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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SCOPING REVIEW

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Keywords:	Injury, value-based care, cost-effectiveness, low-value clinical practices

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SCOPING REVIEW

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ABSTRACT

Introduction:

Underuse of high-value clinical practices and overuse of low-value practices are major sources of inefficiencies in modern healthcare systems. Injuries are second only to cardiovascular disease in terms of acute care costs but data on the economic impact of clinical practices for injury admissions is lacking. This study aims to summarize evidence on the cost-effectiveness of intra-hospital clinical practices for injury care.

Methods and analysis:

We will perform a scoping review to identify research articles that evaluate cost-effectiveness, cost-utility, cost-benefit or cost-minimization of intra-hospital clinical practices in acute injury care. We will search Medline, Embase, Web of Science and the Cochrane Central Register for randomized or non-randomized controlled trials and observational studies reporting an economic evaluation of intra-hospital clinical practices for injury using a combination of keywords and controlled vocabulary. We will consider the following outcomes relative to economic evaluations: Incremental Cost-Effectiveness Ratio (ICER), Incremental Cost-Utility Ratio (ICUR), incremental Net Health Benefit (iNHB), incremental Net Monetary Benefit (iNMB) and Cost-Benefit Ratio. Pairs of independent reviewers will evaluate studies that meet eligibility criteria and extract data from included articles using an electronic data extraction form. All outcomes will be converted into iNMB. We will report iNMB for practices classified by type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-device, therapeutic-other). Results obtained with each of the four ceiling ratios ($0, $50,000, $100,000, and $200,000 per QALY) for identified clinical practices will be summarized by charting forest plots and/or league tables.

Ethics and dissemination:

Ethics approval is not required as original data will not be collected. This study will summarize existing evidence on the cost-effectiveness of clinical practices in injury care. Results will be used to advance knowledge on value-based care for injury admissions and will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations.

Strengths and limitations of this study

- Fill a major knowledge gap on cost-effectiveness of intra-hospital clinical practices for acute injury care.
- Advance the agenda on value-based healthcare for injury admissions.
- Inform research priorities.
- Represents a crucial step towards the de-adoption of low-value clinical practices in acute injury care.
- For feasibility reasons, restricted to studies published since 2008.
- Scoping design means no appraisal of methodological quality—this will be evaluated in ensuing systematic reviews.

INTRODUCTION

In Canada, injuries represent the leading cause of potential years of life lost and cost more than heart and stroke diseases combined[1]. In 2035, the direct costs of injury are expected to reach $CAN 75 billion while they were estimated at $CAN 27 billion in 2007[1], representing an increase of almost 200% [2]. Injuries represent the third leading cause of potential years of life lost in the United States [3]. The estimated total lifetime medical and work loss costs associated with fatal and non-fatal injuries in the US were $671 billion in 2013 [4].

Regional variations in injury outcomes between healthcare providers have been observed in Canada, the United States and the United Kingdom that are not explained by patient case mix [5-7]. This evidence of suboptimal injury outcomes suggests that efforts must be made to optimise clinical practices in injury care. Value-based health care is defined as "care that is tailored for optimising health and wellbeing by delivering what is needed, wanted, clinically effective, affordable, equitable, and responsible in its use of resources"[8, 9]. When patients do not receive tests and treatments that have been shown to be effective for their condition, we refer to *underuse[10]*. Up to 50% of patients admitted for injury do not receive recommended care[11]. When patients undergo tests and treatments that are not supported by evidence and/or could expose them to unnecessary harm, they receive low-value care, widely referred to as *overuse[12]*. Overuse is driven by low-value clinical practices, which consume up to 30% of healthcare resources and threaten the sustainability of affordable and accessible health care [13-16]. More importantly, low-value practices expose patients to adverse events and delays to effective treatment [17]. The estimated overuse of healthcare services in the US amounts to $780 billion annually[18].

To achieve value-based care, guidelines and recommendations should target both underuse and overuse and be supported by data on cost-effectiveness[19]. However, current guidelines on clinical practices in injury care focus almost exclusively on underuse and are rarely supported by evidence of cost-effectiveness [20-23]. This scoping review aims to review evidence of the cost-effectiveness of intra-hospital clinical practices in acute injury care to advance knowledge on value-based care in this patient population.

