effect estimates obtained in the network meta-analysis (adjusted mean differences or log odds ratios) will be provided with 95% credibility intervals. Furthermore, a treatment ranking based on the probability of being the most efficient arm will be carried out.

To evaluate the risk of publication bias, funnel plots will be created and tested for asymmetry using the Harbord test [30] if more than 10 trials are available for a living meta-analysis.

Creating the evidence map

The evidence map of pancreatic surgery will be freely accessible for everyone via the internet. An example how the structure of the evidence map, its instructions and information on a research topic (e.g. pylorus-resection vs. pylorus-preservation in pancreaticoduodenectomy) might look is accessible here: www.evidencemap.surgery.

The quantitative and qualitative analyses are only one part of the added value by the evidence map. The evidence map will be configured as a mind map leading its reader from the center (pancreatic surgery) to a research topic e.g. pylorus-resection vs. pylorus-preservation in pancreaticoduodenectomy (Figure 1). In the center of the map the icon behind the map version, Pancreatic surgery V0 in the example, will provide a summary of the evidence map including a PRISMA flow chart of the actual version. Further, for every type of operation a pooled estimate of mean with 99% confidence interval and median with interquartile ranges from all RCT for the outcomes will be calculated and presented for bench marking purposes. Furthermore, two bubble plots will be created, mapping all RCT by types of operation to types of intervention and types of disease to types of intervention. Within the bubble plots sample size of the trials will be expressed by bubble size and the geographical region by a color code. This will allow concluding on overall evidence gaps in pancreatic surgery and differences between geographical regions.

Through logical connections the reader will be guided to research topics. These are marked with symbols indicating the presence or absence of RCT and SR (a tick means that RCT are existing, a cross means that RCT on the research topic are missing; a star means that SR are existing and an exclamation mark means that SR are missing). In this example the symbols mean that there is at least one RCT and

SR/MA available for the research topic. In this fashion the evidence map gives an intuitive presentation of available evidence and evidence gaps become visible.

For every research topic the reader can look at the existing RCT and SR (Figure 2).

For RCT and SR the name of the first author and the year of publication are displayed. Behind the year of publication three icons are shown. The first icon gives the original conclusion of the article and the full reference. The second icon is a link to the article on the journal homepage or if the manuscript is published open access the full text is directly downloadable. The third icon is available for RCT only and contains the extracted data as an exportable and processable file (.xlsx).

Finally, from the “Living MA and GRADE” field a summary of findings table (GRADE), the forest plots and the funnel plots for all outcomes of a research topic will be downloadable from the evidence map.

Additionally, the evidence map will have a comment function and will allow physicians, researchers and patients to interact with the evidence map by adding comments. In this way researchers can report their new research directly or patients can comment on the importance of future research within research topics. There will be an administrator answering comments and additionally reacting on important subjects via social media.

Living systematic review and meta-analyses

After its induction, a periodically update including the steps of literature search, screening and extraction is planned at least every 6 months. If new RCT and SR are available upon these searches, they will be added to the research topics and the

meta-analyses will be renewed resulting in living meta-analyses. Version numbers and date of last updates will be displayed on the map itself and on every research topic.

Patient involvement

In order to adequately incorporate patients, a priority setting partnership (PSP) for pancreatic cancer treatments in Germany (www.europaeisches-pankreaszentrum.de/extrainfo/psp-pankreaskarzinom/) is performed. The objective of this project is to involve patients, their families, caregivers, specialists, nurses and other stakeholders to identify and prioritise unanswered scientific questions in the treatment of pancreatic cancer. From these responses unidentified research topics may emerge. In a second step patients as well as experts will be asked to rank the existing research topics for priority. Results of the PSP in conjunction with the living evidence map would allow a transparent, objective and patient-centred identification of the most urgent future research topics in pancreatic cancer.

Moreover, national and international patient representative organisations will be involved during the beta-test phase of the evidence map to invite them for their comments especially on importance of the research topics presented. Furthermore, these organisations will be invited to link the map on their internet presences.

Dissemination

The aim of this project is to develop and maintain an evidence map of pancreatic surgery i.e. a living systematic review with meta-analyses and mapping of the evidence. The map will contain all existing evidence from randomised-controlled trials and systematic reviews on pancreatic surgery plotted as an intuitive and interactive mind map. The presented evidence is based on a comprehensive systematic literature search and comprehensibly selection of literature. By a preliminary literature search in MEDLINE, Web of Sciences and Cochrane Central Register of Controlled Trials more than 30´000 potentially eligible articles were identified. It is expected that the first version of the evidence map will contain more than 250 RCT, 400 SR/MA on 100 research topics with living meta-analyses. During the periodically searches about 1´000 new articles must be screened. Through www.evidencemap.surgery a permanently updated evidence map of pancreatic surgery will be disseminated to patients, physicians, researchers and funding bodies.

The living evidence map of pancreatic surgery will serve different purposes for researches, clinicians, patients and funding bodies. For researchers, the evidence map in pancreatic surgery will be a help to get a quick overview about existing research questions. Notably, this is not an attempt to substitute single SR on a specific subject. Much more, the intention is to provide a strong reference as a comparator. Moreover, it will speed up and harmonise the conduct of future SR as researchers can rely on the performed literature search, on the extracted data and critical appraisal. This map would be highly relevant to patient care and the health care system because it would show “what works” and “what is missing” at a glance and in an intuitive fashion. Clinicians could use the map to inform their patients on

benefits and harms of different pancreatic surgery interventions based on up-to-date high-quality data. The difference to follow a guideline is that clinicians can interpret the primary literature from RCT and SR for their individual patients instead of applying recommendations from guidelines. In the same manner, patients will have access to primary data sorted by logical connections which will allow them to find evidence appropriate for their cases. Moreover, researchers, clinicians and patients will be able to comment on research topics and interact with the pancreatic surgery community. Finally, such an evidence map should be of interest for funding bodies because an objective assessment of which research project is most pressing to be funded becomes possible.

The project will be presented at national and international congresses. Moreover, after the evidence map is accessible via the internet, the project will be published in an international peer-reviewed journal as an open access article. Furthermore, it is planned to publish update articles with each meaningful update of the evidence map. As social media become more and more important in the dissemination of scientific results, the evidence map will be promoted on Facebook and twitter [31]. Therefore, updates and living meta-analyses will be blogged and tweets/ re-tweets will be done to surgeons and surgical journals. Finally, to our knowledge the proposed evidence map would be the first of its kind. Therefore, this project would also inspire other researchers to follow and create such maps in their medical fields.

Figures and Tables

Figure 1: Example of the possible structure of the evidence map (from www.evidencemap.surgery)

Figure 2: Example of existing literature (RCT and SR) and living meta-analysis for a research topic (from www.evidencemap.surgery)

Appendix 1: Full search strategy for Web of Science and CENTRAL

Appendix 2: Extracted items for RCT and SR

References

1. Hüttner FJ, Capdeville L, Pianka F, Ulrich A, Hackert T, Büchler MW, Probst P, Diener MK. Systematic review of the quantity and quality of randomized clinical trials in pancreatic surgery. Br J Surg. 2019 Jan;106(1):23-31.

2. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? Ann Surg. 2008;247(3):456-62.

3. Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387(10031):1957-66.

4. Sánchez-Velázquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, Javed AA, Inoue Y, Beghdadi N, Kalisvaart M, Vigia E, Walsh CD, Lovasik B, Busquets J, Scandavini C, Robin F, Yoshitomi H, Mackay TM, Busch OR, Hartog H, Heinrich S, Gleisner A, Perinel J, Passeri M, Lluis N, Raptis DA, Tschuor C, Oberkofler CE, DeOliveira ML, Petrowsky H, Martinie J, Asbun H, Adham M, Schulick R, Lang H, Koerkamp BG, Besselink MG, Han HS, Miyazaki M, Ferrone CR, Fernández-Del Castillo C, Lillemoe KD, Sulpice L, Boudjema K, Del Chiaro M, Fabregat J, Kooby DA, Allen P, Lavu H, Yeo CJ, Barroso E, Roberts K, Muiesan P, Sauvanet A, Saiura A, Wolfgang CL, Cameron JL, Boggi U, Yoon DS, Bassi C, Puhan MA, Clavien PA. Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Ann Surg. 2019 Feb 27. doi: 10.1097/SLA.0000000000003223. [Epub ahead of print]

5. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161(3):584-91.

6. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761-8.

7. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20-5.

8. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. Milbank Q. 2016 Sep;94(3):485-514.

9. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al. Living systematic review: 1. Introduction-the why, what, when, and how. J Clin Epidemiol. 2017;91:23-30.

10. Sutton AJ. Not enough I say! Expand the remit of living systematic reviews to inform future research. J Clin Epidemiol. 2017;91:54-5.

11. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The Global Evidence Mapping Initiative: scoping research in broad topic areas. BMC Med Res Methodol. 2011;11:92.

12. Miake-Lye IM, Hempel S, Shanman R, Shekelle PG. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Syst Rev. 2016;5:28.

13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

14. Simmonds M, Salanti G, McKenzie J, Elliott J, Living Systematic Review N. Living systematic reviews: 3. Statistical methods for updating meta-analyses. J Clin Epidemiol. 2017;91:38-46.

15. Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schunemann HJ, Living Systematic Review N. Living systematic reviews: 4. Living guideline recommendations. J Clin Epidemiol. 2017;91:47-53.

16. Goossen K, Tenckhoff S, Probst P, Grummich K, Mihaljevic AL, Buchler MW, et al. Optimal literature search for systematic reviews in surgery. Langenbecks Arch Surg. 2018;403(1):119-29.

17. Higgins J, Green S. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: http://handbook.cochrane.org. Accessed 13.06.2019

18. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

19. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

20. Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.

21. Probst P, Zaschke S, Heger P, Harnoss JC, Hüttner FJ, Mihaljevic AL, Knebel P, Diener MK. Evidence-based recommendations for blinding in surgical trials. Langenbecks Arch Surg. 2019;404(3):273-284.

22. Probst P, Knebel P, Grummich K, Tenckhoff S, Ulrich A, Büchler MW, Diener MK. Industry Bias in Randomized Controlled Trials in General and Abdominal Surgery: An Empirical Study. Ann Surg. 2016 Jul;264(1):87-92.

23. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011;149(5):680-8.

24. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. Surgery. 2017;161(2):365-72.

25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

27. GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from: http://gradepro.org/. Accessed 13.06.2019

28. R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. Available from: http://www.R-project.org. Accessed 13.06.2019

29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standarad deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology 2014, 14: 135.

30. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25(20):3443-57.

31. Reinisch A, Schröder SR, Ulrich F, Padberg W, Liese J. Antibiotic-treated acute appendicitis-reception in social media. Langenbecks Arch Surg. 2019;404(3):343-349

Acknowledgement

None.

Author's contribution

PP, FJH, OM, EK, HGK and AM made substantial contributions to the conception or design of the work or the acquisition of data and drafted the work.

RK, KJ, TH, MWB and MKD made substantial contributions to the conception or design of the work or the acquisition of data and revised the work critically for important intellectual content.

All authors gave their final approval to the publication of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

This work was supported by the Heidelberg Foundation for Surgery (Heidelberger Stiftung Chirurgie, www.stiftung-chirurgie.de), Heidelberg, Germany. The Heidelberg Foundation for Surgery had no role in planning of the study and will not be involved in the conduct of the study.

Competing interests

None of the authors has a secondary interest according to the ICMJE guidelines that inappropriately influences his contribution to this work.

Ethics/ Patient consent for publication

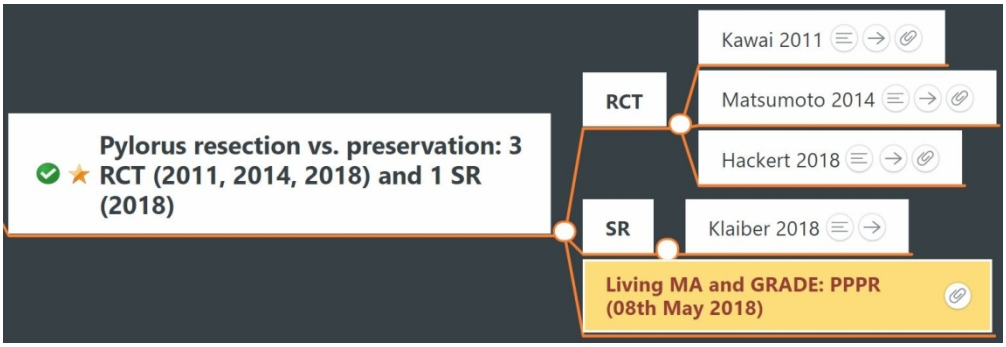
Not required.

Word count

3430 words

Example of the possible structure of the evidence map (from www.evidencemap.surgery)

380x186mm (96 x 96 DPI)



Example of existing literature (RCT and SR) and living meta-analysis for a research topic (from www.evidencemap.surgery)

407x137mm (96 x 96 DPI)

Appendix 1: Full search strategy for Web of Science and CENTRAL.

