BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

BMJ Open

Adverse Events Associated with Endoscopic Retrograde Cholangiopancreatography: Protocol for a Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053302
Article Type:	Protocol
Date Submitted by the Author:	10-May-2021
Complete List of Authors:	Forbes, Nauzer; University of Calgary, Medicine Leontiadis, GI ; McMaster University, Vaska, Marcus; Alberta Health Services, Knowledge Resource Service; Elmunzer, B.; Medical University of South Carolina Yuan, Yuhong ; McMaster University, Bishay, Kirles; University of Calgary, Medicine Meng, Zhao Wu; University of Calgary, Medicine Iannuzzi, Jordan; University of Calgary, Medicine O'Sullivan, Dylan; University of Calgary, Medicine Mah, Brittany; University of Calgary, Medicine Partridge, Arun; University of Calgary, Medicine Keswani, Rajesh; Northwestern University Feinberg School of Medicine Wani, Sachin; University of Colorado - Anschutz Medical Campus Bridges, Ronald; University of Calgary, Medicine Heitman, Steven; University of Calgary, Medicine Hilsden, Robert; University of Calgary, Medicine Ruan, Yibing; Alberta Health Services, Cancer Epidemiology and Prevention Research Brenner, Darren; University of Calgary Cumming School of Medicine, Oncology
Keywords:	Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Pancreatic disease < GASTROENTEROLOGY

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Adverse Events Associated with Endoscopic Retrograde Cholangiopancreatography: Protocol for a Systematic Review and Meta-analysis

Nauzer Forbes MD MSc[1,2], Grigorios I. Leontiadis MD PhD[3,4], Marcus Vaska MLIS[5], B. Joseph Elmunzer MD MSc[6], Yuhong Yuan PhD[4], Kirles Bishay MD[1,2], Zhao Wu Meng MD[1,2], Jordan Iannuzzi MD[1], Dylan E. O'Sullivan PhD[2,7], Brittany Mah BSc[1], Arun C.R. Partridge MD[1], Rajesh N. Keswani MD MS[8], Sachin Wani MD[9], Ronald J. Bridges MD[1], Steven J. Heitman MD MSc[1,2], Robert J. Hilsden MD PhD[1,2], Yibing Ruan PhD MPH[8,10], Darren R. Brenner PhD[2,8,10]

1. Department of Medicine, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB, Canada
2. Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada
3. Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, ON, Canada
4. Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada
5. Knowledge Resource Service, Alberta Health Services, Calgary, AB, Canada
6. Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston, SC, USA
7. Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
8. Division of Gastroenterology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
9. Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
10. Department of Cancer Epidemiology and Prevention Research, Cancer Control Alberta, Alberta Health Services, Calgary, AB, Canada

Corresponding Author:

Nauzer Forbes, MD, MSc
Assistant Professor of Medicine
Division of Gastroenterology
University of Calgary
TRW 6D19, 3280 Hospital Drive NW
Calgary, AB T2N 4Z6
Tel: 403.592.5089 Fax: 403.592.5090
E-mail: nauzer.forbes@ucalgary.ca

AUTHOR CONTRIBUTIONS

- conception and design: NF, GIL
- analysis plan: NF, GIL, MV, YY, DEO, BJE, DRB
- drafting of the article: NF
- critical revision of the article for important intellectual content: all authors
- final approval of the article: all authors

DISCLOSURES/ CONFLICTS OF INTEREST

None relevant.

FUNDING

The N.B. Hershfield Chair in Therapeutic Endoscopy (Grant number not applicable – N/A).

WORD COUNT

243 (abstract); 2,590 (main text).

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

ABSTRACT

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is performed to diagnose and manage conditions of the biliary and pancreatic ducts. Though effective, it is associated with common adverse events (AEs). The purpose of this study is to systematically review ERCP AE rates and report up-to-date pooled estimates.

Methods and Analysis

A comprehensive electronic search will be conducted. A study team of eight data abstracters will independently determine study eligibility, assess quality, and abstract data in parallel, with any two concordant entries constituting agreement and with discrepancies resolved by consensus. The primary outcome will be the pooled incidence of post-ERCP pancreatitis (PEP), with secondary outcomes including post-ERCP bleeding, cholangitis, perforation, cholecystitis, sedation-related cardio-pulmonary events, and unplanned healthcare encounters (UHE). Secondary outcomes will also include rates of specific and overall adverse events within clinically relevant subgroups determined *a priori*. DerSimonian and Laird random effects models will be used to perform meta-analyses of these outcomes. Sources of heterogeneity will be explored via meta-regression. Subgroup analyses based on median dates of data collection across studies will be performed to determine whether AE rates have changed over time.

Conclusion

Given that ERCP is widely performed around the world, endoscopists and patients should have access to up-to-date estimates of procedural risk. Our meta-analysis will bridge these important knowledge gaps so that all relevant stakeholders are well-informed.

PROSPERO Registration Number

CRD42020220221.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Keywords

ERCP; endoscopic retrograde cholangiopancreatography; adverse event; pancreatitis; hemorrhage; cholangitis.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and Limitations of the Proposed Study

- Our meta-analysis will provide to up-to-date estimates of procedural risks associated with the performance of ERCP.
- A comprehensive search strategy will be employed to capture all relevant studies and answer our study question.
- The strength of the body of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.
- A limitation of our approach is the likelihood of pooling outcome estimates using variable definitions of outcomes across studies, which we will partially mitigate by performing sensitivity analyses based on outcome definitions.
- We have also made the decision to exclude conference abstracts from our study. Though this potentially disposes to publication bias, we feel that the unclear or ambiguous methodology often available from conference abstracts would add to potential study heterogeneity.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential and commonly performed advanced endoscopic procedure used in the diagnosis and treatment of several categories of biliary and pancreatic pathology.[1-4] Although the role of standard ERCP has transitioned to that of a primarily therapeutic procedure, ERCP volumes have nevertheless risen over the past 10-15 years in the United States (US).[5, 6] ERCP is performed across high- and low-volume centers, and by endoscopists of variable experience and specialties.[7] A steep learning curve during a specialized period of training results in an advanced skill set required to perform safe and effective ERCP.[8, 9]

While very effective overall,[10] ERCP is widely known to have the highest adverse event (AE) profile among all commonly performed endoscopic procedures, with a collective AE rate of >10%.[11] Common AEs include post-ERCP pancreatitis (PEP), bleeding, infection, cholecystitis, perforation, and cardiopulmonary events.[11, 12] PEP is the most common, with estimated rates of 5-10% in all-comers, approaching or exceeding 20% in higher-risk cases.[11-13] Despite an emphasis on training and quality, both the incidence of PEP and its associated mortality are rising in the US.[14] Rates of post-ERCP bleeding range between 0.3% and 2%.[15-17] Symptomatic post-ERCP infection (cholangitis with or without sepsis) is also a common AE following ERCP, with a reported range between 0.5% and 3%,[11] and is of particular interest in recent years given the rise of duodenoscope-related infections.[18-21]

ERCP AEs are commonly reported in studies of varying designs; however, few systematic reviews have synthesized available incidence rates of specific or overall AEs following ERCPs. A 2015 study synthesized the rates of PEP from randomized trials,[13] but their search is now nearly 8 years out of date. Furthermore, other adverse event rates were not considered, and observational studies were not included. Observational studies are a required element of understanding true population rates of AEs,[22, 23] given that the patient mixes therein are more representative of the actual patient population in clinical practice compared to the highly selected participants in randomized trials. Given the frequency with which these events occur and their significant burden on the healthcare system,[24, 25] it is crucial to obtain accurate, up-to-date data on which to base estimates of incidence. Furthermore, AE rates differ depending on clinically relevant patient- and procedure-related parameters, but pooled estimates of incidences within these subgroups are unavailable.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

These estimates could be important so that patients and endoscopists are aware of specific risks associated with each procedure. Therefore, we propose a systematic review and meta-analysis to determine the incidence of adverse events following ERCP, both overall and within clinically relevant patient- and procedure-related subgroups.

METHODS

Overview and Objectives

Our meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations.[26, 27] Our protocol has been registered on PROSPERO (CRD42020220221).

The primary objective will be to determine the pooled overall incidence of PEP in adult patients undergoing ERCP. The secondary objectives will be to determine the pooled incidences of post-ERCP bleeding, cholangitis, perforation, cholecystitis, sedation-related cardio-pulmonary events, unplanned healthcare encounters, and death, in addition to determining the rates of specific and overall adverse events within clinically relevant subgroups determined *a priori* and described below. No research ethics approval is required for this study given the lack of patient-specific data being collected.

