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HEPATITIS C VIRUS INFECTION AND HOSPITAL-RELATED OUTCOMES: A SYSTEMATIC REVIEW PROTOCOL

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Keywords:	hepatitis C virus, hospital, acute care, protocol, systematic review

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ABSTRACT

Introduction: People living with hepatitis C virus (HCV) infection are disproportionately overrepresented in the healthcare system due to various individual and contextual circumstances, including comorbidities and socioeconomic marginalization. With growing trends in morbidity and mortality related to HCV infection, HCV is becoming a significant health and financial burden on the healthcare system, particularly in acute hospital settings. It is noteworthy that with the advent of direct-acting antiviral (DAA) therapy, the increasing number of patients who are cured of HCV could potentially result in different patterns of hospital-related outcomes over time.

Methods and analysis: We will conduct a systematic review of published literature to retrieve quantitative research articles pertaining to hospital outcomes among patients living with HCV. Primary outcomes include: hospitalization rates, length of stay, leaving against medical advice, readmission, and in-hospital mortality. In total, five databases will be searched (MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science). Titles, abstracts, and full-texts will be independently reviewed by two investigators in three separate stages. The methodological quality of included quantitative research studies will be assessed using a validated tool. Data from included articles will be extracted using a standardized form and synthesized in a narrative account.

Ethics and dissemination: Results of this systematic review could provide a better understanding on how to optimize health systems and services to improve patient outcomes and care. The results of this study may provide future research with a foundation to guide decision-making and for designing and implementing systems-level interventions to improve treatment and care delivery for people living with HCV. Ethical approval for this study was received by the University of British Columbia/Providence Health Care Research Ethics Board. Findings from this study will be disseminated through peer-reviewed publications, presentations, reports, and community forums

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Strengths and limitations of this study:

- This study will be the first to systematically assess the literature on the impact of HCV infection on hospital-related outcomes.
- All included articles will be assessed for methodological quality using a validated tool, the Downs and Black checklist.
- There may be some heterogeneity in the way that the main exposure, HCV infection, and the hospital-related outcomes are defined, which may bias individual studies.

INTRODUCTION

The harms associated with hepatitis C virus (HCV) constitute a major public health challenge globally. It is estimated that 71 million people are living with chronic HCV infection, with a significant proportion who are at high risk of developing advanced liver disease, cirrhosis, or liver cancer [1]. In fact, a review of the literature revealed that the risk of hepatocellular carcinoma increases up to 17-fold in patients living with chronic HCV compared to their HCV-negative counterparts [2,3]. If left untreated, approximately 399,000 people die annually from consequences associated with HCV, mostly from advanced liver disease and hepatocellular carcinoma [4–6]. According to national and international surveillance data, HCV-related deaths are at an all-time high, with more individuals dying as a result of HCV infection compared to all other notifiable conditions, including HIV and tuberculosis [1,7].

People living with chronic HCV infection are often overrepresented in the healthcare system [8,9]. Previous studies have demonstrated that these individuals are large users of inpatient, emergency department, and outpatient health services, which is likely a result of a number of individual and contextual circumstances, including comorbidities and socioeconomic marginalization [10,11]. For example, a national study conducted in the United States indicated that inpatient admissions among HCV-infected individuals born between 1945 and 1965 (i.e., baby boomers) increased by greater than 60% (2.6% in 2001 to 4.2% in 2010, $p < 0.001$) over a nine-year period [11]. The health burden on patients living with HCV infection is also increasing due to the

advancing age of this population, where most were infected as a result of nosocomial or iatrogenic practices in healthcare settings prior to the introduction of blood and organ screening [12]. Furthermore, an advancing age coincides with the slow progression of the infection's clinical manifestations [13]. There are also significant healthcare costs associated with increasing chronic HCV severity, with acute inpatient costs being the largest contributor to the financial burden on the health system [14].