Web of Science Core Collection

9 #8 OR #7
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

8 (#4 OR #3) *AND* **DOCUMENT TYPES:** (Review)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

7 #6 AND #5
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

6 TS = (random* OR RCT OR meta-analysis OR review)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

5 #4 OR #3
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

4 #2 AND #1
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

3 TS = (pancreaticoduodenectom* OR pancreatoduodenectom* OR pancreato-duodenectom* OR duodenopancreatectom* OR pancreatectom* OR Whipple OR Kausch-Whipple OR ppWhipple OR dpphr OR PPPD)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

2 TS = (resection* OR removal OR surger* OR surgical OR laparotom* OR enucleation* OR operation* OR operated)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

1 TS = (pancreas OR pancreatic OR pancreato*)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

CENTRAL (Cochrane Central Register of Controlled Trials)

#1 (pancreas OR pancreatic OR pancreato*) NEAR (resection* OR removal OR surger* OR surgical OR laparotom* OR enucleation* OR operation* OR operated)

#2 MeSH descriptor: [Pancreas] explode all trees and with qualifier(s): [surgery - SU]

#3 (pancreaticoduodenectom* OR pancreatoduodenectom* OR pancreatoÔÇÉduodenectom* OR duodenopancreatectom* OR pancreatectom* OR Whipple OR Kausch-Whipple OR ppWhipple OR dpphr OR PPPD)

#4 MeSH descriptor: [Pancreaticoduodenectomy] explode all trees

#5 MeSH descriptor: [Pancreatic Diseases] explode all trees and with qualifier(s): [surgery - SU]

#6 MeSH descriptor: [Pancreatectomy] explode all trees

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

Appendix 2 - Randomized Controlled Trials

Item	Unit	Format
ID	RCT - NUMBER	Int
Title	-	Txt
First author	-	Txt
Journal Index medicus	-	Txt
Year of publication	Years	Int
Volume(issue):pages	-	Text
Region of publication	Europe, North America, South America, Africa, Asia, Australia/ New-Zealand	Selection ≥1
Type of operation	Distal Pancreatectomy, Duodenum preserving pancreatic head resection, Enucleation, Partial pancreaticoduodenectomy, total pancreatectomy, Other	Selection ≥1
Type of intervention	Drug, Nutrition, Medical device, perioperative management, surgical strategy, Other	Selection =1
Description of intervention arm	-	Txt
Description of control arm	-	Txt
Description of other arm 3 (optional)	-	Txt
Description of other arm 4 (optional)	-	Txt
Type of disease	Ampullary carcinoma, Bile duct carcinoma, Chronic pancreatitis, Acute pancreatitis, Cystic neoplasms, Duodenal carcinoma, Intraductal papillary mucinous neoplasms, Neuroendocrine tumors, Pancreatic adenocarcinoma, trauma, Other	Selection ≥1
Lowest age included	Years	int
Highest age included	Years	Int
Were relaparotomies excluded	-	Selection =1
Which comorbidities were excluded?	-	Txt
Which cancer stages were excluded?	-	Txt
Which other patients were excluded?	-	Txt
Overall randomized sample size	-	Int
Randomized in intervention, control and other groups	n	Int
Followup	Months	Int
Mean age at baseline	Years	Int
Sex	-	Selection =1
Mortality as event in groups	n	Int
Overall POPF as event in groups	n	Int
POPF grades as event in groups	n	Int
POPF definition used?	-	Txt
Overall DGE as event in groups	n	Int
DGE grades as event in groups	n	Int
DGE definition used?	-	Txt
Overall PPH as event in groups	n	Int
PPH grades as event in groups	n	Int
PPH definition used?	-	Txt
Overall bile leak as event in groups	n	Int
Bile leak grades as event in groups	n	Int
Bile leak definition used?	-	Txt
Overall chyle leak as event in groups	n	Int
Chyle leak grades as event in groups	n	Int
Chyle leak definition used?	-	Txt
Overall Intraabdominal fluid collection as event in groups	n	Int
Intraabdominal fluid collection grades as event in groups	n	Int
Fluid collection definition used?	-	Txt
Morbidity and mortality according to Clavien-Dindo as event in groups	n	Int
1 to 5 year survival as event in groups	n	Int
Overall survival as mean with sd in groups	-	real number
Mean operation time with sd in groups	Minutes	real number
Mean length of hospital stay with sd in groups	Days	real number
Patient related outcome measures assessed?	-	Selection =1
Bias arising from the randomization process	High, some concerns, low	Selection =1
Bias due to deviations from intended interventions	High, some concerns, low	Selection =1
Bias due to missing outcome data	High, some concerns, low	Selection =1
Bias in measurement of the outcome	High, some concerns, low	Selection =1
Bias in selecting of the reported result	High, some concerns, low	Selection =1
Overall risk-of-bias judgement	High, some concerns, low	Selection =1
Funding source	Industry, Independent, not reported	Selection =1
Important notes	-	Txt

Appendix 2 - Systematic Reviews

Item	Unit	Format
ID	SR - NUMBER	Int
Title	-	Txt
First author	-	Txt
Journal Index medicus	-	Txt
Year of publication	Years	Int
Volume(issue):pages	-	Txt
Region of publication	Europe, North America, South America, Africa, Asia, Australia/ New-Zealand	Selection ≥1
Type of operation	Distal Pancreatectomy, Duodenum preserving pancreatic head resection, Enucleation, Partial pancreaticoduodenectomy, total pancreatectomy, Other	Selection ≥1
Type of intervention	Drug, Nutrition, Medical device, perioperative management, surgical strategy, Other	Selection =1
Type of disease	Ampullary carcinoma, Bile duct carcinoma, Chronic pancreatitis, Acute pancreatitis, Cystic neoplasms, Duodenal carcinoma, Intraductal papillary mucinous neoplasms, Neuroendocrine tumors, Pancreatic adenocarcinoma, trauma, Other	Selection ≥1
Important notes	-	Txt

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 + 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	22
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	22
Sponsor	5b	Provide name for the review funder and/or sponsor	22
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	22
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4/5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7/8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6/7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7 + Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7/8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7/8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8/9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9/10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9/10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9 + 10/11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10/11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10/11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Evidence Map of Pancreatic Surgery - Protocol for a Living Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032353.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Sep-2019
Complete List of Authors:	Probst, Pascal; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Hüttner, Felix; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Meydan, Ömer; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Kalkum, Eva; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Kretschmer, Rüdiger; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Jensen, Katrin; University of Heidelberg, Institute of Medical Biometry and Informatics Kenngott, Hannes; University of Heidelberg, Department of General, Visceral and Transplantation Surgery Mihaljevic, A; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC) Thilo, Hackert; University of Heidelberg, Department of General, Visceral and Transplantation Surgery Buchler, Markus W.; University of Heidelberg, Department of General, Visceral and Transplantation Surgery Diener, M. K.; University of Heidelberg, Department of General, Visceral and Transplantation Surgery; University of Heidelberg, The Study Center of the German Surgical Society (SDGC)
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Evidence based practice, Health services research, Oncology, Communication
Keywords:	Evidence map, evidence management, Pancreatic surgery < SURGERY, systematic review, meta-analysis, living review

Evidence Map of Pancreatic Surgery - Protocol for a Living Systematic Review and Meta-Analysis