METHODS AND ANALYSIS

The structure of the protocol follows the six stages of published guidelines for scoping reviews[24]. As is common with scoping reviews, the methods may be modified as the review progresses [25-28]. Any changes to the protocol will be documented in the final published report.

Research question

Our project steering committee comprising 2 emergency physicians, 2 trauma surgeons, 3 critical care physicians, 2 trauma system managers and a healthcare economist defined our research question as follows: which intra-hospital clinical practices in acute injury care have evidence of being cost-effective or of not being cost-effective?

Relevant studies

Inclusion criteria

We will include research articles, systematic reviews, reports and guidelines on cost-effectiveness analyses (e.g. cost per life year gained), cost-utility analyses (e.g. cost per quality-adjusted life year gained or cost per disability-adjusted life year), cost-benefit and cost-minimization analyses of intra-hospital clinical practices specific to acute injury care. Clinical practices could include admissions, transfers, consultations, as well as diagnostic or therapeutic procedures. A "do nothing" strategy, standard care or any other strategy will be considered as potential comparators.

The following outcomes of economic evaluation will be considered: Incremental Cost-Effectiveness Ratio “ICER”, Incremental Cost-Utility Ratio “ICUR”, incremental Net Monetary Benefit “iNMB”, incremental Net Health Benefit “iNHB” and the incremental Cost-Benefit ratio. Studies identifying the results of the economic evaluation as one clinical practice being dominant or dominated will be included. Such results would indicate that one comparator is less costly and more effective than the other.

Exclusion criteria

We will not include cost-consequences analyses, budget impact studies, narrative reviews, research protocols or conference abstracts. Studies providing incremental costs without incremental effectiveness or vice versa will not be included. Studies on experimental interventions, military injuries, cadavers or animals will be excluded. Studies in which there is no comparator group will be excluded. We will restrict the review to studies published in the last ten years (from January 2008) to ensure feasibility of the review and results that are current.

Information sources

We will search MEDLINE, EMBASE, NHS Economic Evaluation Database, Health Technology Assessment Database, EconLit, Tufts CEA Registry, Cochrane CENTRAL, BIOSIS, and CINAHL to identify research articles on economic evaluation of clinical practices specific to intrahospital acute injury care. The grey literature will be searched through thesis repositories, injury association websites, healthcare quality websites and the Web of Knowledge. Thesis repositories include Thesis portal Canada, Electronic Thesis Online Service (EThOS), Digital Access to Research Theses (DART)-Europe E-Theses Portal, the National Library of Australia’s Trove and ProQuest Dissertations & Theses Global. Healthcare quality websites include the World Health Organization, National Institute for Health and Care Excellence, National Association for Healthcare Quality, National Quality Forum, Lown Institute, Agency for Healthcare Research and Quality, Choosing Wisely, Canadian Institutes for Health Information, Australasian Association for Quality in Healthcare. Injury organisations include the American College of Surgeons, Trauma Association of Canada, International Association for Trauma Surgery and Intensive Care, Australasian Trauma Society, Trauma Audit Research Network, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, American Trauma Society, British Trauma Society, Orthopaedic Trauma Association,

Western Trauma Association, Trauma.org, The Society of Trauma Nurses, International Trauma Anaesthesia and Critical Care Society, the BrainTrauma Foundation and patient advocacy organisations including Safer Healthcare Now!

Search strategy

A rigorous strategy will be designed using a combination of Boolean terms with relevant keywords and subject headings covering 'injury', 'trauma' and 'economic evaluation' for EMBASE (EMBASE tree; EMTREE) and MEDLINE (Medical Subject Headings; MeSH), and then adapted to the remaining databases (see Appendix 1 for the preliminary search strategy). Clinicians in the project steering committee and information specialists will be consulted to refine the search strategy using the Peer Review of Electronic Search Strategies checklist[29]. The sensitivity of our search strategy will be evaluated by identifying between five and ten sentinel articles and checking whether they are detected.

Select studies

Data management

Citations will be managed using EndNote software (version X7.0.1, New York City: Thomson Reuters, 2011). Duplicates will be identified and removed via electronic and manual screening. If multiple publications based on the same dataset are identified, we will select the most recent study or the one with the largest sample size.