In recent years, the advent of direct-acting antiviral based therapies has made controlling the HCV epidemic a realistic probability [15,16]. By extension, this would result in a significant reduction in hospital and health service utilization and would likely have a beneficial effect on the resource burden currently imposed on the health system. To date, there has been no explicit systematic review that has examined the impact of HCV infection on hospital-related outcomes, including hospital admission rates, length of stay, leaving hospital against medical advice, readmissions, and in-hospital mortality, and the potential impact of DAAs on these outcomes. Most of the previously reviewed literature has been focused on hospital outcomes among people living with HIV/AIDS, a population that overlaps significantly with people living with HCV infection due to shared transmission routes [17]. Therefore, the purpose of this systematic review is to comprehensively assess the literature on this topic to provide a better understanding on how to optimize health systems and services to improve patient outcomes and care.

METHODS AND ANALYSIS

Protocol and registration

This systematic review protocol conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (Additional File 1) and we will adhere to the PRISMA guidelines for the development of this systematic review [18,19]. This protocol has been registered in the PROSPERO database (CRD42017081082).

Research question

The proposed systematic review will aim to answer the following research question: what is the impact of HCV infection on hospital-related outcomes among adults?

Eligibility

The research question being addressed is best described by the population, exposure, and outcomes (PEO) framework: the population of interest will include adults greater than or equal to 18 years of age (at baseline); the exposure of interest will be acute or chronic HCV infection; the outcome of interest will be hospital-related outcomes, which will include the following: hospitalization; length of stay; leaving hospital against medical advice; readmission; and in-hospital mortality. While the introduction of DAAs has been relatively recent, efforts will also be made to examine the potential impact of expanded access to DAAs on these hospital-related outcomes.

For the present study, only original quantitative research studies that report on HCV and hospital-related outcomes will be included. Commentaries, letters to the editors, editorials, and other types of opinion pieces will be excluded. We will also exclude literature reviews, but will conduct back referencing to ensure that all relevant studies from the literature review are captured. The search will be restricted to publications in English, but in order to capture a comprehensive list of relevant articles, will not be restricted to setting or publication date.

Information sources and search strategy

We will conduct a comprehensive search strategy to identify articles that meet the eligibility criteria. Specifically, we will search the following databases: MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science. As indicated above, search terms will be based on the PEO framework, and these terms will be mapped to database-specific medical subject headings and controlled vocabulary terms when available (Additional File 2). Additionally, we will search reference lists of research articles and systematic reviews to identify relevant articles not otherwise captured in the search strategy. To ensure the robustness of the search strategy, we have consulted with a medical reference librarian with expertise in systematic reviews and population and public health at the University of British Columbia (U. Ellis, personal communication, October 5, 2017).

Study records

We will conduct database searches and import the full-text articles from the search strategy into Endnote X8. Then, we will remove any duplicates prior to reviewing the titles, abstracts, and full-text articles. This will be conducted independently in three separate stages by two investigators. At each review stage, studies clearly not meeting the inclusion criteria will be excluded from further review and the reason for exclusion will be recorded. If the two investigators are not able to come to a consensus regarding the inclusion or exclusion of an article, this will be resolved by discussion with a third investigator.

Risk of bias in individual studies

The methodological quality, including risk of bias, of included quantitative research studies will be assessed using a modified version of the Downs and Black checklist for the reporting of healthcare studies [20,21]. This checklist has been shown to be a valid and reliable tool in assessing the quality of research studies. Higher scores out of a total score of 18 represent higher overall methodological quality. Each article will be independently scored by two investigators. If the two investigators are not able to come to a consensus regarding the inclusion or exclusion of an article, this will be resolved by mutual consent and discussion with a third investigator.

Data synthesis

A PRISMA flow chart will be created to outline the article selection process [22]. Data from included studies will be extracted using a standardized form developed to capture study characteristics and main findings and summarized in a table. Specifically, information on study characteristics (e.g., study setting, study design, study period, study population), participant characteristics (e.g., age, sex/gender); study objectives; outcome variable(s), and main study findings will be extracted from individual studies. Should there be multiple articles pertaining to the same study population and setting, we plan to extract comprehensive data across the articles but they will be linked together as one unique study. Findings from the included studies will then be synthesized in a narrative account that addresses the objectives of this systematic review.