Eligibility Criteria

Given the comprehensive nature of the study question and outcomes of interest, two separate electronic searches will be conducted, with studies captured within either search being eligible for inclusion in the overall systematic review. The first search will focus on randomized trials only, while the second search will also include observational studies. For the first search, a study will be included in the final review if it meets ALL of the following criteria: (1) it presents original data in the form of a randomized clinical trial (with any primary research question), (2) the interventional arm or control arm represents adult patients receiving ERCP, (3) it makes reference to the determination of overall or specific ERCP-related adverse event(s) as a primary or secondary outcome; (4) it reports the incidence of at least one post-ERCP adverse event (including any of PEP, bleeding, symptomatic infection or cholangitis, perforation, cholecystitis, sedation-related cardio-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

pulmonary events, death, or unplanned presentation to a healthcare facility within any follow-up period up to 30 days after the index procedure); (5) it is published in English; and (6) at least 75% of study patients received their ERCP in the year 2000 or later. The year 2000 was chosen as a cut-off so that only studies representative of the current 'era' of ERCP are included. For the first search, a study will be excluded from the review if (1) it is a conference abstract; or (2) if it reports data that overlaps with another study's patient population in part or in whole for the same outcome of interest. In the latter case, the study that includes the largest number of patients that had their ERCP conducted in the year 2000 or later will be included while any others are excluded.

For the second search, a study will be included in the final review if it meets ALL of the following criteria: (1) it is an observational study of any design; (2) its primary or secondary objective is to assess post-ERCP adverse event rates or outcomes in adults; (3) it reports the incidence of a specific post-ERCP adverse event, including any of the following: PEP, bleeding, symptomatic infection or cholangitis, perforation, cholecystitis, sedation-related cardio-pulmonary events, and unplanned presentation to a healthcare facility within 30 days of the index procedure; (4) it is published in English; and (5) at least 75% of study patients received their ERCP in the year 2000 or later. For the second search, a study will be excluded from the review if it meets ANY of the following criteria: (1) it is a case report; (2) it is a smaller study (fewer than 500 total study patients, with this threshold set to mitigate small study effects due to random error and to reduce the likelihood of including zero-event studies, which are problematic to meta-analyze); (3) it represents the experience of a single endoscopist; (4) it is a conference abstract; or (5) it reports data that overlaps with another study's patient population in part or in whole for the same outcome. In the latter case, the study that includes the largest number of patients that had their ERCP conducted in the year 2000 or later will be included while any others are excluded. Eligibility criteria for both aspects of the overall search strategy are summarized in **Table 1**.

Search Strategy and Terms

A comprehensive electronic search will be designed by a health research librarian and carried out in the electronic databases MEDLINE (Ovid), PubMed, CINAHL, EMBASE, Scopus, Web of Science, and Evidence Based Medicine (EBM) Reviews based on the eligibility criteria

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

detailed above, from inception of each data source to the search date. English language citations from 2000 or later will be included. A combination of Medical Subject Heading (MeSH) and free-text terms will be used along with spelling variations and synonyms to create the two search strategies outlined above. A detailed list of search terms is provided in **Table 2**, with a full search planning document provided in the **Supplementary Materials**.

Study Selection and Data Abstraction

All citations will be imported into DistillerSR (Evidence Partners, Ottawa, Canada) and any duplicate entries will be removed. Given the large volume of anticipated citations identified in the initial searches, 7 reviewers (KB, ZWM, JCD, JI, DEO, BM, AP) will be randomly assigned roughly equal numbers of citations and will independently screen titles and abstracts to identify citations for full-text review. A vote of 'both include' or 'both exclude' by any 2 of the 8 reviewers will be considered definitive. Discrepancies will be resolved by consensus of an *a priori* committee of study investigators (NF, YR, DRB). All included citations will then undergo independent duplicate full-text inclusion or exclusion by 2 reviewers (of the same pool of 8), with discrepancies again being resolved by consensus. Data will then be extracted into standardized abstraction forms in duplicate, with separate forms for each aspect of the search strategy. Forms will include authors, year of publication, study design, country(ies) in which the research was carried out, study setting, recruitment period, sample sizes, patient sex, age, and comorbidity, procedural indication(s), description of intervention(s), rates of adverse events (in absolute numbers and proportions), outcome definitions and follow-up periods. Data will be abstracted both on the patient level as well as the procedure level, as available. Relevant subgroups (**Table 3**) will also be abstracted.

Outcome Definitions

A particular challenge with pooling rates of ERCP AEs is that non-universal definitions of outcomes are employed across studies. Detailed study-specific outcome definitions will be abstracted to help address this issue. Outcome definitions will be compared against those described in the American Society for Gastrointestinal Endoscopy (ASGE) Lexicon.[28] Studies not reporting clear outcomes definitions or those employing non-lexicon definitions will be

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

flagged for sensitivity analyses. Study-specific mechanisms of outcome capture will also be abstracted so that these can be considered separately.[29]

Risk of Bias

Two authors will independently conduct risk of bias assessments for all included studies. Assessment of included randomized studies will be performed using the Cochrane Risk of Bias tool, version 2 (RoB 2),[29] while the quality of observational studies will be assessed using the ROBINS-I tool.[30] Discrepancies will be resolved by consensus.

Statistical Analysis, Subgroup and Sensitivity Analyses

We will perform DerSimonian and Laird random effects meta-analyses to report the pooled incidence rates of individual post-ERCP AEs along with 95% confidence intervals (CIs). Incidence rates from observational studies and randomized trials will be pooled separately (at no point being combined). Subgroup analyses will be performed using relevant study-, procedure- and patient-related characteristics selected *a priori*. These are summarized in **Table 3**. Sources of heterogeneity will also be tested by performing meta-regression. To determine whether adverse event rates have changed over time, we will perform subgroup analyses based on the median dates of data collection in individual studies for each type of adverse event. Median data collection will be assigned a single value per study and studies will be separated into three periods: a) 2000-2009, b) 2010-2014, and c) 2015-present. Meta-regression will be performed to determine whether there are any significant differences in specific or overall AE rates between periods. Periods were chosen based on the 2012 publication of the seminal manuscript on rectal non-steroidal anti-inflammatory agents to prevent PEP[31] and a 3-year lag period between study dissemination and clinical practice adoption.

We will also conduct a series of sensitivity analyses whereby studies of varying quality as per ROBINS-I and RoB 2 are considered separately and whereby studies employing non-ASGE-lexicon AE definitions will be considered separately. Inter-study heterogeneity will be assessed using the Cochrane I^2 statistic. Publication bias will be assessed by visual inspection of funnel plots in addition to performing Egger's and Begg's tests.[32, 33] The statistical packages Revman 5.1 (Cochrane Collaboration) and Stata 14.0

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

(StataCorp) will be used for all analyses. The strength of the body of evidence will then be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.[34]

Patient and Public Involvement

No patients or public involved.

DISCUSSION

This systematic review and meta-analysis will provide up-to-date estimates of incidences of the most common adverse events associated with the performance of ERCP. Though ERCP in 2020 is primarily a therapeutic procedure, with minimal diagnostic indications, it remains one of the most commonly performed endoscopic procedures in the US and world-wide, with volumes having increased over time.[5, 6] Even though ERCP is a relatively safe procedure overall, AEs are more prevalent with its performance than any other endoscopic procedure. Thus, it behooves endoscopists performing ERCP to be acutely aware of the most precise and up-to-date estimates of risk possible. If possible, patient- and procedure-specific estimates of risk should also be ascertained, which is also a goal of the proposed study. Obtaining these estimates could help set up appropriate patient expectations of risk and could also serve to optimize the peri-procedural management of ERCP patients.

Specific knowledge gaps are particularly important to bridge regarding ERCP AEs. In particular, accurate estimates of the rate of post-ERCP symptomatic infections (cholangitis or sepsis) are particularly important given the growing concerns around duodenoscope-related infections.[18-21] Obtaining accurate estimates of the overall burden of post-ERCP infection is the first step toward describing the relatively smaller infection risk attributable directly to duodenoscope contamination and transmission. Similarly, estimates of post-sphincterotomy and/or post-sphincteroplasty bleeding are variable,[15-17] and no pooled estimates to date are available. With regards to rarer AEs such as cholecystitis and perforation, evidence is even more scarce. Thus, an urgent but unmet need is present to accurately define the overall and specific AE profile associated with ERCP.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Though this protocol was designed to limit sources of bias through rigorous methodology, there are nevertheless potential limitations that require acknowledgment. As with any meta-analysis, the certainty of pooled estimates is limited by the quality of input studies. With this topic in particular, it is anticipated that study cohorts will be described using variable levels of detail regarding demographics, comorbidities, procedural indications, and procedural interventions. To mitigate this, we divided our study into two main analyses; the first, inclusive of randomized controlled trials, is expected to be more granular in terms of these details and is thus expected to yield more robust patient- and procedure-specific estimates of risk. The second, inclusive of only large observational studies, is expected to yield more pragmatic 'real-world' estimates of risk. For this analysis, a pre-set cutoff point of 500 patients was chosen to mitigate small study effects.