Selection process

Pairs of independent reviewers (LM, BC, PAT, IF, TM, KS, SB) will screen all titles, abstracts, and full texts to identify eligible studies. Prior to selection, we will evaluate inter-reviewer agreement on eligibility using the first 500 citations to clarify the inclusion criteria. Discrepancies between reviewers will be resolved by consensus. We will re-specify eligibility criteria, if necessary, and repeat the selection process until an acceptable inter-rater agreement is attained. A third reviewer will adjudicate if necessary (JRG). The level of agreement between reviewers will be assessed with Kappa coefficients[30] and agreement will be considered acceptable if kappa > 0.9. If information on eligibility is unavailable or unclear, study authors will be contacted.

Chart material

Data collection

An electronic data abstraction form will be developed with a detailed instruction manual and piloted on a representative sample of 10 publications. An example of the extraction grid is presented in Appendix 2. Pairs of reviewers with methodological and content expertise (BC, IF, PAT, MAG) will extract the following information from eligible articles: study design (systematic review, randomized controlled trial (RCT), observational study, model-based study), setting (country, year, hospital), type of economic evaluation (cost-effectiveness, cost-minimization, cost-utility, cost-benefit), perspective of economic evaluation (patient, hospital/clinic, healthcare system or societal), population (age, type of injury, injury severity, sample size), treatment and comparator, primary outcomes of the economic evaluation as stated above and authors' conclusions. Any discrepancies between reviewers will be resolved by consensus and a third reviewer will adjudicate if necessary

(JRG). If important information is missing or requires clarification, we will contact study authors using up to three email attempts over 1 month to all listed authors.

Collate, summarise and report on results

Two reviewers (BC, MAG) will independently classify clinical practices according to the type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-device, therapeutic-other). Any disagreements will be adjudicated by a third reviewer (LM). The methodological quality of included studies will not be evaluated, as is common in scoping reviews[25]. Evidence of cost-effectiveness (or lack of cost-effectiveness) for clinical practices will be presented by the type and number of studies as well as measures of cost-effectiveness. All cost-effectiveness and cost-utility measures will be converted into iNMB using ceiling ratios (i.e., the maximum acceptable willingness to pay per unit of health gain) of $0, $50,000, $100,000, and $200,000 per QALY gained. Results obtained with each of the four ceiling ratios for identified clinical practices will be summarized by charting forest plots or league tables. In the consultation phase, we will ask the project advisory committee to assess the clinical significance of results and give feedback on interpretation and presentation.

ETHICS AND DISSEMINATION

The results of this scoping review will fill a major knowledge gap on the cost-effectiveness of clinical practices in acute injury care. They will be used to advance knowledge on value-based healthcare in this population. Results will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations. Ethics approval is not required as original data will not be collected.

Appendix 1. Search strategy within Pubmed (10-12-2018)