ETHICS AND DISSEMINATION

The proposed systematic review will be the first to synthesize the literature to identify the burden of HCV infection on the healthcare system, particularly as it pertains to acute inpatient hospital care. The results from this review will provide evidence to help health system leaders and policy makers develop effective health policies and strategies that will positively influence how care is delivered to patients living with HCV. Additionally, these findings may reveal efficient models of treatment

and care that would promote retention and continuity of care for patients and minimize any gaps in the healthcare system.

We plan to conduct a comprehensive and reproducible search and analysis of the available literature while recognizing that there may be some limitations. First, the investigators are aware that biases may be present even in studies that have been well designed. To address this, the proposed review will be evaluated on its risk of bias using a validated tool and will be conducted independently by two investigators. Second, there may be some heterogeneity in the way that the main exposure and outcomes are defined, which may bias individual studies. While we plan to include all studies that fit the eligibility criteria with no restrictions on measurement, we plan to record and report these in our data extraction table. Third, it is possible that some eligible studies may be missed in our search strategy, though we have sought expert advice from an experienced librarian to ensure that our search strategy is as inclusive as possible.

Upon completion of the proposed systematic review, a robust knowledge dissemination and exchange strategy will be implemented. We plan to submit the findings of this review for publication in a peer-reviewed open access journal to ensure that the results are accessible to the appropriate scientific and clinical audiences. We also plan to present the results at relevant scientific conferences and meetings both nationally and internationally (e.g., Conference on Retroviruses and Opportunistic Infections, The Liver Meeting, The Canadian Network on Hepatitis C Meeting). Recognizing that the publication of research findings through scientific avenues may

not necessarily be easily accessible to public and community end users, our findings will also be disseminated through newsletters and plain language summaries throughout local hospitals and clinical programs for timely and effective uptake of the research findings. This study has received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

In sum, the proposed systematic review will examine and quantify the effect of HCV infection on hospital-related outcomes, and, whenever possible, the effect of expanded access to DAAs on these outcomes. Findings from this review may lead to the identification of current gaps in the literature regarding this topic and the development of new research questions to be answered. In addition, this review may discover effective quality improvement strategies in an effort to minimize the health, societal, and financial burden imposed on the hospital and healthcare system.

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DECLARATIONS

Authors' contributions:

LT led the development of the protocol, and planned and designed the systematic review protocol. LT prepared the first draft. MN and LA will bet implementing the systematic review protocol. MN, LA, and MPC reviewed and critically revised the first and successive draft of the manuscript. All authors read and approved the final manuscript.

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Competing interests:

The authors declare that they have no competing interests.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	7
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	240
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	☐	X	
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	237
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	237
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	237
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	70

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	107
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	123
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	138
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	X	☐	138
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	151
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	151
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	151
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	123
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	123
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	X	☐	161
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	171
	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 (e.g., I^2, Kendall's tau)	☐	X	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	X	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X	☐	171
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	X	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X	☐	171

Additional File 2

Search strategy in OVID Medline performed 2017-06-15

Number	Search statement	Number of results
1	exp Hepatitis C/ or Hepatitis C, Chronic/ or hepatitis c.mp. or HCV.mp.	88405
2	hospitalization.mp. or exp Hospitalization/ or hospital*.ti.	494402
3	length of stay.mp. or "Length of Stay"/	101326
4	Patient Readmission/ or readmission.mp. or re-admission.mp.	22407
5	in-hospital mortality.mp. or Hospital Mortality/ or hospital mortality.mp.	49183
6	Patient Discharge/ or discharge against medical advice.mp. or against medical advice.mp.	26345
7	2 or 3 or 4 or 5 or 6	542070
8	1 and 7	1505

