Efficacy and safety of modified-release paracetamol for acute and chronic pain: a systematic review protocol

Zeljana Margan Koletic,1 Svjetlana Dosenovic,2 Livia Puljak3

ABSTRACT
Introduction Paracetamol (acetaminophen) is widely used for management of mild-to-moderate pain and reduction of fever. It is available as immediate release (IR) and modified-release (MR) formulation. In 2017, European Medicines Agency recommended a suspension of marketing of MR paracetamol in the European Union. Benefit-risk balance of these products has been assessed as negative as data showed that existing procedures for overdose management may not be efficient. Since MR paracetamol is still available in other countries (Australia and USA) and there is no available systematic review (SR) of efficacy and safety of MR paracetamol in the literature, we have decided to perform one to evaluate available data from randomised clinical trials (RCTs).

Methods and analysis Using predefined search criteria, we will search EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform to identify RCTs evaluating efficacy and safety of MR paracetamol alone in any dose or duration for any pain. Participants are defined as adults and adolescents (over 12 years). Primary efficacy outcomes will be pain intensity, pain relief and sleep. Primary safety outcomes will be the number of patients experiencing any (serious) adverse event, the number of patients withdrawn due to adverse events and the number of patients experiencing any (serious) adverse event, the number of patients withdrawn due to adverse events and the number of patients experiencing any (serious) adverse event. Data analysis will be subdivided based on different clinical syndromes. Meta-analysis will be conducted if possible. Cochrane risk of bias (RoB) tool with seven dimensions will be used to assess RoB of individual studies.

Ethics and dissemination This SR will include only data collected from trial reports; therefore, an ethical approval will not be sought. We will publish the protocol and our findings in peer-reviewed journals.

PROSPERO registration number CRD42018115769.

INTRODUCTION
Rationale Paracetamol (known as acetaminophen in USA) is used alone for management of mild-to-moderate pain in patients ≥2 years of age or in combination with opioids for management of moderate-to-severe pain in patients ≥2 years. It is also used for temporary reduction of fever. Paracetamol-containing products are available for oral, rectal and parenteral use, both as over-the-counter and prescription medicines.1

Besides immediate release (IR) formulations for oral use, such as tablets, oral suspensions and effervescent tablets, there are modified-release (MR) formulations of paracetamol available as well. In the literature, depending on the authors, MR formulations are sometimes also referred to as prolonged-release (PR), slow-release/sustained-release, controlled-release, delayed or extended-release (ER) formulations, and they were developed to ensure longer duration of action and pain relief.2–4

Independently of the formulation, the main safety concern related to paracetamol use is its hepatotoxic effect, especially when used in doses above those clinically recommended (≥4g/day in adults).5 6 Depending on patients’ risk factors, ingested amount and management of overdose, ingestion of paracetamol can cause acute liver failure, sometimes resulting in liver transplant and death.7 8 Risk assessment is based on amount of ingested paracetamol in mg/kg and time elapsed since ingestion. Some studies indicate that existing overdose treatment guidelines...
are not applicable if patients ingested MR paracetamol containing products.9

Although paracetamol is effective in acute pain, data indicate it is somewhat less effective than non-steroidal anti-inflammatory drugs (NSAIDs).10 Also, some published studies show its modest efficacy for certain types of chronic pain, such as low back pain or pain in arthritis11 and osteoarthritis.12 13

In 2017, European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) recommended a suspension of marketing authorisation of MR paracetamol containing products. This decision was reached after detailed review through a referral procedure conducted by PRAC concluded that benefits of these products are outweighed by the risks related to overdose, especially management of overdose.14

Given the European Union recommendation regarding benefit risk ratio (BRR) of medicines containing MR paracetamol as well as lack of high-level evidence synthesis in literature, we aim to conduct a systematic review (SR) of randomised controlled trials (RCTs) that have assessed efficacy and safety of the MR paracetamol.

**Objective**
The objective of this SR is to evaluate available data from RCTs about efficacy and safety of MR paracetamol compared to any other comparator(s) for acute and chronic pain in adults and adolescents (over 12 years of age).

**METHODS AND ANALYSIS**
This SR of the literature will be conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.15 For the development of SR protocol, Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 checklist was used.16 The systematic review is registered in International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018115769) and any subsequent changes to the protocol will be recorded there.17

**Patient and public involvement**
Design of this study protocol for an SR was done without patient or public involvement.