Concepts	keywords	Research	# Results
Trauma (injuries) (free text)	"injure"[TIAB] OR "injured"[TIAB] OR "injures"[TIAB] OR "injuries"[TIAB] OR "injury"[TIAB] OR "Injuries and Wounds"[TIAB] OR "Wounds and Injury"[TIAB] OR "Injury and Wounds"[TIAB] OR "Wounds, Injury"[TIAB] OR "Injuries, Wounds"[TIAB] OR "Wounds"[TIAB] OR "Wound"[TIAB] OR "Research-Related Injuries"[TIAB] OR "Injuries, Research-Related"[TIAB] OR "Injury, Research-Related"[TIAB] OR "Research Related Injuries"[TIAB] OR "Research-Related Injury"[TIAB] OR Trauma*[TIAB]	#1	1,068,915
Trauma (controlled vocabulary)	"Wounds and Injuries"[Mesh]	#2	849,041
Total trauma	#1 OR #2	#3	1,536,583
Economic evaluation (controlled vocabulary)	"Cost-Benefit Analysis"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Budgets"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Resource Allocation"[Mesh] OR "Health Care Costs"[Mesh]	#4	175,846
Economic evaluation (free text)	Cost[TIAB] OR costs[TIAB] OR economic*[TIAB] OR marginal analys*[TIAB] OR budget*[TIAB] OR fee[TIAB] OR fees[TIAB] OR finance*[TIAB] OR price*[TIAB] OR pricing[TIAB] OR resource allocat*[TIAB] OR monetary value[TIAB] OR (value[TIAB] AND money*[TIAB])	#5	726,701
Total economic evaluation	#4 OR #5	#6	79,394
Total trauma and economic evaluation	#3 AND #6	#7	38,845
Filter for humans	"animals"[Mesh] NOT "Humans"[Mesh]	#8	4,514,521
Total in humans	#7 NOT #8	#9	37,393
Filter for studies	Epidemiologic studies[MeSH:noexp] OR case control studies[MeSH] OR cohort studies[MeSH] OR Cross-sectional studies[MeSH:noexp] OR "Observational Study" [Publication Type] OR (Case control[TIAB] OR (cohort[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Cohort analy*[TIAB] OR (Follow up[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (observational[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Longitudinal[TIAB] OR Retrospective[TIAB] OR Cross sectional[TIAB] OR prospective[TIAB] OR (epidemiologic*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (correlational*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (clinical*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (famil*[TIAB] AND (study[TIAB] OR studies[TIAB]))) OR ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]))	#10	7,380,383
Total studies	#9 AND #10	#11	20,547
Date of publication	2008[DP] OR 2009[DP] OR 2010[DP] OR 2011[DP] OR 2012[DP] OR 2013[DP] OR 2014[DP] OR 2015[DP] OR 2016[DP] OR 2017[DP] OR 2018[DP]	#12	10,685,930
Total since 2008	#11 AND #12 Limits French and English	#13	12,462

1. Study a) Author b) Year of publication c) Journal	2. Type of economic evaluation	3. Design	4. Population a) age, b) type of injury c) Sample size	5. Perspective of economic evaluation	5. Treatments a) New treatment b) Comparator	5. New Intervention a) cost b) outcome of Effectiveness	6. Comparator a) cost b) outcome of Effectiveness	ICER / iNMB / iNHB / C/B	9. Authors' conclusion
a) Xiao Wu et al. b) 2017 c) Annals of Emergency Medicine	Cost-utility analysis	Simulation	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after a negative CT b) no follow-up after CT	a) $11,477 b) 24.03 Qaly	a) $6,432 b) 24.08 Qaly	$100,900/QALY	No follow-up dominates MRI. MRI is not cost-effective
a) Xiao Wu et al. b) 2018 c) JAMA	Cost-utility analysis	Simulation	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after normal CT b) no follow-up after CT	a) $14,185 b) 24.02 Qaly	a) $1,059 b) 24.11 Qaly	$145,844/QALY	MRI is not cost-effective for patients with Obtunded Blunt Trauma After a Normal CTS
a) Arturo Garcia et al. b) 2013 c) J Trauma Acute Care Surg	Cost-utility analysis	Simulation	a) hypothetical cohort of 20-year-old males b) penetrating trauma (All) c)N/A	Societal	a) routine prehospital spine immobilization b) no PHSI	a) $930,446 s b) 25.44 Qaly	a) $929,883 b) 25.44 Qaly	N/A No PHSI dominates routine PHSI	PHSI was not cost-effective for patients with torso or extremity penetrating trauma
a) Van Oudenaarde, K. et al. b) 2018 c) Skeletal radiology	Cost-utility analysis	RCT	a) 18-45 years b) traumatic knee complaints c) 356 patients	Societal and healthcare	a) MR imaging within 2 weeks b) no MR scan, but referral to an orthopedic surgeon when conservative treatment was unsatisfactory	a) $1,109 b) 0.888 Qaly	a) $837 b) 0.899 Qaly	$24,727.3/QALY	MR scan referral by the general practitioner was not cost-effective in patients with traumatic knee complaints, MR imaging led to more healthcare costs without improving health outcomes.
a) Cotton, B. A.et al. b) 2011 c) J Trauma	Cost-utility analysis	RCT	a) N/A b) Early posttraumatic Brain injury seizure prophylaxis c) N/A	Healthcare (trauma center Level I)	a) levetiracetam b) phenytoin	a) $480 b) 23.2 Qaly	a) $37.50 b) 23.6 Qaly	Levetiracetam was dominated	Phenytoin is more cost-effective than levetiracetam at all reasonable prices and at all clinically plausible reductions in post-TBI seizure potential.