Pascal Probst[1,2] (PP): pascal.probst@med.uni-heidelberg.de

Felix J. Hüttner[1,2] (FJH) : felix.huettner@med.uni-heidelberg.de

Ömer Meydan [2] (OM): meydan@stud.uni-heidelberg.de

Eva Kalkum[2] (EK): eva.kalkum@med.uni-heidelberg.de

Rüdiger Kretschmer[2] (RK): kretschmer@evidencemap.surgery

Katrin Jensen[3] (KJ): jensen@imbi.uni-heidelberg.de

Hannes G. Kenngott[1] (HGK): hannes.kenngott@med.uni-heidelberg.de

André Mihaljevic[1,2] (AM): andre.mihaljevic@med.uni-heidelberg.de

Thilo Hackert[1] (TH): thilo.hackert@med.uni-heidelberg.de

Markus W Büchler[1] (MWB): markus.buechler@med.uni-heidelberg.de

Markus K. Diener[1,2] (MKD): markus.diener@med.uni-heidelberg.de

[1]Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

[2]The Study Center of the German Surgical Society (SDGC), University of Heidelberg, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany

[2]Institute of Medical Biometry and Informatics, University of Heidelberg, Im Neuenheimer Feld 130.3, 69120 Heidelberg, Germany

Corresponding author:

Pascal Probst, MD, MSc

Department of General, Visceral and Transplantation Surgery

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg

Germany

T: +496221 56 6110

E-Mail: pascal.probst@med.uni-heidelberg.de

Abstract

Introduction

Pancreatic surgery is a large and complex field of research. Several evidence gaps exist for specific diseases or surgical procedures. An overview on existing knowledge is needed to plan and prioritise future research. The aim of this project is to create a systematic and living evidence map of pancreatic surgery.

Methods and analysis

A systematic literature search in MEDLINE (via PubMed), Web of Science and CENTRAL will be performed searching for all randomised controlled trials (RCT) and systematic reviews (SR) on pancreatic surgery. RCT and SR will be grouped in research topics. Baseline and outcome data from RCT will be extracted, presented and effect sizes meta-analysed. Data from SR will be used to identify evidence gaps. A freely accessible web-based evidence map in the format of a mind map will be created. The evidence map and meta-analyses will be updated periodically.

Dissemination

After completion of the project, a permanently updated evidence map of pancreatic surgery will be available to patients, physicians, researchers and funding bodies via www.evidencemap.surgery. Its use will allow clinical decision making based on primary data and prioritisation of future research endeavours.

Systematic review registration: PROSPERO 2019 CRD42019133444

Keywords: Evidence map, evidence management, pancreatic surgery, systematic review, meta-analysis, living review

Strengths and limitations

- Through a comprehensive search and selection of high-quality articles the best available evidence for pancreatic surgery will be gathered.
- Contrary to medical databases the evidence map in the form of a mind map will present randomised-controlled trials and systematic reviews ordered by research topics in an intuitive fashion.
- The evidence map of pancreatic surgery will strengthen the visibility of primary research results in pancreatic surgery.

Background

Quantity and quality of randomised controlled trials (RCT) for pancreatic surgery is increasing, however, there are still blind spots regarding specific operations and diseases [1]. Socio-economic pressure demands for prioritisation of relevant research projects in the field of pancreatic surgery. Since pancreatic diseases are devastating for patients and highly impair their quality of life [2,3], there is an urgent need for the best treatment, which should be based on the best available evidence. Consequently, patients undergoing pancreatic surgery should be included in prospective trials whenever evidence is lacking. Therefore, pancreatic surgery research should be performed according to an objective priority setting.

The two main surgically treated diseases of the pancreas are tumours and chronic pancreatitis [1]. For both entities, surgery remains the only chance of cure or long-term increase of quality of life, respectively [2,3]. Therefore, all patients bear the burden of a severe disease in need of major surgery, but also must carry the risk of postoperative morbidity which is as high as 73% [4]. Therefore, one of the major research interests is to find the most effective and safe way to operate patients. Since perioperative mortality in specialised centres is low nowadays [4], the focus lies on reduction of pancreas-specific complications like postoperative pancreatic fistula (POPF) [5], delayed gastric emptying (DGE) [6] or post-pancreatectomy haemorrhage (PPH) [7].

To systematically investigate the field of pancreatic surgery, two innovative methods of evidence-based medicine are combined: the living systematic review (SR) and evidence mapping.

Living SR follow the established methods of a SR. However, they overcome the difficulty that normal SR are soon outdated or redundant after their publication [8]. Living SR are assumed to achieve a greater validity with increased benefits for physicians and patients at lower spending of resources over time [9]. Some experts even think that living SR should become the flagship of synoptic evidence and the research community should have a strong interest to establish living SR in their fields [10].

Evidence mapping is also an emerging approach to systematic assessment of quantitative and qualitative aspects [11]. Although there is no universally applied definition of evidence mapping yet, its aim is usually to summarize evidence and identify gaps in the body of knowledge regarding a specific area of research. In times of scarcity of health system resources and overload of information, this approach may enable researchers and funding bodies to prioritise future research questions [12].

The combination of the methods of living SR and evidence mapping applied on pancreatic surgery will result in an intuitive and permanently up-to-date map of available evidence including living meta-analyses (MA). Through visualisation of available evidence, health-care professionals, patients and funding bodies gain direct access to highly relevant data.

Aim

The major problem of evidence management is that most research activities are not harmonised with clinical and political relevance. This results in production of waste-evidence, rather than needed evidence by prioritisation. The first step in priority setting would be an up-to-date characterisation of existing knowledge, lack of knowledge and research questions. Thus, the aim of this project is to create a systematic and living evidence map of pancreatic surgery.

Methods/ Design

The PRISMA-P guideline was followed [13]. Further, the living systematic review network guidelines on how living SR should be published [10], how living MA should be updated [14] and how living recommendations should be formed [15] will be followed wherever applicable. The project was prospectively registered (PROSPERO 2019 CRD42019133444) and for full transparency the protocol is herewith published open access.

Systematic literature search

A systematic literature search in all major electronic bibliographic databases with relevance for surgical literature will be searched [16]: MEDLINE (via PubMed), Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL). No restrictions will be applied regarding language or publication date. The full search strategy for MEDLINE (via PubMed) will be:

"((pancreas[MeSH terms] OR pancreas[tiab] OR pancreatic[tiab] OR pancreato*[tiab]) AND (resection* [tiab] OR removal [tiab] OR surger* [tiab] OR surgical [tiab] OR laparotom*[tiab] OR enucleation* [tiab] OR operation* [tiab] OR operated [tiab] OR "surgical procedures, operative"[MeSH terms] OR "general surgery"[MeSH terms])) OR (pancreaticoduodenectom*[tiab] OR pancreatoduodenectom*[tiab] OR pancreatoduodenectom*[tiab] OR duodenopancreatectom*[tiab] OR pancreatectom*[tiab] OR Whipple[tiab] OR Kausch-Whipple[tiab] OR ppWhipple[tiab] OR dpphr[tiab] OR PPPD[tiab] OR pancreaticoduodenectomy[MeSH] OR pancreatectomy[MeSH] OR "Pancreas/surgery"[Mesh] OR "Pancreatic Diseases/surgery"[Mesh] AND (randomized controlled trial [pt] OR random*[tw] OR RCT [tw] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [pt] OR systematic review [pt] OR meta-analysis [pt] OR re-view [pt] OR meta-analysis [tw] OR review [tw])". The full search strategy for Web of Science and CENTRAL is displayed in appendix 1.