Another limitation of our approach is the possibility of pooling outcome estimates using variable definitions of outcomes across studies. To mitigate this, we will abstract study-specific outcome definitions and perform sensitivity analyses whereby studies with unclear or absent definitions are separately analyzed. Even with this approach, we expect there to be some degree of (acceptable) variability between study definitions, but we will compare study-specific definitions against the ASGE Lexicon's AE definitions[28] to ensure that we only pool studies adhering to minimal thresholds for attribution of AEs. For instance, for post-ERCP bleeding, we will ensure that at minimum, studies require a hemoglobin drop of > 2 g as part of their definition, in order to prevent inclusion of patients with intraprocedural or non-clinically-significant post-procedural bleeding, which has been demonstrated to be of limited consequence.[12] Another limitation includes missing studies due to our decision to restrict our inclusions to English studies with the majority of data collected after the year 2000. While this is a valid concern, we felt it was more important to capture evidence most representative of current practices, techniques and technologies. Therefore, studies with a significant volume of study procedures performed prior to the year 2000 were deemed to be at risk of not representing current ERCP practice. Finally, we have made the decision to exclude conference abstracts from our study. Though this potentially disposes to publication bias, we feel that the unclear or ambiguous methodology often available from conference abstracts would add to potential study heterogeneity.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Overall, despite these limitations, we anticipate that our study will bridge important knowledge gaps pertaining to ERCP-associated adverse events. Our results could potentially improve patient care and satisfaction by providing more detailed and up-to-date estimates of ERCP-related risk. Accurate AE estimates will also facilitate the design of future prospective ERCP studies including randomized trials and could potentially have meaningful implications on training and practice standards.

For peer review only

Table 1. Eligibility criteria for both aspects of the overall search strategy.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

	Inclusion criteria	Exclusion criteria
Search Aspect 1	• original data • randomized controlled trial (with any research question) • interventional OR control arm of RCT represents adult patients receiving ERCP • an adverse event is a primary and/or secondary outcome	• non-English publication • data overlaps with data from another study (in part or in whole) • over 25% of study procedures performed prior to 2000 • conference abstract
Search Aspect 2	• original data • observational study (prospective or retrospective) • reports on adult patients receiving ERCP • primary or secondary objective of study is determination of ERCP adverse event(s)	• small cohort of patients (fewer than 500) • represents the experience of a single endoscopist • non-English publication • data overlaps with data from another study (in part or in whole) • over 25% of study procedures performed prior to 2000 • conference abstract

RCT, randomized controlled trial; ERCP, endoscopic retrograde cholangiopancreatography.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Table 2. Summary of electronic database search terms.*

Search Aspect 1: Randomized Controlled Trials
(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to RCTs (ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to RCTs
Search Aspect 2: Observational Studies
(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to cohort/observational studies (ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to cohort/observational studies

*Full electronic search strategy provided in **Supplementary Materials**.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Table 3. Planned subgroup analyses.

Category	Subgroups
Patient demographics and characteristics	• Female versus male sex • Age < 50 versus ≥ 50 • Inpatient versus outpatient status • Degree of comorbidity (Charlson Comorbidity Index or other, TBD) • Underlying primary sclerosing cholangitis • Liver transplant status • Presence of antiplatelet or anticoagulant medications • Presence versus absence of PEP prophylaxis
Practice settings	• Academic institutions versus community practices • Low-volume versus high-volume centers and/or endoscopists (cutoff points TBD)
Procedural indications	• Pancreatic versus biliary indications • Choledocholithiasis (suspected or confirmed) • Malignant obstruction • Benign obstruction
Intra-procedural techniques	• Sphincterotomy • Sphincteroplasty • Pre-cut sphincterotomy • Needle knife papillotomy • Biliary stent placement • Mechanical lithotripsy • Cholangioscopy and/or pancreatoscopy • Pancreatic versus common bile duct cannulation
Study methodology	• North American versus European versus Asian-Pacific • Study publication date • Median data collection date (2000-2009, 2010-2014, 2015-present) • Study design (retrospective versus prospective observational versus randomized controlled trial) • ASGE Lexicon versus non-lexicon definition(s) of outcomes

PEP, post-ERCP pancreatitis; TBD, to be determined; ASGE, American Society for Gastrointestinal Endoscopy.

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

REFERENCES

[1] Maple JT, Ikenberry SO, Anderson MA, et al. The role of endoscopy in the management of choledocholithiasis. Gastrointest Endosc 2011;74:731-44.

[2] Adler DG, Baron TH, Davila RE, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. Gastrointest Endosc 2005;62:1-8.

[3] Anderson MA, Appalaneni V, Ben-Menachem T, et al. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointest Endosc 2013;77:167-74.

[4] Chandrasekhara V, Chathadi KV, Acosta RD, et al. The role of endoscopy in benign pancreatic disease. Gastrointest Endosc 2015;82:203-14.

[5] Kröner PT, Bilal M, Samuel R, et al. Use of ERCP in the United States over the past decade. Endosc Int Open 2020;8:E761-e769.

[6] Ahmed M, Kanotra R, Savani GT, et al. Utilization trends in inpatient endoscopic retrograde cholangiopancreatography (ERCP): A cross-sectional US experience. Endosc Int Open 2017;5:E261-e271.

[7] Testoni PA, Mariani A, Giussani A, et al. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. Am J Gastroenterol 2010;105:1753-61.

[8] Wani S, Keswani RN, Han S, et al. Competence in Endoscopic Ultrasound and Endoscopic Retrograde Cholangiopancreatography, From Training Through Independent Practice. Gastroenterology 2018;155:1483-1494.e7.

[9] Wani S, Han S, Simon V, et al. Setting minimum standards for training in EUS and ERCP: results from a prospective multicenter study evaluating learning curves and competence among advanced endoscopy trainees. Gastrointest Endosc 2019;89:1160-1168.e9.

[10] Mariani A, Segato S, Anderloni A, et al. Prospective evaluation of ERCP performance in an Italian regional database study. Dig Liver Dis 2019;51:978-984.

[11] Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc 2017;85:32-47.

[12] Rustagi T, Jamidar PA. Endoscopic retrograde cholangiopancreatography-related adverse events: general overview. Gastrointest Endosc Clin N Am 2015;25:97-106.

[13] Kochar B, Akshintala VS, Afghani E, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc 2015;81:143-149.e9.

[14] Mutneja H, Vohra I, Go A, et al. Temporal Trends and Mortality of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis in the United States: A Nationwide Analysis. Endoscopy 2020.

[15] Cotton PB, Garrow DA, Gallagher J, et al. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.

[16] Christensen M, Matzen P, Schulze S, et al. Complications of ERCP: a prospective study. Gastrointest Endosc 2004;60:721-31.