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Lynne Moore led the development of the protocol and drafted the manuscript. She acts as guarantor for the review.

Jason Robert Guertin contributed to the development of research objectives and inclusion criteria, elaborated keywords, validated the data extraction form, critically revised the manuscript and approved the final version.

Pier-Alexandre Tardif contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Imen Farhat contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Thomas Moore contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Samy Bouderba contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Kahina Soltana contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Patrick Archambault contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Simon Berthelot contributed to the development of research objectives and inclusion criteria, elaborated keywords, critically revised the manuscript and approved the final version.

François Lauzier contributed to developing keywords, validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Alexis F. Turgeon elaborated inclusion criteria and clinically significant outcomes, validated the search strategy, elaborated keywords, revised the manuscript and approved the final version.

Henry Thomas Stelfox contributed to the development of research objectives, inclusion criteria, the search strategy and the extraction form, developed keywords, revised the manuscript and approved the final version.

Michael Chassé validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Jeffrey Hoch contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

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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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
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
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
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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)
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
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	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)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.**

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

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ABSTRACT

Introduction:

Underuse of high-value clinical practices and overuse of low-value practices are major sources of inefficiencies in modern healthcare systems. Injuries are second only to cardiovascular disease in terms of acute care costs but data on the economic impact of clinical practices for injury admissions is lacking. This study aims to summarize evidence on the economic value of intra-hospital clinical practices for injury care.

Methods and analysis:

We will perform a systematic review to identify research articles, reports or guidelines that evaluate cost-effectiveness, cost-utility, cost-benefit or cost-minimization of intra-hospital clinical practices in acute injury care. We will search Medline, Embase, Web of Science and the Cochrane Central Register for randomized or non-randomized controlled trials (RCTs) and observational studies reporting an economic evaluation of intra-hospital clinical practices for injury using a combination of keywords and controlled vocabulary. We will consider the following outcomes relative to economic evaluations: Incremental Cost-Effectiveness Ratio (ICER), Incremental Cost-Utility Ratio (ICUR), incremental Net Health Benefit (iNHB), incremental Net Monetary Benefit (iNMB) and incremental Cost-Benefit Ratio. Pairs of independent reviewers will evaluate studies that meet eligibility criteria and extract data from included articles using an electronic data extraction form. All outcomes will be converted into iNMB. We will report iNMB for practices classified by type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-device, therapeutic-other). Results obtained with each of the four ceiling ratios ($0, $50,000, $100,000, and $200,000 per QALY gained) for identified clinical practices will be summarized by charting forest plots and/or league tables. In line with Cochrane recommendations for systematic reviews of economic evaluations, meta-analyses will not be conducted. We will assess methodological quality using the Consensus on Health Economic Criteria.

Ethics and dissemination:

Ethics approval is not required as original data will not be collected. This study will summarize existing evidence on the economic value of clinical practices in injury care. Results will be used to advance knowledge on value-based care for injury admissions and will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations.

Strengths and limitations of this study

- Fill a major knowledge gap on the economic value of intra-hospital clinical practices for acute injury care.
- Advance the agenda on value-based healthcare for injury admissions.
- Inform research priorities.
- Represents a crucial step towards the de-adoption of low-value clinical practices in acute injury care.
- For feasibility reasons, restricted to studies published in English since 2009.

INTRODUCTION

In Canada, injuries represent the leading cause of potential years of life lost and cost more than heart and stroke diseases combined[1]. In 2035, the direct costs of injury are expected to reach $CAN 75 billion while they were estimated at $CAN 27 billion in 2007[1], representing an increase of almost 200% [2]. Injuries represent the third leading cause of potential years of life lost in the United States [3]. The estimated total lifetime medical and work loss costs associated with fatal and non-fatal injuries in the US were $671 billion in 2013 [4].