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Secondary Subject Heading:	Health services research
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INTRODUCTION

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People living with chronic HCV infection are often overrepresented in the healthcare system [9,10]. Previous studies have demonstrated that these individuals are large users of inpatient, emergency department, and outpatient health services, which is likely a result of a number of individual and contextual circumstances, including comorbidities and socioeconomic marginalization [11,12]. For example, a national study conducted in the United States indicated that inpatient admissions among HCV-infected individuals born between 1945 and 1965 (i.e., baby boomers) increased by

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Research question

The proposed systematic review will aim to answer the following research question: what is the impact of HCV infection on hospital-related outcomes among adults?

Patient and public involvement

No patients were involved in the design of the study. However, results will be disseminated to appropriate patient groups as described in the discussion section.

Eligibility

The research question being addressed is best described by the population, exposure, and outcomes (PEO) framework: the population of interest will include

adults greater than or equal to 18 years of age (at baseline); the exposure of interest will be acute or chronic HCV infection; the outcome of interest will be hospital-related outcomes, which will include the following: proportion or rates of hospitalization; length of stay; proportion or rates of leaving hospital against medical advice; proportion or rates of readmission; and proportion or rates of in-hospital mortality. While the introduction of DAAs has been relatively recent, efforts will also be made to examine the potential impact of expanded access to DAAs on these hospital-related outcomes.

For the present study, only original quantitative research studies that report on HCV and hospital-related outcomes will be included. Commentaries, letters to the editors, editorials, and other types of opinion pieces will be excluded. We will also exclude literature reviews, but will conduct back referencing to ensure that all relevant studies from the literature review are captured. The search will be restricted to publications in English, but in order to capture a comprehensive list of relevant articles, will not be restricted to setting or publication date; however, these will be recorded during data extraction and synthesis. The planned start date for this study is February 2018.

Information sources and search strategy

We will conduct a comprehensive search strategy to identify articles that meet the eligibility criteria. Specifically, we will search the following databases: MEDLINE, EMBASE, CINAHL, PsycINFO, and Web of Science. As indicated above, search terms will be based on the PEO framework, and these terms will be mapped to database-

specific medical subject headings and controlled vocabulary terms when available (Additional File 2). Additionally, we will search reference lists of research articles and systematic reviews to identify relevant articles not otherwise captured in the search strategy. To ensure the robustness of the search strategy, we have consulted with a medical reference librarian with expertise in systematic reviews and population and public health at the University of British Columbia (U. Ellis, personal communication, October 5, 2017).

Study records

We will conduct database searches and import the full-text articles from the search strategy into Endnote X8. Then, we will remove any duplicates prior to reviewing the titles, abstracts, and full-text articles. This will be conducted independently in three separate stages by two investigators. At each review stage, studies clearly not meeting the inclusion criteria will be excluded from further review and the reason for exclusion will be recorded. If the two investigators are not able to come to a consensus regarding the inclusion or exclusion of an article, this will be resolved by discussion with a third investigator.

Risk of bias in individual studies

The methodological quality, including risk of bias, of included quantitative research studies will be assessed using the Downs and Black checklist for the reporting

of healthcare studies [22,23]. This 27-item checklist has been shown to be a valid and reliable tool in assessing the quality of research studies. Higher scores represent higher overall methodological quality. Each article will be independently scored by two investigators. If the two investigators are not able to come to a consensus regarding the inclusion or exclusion of an article, this will be resolved by mutual consent and discussion with a third investigator.

Data synthesis

A PRISMA flow chart will be created to outline the article selection process [24]. Data from included studies will be extracted using a standardized form developed to capture study characteristics and main findings and summarized in a table. Specifically, information on study characteristics (e.g., geographical setting, study design, study period (including therapeutic periods [i.e., interferon-based therapy era, first generation DAA-based therapy era, second generation DAA-based therapy era]), study population), participant characteristics (e.g., age, sex/gender); study objectives; outcome variable(s), and main study findings will be extracted from individual studies. Should there be multiple articles pertaining to the same study population and setting, we plan to extract comprehensive data across the articles but they will be linked together as one unique study. Findings from the included studies will then be synthesized in a narrative account that addresses the objectives of this systematic review.