[17] Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

[18] Preventable tragedies: Superbugs and How Ineffective Monitoring of Medical Device Safety Fails Patients In: U.S. Senate Health E, Labor, and Pensions Committee, ed, 2016.
[19] Muscarella LF. Risk of transmission of carbapenem-resistant Enterobacteriaceae and related "superbugs" during gastrointestinal endoscopy. World J Gastrointest Endosc 2014;6:457-74.
[20] Humphries RM, McDonnell G. Superbugs on Duodenoscopes: the Challenge of Cleaning and Disinfection of Reusable Devices. J Clin Microbiol 2015;53:3118-25.
[21] Forbes N, Heitman S, McCulloch P. Infection Control in ERCP: a Human Factors Perspective. Clin Transl Gastroenterol 2020;11:e00214.
[22] Page MJ, McKenzie JE, Kirkham J, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. Cochrane Database Syst Rev 2014:Mr000035.
[23] Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLoS Med 2011;8:e1001026.
[24] Fagenholz PJ, Fernández-del Castillo C, Harris NS, et al. Direct medical costs of acute pancreatitis hospitalizations in the United States. Pancreas 2007;35:302-7.
[25] Inamdar S, Sejpal DV, Ullah M, et al. Weekend vs. Weekday Admissions for Cholangitis Requiring an ERCP: Comparison of Outcomes in a National Cohort. Am J Gastroenterol 2016;111:405-10.
[26] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[27] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000;283:2008-12.
[28] Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446-54.
[29] Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions, 2011.
[30] Sterne J, Hernan M, Reeves B, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
[31] Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.
[32] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629-34.
[33] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
[34] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Supplementary Materials – Search Planning Document

Keywords

Concept	Synonym
ERCP	ERCP [Keyword]; "endoscopic retrograde cholangiopancreatography" [Keyword]; cholangiopancreatography, endoscopic retrograde [MeSH]
Adverse Events	"adverse event*" [Keyword]; "adverse effect*" [Keyword]; "adverse reaction*" [Keyword]; long term adverse effects [MeSH]; "post-ERCP pancreatitis" [Keyword]; "post-endoscopic retrograde cholangiopancreatography pancreatitis" [Keyword]; pancreatitis [Keyword, MeSH]; hemorrhage [Keyword, MeSH]; haemorrhage [Keyword]; cholangitis [Keyword, MeSH]; bleeding [Keyword]; infection* [Keyword]; infections [MeSH]; cholecystitis [Keyword, MeSH]; perforation [Keyword]; cardiopulmonary [Keyword]; sepsis [Keyword, MeSH]; complication* [Keyword]; unplanned [Keyword]; event* [Keyword]; sedation [Keyword]; cholecystectomy [Keyword, MeSH]; choledocholithiasis [Keyword, MeSH]; "risk factor*" [Keyword]; risk factors [MeSH]; "postoperative complication*" [Keyword]; postoperative complications [MeSH]; "treatment outcome*" [Keyword]; treatment outcome [MeSH]; inflammation [Keyword, MeSH]; rupture [Keyword, MeSH];
RCTs*	RCT [Keyword]; "randomized controlled trial*" [Keyword]; randomized controlled trial [MeSH]; randomized controlled trials as topic [MeSH]; "clinical trial*" [Keyword]; clinical trial [MeSH]; clinical trials as topic [MeSH]
Cohort/Observational Studies*	"observational study" [Keyword, MeSH]; "cohort study" [Keyword]; cohort studies [MeSH]

*a combination of MeSH headings, publication types, and methodological search filters, https://guides.library.ualberta.ca/health-sciences-search-filters/study-type-filters will be used

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Suggested Search Strings

Search Aspect #1: RCTs

(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to RCTs

(ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to RCTs

Search Aspect #2: Cohort/Observational Studies

(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to cohort/observational studies

(ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to cohort/observational studies

MEDLINE (Ovid) Search Strategy

1. ERCP.ab,ti.
2. "endoscopic retrograde cholangiopancreatography".ab,ti.
3. exp Cholangiopancreatography, Endoscopic Retrograde/
4. 1 or 2 or 3
5. "adverse event* ".ab,ti.
6. "adverse effect* ".ab,ti.
7. "adverse reaction* ".ab,ti.
8. exp Long Term Adverse Effects/
9. "post-ERCP pancreatitis".ab,ti.
10. "post-endoscopic retrograde cholangiopancreatography pancreatitis".ab,ti.
11. pancreatitis.ab,ti.
12. exp Pancreatitis/
13. exp Hemorrhage/
14. hemorrhage.ab,ti.
15. haemorrhage.ab,ti.
16. cholangitis.ab,ti.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

17. exp Cholangitis/
18. bleeding.ab,ti.
19. "infection*".ab,ti.
20. exp Infections/
21. exp Cholecystitis/
22. cholecystitis.ab,ti.
23. perforation.ab,ti.
24. cardiopulmonary.ab,ti.
25. sepis.ab,ti.
26. exp Sepsis/
27. "complication*".ab,ti.
28. unplanned.ab,ti.
29. "event*".ab,ti.
30. sedation.ab,ti.
31. cholecystectomy.ab,ti.
32. exp Cholecystectomy/
33. exp Choledocholithiasis/
34. choledocholithiasis.ab,ti.
35. "risk factor* ".ab,ti.
36. exp Risk Factors/
37. "postoperative complication* ".ab,ti.
38. exp Postoperative Complications/
39. exp Treatment Outcome/
40. "treatment outcome* ".ab,ti.
41. inflammation.ab,ti.
42. rupture.ab,ti.
43. exp Inflammation/
44. exp Rupture/
45. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. randomized controlled trial.pt.
47. clinical trial.pt.
48. randomi?ed.ti,ab.
49. placebo.ti,ab.
50. dt.fs.
51. randomly.ti,ab.
52. trial.ti,ab.
53. groups.ti,ab.
54. or/46-53
55. animals/
56. humans/
57. 55 not (55 and 56)
58. 54 not 57
59. RCT.ab,ti.
60. "randomized controlled trial* ".ab,ti.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

61. "clinical trial* ".ab,ti.
62. exp Randomized Controlled Trial/
63. exp Randomized Controlled Trials as Topic/
64. exp Clinical Trial/
65. exp Clinical Trials as Topic/
66. 59 or 60 or 61 or 62 or 63 or 64 or 65
67. "observational study".ab,ti.
68. "cohort study".ab,ti.
69. exp Observational Study/
70. exp Cohort Studies/
71. 67 or 68 or 69 or 70
72. 4 and 45
73. limit 72 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial)
74. limit 72 to observational study
75. limit 4 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial)
76. limit 4 to observational study
77. 58 or 66
78. 4 and 77
79. 4 and 71
80. 75 or 78
81. 76 or 79
82. limit 80 to (english language and yr="2000 -Current")
83. limit 81 to (english language and yr="2000 -Current")
84. 72 and 77
85. 71 and 72
86. 73 or 84
87. 74 or 85
88. limit 86 to (english language and yr="2000 -Current")
89. limit 87 to (english language and yr="2000 -Current")
90. 82 or 83 or 88 or 89
91. remove duplicates from 90

Databases

MEDLINE (Ovid); PubMed; CINAHL; EMBASE; Scopus; Web of Science; Evidence-Based Medicine (EBM) Reviews

Limits

Language: English
Publication Date: 2000 – present

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 5
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	1
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
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)	5

bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only

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	5-6
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	Tables 1, 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
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
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	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9

For peer review only

http://bmjopen.bmj.com/ on April 20, 2021 by guest. Protected by copyright.

	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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.

For peer review only

bmjopen-2021-053662 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

BMJ Open

Adverse Events Associated with Endoscopic Retrograde Cholangiopancreatography: Protocol for a Systematic Review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-053302.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Jul-2021
Complete List of Authors:	Forbes, Nauzer; University of Calgary, Medicine Leontiadis, GI ; McMaster University, Vaska, Marcus; Alberta Health Services, Knowledge Resource Service; Elmunzer, B.; Medical University of South Carolina Yuan, Yuhong ; McMaster University, Bishay, Kirles; University of Calgary, Medicine Meng, Zhao Wu; University of Calgary, Medicine Iannuzzi, Jordan; University of Calgary, Medicine O'Sullivan, Dylan; University of Calgary, Medicine Mah, Brittany; University of Calgary, Medicine Partridge, Arun; University of Calgary, Medicine Henderson, Amanda; University of Calgary, Medicine Qureshi, Aatif; University of Calgary, Medicine Keswani, Rajesh; Northwestern University Feinberg School of Medicine Wani, Sachin; University of Colorado - Anschutz Medical Campus Bridges, Ronald; University of Calgary, Medicine Heitman, Steven; University of Calgary, Medicine Hilsden, Robert; University of Calgary, Medicine Ruan, Yibing; Alberta Health Services, Cancer Epidemiology and Prevention Research Brenner, Darren; University of Calgary Cumming School of Medicine, Oncology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Evidence based practice
Keywords:	Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Pancreatic disease < GASTROENTEROLOGY

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Adverse Events Associated with Endoscopic Retrograde Cholangiopancreatography: Protocol for a Systematic Review and Meta-analysis