Regional variations in injury outcomes between healthcare providers have been observed in Canada, the United States and the United Kingdom that are not explained by patient case mix [5-7]. This evidence of suboptimal injury outcomes suggests that efforts must be made to optimise clinical practices in injury care[8]. Value-based health care is defined as "care that is tailored for optimising health and wellbeing by delivering what is needed, wanted, clinically effective, affordable, equitable, and responsible in its use of resources"[9, 10]. When patients do not receive tests and treatments that have been shown to be effective for their condition, we refer to *underuse[11]*. Up to 50% of patients admitted for injury do not receive recommended care[12]. When patients undergo tests and treatments that are not supported by evidence and/or could expose them to unnecessary harm, they receive low-value care, widely referred to as *overuse[13]*. Overuse is driven by low-value clinical practices, which consume up to 30% of healthcare resources and threaten the sustainability of affordable and accessible health care [14-17]. More importantly, low-value practices expose patients to adverse events and delays to effective treatment [18]. The estimated overuse of healthcare services in the US amounts to $780 billion annually[19].

To achieve value-based care, guidelines and recommendations should target both underuse and overuse and be supported by data provided from economic evaluations[20]. However, current guidelines on clinical practices in injury care focus almost exclusively on underuse and are rarely supported by evidence of cost-effectiveness [21-24]. This systematic review aims to review evidence of the economic value of intra-hospital clinical practices in acute injury care to advance knowledge on value-based care in this patient population.

METHODS AND ANALYSIS

The structure of the protocol follows PRISMA-P guidelines for systematic reviews[25]. Any changes to the protocol will be documented in the final published report.

Patient and Public Involvement

No patient involved

Research question

Our project steering committee comprising 2 emergency physicians, 2 trauma surgeons, 3 critical care physicians, 2 trauma system managers and a healthcare economist defined our research question as follows: which intra-hospital clinical practices in acute injury care have evidence of being cost-effective or of not being cost-effective?

Relevant studies

Inclusion criteria

We will include research articles, systematic reviews, reports and guidelines on cost-effectiveness analyses (e.g. cost per life year gained), cost-utility analyses (e.g. cost per quality-adjusted life year gained or cost per disability-adjusted life year averted), cost-benefit and cost-minimization analyses of intra-hospital clinical practices for patients treated in hospital for injury. Clinical practices could include admissions, transfers, consultations, as well as diagnostic or therapeutic procedures. A "do nothing" strategy, standard care or any other strategy will be considered as potential comparators.

The following outcomes of economic evaluation will be considered: Incremental Cost-Effectiveness Ratio “ICER”, Incremental Cost-Utility Ratio “ICUR”, incremental Net Monetary Benefit “iNMB”, incremental Net Health Benefit “iNHB” and the incremental Cost-Benefit ratio. Studies identifying the results of the economic evaluation as one clinical practice being dominant or dominated will be included. Such results would indicate that one comparator is less costly and more effective than the other. We will restrict the review to studies published in English in the last ten years (from January 2009) to ensure feasibility of the review and results that are current.

Exclusion criteria

We will not include cost-consequences analyses, budget impact studies, narrative reviews, research protocols or conference abstracts. Studies providing incremental costs without incremental effectiveness or vice versa will not be included. Studies on experimental interventions, military injuries, cadavers or animals will be excluded. Studies in which there is no comparator group will be excluded.

Information sources

We will search MEDLINE (via PubMed), EMBASE, NHS Economic Evaluation Database, Health Technology Assessment Database, EconLit, Tufts CEA Registry, Cochrane CENTRAL, BIOSIS, and CINAHL to identify research articles on economic evaluation of clinical practices specific to intrahospital acute injury care. The grey literature will be searched through thesis repositories, injury association websites, healthcare quality websites and the Web of Knowledge. Thesis repositories include Thesis portal Canada, Electronic Thesis Online Service (EThOS), Digital Access to Research Theses (DART)-Europe E-Theses Portal, the National Library of Australia’s Trove and ProQuest Dissertations & Theses Global. Healthcare quality websites include the World Health

Organization, National Institute for Health and Care Excellence, National Association for Healthcare Quality, National Quality Forum, Lown Institute, Agency for Healthcare Research and Quality, Choosing Wisely, Canadian Institutes for Health Information, Australasian Association for Quality in Healthcare. Injury organisations include the American College of Surgeons, Trauma Association of Canada, International Association for Trauma Surgery and Intensive Care, Australasian Trauma Society, Trauma Audit Research Network, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, American Trauma Society, British Trauma Society, Orthopaedic Trauma Association, Western Trauma Association, Trauma.org, The Society of Trauma Nurses, International Trauma Anaesthesia and Critical Care Society, the BrainTrauma Foundation and patient advocacy organisations including Safer Healthcare Now!