ETHICS AND DISSEMINATION

The proposed systematic review will be the first to synthesize the literature to identify the burden of HCV infection on the healthcare system, particularly as it pertains to acute inpatient hospital care. The results from this review will provide evidence to help health system leaders and policy makers develop effective health policies and strategies that will positively influence how care is delivered to patients living with HCV. Additionally, these findings may reveal efficient models of treatment and care that would promote retention and continuity of care for patients and minimize any gaps in the healthcare system.

We plan to conduct a comprehensive and reproducible search and analysis of the available literature while recognizing that there may be some limitations. First, the investigators are aware that biases may be present even in studies that have been well designed. To address this, the proposed review will be evaluated on its risk of bias using a validated tool and will be conducted independently by two investigators. Second, there may be some heterogeneity in the way that the main exposure and outcomes are defined, which may bias individual studies. While we plan to include all studies that fit the eligibility criteria with no restrictions on measurement, we plan to record and report these in our data extraction table. Third, it is possible that some eligible studies may be missed in our search strategy, though we have sought expert

advice from an experienced librarian to ensure that our search strategy is as inclusive as possible.

Upon completion of the proposed systematic review, a robust knowledge dissemination and exchange strategy will be implemented. We plan to submit the findings of this review for publication in a peer-reviewed open access journal to ensure that the results are accessible to the appropriate scientific and clinical audiences. We also plan to present the results at relevant scientific conferences and meetings both nationally and internationally (e.g., Conference on Retroviruses and Opportunistic Infections, The Liver Meeting, The Canadian Network on Hepatitis C Meeting). Recognizing that the publication of research findings through scientific avenues may not necessarily be easily accessible to public and community end users, our findings will also be disseminated through newsletters and plain language summaries throughout local hospitals and clinical programs for timely and effective uptake of the research findings. This study has received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

In sum, the proposed systematic review will examine and quantify the effect of HCV infection on hospital-related outcomes, and, whenever possible, the effect of expanded access to DAAs on these outcomes. Findings from this review may lead to the identification of current gaps in the literature regarding this topic and the development of new research questions to be answered. In addition, this review may discover effective quality improvement strategies in an effort to minimize the health, societal, and financial burden imposed on the hospital and healthcare system.

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DECLARATIONS

Authors' contributions:

LT led the development of the protocol, and planned and designed the systematic review protocol. LT prepared the first draft. MN, LA, and MPC reviewed and critically revised the first and successive draft of the manuscript. All authors read and approved the final manuscript.

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Competing interests:

The authors declare that they have no competing interests.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	74
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X	☐	7
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	332
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	☐	X	
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	337
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	337
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	337
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	89

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	107
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	145
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	166
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	X	☐	166
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	179
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	179
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	179
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	145
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	150
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	X	☐	189
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	199
	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 (e.g., I^2, Kendall's tau)	☐	X	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	X	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X	☐	199
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	X	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X	☐	189

Additional File 2

Search strategy in OVID Medline performed 2017-06-15

Number	Search statement	Number of results
1	exp Hepatitis C/ or Hepatitis C, Chronic/ or hepatitis c.mp. or HCV.mp.	88405
2	hospitalization.mp. or exp Hospitalization/ or hospital*.ti.	494402
3	length of stay.mp. or "Length of Stay"/	101326
4	Patient Readmission/ or readmission.mp. or re-admission.mp.	22407
5	in-hospital mortality.mp. or Hospital Mortality/ or hospital mortality.mp.	49183
6	Patient Discharge/ or discharge against medical advice.mp. or against medical advice.mp.	26345
7	2 or 3 or 4 or 5 or 6	542070
8	1 and 7	1505