By a preliminary literature search in MEDLINE (via PubMed), Web of Sciences and Cochrane Central Register of Controlled Trials more than 30´000 potentially eligible articles were identified. It is expected that the first version of the evidence map will contain more than 250 RCT and 400 SR/MA.

Study selection

The PICO question is shown in Table 1. Following the recommendations of the Cochrane Collaboration [17], titles, abstracts and full texts of identified articles will be screened independently by two reviewers. If there is a disagreement between the two

reviewers, this will be resolved by a third reviewer. The screening process will be done with the bibliographic software EndNote X9 (Clarivate Analytics).

Eligible study designs to be included will be RCT and SR with or without MA. SR will only be eligible if they meet minimal quality requirements i.e. SR must search at least two established literature databases and provide a critical appraisal with validated tools like the Cochrane Collaboration tool for assessing risk of bias [18] for RCT or like the ROBINS-I for non-randomised studies [19].

The focus of this evidence map is pancreatic surgery. Interventions to be included should aim to affect the surgical outcome i.e. medical devices (e.g. stapler versus scalpel resection in distal pancreatectomy), perioperative management (e.g. prehabilitation of patients, or intraoperative fluid management), surgical strategy (e.g. open versus laparoscopic access to the abdominal cavity), drug (e.g. somatostatin analogues to influence POPF) and nutrition (e.g. immunonutrition to avoid complications). Interventions like endoscopic retrograde cholangiopancreatography, radiologically guided punctures or similar interventions will only be assessed as control groups to the above mentioned interventions. Moreover, studies on neo-/adjuvant treatment, or pancreatic transplantation will be excluded.

Data extraction

All stages of data extraction and quality assessment will be carried out independently by two reviewers using predefined items. Any disagreement will be resolved by consensus, or by consultation with a third reviewer. The items are directly extracted to a user interface (Microsoft .NET framework, Windows Forms) with automated plausibility checks. The data will be saved in a database (Microsoft SQL Server 2017

Express) tailored for this project. The database will allow saving resources during data extraction and making data usable for presentation on the evidence map and for statistical analysis. After validation of the extracted data, the relational database will be able to export the extracted data in the exact form needed for presentation on the evidence map. Further, the database will have an interface to the statistical program to export data needed for the meta-analyses. All extracted items for RCT and SR within the user interface are shown in appendix 2.

Further, the methodological quality of included RCT will be assessed using the newly suggested Cochrane Collaboration tool for assessing risk of bias 2.0 [20]. The tool includes five standard domains of bias: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selecting of the reported result. These domains will be rated as 'high risk', 'low risk' of bias, or some concerns. Finally, an overall risk of bias judgement will be made. As recently recommended for surgical trials, detailed information on blinding will be recorded and reported [21]. Furthermore, industrial funding will be considered as another potential threat to validity [22].

Data synthesis for creation of the evidence map

All included RCT and SR will be clustered according to the type of operation, the type of disease and the type of interventions. Consequently, studies on the same research topics will be grouped e.g. pylorus-resecting versus pylorus-preserving (intervention: surgical strategy) in partial pancreatoduodenectomy (operation) for tumours or chronic pancreatitis (disease).

Information on existing SR will be shown within the evidence map and will be used for identification of evidence gaps in the research topics i.e. missing RCT. Therefore, no quantitative data will be extracted and no critical appraisal of SR will be performed. Including SR in the evidence map is preferred to the inclusion of all other primary study types like non-randomised prospective trials or retrospective studies.

Information on existing RCT will also be shown within the evidence map and the extracted data will be used for pooling in meta-analyses. For each research topic the following set of outcomes will be reported in the meta-analyses: mortality, postoperative pancreatic fistula (graded as biochemical leak, B, C if the International Study Group of Pancreatic Surgery (ISGPS) definition [5] is used), delayed gastric emptying (graded as A, B, C if the ISGPS definition [6] is used), post-pancreatectomy haemorrhage (graded as A, B, C if the ISGPS definition [7] is used), bile leak (graded as A, B, C if the International Study Group of Liver Surgery definition [23] is used), chyle leak (graded as A, B, C if the ISGPS definition [24] is used), intraabdominal fluid collection/abscess, overall morbidity (if available according to the Clavien-Dindo classification [25]), Overall survival (as 1, 2, 3, 4 and 5 year survival rate and median overall survival), length of hospital stay and operation time. Protocols of ongoing RCT will be displayed within the evidence map until the final results are available.

Furthermore, for each outcome the certainty of the evidence will be rated using the GRADE system [26,27]. This includes limitations in the design from the risk of bias assessment (see above), indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and publication bias. Thus, the certainty of the evidence will be rated to be very low, low, moderate or high for each outcome.

Statistical analysis

If more than 3 RCT investigate the same research topic e.g. pylorus-resection vs. pylorus-preservation in pancreaticoduodenectomy, the above-mentioned outcomes of these RCT will be pooled in living meta-analyses.

Statistical analyses will be performed with R [28]. Dichotomous data (mortality, postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy hemorrhage, bile leak, chyle leak, intraabdominal fluid collection/ abscess, overall morbidity, survival rate) will be pooled in a Mantel–Haenszel model to estimate odds ratios and associated 95% confidence intervals. For complications defined by the ISGPS the meta-analyses will discriminate grade A complications from clinically relevant B/C complications. For continuous data (mean overall survival, length of hospital stay, operation time) mean differences and associated 95% confidence intervals will be calculated using an inverse-variance model. A two-sided level of significance below 5 per cent will be considered statistically significant. Continuous values reported as median with range will be converted to mean and sd [29]. For dichotomous and continuous data, a prediction interval will be calculated. Statistical heterogeneity among trials will be evaluated by means of the I^2 statistic. We will consider I^2 < 25% to indicate low statistical heterogeneity and I^2 > 75% to indicate high statistical heterogeneity. A random-effects rather than a fixed-effects model will be used for meta-analysis when clinical heterogeneity is assumed and at least 5 RCT are available.

If more than two interventions are compared within a research topic, a state-of-the art Bayesian network meta-analysis will be performed. Either linear or logistic random effects models will be applied. Pooled effect estimates obtained in the network meta-analysis (adjusted mean differences or log odds ratios) will be provided with 95%

credibility intervals. Furthermore, a treatment ranking based on the probability of being the most efficient arm will be carried out.

To evaluate the risk of publication bias, funnel plots will be created and tested for asymmetry using the Harbord test [30] if more than 10 trials are available for a living meta-analysis.

Creating the evidence map

The evidence map of pancreatic surgery will be freely accessible for everyone via the internet. An example how the structure of the evidence map, its instructions and information on a research topic (e.g. pylorus-resection vs. pylorus-preservation in pancreaticoduodenectomy) might look is accessible here: www.evidencemap.surgery.