Search strategy

A rigorous strategy will be designed using a combination of Boolean terms with relevant keywords and subject headings covering 'injury', 'trauma' and 'economic evaluation' for EMBASE (EMBASE tree; EMTREE) and PubMed (Medical Subject Headings; MeSH), and then adapted to the remaining databases (see Appendix 1 in supplementary file for the preliminary search strategy of December 28, 2019). Clinicians in the project steering committee and information specialists will be consulted to refine the search strategy using the Peer Review of Electronic Search Strategies checklist[26]. The sensitivity of our search strategy will be evaluated by identifying between five and ten sentinel articles and checking whether they are detected.

Select studies

Data management

Citations will be managed using EndNote software (version X7.0.1, New York City: Thomson Reuters, 2011). Duplicates will be identified and removed via electronic and manual screening. If multiple publications based on the same dataset are identified, we will select the most recent study or the one with the largest sample size.

Selection process

Pairs of independent reviewers (LM, BC, PAT, IF, TM, KS, SB) will screen all titles, abstracts, and full texts to identify eligible studies. Prior to selection, we will evaluate inter-reviewer agreement on eligibility using the first 500 citations. Discrepancies between reviewers will be resolved by consensus. We will re-specify eligibility criteria if necessary and repeat the selection process until an acceptable inter-rater agreement is attained. A third reviewer will adjudicate if necessary (JRG). The level of agreement between reviewers will be assessed with Kappa coefficients[27] and agreement will be considered acceptable if kappa > 0.9. If information on eligibility is unavailable or unclear, study authors will be contacted.

Chart material

Data collection

An electronic data abstraction form will be developed with a detailed instruction manual and piloted on a representative sample of 10 publications. An example of the extraction grid is presented in Appendix 2 (in supplementary file). Pairs of reviewers with methodological and content expertise (BC, IF, PAT, MAG) will extract the following information from eligible articles: study design (systematic review, randomized controlled trial (RCT), observational study, simulation study), setting (country, year, hospital), type of economic evaluation (cost-effectiveness, cost-minimization, cost-utility, cost-benefit), perspective of economic evaluation (patient, hospital/clinic, healthcare system or societal), population (age, type of injury, injury severity, sample size), treatment and comparator, primary outcomes of the economic evaluation as stated above and authors' conclusions. Any discrepancies between reviewers will be resolved by consensus and a third reviewer will adjudicate if necessary (JRG). If important information is missing or requires clarification, we will contact study authors using up to three email attempts over 1 month to all listed authors.

Collate, summarise and report on results

Two reviewers (BC, MAG) will independently classify clinical practices according to the type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-device, therapeutic-other). Any disagreements will be adjudicated by a third reviewer (LM). Evidence of cost-effectiveness, cost-utility, cost-benefit or cost-minimization (or lack of cost-effectiveness, cost-utility or cost-benefit) for clinical practices will be presented by the type and number of studies as well as measures of economic value. All measures will be converted into iNMB using ceiling ratios (i.e., the maximum acceptable willingness to pay per unit of health gain) of $0, $50,000, $100,000, and $200,000 per QALY gained. Results obtained with each of the four ceiling ratios for identified clinical practices will be summarized by charting forest plots or league tables. We anticipate that meta-analyses will be inappropriate due to the heterogeneity of cost estimates both within and between settings[28].

Methodological quality of included studies

Two content experts will independently assess methodological quality using the Consensus on Health Economic Criteria[29].

ETHICS AND DISSEMINATION

The results of this systematic review will fill a major knowledge gap on the economic value of clinical practices in acute injury care. They will be used to advance knowledge on value-based healthcare in this population. Results will be disseminated through a peer-reviewed

article, international scientific meetings and clinical and healthcare quality associations. Ethics approval is not required as original data will not be collected.

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Samy Bouderba contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Kahina Soltana contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Patrick Archambault contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Simon Berthelot contributed to the development of research objectives and inclusion criteria, elaborated keywords, critically revised the manuscript and approved the final version.

François Lauzier contributed to developing keywords, validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Alexis F. Turgeon elaborated inclusion criteria and clinically significant outcomes, validated the search strategy, elaborated keywords, revised the manuscript and approved the final version.