Nauzer Forbes MD MSc[1,2], Grigorios I. Leontiadis MD PhD[3,4], Marcus Vaska MLIS[5], B. Joseph Elmunzer MD MSc[6], Yuhong Yuan PhD[4], Kirles Bishay MD[1,2], Zhao Wu Meng MD[1,2], Jordan Iannuzzi MD[1], Dylan E. O'Sullivan PhD[2,7], Brittany Mah BSc[1], Arun C.R. Partridge MD[1], Amanda M. Henderson BSc[1], Aatif Qureshi MD[1], Rajesh N. Keswani MD MS[8], Sachin Wani MD[9], Ronald J. Bridges MD[1], Steven J. Heitman MD MSc[1,2], Robert J. Hilsden MD PhD[1,2], Yibing Ruan PhD MPH[8,10], Darren R. Brenner PhD[2,8,10]

1. Department of Medicine, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB, Canada
2. Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada
3. Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, ON, Canada
4. Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada
5. Knowledge Resource Service, Alberta Health Services, Calgary, AB, Canada
6. Division of Gastroenterology and Hepatology, Medical University of South Carolina, Charleston, SC, USA
7. Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
8. Division of Gastroenterology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
9. Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
10. Department of Cancer Epidemiology and Prevention Research, Cancer Control Alberta, Alberta Health Services, Calgary, AB, Canada

Corresponding Author:

Nauzer Forbes, MD, MSc
Assistant Professor of Medicine
Division of Gastroenterology
University of Calgary
TRW 6D19, 3280 Hospital Drive NW
Calgary, AB T2N 4Z6
Tel: 403.592.5089 Fax: 403.592.5090
E-mail: nauzer.forbes@ucalgary.ca

AUTHOR CONTRIBUTIONS

- conception and design: NF, GIL
- analysis plan: NF, GIL, MV, YY, DEO, BJE, DRB
- drafting of the article: NF
- critical revision of the article for important intellectual content: NF, GIL, MV, BJE, YY, KB, ZWM, JI, DEO, BM, ACRP, AMH, AQ, RNK, SW, RJB, SJH, RJH, YR, DRB.
- final approval of the article: NF, GIL, MV, BJE, YY, KB, ZWM, JI, DEO, BM, ACRP, AMH, AQ, RNK, SW, RJB, SJH, RJH, YR, DRB.

DISCLOSURES/ CONFLICTS OF INTEREST

None relevant.

FUNDING

The N.B. Hershfield Chair in Therapeutic Endoscopy (Grant number not applicable – N/A).

WORD COUNT

236 (abstract); 2845 (main text).

KEYWORDS

ERCP; endoscopic retrograde cholangiopancreatography; adverse event; pancreatitis; hemorrhage; cholangitis.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

ABSTRACT

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is performed to diagnose and manage conditions of the biliary and pancreatic ducts. Though effective, it is associated with common adverse events (AEs). The purpose of this study is to systematically review ERCP AE rates and report up-to-date pooled estimates.

Methods and Analysis

A comprehensive electronic search will be conducted of relevant medical databases through November 10, 2020. A study team of eight data abstracters will independently determine study eligibility, assess quality, and abstract data in parallel, with any two concordant entries constituting agreement and with discrepancies resolved by consensus. The primary outcome will be the pooled incidence of post-ERCP pancreatitis (PEP), with secondary outcomes including post-ERCP bleeding, cholangitis, perforation, cholecystitis, death, and unplanned healthcare encounters (UHE). Secondary outcomes will also include rates of specific and overall adverse events within clinically relevant subgroups determined *a priori*. DerSimonian and Laird random effects models will be used to perform meta-analyses of these outcomes. Sources of heterogeneity will be explored via meta-regression. Subgroup analyses based on median dates of data collection across studies will be performed to determine whether AE rates have changed over time.

Ethics and Dissemination

Our protocol was registered on PROSPERO (CRD42020220221). Ethics approval is not required for this study as it is a planned meta-analysis of previously published data. Participant consent is similarly not required. Dissemination is planned via presentation at relevant conferences in addition to publication in peer-reviewed journals.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and Limitations of the Proposed Study

- Our meta-analysis will provide to up-to-date estimates of procedural risks associated with the performance of ERCP.
- A comprehensive search strategy will be employed to capture all relevant studies and answer our study question.
- The strength of the body of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.
- A limitation of our approach is the likelihood of pooling outcome estimates using variable definitions of outcomes across studies, which we will partially mitigate by performing sensitivity analyses based on outcome definitions.
- Though the decision to exclude conference abstracts potentially disposes to publication bias, we feel that the unclear or ambiguous methodology often available from conference abstracts would add to potential study heterogeneity.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential and commonly performed advanced endoscopic procedure used in the diagnosis and treatment of several categories of biliary and pancreatic pathology.[1-4] Although the role of standard ERCP has transitioned to that of a primarily therapeutic procedure, ERCP volumes have nevertheless risen over the past 10-15 years in the United States (US).[5, 6] ERCP is performed across high- and low-volume centers, and by endoscopists of variable experience and specialties.[7] A steep learning curve during a specialized period of training results in an advanced skill set required to perform safe and effective ERCP.[8, 9]

While very effective overall,[10] ERCP is widely known to have the highest adverse event (AE) profile among all commonly performed endoscopic procedures, with a collective AE rate of >10%.[11] Common AEs include post-ERCP pancreatitis (PEP), bleeding, infection, cholecystitis, perforation, and cardiopulmonary events.[11, 12] PEP is the most common, with estimated rates of 5-10% in all-comers, approaching or exceeding 20% in higher-risk cases.[11-13] Despite an emphasis on training and quality, both the incidence of PEP and its associated mortality are rising in the US.[14] Rates of post-ERCP bleeding range between 0.3% and 2%.[15-17] Symptomatic post-ERCP infection (cholangitis with or without sepsis) is also a common AE following ERCP, with a reported range between 0.5% and 3%,[11] and is of particular interest in recent years given the rise of duodenoscope-related infections.[18-21]

ERCP AEs are commonly reported in studies of varying designs; however, few systematic reviews have synthesized available incidence rates of specific or overall AEs following ERCPs. A 2015 study synthesized the rates of PEP from randomized trials,[13] but their search is now nearly 8 years out of date. Furthermore, other adverse event rates were not considered, and observational studies were not included. Observational studies are a required element of understanding true population rates of AEs,[22, 23] given that the patient mixes therein are more representative of the actual patient population in clinical practice compared to the highly selected

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only

participants in randomized trials. Given the frequency with which these events occur and their significant burden on the healthcare system,[24, 25] it is crucial to obtain accurate, up-to-date data on which to base estimates of incidence. Furthermore, AE rates differ depending on clinically relevant patient- and procedure-related parameters, but pooled estimates of incidences within these subgroups are largely unavailable. These estimates could be important so that patients and endoscopists are aware of specific risks associated with each procedure.

Prior meta-analyses on this topic have focused only on pediatric patients[26] or instead on specific AEs or specific patient subgroups.[13, 27, 28] Therefore, we propose an up-to-date, comprehensive, and methodologically rigorous systematic review and meta-analysis to determine the incidence of adverse events following ERCP in adult patients, both overall and within clinically relevant patient- and procedure-related subgroups.

METHODS

Overview and Objectives

Our meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations.[29, 30]

The primary objective will be to determine the pooled overall incidence of PEP (the primary outcome) in adult patients undergoing ERCP. The secondary objectives will be to determine the pooled incidences of post-ERCP bleeding, cholangitis, perforation, cholecystitis, death, and unplanned healthcare encounters, in addition to determining the rates of specific and overall adverse events within clinically relevant subgroups determined *a priori* and described below.

Eligibility Criteria

Given the comprehensive nature of the study question and outcomes of interest, two separate electronic searches will be conducted, with studies captured within either search being

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

eligible for inclusion in the overall systematic review. The first search will focus on randomized trials only, while the second search will also include observational studies. For the first search, a study will be included in the final review if it meets *all* of the following criteria: (1) it presents original data in the form of a randomized clinical trial (with any primary research question), (2) the interventional arm or control arm represents adult patients receiving ERCP, (3) it makes reference to the determination of overall or specific ERCP-related adverse event(s) as a primary or secondary outcome; (4) it reports the incidence of at least one post-ERCP adverse event (including any of PEP, bleeding, symptomatic infection or cholangitis, perforation, cholecystitis, death, or unplanned presentation to a healthcare facility within any follow-up period up to 30 days after the index procedure); (5) it is published in English; and (6) at least 75% of study patients received their ERCP in the year 2000 or later. The year 2000 was chosen as a cut-off so that only studies representative of the current 'era' of ERCP are included. For the first search, a study will be excluded from the review if (1) it is a conference abstract; or (2) if it reports data that overlaps with another study's patient population in part or in whole for the same outcome of interest. In the latter case, the study that includes the largest number of patients that had their ERCP conducted in the year 2000 or later will be included while any others are excluded.