The quantitative and qualitative analyses are only one part of the added value by the evidence map. The evidence map will be configured as a mind map leading its reader from the center (pancreatic surgery) to a research topic e.g. pylorus-resection vs. pylorus-preservation in pancreaticoduodenectomy (Figure 1). In the center of the map the icon behind the map version, Pancreatic surgery V0 in the example, will provide a summary of the evidence map including a PRISMA flow chart of the actual version. Further, for every type of operation a pooled estimate of mean with 99% confidence interval and median with interquartile ranges from all RCT for the outcomes will be calculated and presented for bench marking purposes. Furthermore, two bubble plots will be created, mapping all RCT by types of operation to types of intervention and types of disease to types of intervention. Within the bubble plots sample size of the trials will be expressed by bubble size and the

geographical region by a color code. This will allow concluding on overall evidence gaps in pancreatic surgery and differences between geographical regions.

Through logical connections the reader will be guided to research topics. These are marked with symbols indicating the presence or absence of RCT and SR (a tick means that RCT are existing, a cross means that RCT on the research topic are missing; a star means that SR are existing and an exclamation mark means that SR are missing). In this example the symbols mean that there is at least one RCT and SR/MA available for the research topic. In this fashion the evidence map gives an intuitive presentation of available evidence and evidence gaps become visible.

For every research topic the reader can look at the existing RCT and SR (Figure 2).

For RCT and SR the name of the first author and the year of publication are displayed. Behind the year of publication three icons are shown. The first icon gives the original conclusion of the article and the full reference. The second icon is a link to the article on the journal homepage or if the manuscript is published open access the full text is directly downloadable. The third icon is available for RCT only and contains the extracted data as an exportable and processable file (.xlsx).

Finally, from the “Living MA and GRADE” field a summary of findings table (GRADE), the forest plots and the funnel plots for all outcomes of a research topic will be downloadable from the evidence map.

Additionally, the evidence map will have a comment function and will allow physicians, researchers and patients to interact with the evidence map by adding comments. In this way researchers can report their new research directly or patients can comment on the importance of future research within research topics. There will

be an administrator answering comments and additionally reacting on important subjects via social media.

Living systematic review and meta-analyses

After its induction, a periodically update including the steps of literature search, screening and extraction is planned at least every 6 months. If new RCT and SR are available upon these searches, they will be added to the research topics and the meta-analyses will be renewed resulting in living meta-analyses. Version numbers and date of last updates will be displayed on the map itself and on every research topic.

Patient involvement

In order to adequately incorporate patients, a priority setting partnership (PSP) for pancreatic cancer treatments in Germany (www.europaeisches-pankreaszentrum.de/extrainfo/psp-pankreaskarzinom/) is performed. The objective of this project is to involve patients, their families, caregivers, specialists, nurses and other stakeholders to identify and prioritise unanswered scientific questions in the treatment of pancreatic cancer. From these responses unidentified research topics may emerge. In a second step patients as well as experts will be asked to rank the existing research topics for priority. Results of the PSP in conjunction with the living evidence map would allow a transparent, objective and patient-centred identification of the most urgent future research topics in pancreatic cancer.

Moreover, national and international patient representative organisations will be involved during the beta-test phase of the evidence map to invite them for their comments especially on importance of the research topics presented. Furthermore, these organisations will be invited to link the map on their internet presences.

Dissemination

The aim of this project is to develop and maintain an evidence map of pancreatic surgery i.e. a living systematic review with meta-analyses and mapping of the evidence. The map will contain all existing evidence from randomised-controlled trials and systematic reviews on pancreatic surgery plotted as an intuitive and interactive mind map. The presented evidence is based on a comprehensive systematic literature search and comprehensibly selection of literature. Through www.evidencemap.surgery a permanently updated evidence map of pancreatic surgery will be disseminated to patients, physicians, researchers and funding bodies.

The living evidence map of pancreatic surgery will serve different purposes for researches, clinicians, patients and funding bodies. For researchers, the evidence map in pancreatic surgery will be a help to get a quick overview about existing research questions. Notably, this is not an attempt to substitute single SR on a specific subject. Much more, the intention is to provide a strong reference as a comparator. Moreover, it will speed up and harmonise the conduct of future SR as researchers can rely on the performed literature search, on the extracted data and critical appraisal. This map would be highly relevant to patient care and the health care system because it would show “what works” and “what is missing” at a glance and in an intuitive fashion. Clinicians could use the map to inform their patients on benefits and harms of different pancreatic surgery interventions based on up-to-date high-quality data. The difference to follow a guideline is that clinicians can interpret the primary literature from RCT and SR for their individual patients instead of applying recommendations from guidelines. In the same manner, patients will have access to primary data sorted by logical connections which will allow them to find

evidence appropriate for their cases. Moreover, researchers, clinicians and patients will be able to comment on research topics and interact with the pancreatic surgery community. Finally, such an evidence map should be of interest for funding bodies because an objective assessment of which research project is most pressing to be funded becomes possible.

The first version will be presented at the World Pancreas Forum (Bern, Switzerland; www.worldpancreasforum.com) on February 6th 2020. The first citable version i.e. a version of which cornerstone data will be published in a peer-reviewed journal is planned for the end of 2020. After this the online version will be updated every 6 months and a new citable version is planned after 2 and 4 years. Thereafter, the impact on literature and research of the evidence map will be re-evaluated. As social media become more and more important in the dissemination of scientific results, the evidence map will be promoted on Facebook and twitter [31]. Therefore, updates and living meta-analyses will be blogged and tweets/ re-tweets will be done to surgeons and surgical journals. Finally, to our knowledge the proposed evidence map would be the first of its kind. Therefore, this project would also inspire other researchers to follow and create such maps in their medical fields.

Figures and Tables

Figure 1: Example of the possible structure of the evidence map (from www.evidencemap.surgery)

Figure 2: Example of existing literature (RCT and SR) and living meta-analysis for a research topic (from www.evidencemap.surgery)

Table: 1: PICO Question

Appendix 1: Full search strategy for Web of Science and CENTRAL

Appendix 2: Extracted items for RCT and SR

References

1. Hüttner FJ, Capdeville L, Pianka F, Ulrich A, Hackert T, Büchler MW, Probst P, Diener MK. Systematic review of the quantity and quality of randomized clinical trials in pancreatic surgery. Br J Surg. 2019 Jan;106(1):23-31.

2. Schnelldorfer T, Ware AL, Sarr MG, Smyrk TC, Zhang L, Qin R, et al. Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: is cure possible? Ann Surg. 2008;247(3):456-62.

3. Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387(10031):1957-66.