**Eligibility criteria**
Studies will be selected according to the below described criteria.

**Study designs**
RCTs investigating safety and efficacy of MR paracetamol containing medicines used as a pharmacological intervention for any type of acute or chronic pain will be included in this SR.

**Participants**
Participants are defined as adults and adolescents over 12 years of age receiving MR paracetamol products for any type of acute or chronic pain. Studies conducted in vitro or in animals will be excluded.

**Interventions**
We will consider studies where MR paracetamol containing medicines were used as an intervention. No restrictions regarding dose or duration of use will be applied. We will not include fixed-dose combination products or studies, which have used MR paracetamol in combination with any other intervention.

**Comparators**
Any type of pharmacological or non-pharmacological comparators will be eligible for inclusion. When analysing data, the extracted data will be divided into categories based on comparator used in the studies.

**Outcomes**
Primary efficacy outcomes will be pain intensity, pain relief and sleep. Primary safety outcomes will be the number of patients experiencing any adverse event, the number of patients experiencing any serious adverse event, the number of patients withdrawn from study due to adverse events, and the number of patients with gastrointestinal and hepatic adverse events.

Secondary outcomes will be physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment.

Outcome measures, number of participants and numerical data for each outcome will be extracted. If available, we will report the definition of the harm and seriousness used by each included study and if multiple events occurred in the same individuals.

**Setting**
We will extract data about setting, that is, whether patients were treated in the setting of primary, secondary, tertiary or community care setting.

**Language**
We will consider studies published in any language for inclusion. Studies in languages other than English will be translated. If translation will not be possible, we will include full references for those studies and report them transparently.

**Information sources**
To identify studies of interest, we will conduct a search of following electronic databases: EMBASE and MEDLINE via OVID and Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library from the start of indexing to the search date that will be defined after publication of the protocol.
To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.

**Selection of studies**

For ensuring consistency between reviewers, we will conduct calibration exercise for all methodological steps of the review process before proceeding to the independent assessment stages.

In the first phase of the literature screening two authors will independently screen bibliographic records (titles and abstracts) retrieved by database search according to the inclusion criteria. If not clear from the title or abstract, we will mark the record as maybe eligible, and

To complement the search, we will also search clinical trial registries ClinicalTrials.gov (www.clinicaltrials.gov) and WHO International Clinical Trials Registry Platform (www.who.int/ictrp/en/) and we will screen references and citations of included RCTs to potentially retrieve additional studies that were missed during the search and screening of electronic databases.

Search will be conducted by using predefined search strategies. We will contact first authors of selected studies if specific data are missing and authors of abstracts to retrieve a full manuscript if possible.

**Search strategy**

A combination of relevant keywords was used to construct search strategies shown in table 1. No search limits are going to be applied. We will use validated search filters for identifying RCTs in PubMed and EMBASE as recommended in the Cochrane Handbook for Systematic Reviews of Interventions. 19 We will consider studies published in any language for inclusion, however during selection process only studies conducted in humans will be included for further review.

Search results from all databases will be exported in the EndNote X9 library (Clarivate Analytics, New York, NY, USA) and duplicates removed via software and then manually. If we find duplicate publications, we will avoid including duplicates to avoid double counting. We will count multiple reports of a single study as one included study, and we will report details of such reports.
we will further verify for all records retained in the first screening phase whether inclusion criteria are met after the review of the full text in the next phase.

In the second phase of the literature screening, two authors will independently analyse full texts of all potentially relevant studies. Disagreements will be resolved by discussion leading to a consensus and involvement of the third author if necessary. We will record reasons for exclusion of studies analysed in full text.

In the third phase of screening, references and citations of included studies will be downloaded from Web of Science by two authors and they will screen them independently, in order to identify potential additional citations that may have been missed via database searching. We will contact corresponding authors for additional data if necessary.

A flow diagram of selection process developed according to the PRISMA guideline will be included as well (21).

Data extraction and management

Two authors will manually and independently extract data from included RCTs and insert extracted data into Microsoft Excel spreadsheet. For data presented as graphs or figures only, PlotDigitizer software will be used.20 21

We will contact corresponding authors if reported outcome data are not suitable for quantitative pooling in a meta-analysis.