For the second search, a study will be included in the final review if it meets *all* of the following criteria: (1) it is an observational study of any design; (2) its primary or secondary objective is to assess post-ERCP adverse event rates or outcomes in adults; (3) it reports the incidence of a specific post-ERCP adverse event, including any of the following: PEP, bleeding, symptomatic infection or cholangitis, perforation, cholecystitis, death, or unplanned presentation to a healthcare facility within 30 days of the index procedure; (4) it is published in English; and (5) at least 75% of study patients received their ERCP in the year 2000 or later. For the second search, a study will be excluded from the review if it meets *any* of the following criteria: (1) it is a case report; (2) it is a smaller study (fewer than 500 total study patients, with this threshold set to mitigate small study effects due to random error and to reduce the likelihood of including zero-

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

event studies, which are problematic to meta-analyze); (3) it represents the experience of a single endoscopist; (4) it is a conference abstract; or (5) it reports data that overlaps with another study's patient population in part or in whole for the same outcome. In the latter case, the study that includes the largest number of patients that had their ERCP conducted in the year 2000 or later will be included while any others are excluded. Eligibility criteria for both aspects of the overall search strategy are summarized in **Table 1**.

Search Strategy and Terms

A comprehensive electronic search will be designed by a health research librarian and carried out in the electronic databases MEDLINE (Ovid), PubMed, CINAHL, EMBASE, Scopus, Web of Science, and Evidence Based Medicine (EBM) Reviews based on the eligibility criteria detailed above, from inception of each data source to the search date of November 10, 2020. English language citations from 2000 or later will be included. A combination of Medical Subject Heading (MeSH) and free-text terms will be used along with spelling variations and synonyms to create the two search strategies outlined above. A detailed list of search terms is provided in **Table 2**, with a full search planning document provided in the **Supplementary Materials**.

Study Selection and Data Abstraction

All citations will be imported into DistillerSR (Evidence Partners, Ottawa, Canada) and any duplicate entries will be removed. Given the large volume of anticipated citations identified in the initial searches, 8 reviewers (KB, ZWM, JI, DEO, BM, ACRP, AMH, AQ) will be randomly assigned roughly equal numbers of citations. Assessments by the first 2 reviewers will be used for titles and abstracts to identify citations for potential full-text review. A vote of 'both include' or 'both exclude' by any 2 of the 8 reviewers will be considered definitive. Discrepancies will be resolved by consensus of an *a priori* committee of study investigators (NF, YR, DRB). All included citations will then undergo independent duplicate full-text abstraction by 2 reviewers (of the same pool of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

8), with discrepancies again being resolved by consensus. Data will then be extracted into standardized abstraction forms in duplicate, with separate forms for each aspect of the search strategy. Forms will include authors, year of publication, study design, country(ies) in which the research was carried out, study setting, recruitment period, sample sizes, patient sex, age, and comorbidity, procedural indication(s), relevant pre-procedural parameters (including imaging studies and bilirubin levels) description of intervention(s), rates of adverse events (in absolute numbers and proportions), outcome definitions and follow-up periods. Where possible, the severity of AEs will also be captured, including as an example mild, moderate, and severe pancreatitis according to the Atlanta classification,[31] so that pooled data can also be reported according to severity. Data will be abstracted both on the patient level as well as the procedure level, as available. Relevant subgroups (**Table 3**) will also be abstracted.

Outcome Definitions

A challenge with pooling rates of ERCP AEs is that non-universal definitions of outcomes are employed across studies. Detailed study-specific outcome definitions will be abstracted to help address this issue. Outcome definitions will be compared against those described in the American Society for Gastrointestinal Endoscopy (ASGE) Lexicon[32] and the European Society for Gastrointestinal Endoscopy (ESGE) Guideline.[33] Studies not reporting clear outcomes definitions or those employing non-guideline/lexicon definitions will be flagged for sensitivity analyses. Study-specific mechanisms of outcome capture will also be abstracted so that these can be considered separately.[34] For the primary outcome (PEP), the ASGE Lexicon definition requires typical pain with amylase or lipase greater than 3 times the upper limit of normal.[32]

Risk of Bias

Two authors will independently conduct risk of bias assessments for all included studies. Assessment of included randomized studies will be performed using the Cochrane Risk of Bias

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

tool, version 2 (RoB 2),[34] while the quality of observational studies will be assessed using the ROBINS-I tool.[35] Discrepancies will be resolved by consensus.

Statistical Analysis, Subgroup and Sensitivity Analyses

We will perform DerSimonian and Laird random effects meta-analyses to report the pooled incidence rates of individual post-ERCP AEs along with 95% confidence intervals (CIs). Study weights will be measured using the inverse variance method. Incidence rates from observational studies and randomized trials will be pooled separately (at no point being combined). Heterogeneity between studies will be assessed with the I^2 and χ^2 statistics. We will consider p values of <0.10 for the χ^2 statistic or an I^2 value >50% to indicate substantial heterogeneity, which will be further investigated with subgroup analyses. Subgroup analyses will be performed using relevant study-, procedure- and patient-related characteristics selected *a priori*. These are summarized in **Table 3**. In addition, sources of heterogeneity will also be tested by performing meta-regression on these *a priori* selected characteristics. We will examine the I^2 and adjusted R^2 statistics to estimate the fraction of heterogeneity accounted for by these characteristics.

To determine whether adverse event rates have changed over time, we will perform subgroup analyses based on the median dates of data collection in individual studies for each type of adverse event. Median data collection will be assigned a single value per study and studies will be separated into three periods: a) 2000-2009, b) 2010-2014, and c) 2015-present. Meta-regression will be performed to determine whether there are any significant differences in specific or overall AE rates between periods. Periods were chosen based on the 2012 publication of the seminal manuscript on rectal non-steroidal anti-inflammatory agents to prevent PEP[36] and a 3-year lag period between study dissemination and clinical practice adoption.

We will also conduct a series of sensitivity analyses whereby studies of varying quality as per ROBINS-I and RoB 2 are considered separately and whereby studies employing non-ASGE-lexicon AE definitions will be considered separately. Inter-study heterogeneity will be assessed

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

using the Cochrane I^2 statistic. Publication bias will be assessed by visual inspection of funnel plots in addition to performing Egger's and Begg's tests.[37, 38] The statistical packages Revman 5.1 (Cochrane Collaboration) and Stata 14.0 (StataCorp) will be used for all analyses. The strength of the body of evidence will then be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework.[39]

Patient and Public Involvement

No patients or public were involved in study design.

ETHICS AND DISSEMINATION

Our protocol was registered on PROSPERO (CRD42020220221). Ethics approval is not required for this study as it is a planned meta-analysis of previously published data. Participant consent is similarly not required. Dissemination is planned via presentation at relevant conferences in addition to publication in peer-reviewed journals.

DISCUSSION

This systematic review and meta-analysis will provide up-to-date estimates of incidences of the most common adverse events associated with the performance of ERCP. Though ERCP in 2020 is primarily a therapeutic procedure, with minimal diagnostic indications, it remains one of the most commonly performed endoscopic procedures in the US and world-wide, with volumes having increased over time.[5, 6] Even though ERCP is a relatively safe procedure overall, AEs are more prevalent with its performance than any other endoscopic procedure. Thus, it behooves endoscopists performing ERCP to be acutely aware of the most precise and up-to-date estimates of risk possible. If possible, patient- and procedure-specific estimates of risk should also be ascertained, which is also a goal of the proposed study. Obtaining these estimates could help set

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

up appropriate patient expectations of risk and could also serve to optimize the peri-procedural management of ERCP patients.

Specific knowledge gaps are particularly important to bridge regarding ERCP AEs. In particular, accurate estimates of the rate of post-ERCP symptomatic infections (cholangitis or sepsis) are particularly important given the growing concerns around duodenoscope-related infections.[18-21] Obtaining accurate estimates of the overall burden of post-ERCP infection is the first step toward describing the relatively smaller infection risk attributable directly to duodenoscope contamination and transmission. Similarly, estimates of post-sphincterotomy and/or post-sphincteroplasty bleeding are variable,[15-17] and no pooled estimates to date are available. With regards to rarer AEs such as cholecystitis and perforation, evidence is even more scarce. Thus, an urgent but unmet need is present to accurately define the overall and specific AE profile associated with ERCP.