4. Sánchez-Velázquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, Javed AA, Inoue Y, Beghdadi N, Kalisvaart M, Vigia E, Walsh CD, Lovasik B, Busquets J, Scandavini C, Robin F, Yoshitomi H, Mackay TM, Busch OR, Hartog H, Heinrich S, Gleisner A, Perinel J, Passeri M, Lluis N, Raptis DA, Tschuor C, Oberkofler CE, DeOliveira ML, Petrowsky H, Martinie J, Asbun H, Adham M, Schulick R, Lang H, Koerkamp BG, Besselink MG, Han HS, Miyazaki M, Ferrone CR, Fernández-Del Castillo C, Lillemoe KD, Sulpice L, Boudjema K, Del Chiaro M, Fabregat J, Kooby DA, Allen P, Lavu H, Yeo CJ, Barroso E, Roberts K, Muiesan P, Sauvanet A, Saiura A, Wolfgang CL, Cameron JL, Boggi U, Yoon DS, Bassi C, Puhan MA, Clavien PA. Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Ann Surg. 2019 Feb 27. doi: 10.1097/SLA.0000000000003223. [Epub ahead of print]

5. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161(3):584-91.

6. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142(5):761-8.

7. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142(1):20-5.

8. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. Milbank Q. 2016 Sep;94(3):485-514.

9. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al. Living systematic review: 1. Introduction-the why, what, when, and how. J Clin Epidemiol. 2017;91:23-30.

10. Sutton AJ. Not enough I say! Expand the remit of living systematic reviews to inform future research. J Clin Epidemiol. 2017;91:54-5.

11. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The Global Evidence Mapping Initiative: scoping research in broad topic areas. BMC Med Res Methodol. 2011;11:92.

12. Miake-Lye IM, Hempel S, Shanman R, Shekelle PG. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Syst Rev. 2016;5:28.

13. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

14. Simmonds M, Salanti G, McKenzie J, Elliott J, Living Systematic Review N. Living systematic reviews: 3. Statistical methods for updating meta-analyses. J Clin Epidemiol. 2017;91:38-46.

15. Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schunemann HJ, Living Systematic Review N. Living systematic reviews: 4. Living guideline recommendations. J Clin Epidemiol. 2017;91:47-53.

16. Goossen K, Tenckhoff S, Probst P, Grummich K, Mihaljevic AL, Buchler MW, et al. Optimal literature search for systematic reviews in surgery. Langenbecks Arch Surg. 2018;403(1):119-29.

17. Higgins J, Green S. (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: http://handbook.cochrane.org. Accessed 13.06.2019

18. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

19. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

20. Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.

21. Probst P, Zaschke S, Heger P, Harnoss JC, Hüttner FJ, Mihaljevic AL, Knebel P, Diener MK. Evidence-based recommendations for blinding in surgical trials. Langenbecks Arch Surg. 2019;404(3):273-284.

22. Probst P, Knebel P, Grummich K, Tenckhoff S, Ulrich A, Büchler MW, Diener MK. Industry Bias in Randomized Controlled Trials in General and Abdominal Surgery: An Empirical Study. Ann Surg. 2016 Jul;264(1):87-92.

23. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011;149(5):680-8.

24. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. Surgery. 2017;161(2):365-72.

25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

27. GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from: http://gradepro.org/. Accessed 13.06.2019

28. R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. Available from: http://www.R-project.org. Accessed 13.06.2019

29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standarad deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology 2014, 14: 135.

30. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25(20):3443-57.

31. Reinisch A, Schröder SR, Ulrich F, Padberg W, Liese J. Antibiotic-treated acute appendicitis-reception in social media. Langenbecks Arch Surg. 2019;404(3):343-349

Table 1

PICO Question

Population	Inclusion: Patients with any kind of pancreatic disease that requires surgery Exclusion: Patients with pancreatic diseases that does not require surgery
Interventions	Inclusion: All kind of interventions will be included as long as they are aimed to affect the surgical outcome i.e. medical devices, perioperative management, surgical strategy, drug and nutrition. Exclusion: Endoscopic retrograde cholangiopancreatography, radiologically guided punctures or similar interventions. Systemic cancer therapies and pancreatic transplantation
Control	Any other kind of control compared to the above-mentioned intervention including endoscopic retrograde cholangiopancreatography, radiologically guided punctures or similar interventions.
Outcomes	Mortality, postoperative pancreatic fistula, delayed gastric emptying, post-pancreatectomy haemorrhage, bile leak, chyle leak, intraabdominal fluid collection/abscess, overall morbidity, Overall survival, length of hospital stay and operation time

Acknowledgement

None.

Author's contribution

PP, FJH, OM, EK, HGK and AM made substantial contributions to the conception or design of the work or the acquisition of data and drafted the work.

RK, KJ, TH, MWB and MKD made substantial contributions to the conception or design of the work or the acquisition of data and revised the work critically for important intellectual content.

All authors gave their final approval to the publication of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

This work was supported by the Heidelberg Foundation for Surgery (Heidelberger Stiftung Chirurgie, www.stiftung-chirurgie.de), Heidelberg, Germany. The Heidelberg Foundation for Surgery had no role in planning of the study and will not be involved in the conduct of the study.

Competing interests

None of the authors has a secondary interest according to the ICMJE guidelines that inappropriately influences his contribution to this work.

Ethics/ Patient consent for publication

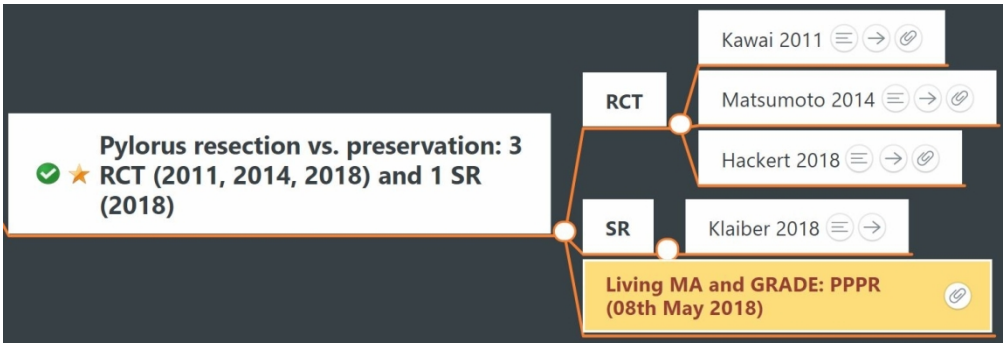
Not required.

Word count

3525 words

Example of the possible structure of the evidence map (from www.evidencemap.surgery)

380x186mm (96 x 96 DPI)



Example of existing literature (RCT and SR) and living meta-analysis for a research topic (from www.evidencemap.surgery)

407x137mm (96 x 96 DPI)

Appendix 1: Full search strategy for Web of Science and CENTRAL.