Discrepancies will be resolved by discussion leading to a consensus, however if a consensus cannot be reached, the third author will be consulted.

Handling missing data

Corresponding authors of included RCTs will be contacted by emails (up to three times if not responding) to try to obtain clarifications and missing data, if necessary.

Risk of bias of individual studies

Cochrane risk of bias (RoB) tool, with seven dimensions, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selection outcome reporting and other potential threats to study validity will be used. We will assess RoB in line with instructions from the Cochrane Handbook for Systematic Reviews of Interventions22 to avoid mistakes review authors frequently make when conducting RoB assessments with this tool.23–27 For each study, we will create a RoB domain, which will have a RoB judgement for each domain (high, low or unclear risk) and an accompanying supporting comment to explain the RoB judgement. Two authors will assess RoB independently; discrepancies will be resolved via discussion or involvement of the third author if necessary.

Data synthesis

Data analysis will be subdivided based on acute versus chronic pain (defined as pain lasting 3 months or more). Chronic pain will be subdivided to chronic cancer pain and chronic non-cancer pain. Where applicable, we will also conduct analyses based on individual clinical pain syndromes.

Data that are measured with compatible measures, such as Visual Analogue scale and numerical rating scale for pain intensity, and outcome measures for pain reduction using the same percentage (ie, participant-reported pain relief of 30% or greater, over baseline; participant-reported pain relief of 50% or greater, over baseline) will be pooled together. Descriptive scales for pain will not be pooled with such scales.

If possible, meta-analysis will be conducted for outcomes that will be reported in more than one homogeneous RCT. Random-effect meta-analysis will be conducted using Cochrane RevMan V.5 software (The Cochrane Collaboration, 2014, The Nordic Cochrane Centre, Copenhagen, Denmark). Unit of analysis will be a randomised individual. If we find crossover study, we will extract data for the first period only. If not possible, narrative synthesis of the finding will be presented/data will be summarised descriptively.

We will report dichotomous data using risk ratio and risk difference with respective 95% confidence interval (CI). We will report continuous data using mean difference with 95% CI. We will assess heterogeneity by using the I² statistic in RevMan 5 in order to ensure that pooling of data will be valid. We will grade the degree of heterogeneity as: low, moderate and high, corresponding to the I² values of 25%, 50% and 75%, respectively. If we find substantial heterogeneity, we will explore its potential causes in subgroup and sensitivity analyses. The following a priori variables that may cause or explain heterogeneity, for which subgroup analyses will be conducted if there will be sufficient data available, are: (1) studies with high RoB (defined as studies with at least one judgement for high risk in the key RoB domains, and as key RoB domains we defined random sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcome assessors), (2) commercial funding and (3) different doses.

Sensitivity analysis will be conducted to explore the effect of studies with high RoB that will be judged as having high RoB in one or more of the following key domains: sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcome assessors.

We will use MedCalc (MedCalc, Mariakerke, Belgium) to analyse descriptive statistics if necessary. We will use Cochrane’s RevMan V.5 for data synthesis in an SR, if applicable.

Metabias(es)

RoB while conducting an SR will be minimised by using two duplicate authors for each crucial step in methodology.

If we will be able to pool more than 10 trials, we will create and examine a funnel plot to explore possible publication bias.
Ethics and dissemination
This SR will include only data collection from trial reports; therefore, an ethical approval will not be sought. We will publish the protocol and our findings in peer-reviewed journals.

Expected timeline
We registered our SR protocol in PROSPERO on 26 November 2018. First draft of this manuscript containing SR protocol was finalised on 7 February 2019 and submitted to the BMJ Open. The review did not progress any further from the draft protocol. We anticipate to start conducting the review only after receiving final reviewers’ comments.

Contributors
ZMK designed the systematic review protocol with the support of LP. ZMK prepared the first draft. SD and LP reviewed and revised the first draft. All authors read and approved the final protocol manuscript.

Funding
The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests
None declared.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc-4.0/.

REFERENCES
22. Barcot O, Boric M, Dosenovic S, et al. Risk of bias assessments for binding of participants and personnel in Cochrane reviews were frequently inadequate. J Clin Epidemiol 2019;113:S0895-4356(19)30275-6