Though this protocol was designed to limit sources of bias through rigorous methodology, there are nevertheless potential limitations that require acknowledgment. As with any meta-analysis, the certainty of pooled estimates is limited by the quality of input studies. With this topic in particular, it is anticipated that study cohorts will be described using variable levels of detail regarding demographics, comorbidities, procedural indications, and procedural interventions. To mitigate this, we divided our study into two main analyses; the first, inclusive of randomized controlled trials, is expected to be more granular in terms of these details and is thus expected to yield more robust patient- and procedure-specific estimates of risk. The second, inclusive of only large observational studies, is expected to yield more pragmatic 'real-world' estimates of risk. For this analysis, a pre-set cutoff point of 500 patients was chosen to mitigate small study effects. The 'delta', or gap between these two types of estimates, will also be a crucial aspect of our findings that we plan on discussing as it relates to implications on evidence interpretation and on clinical practice.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Another limitation of our approach is the possibility of pooling outcome estimates using variable definitions of outcomes across studies. To mitigate this, we will abstract study-specific outcome definitions and perform sensitivity analyses whereby studies with unclear or absent definitions are separately analyzed. Even with this approach, we expect there to be some degree of (acceptable) variability between study definitions, but we will compare study-specific definitions against the ASGE Lexicon's AE definitions[32] to ensure that we only pool studies adhering to minimal thresholds for attribution of AEs. For instance, for post-ERCP bleeding, we will ensure that at minimum, studies require a hemoglobin drop of > 2 g as part of their definition, in order to prevent inclusion of patients with intraprocedural or non-clinically-significant post-procedural bleeding, which has been demonstrated to be of limited consequence.[12] Another limitation includes missing studies due to our decision to restrict our inclusions to English studies with the majority of data collected after the year 2000. While this is a valid concern, we felt it was more important to capture evidence most representative of current practices, techniques and technologies. Therefore, studies with a significant volume of study procedures performed prior to the year 2000 were deemed to be at risk of not representing current ERCP practice. Finally, we have made the decision to exclude conference abstracts from our study. Though this potentially disposes to publication bias, we feel that the unclear or ambiguous methodology often available from conference abstracts would add to potential study heterogeneity.

Overall, despite these limitations, we anticipate that our study will bridge important knowledge gaps pertaining to ERCP-associated adverse events. Our results could potentially improve patient care and satisfaction by providing more detailed and up-to-date estimates of ERCP-related risk. Accurate AE estimates will also facilitate the design of future prospective ERCP studies including randomized trials and could potentially have meaningful implications on training and practice standards.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Table 1. Eligibility criteria for both aspects of the overall search strategy.

	Inclusion criteria	Exclusion criteria
Search Aspect 1	• original data • randomized controlled trial (with any research question) • interventional OR control arm of RCT represents adult patients receiving ERCP • an adverse event is a primary and/or secondary outcome	• non-English publication • data overlaps with data from another study (in part or in whole) • over 25% of study procedures performed prior to 2000 • conference abstract
Search Aspect 2	• original data • observational study (prospective or retrospective) • reports on adult patients receiving ERCP • primary or secondary objective of study is determination of ERCP adverse event(s)	• small cohort of patients (fewer than 500) • represents the experience of a single endoscopist • non-English publication • data overlaps with data from another study (in part or in whole) • over 25% of study procedures performed prior to 2000 • conference abstract

RCT, randomized controlled trial; ERCP, endoscopic retrograde cholangiopancreatography.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Table 2. Summary of electronic database search terms.*

Search Aspect 1: Randomized Controlled Trials
(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to RCTs (ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to RCTs
Search Aspect 2: Observational Studies
(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to cohort/observational studies (ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to cohort/observational studies

*Full electronic search strategy provided in **Supplementary Materials**.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3. Planned subgroup analyses.

Category	Subgroups
Patient demographics and characteristics	• Female versus male sex • Age < 50 versus ≥ 50 • Inpatient versus outpatient status • Degree of comorbidity (Charlson Comorbidity Index or other, TBD) • Underlying primary sclerosing cholangitis • Liver transplant status • Presence of antiplatelet or anticoagulant medications • Presence versus absence of PEP prophylaxis
Practice settings	• Academic institutions versus community practices • Low-volume versus high-volume centers and/or endoscopists (cutoff points TBD)
Procedural indications	• Pancreatic versus biliary indications • Choledocholithiasis (suspected or confirmed) • Malignant obstruction • Benign obstruction
Intra-procedural techniques	• Sphincterotomy • Sphincteroplasty • Pre-cut sphincterotomy • Needle knife papillotomy • Biliary stent placement • Mechanical lithotripsy • Cholangioscopy and/or pancreatoscopy • Pancreatic versus common bile duct cannulation
Study methodology	• North American versus European versus Asian-Pacific • Study publication date • Median data collection date (2000-2009, 2010-2014, 2015-present) • Study design (retrospective versus prospective observational versus randomized controlled trial) • ASGE Lexicon versus non-lexicon definition(s) of outcomes

PEP, post-ERCP pancreatitis; TBD, to be determined; ASGE, American Society for Gastrointestinal Endoscopy.

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

REFERENCES

1. Maple JT, Ikenberry SO, Anderson MA, et al. The role of endoscopy in the management of choledocholithiasis. Gastrointest Endosc 2011;74:731-44.
2. Adler DG, Baron TH, Davila RE, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. Gastrointest Endosc 2005;62:1-8.
3. Anderson MA, Appalaneni V, Ben-Menachem T, et al. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointest Endosc 2013;77:167-74.
4. Chandrasekhara V, Chathadi KV, Acosta RD, et al. The role of endoscopy in benign pancreatic disease. Gastrointest Endosc 2015;82:203-14.
5. Kroner PT, Bilal M, Samuel R, et al. Use of ERCP in the United States over the past decade. Endoscopy International Open 2020;8:E761.
6. Ahmed M, Kanotra R, Savani GT, et al. Utilization trends in inpatient endoscopic retrograde cholangiopancreatography (ERCP): A cross-sectional US experience. Endosc Int Open 2017;5:E261-e271.
7. Testoni PA, Mariani A, Giussani A, et al. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. Am J Gastroenterol 2010;105:1753-61.
8. Wani S, Keswani RN, Han S, et al. Competence in Endoscopic Ultrasound and Endoscopic Retrograde Cholangiopancreatography, From Training Through Independent Practice. Gastroenterology 2018;155:1483-1494.e7.
9. Wani S, Han S, Simon V, et al. Setting minimum standards for training in EUS and ERCP: results from a prospective multicenter study evaluating learning curves and competence among advanced endoscopy trainees. Gastrointest Endosc 2019;89:1160-1168.e9.
10. Mariani A, Segato S, Anderloni A, et al. Prospective evaluation of ERCP performance in an Italian regional database study. Dig Liver Dis 2019;51:978-984.
11. Chandrasekhara V, Khashab MA, Muthusamy VR, et al. Adverse events associated with ERCP. Gastrointest Endosc 2017;85:32-47.
12. Rustagi T, Jamidar PA. Endoscopic retrograde cholangiopancreatography-related adverse events: general overview. Gastrointest Endosc Clin N Am 2015;25:97-106.
13. Kochar B, Akshintala VS, Afghani E, et al. Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials. Gastrointest Endosc 2015;81:143-149.e9.
14. Mutneja H, Vohra I, Go A, et al. Temporal Trends and Mortality of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis in the United States: A Nationwide Analysis. Endoscopy 2020.
15. Cotton PB, Garrow DA, Gallagher J, et al. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointest Endosc 2009;70:80-8.
16. Christensen M, Matzen P, Schulze S, et al. Complications of ERCP: a prospective study. Gastrointest Endosc 2004;60:721-31.
17. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-18.
18. Preventable tragedies: Superbugs and How Ineffective Monitoring of Medical Device Safety Fails Patients In: U.S. Senate Health E, Labor, and Pensions Committee, ed, 2016.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