Web of Science Core Collection

9 #8 OR #7
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

8 (#4 OR #3) *AND* **DOCUMENT TYPES:** (Review)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

7 #6 AND #5
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

6 TS = (random* OR RCT OR meta-analysis OR review)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

5 #4 OR #3
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

4 #2 AND #1
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

3 TS = (pancreaticoduodenectom* OR pancreatoduodenectom* OR pancreato-duodenectom* OR duodenopancreatectom* OR pancreatectom* OR Whipple OR Kausch-Whipple OR ppWhipple OR dpphr OR PPPD)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

2 TS = (resection* OR removal OR surger* OR surgical OR laparotom* OR enucleation* OR operation* OR operated)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

1 TS = (pancreas OR pancreatic OR pancreato*)
Indexes=SCI-EXPANDED, SSCI Timespan=1900-2019

CENTRAL (Cochrane Central Register of Controlled Trials)

#1 (pancreas OR pancreatic OR pancreato*) NEAR (resection* OR removal OR surger* OR surgical OR laparotom* OR enucleation* OR operation* OR operated)

#2 MeSH descriptor: [Pancreas] explode all trees and with qualifier(s): [surgery - SU]

#3 (pancreaticoduodenectom* OR pancreatoduodenectom* OR pancreatoÔÇÉduodenectom* OR duodenopancreatectom* OR pancreatectom* OR Whipple OR Kausch-Whipple OR ppWhipple OR dpphr OR PPPD)

#4 MeSH descriptor: [Pancreaticoduodenectomy] explode all trees

#5 MeSH descriptor: [Pancreatic Diseases] explode all trees and with qualifier(s): [surgery - SU]

#6 MeSH descriptor: [Pancreatectomy] explode all trees

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

Article Info | Baseline | Complications | Clavien-Dindo | Survival | Diverse | Bias

ID: 1

Title: Intervention versus Control for pancreas surgery

First author: Probst

Journal (Index medicus): Langenbecks Arch Surg.

Year of publication: 2019

Volume(issue):pages: 10(1):1-10

Type of intervention (general): Surgical strategy

Description of intervention arm: Intervention

Description of control arm: Control

Description of other arm 3 (optional):

Region of publication

- [x] Europe
- [ ] North America
- [ ] South America
- [ ] Africa
- [ ] Asia
- [ ] Australia/New Zealand

Type of operation

- [x] Distal pancreatectomy
- [ ] Duodenum-preserving pancreatic head resection
- [ ] Enucleation
- [x] Partial pancreaticoduodenectomy
- [ ] Total pancreatectomy
- [ ] Other

Type of disease

- [x] Ampullary carcinoma
- [x] Bile duct carcinoma
- [x] Chronic pancreatitis
- [ ] Acute pancreatitis
- [x] Cystic neoplasms
- [x] Duodenal carcinoma
- [x] Intraductal papillary mucinous neoplasms
- [x] Neuroendocrine tumors
- [x] Pancreatic adenocarcinoma
- [ ] Trauma
- [ ] Other

Document upload: Upload | Show

Important notes:

Conclusion: XYZ

Save | Back

Article Info | Baseline | Complications | Clavien-Dindo | Survival | Diverse | Bias

ID 6

Lowest age included ☑ Not reported

Highest age included ☑ Not reported

Were relaparotomies excluded? ○ Yes ◉ No

Which comorbidities were excluded? Not reported.

Which cancer stages were excluded? Not reported.

Which other patients were excluded? Patients undergoing a nonstandard pancreatic resection or a procedure associated with known greater morbidity.

Overall randomized sample size 233

Randomized in intervention arm 111

Randomized in control arm 111

Followup (months) 3

Mean age at baseline Not reported ☐

	Not reported	Mean value	Standard deviation
Intervention arm	☐	64.3	10.5
Control arm	☐	62.5	13.5

Gender Not reported ☐

	Not reported	Male	Female
Intervention arm	☐	57	54
Control arm	☐	52	59

Save Back

Article Info | Baseline | Complications | Clavien-Dindo | Survival | Diverse | Bias

ID 6

POPF

Not reported ☐

	Not reported	A/BL	B	C	Events	Total
Intervention arm	☐	14	7	3	10	111
Control arm	☐	23	4	4	8	111

Definition ISGPS

Mortality | POPF | DGE | PPH | Bile Leak | Chyle | IAA

Save | Back

EMBS - RCT

Article Info | Baseline | Complications | Clavien-Dindo | Survival | Diverse | Bias

ID 6

Morbidity and Mortality

Not reported ☑

CCI

Not reported ☐

	Not reported	Mean value	Standard deviation
Intervention arm	☐	0	0
Control arm	☐	0	0

Save Back

ID 6

Survival

Not reported ☑

Survival HR

	Not reported	HR	Lower 95%-CI	Upper 95%-CI	Log(HR)	SE
Intervention vs control	☑					

Save Back

Article Info | Baseline | Complications | Clavien-Dindo | Survival | Diverse | Bias

ID 6

Operation time

Not reported ☐

	Not reported	Mean value	Standard deviation
Intervention arm	☐	286	54
Control arm	☐	296	48

Length of stay

Not reported ☐

	Not reported	Mean value	Standard deviation
Intervention arm	☐	12	0
Control arm	☐	12	0

Patient related outcome measures

Assessed ○ Yes ◉ No

Save Back

Article Info | Baseline | Complications | Clavien-Dindo | Survival | Diverse | Bias

ID 6

Bias arising from the randomization process	Low
Reason	
Bias due to deviations from intended interventions	Low
Blinding	
Patient	not reported
Physician	not blinded
Data collector	not reported
Reason	
Bias due to missing outcome data	Low
Reason	
Bias in measurement of the outcome	Low
Blinding	
Outcome assessor	blinded
Statistician	not reported
Reason	
Bias in selecting of the reported result	Low
Reason	
Overall risk-of-bias judgement	Low
Reason	
Funding source	Unclear

Save | Back

ID	1
Title	Intervention versus Control for pancreas surge
First author	Probst
Journal (Index medicus)	Langenbecks Arch Surg.
Year of publication	2019
Volume(issue):pages	10(1):1-10

Type of intervention (general): Surgical strategy

Description of intervention arm	Intervention
Description of control arm	Control
Description of other arm 3 (optional)	

Region of publication

- [ ] Europe
- [ ] North America
- [ ] South America
- [ ] Africa
- [x] Asia
- [ ] Australia/New Zealand

Type of operation

- [x] Distal pancreatectomy
- [x] Duodenum-preserving pancreatic head r...
- [ ] Enucleation
- [x] Partial pancreaticoduodenectomy
- [x] Total pancreatectomy
- [ ] Other

Type of disease

- [x] Ampullary carcinoma
- [x] Bile duct carcinoma
- [x] Chronic pancreatitis
- [ ] Acute pancreatitis
- [x] Cystic neoplasms
- [x] Duodenal carcinoma
- [x] Intraductal papillary mucinous neoplasms
- [x] Neuroendocrine tumors
- [x] Pancreatic adenocarcinoma
- [ ] Trauma
- [ ] Other

Document upload: Upload | Show pdf

Important notes	
Conclusion	XYZ

Save | Back

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 + 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	22
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	22
Sponsor	5b	Provide name for the review funder and/or sponsor	22
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	22
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4/5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7/8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6/7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7 + Appendix 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7/8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7/8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8/9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9/10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9/10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9 + 10/11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10/11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10/11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.