19. Muscarella LF. Risk of transmission of carbapenem-resistant Enterobacteriaceae and related "superbugs" during gastrointestinal endoscopy. World J Gastrointest Endosc 2014;6:457-74.
20. Forbes N, Heitman S, McCulloch P. Infection Control in ERCP: a Human Factors Perspective. Clin Transl Gastroenterol 2020;11:e00214.
21. Humphries RM, McDonnell G. Superbugs on Duodenoscopes: the Challenge of Cleaning and Disinfection of Reusable Devices. J Clin Microbiol 2015;53:3118-25.
22. Page MJ, McKenzie JE, Kirkham J, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. Cochrane Database Syst Rev 2014:Mr000035.
23. Golder S, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. PLoS Med 2011;8:e1001026.
24. Fagenholz PJ, Fernández-del Castillo C, Harris NS, et al. Direct medical costs of acute pancreatitis hospitalizations in the United States. Pancreas 2007;35:302-7.
25. Inamdar S, Sejpal DV, Ullah M, et al. Weekend vs. Weekday Admissions for Cholangitis Requiring an ERCP: Comparison of Outcomes in a National Cohort. Am J Gastroenterol 2016;111:405-10.
26. Usatin D, Fernandes M, Allen IE, et al. Complications of Endoscopic Retrograde Cholangiopancreatography in Pediatric Patients; A Systematic Literature Review and Meta-Analysis. J Pediatr 2016;179:160-165.e3.
27. Mashiana HS, Dhaliwal AS, Sayles H, et al. Endoscopic retrograde cholangiopancreatography in cirrhosis - a systematic review and meta-analysis focused on adverse events. World J Gastrointest Endosc 2018;10:354-366.
28. Iqbal U, Anwar H, Khan MA, et al. Safety and Efficacy of Endoscopic Retrograde Cholangiopancreatography in Nonagenarians: A Systematic Review and Meta-Analysis. Dig Dis Sci 2021.
29. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
30. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000;283:2008-12.
31. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
32. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446-54.
33. Dumonceau JM, Kapral C, Aabakken L, et al. ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2020;52:127-149.
34. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions, 2011.
35. Sterne J, Hernan M, Reeves B, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
36. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med 2012;366:1414-22.
37. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315:629-34.
38. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
39. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 2008;336:924-6.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

Supplementary Materials – Search Planning Document

Keywords

Concept	Synonym
ERCP	ERCP [Keyword]; "endoscopic retrograde cholangiopancreatography" [Keyword]; cholangiopancreatography, endoscopic retrograde [MeSH]
Adverse Events	"adverse event*" [Keyword]; "adverse effect*" [Keyword]; "adverse reaction*" [Keyword]; long term adverse effects [MeSH]; "post-ERCP pancreatitis" [Keyword]; "post-endoscopic retrograde cholangiopancreatography pancreatitis" [Keyword]; pancreatitis [Keyword, MeSH]; hemorrhage [Keyword, MeSH]; haemorrhage [Keyword]; cholangitis [Keyword, MeSH]; bleeding [Keyword]; infection* [Keyword]; infections [MeSH]; cholecystitis [Keyword, MeSH]; perforation [Keyword]; cardiopulmonary [Keyword]; sepsis [Keyword, MeSH]; complication* [Keyword]; unplanned [Keyword]; event* [Keyword]; sedation [Keyword]; cholecystectomy [Keyword, MeSH]; choledocholithiasis [Keyword, MeSH]; "risk factor*" [Keyword]; risk factors [MeSH]; "postoperative complication*" [Keyword]; postoperative complications [MeSH]; "treatment outcome*" [Keyword]; treatment outcome [MeSH]; inflammation [Keyword, MeSH]; rupture [Keyword, MeSH];
RCTs*	RCT [Keyword]; "randomized controlled trial*" [Keyword]; randomized controlled trial [MeSH]; randomized controlled trials as topic [MeSH]; "clinical trial*" [Keyword]; clinical trial [MeSH]; clinical trials as topic [MeSH]
Cohort/Observational Studies*	"observational study" [Keyword, MeSH]; "cohort study" [Keyword]; cohort studies [MeSH]

*a combination of MeSH headings, publication types, and methodological search filters, https://guides.library.ualberta.ca/health-sciences-search-filters/study-type-filters will be used

For peer review only

Suggested Search Strings

Search Aspect #1: RCTs

(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to RCTs

(ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to RCTs

Search Aspect #2: Cohort/Observational Studies

(ERCP OR "endoscopic retrograde cholangiopancreatography")→limit to cohort/observational studies

(ERCP OR "endoscopic retrograde cholangiopancreatography") AND ("adverse event*" OR "adverse effect*" OR "adverse reaction*" OR "post-ERCP pancreatitis" OR "post-endoscopic retrograde cholangiopancreatography pancreatitis" OR pancreatitis OR hemorrhage OR haemorrhage OR cholangitis OR bleeding OR infection* OR cholecystitis OR perforation OR cardiopulmonary OR sepsis OR complication* OR unplanned OR event* OR sedation OR cholecystectomy OR choledocholithiasis OR "risk factor*" OR "postoperative complication*" OR "treatment outcome*" OR inflammation OR rupture)→limit to cohort/observational studies

MEDLINE (Ovid) Search Strategy

1. ERCP.ab,ti.
2. "endoscopic retrograde cholangiopancreatography".ab,ti.
3. exp Cholangiopancreatography, Endoscopic Retrograde/
4. 1 or 2 or 3
5. "adverse event* ".ab,ti.
6. "adverse effect* ".ab,ti.
7. "adverse reaction* ".ab,ti.
8. exp Long Term Adverse Effects/
9. "post-ERCP pancreatitis".ab,ti.
10. "post-endoscopic retrograde cholangiopancreatography pancreatitis".ab,ti.
11. pancreatitis.ab,ti.
12. exp Pancreatitis/
13. exp Hemorrhage/
14. hemorrhage.ab,ti.
15. haemorrhage.ab,ti.
16. cholangitis.ab,ti.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

17. exp Cholangitis/
18. bleeding.ab,ti.
19. "infection*".ab,ti.
20. exp Infections/
21. exp Cholecystitis/
22. cholecystitis.ab,ti.
23. perforation.ab,ti.
24. cardiopulmonary.ab,ti.
25. sepis.ab,ti.
26. exp Sepsis/
27. "complication*".ab,ti.
28. unplanned.ab,ti.
29. "event*".ab,ti.
30. sedation.ab,ti.
31. cholecystectomy.ab,ti.
32. exp Cholecystectomy/
33. exp Choledocholithiasis/
34. choledocholithiasis.ab,ti.
35. "risk factor* ".ab,ti.
36. exp Risk Factors/
37. "postoperative complication* ".ab,ti.
38. exp Postoperative Complications/
39. exp Treatment Outcome/
40. "treatment outcome* ".ab,ti.
41. inflammation.ab,ti.
42. rupture.ab,ti.
43. exp Inflammation/
44. exp Rupture/
45. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. randomized controlled trial.pt.
47. clinical trial.pt.
48. randomi?ed.ti,ab.
49. placebo.ti,ab.
50. dt.fs.
51. randomly.ti,ab.
52. trial.ti,ab.
53. groups.ti,ab.
54. or/46-53
55. animals/
56. humans/
57. 55 not (55 and 56)
58. 54 not 57
59. RCT.ab,ti.
60. "randomized controlled trial* ".ab,ti.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

61. "clinical trial* ".ab,ti.
62. exp Randomized Controlled Trial/
63. exp Randomized Controlled Trials as Topic/
64. exp Clinical Trial/
65. exp Clinical Trials as Topic/
66. 59 or 60 or 61 or 62 or 63 or 64 or 65
67. "observational study".ab,ti.
68. "cohort study".ab,ti.
69. exp Observational Study/
70. exp Cohort Studies/
71. 67 or 68 or 69 or 70
72. 4 and 45
73. limit 72 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial)
74. limit 72 to observational study
75. limit 4 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial protocols as topic or clinical trial or controlled clinical trial or randomized controlled trial)
76. limit 4 to observational study
77. 58 or 66
78. 4 and 77
79. 4 and 71
80. 75 or 78
81. 76 or 79
82. limit 80 to (english language and yr="2000 -Current")
83. limit 81 to (english language and yr="2000 -Current")
84. 72 and 77
85. 71 and 72
86. 73 or 84
87. 74 or 85
88. limit 86 to (english language and yr="2000 -Current")
89. limit 87 to (english language and yr="2000 -Current")
90. 82 or 83 or 88 or 89
91. remove duplicates from 90

Databases

MEDLINE (Ovid); PubMed; CINAHL; EMBASE; Scopus; Web of Science; Evidence-Based Medicine (EBM) Reviews

Limits

Language: English
Publication Date: 2000 – present

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

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	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 5
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	1
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	1
Sponsor	5b	Provide name for the review funder and/or sponsor	1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
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)	5

For peer review only

/bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.

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	5-6
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	Tables 1, 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
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
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	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	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)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9

bmjopen-2021-053302 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2021 by guest. Protected by copyright.

For peer review only

	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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.

For peer review only

bmjopen-2021-053662 on 17 August 2021. Downloaded from http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.