Henry Thomas Stelfox contributed to the development of research objectives, inclusion criteria, the search strategy and the extraction form, developed keywords, revised the manuscript and approved the final version.

Michael Chassé validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Jeffrey Hoch contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Lynne Moore led the development of the protocol and drafted the manuscript. She acts as guarantor for the review.

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Appendix 1. Search strategy within Pubmed (28-12-2019)

Concepts	keywords	Research	# Results
Trauma (injuries) (free text)	"injure"[TIAB] OR "injured"[TIAB] OR "injures"[TIAB] OR "injuries"[TIAB] OR "injury"[TIAB] OR "Injuries and Wounds"[TIAB] OR "Wounds and Injury"[TIAB] OR "Injury and Wounds"[TIAB] OR "Wounds, Injury"[TIAB] OR "Injuries, Wounds"[TIAB] OR "Wounds"[TIAB] OR "Wound"[TIAB] OR "Research-Related Injuries"[TIAB] OR "Injuries, Research-Related"[TIAB] OR "Injury, Research-Related"[TIAB] OR "Research Related Injuries"[TIAB] OR "Research-Related Injury"[TIAB] OR Trauma*[TIAB]	#1	1,147,497
Trauma (controlled vocabulary)	"Wounds and Injuries"[Mesh]	#2	884,715
Total trauma	#1 OR #2	#3	1,631,620
Economic evaluation (controlled vocabulary)	"Cost-Benefit Analysis"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Resource Allocation"[Mesh] OR "Health Care Costs"[Mesh]	#4	172,964
Economic evaluation (free text)	Cost[TIAB] OR costs[TIAB] OR economic*[TIAB] OR marginal analys*[TIAB] OR budget*[TIAB] OR fee[TIAB] OR fees[TIAB] OR finance*[TIAB] OR price*[TIAB] OR pricing[TIAB] OR resource allocat*[TIAB] OR monetary value[TIAB] OR (value[TIAB] AND money*[TIAB])	#5	796,642
Total economic evaluation	#4 OR #5	#6	860,748
Total trauma and economic evaluation	#3 AND #6	#7	42,684
Filter for humans	"animals"[Mesh] NOT "Humans"[Mesh]	#8	4,653,747
Total in humans	#7 NOT #8	#9	41,025
Filter for studies	Epidemiologic studies[MeSH:noexp] OR case control studies[MeSH] OR cohort studies[MeSH] OR Cross-sectional studies[MeSH:noexp] OR "Observational Study"[Publication Type] OR (Case control[TIAB] OR (cohort[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Cohort analy*[TIAB] OR (Follow up[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (observational[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Longitudinal[TIAB] OR Retrospective[TIAB] OR Cross sectional[TIAB] OR prospective[TIAB] OR (epidemiologic*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (correlational*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (clinical*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (famil*[TIAB] AND (study[TIAB] OR studies[TIAB]))) OR ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]))	#10	7,919,395
Total studies	#9 AND #10	#11	22,781
Date of publication	2009[DP] OR 2010[DP] OR 2011[DP] OR 2012[DP] OR 2013[DP] OR 2014[DP] OR 2015[DP] OR 2016[DP] OR 2017[DP] OR 2018[DP] OR 2019[DP]	#12	11,331,791
Total since 2009	#11 AND #12 Limits English	#13	13,892

Appendix 2. Example of extraction grid

1. Study a) Author b) Year of publication c) Journal	**2. Type of economic evaluation**	**3. Design**	**4. Population** a) age, b) type of injury c) Sample size	**5. Perspective of economic evaluation**	**6. Treatments** a) New treatment b) Comparator	**7. New Intervention** a) cost b) outcome of Effectiveness	**8. Comparator** a) cost b) outcome of Effectiveness	**9. ICER / iNMB / iNHB / C/B**	**10. Authors' conclusion**
a) Wu et al. b) 2017 c) Annals of Emergency Medicine	Cost-utility analysis	Model-based	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after a negative CT b) no follow-up after CT	a) $11,477 b) 24.03 Qaly	a) $6,432 b) 24.08 Qaly	No follow-up dominates MRI.	MRI follow-up is not cost-effective for further evaluation of unstable injury in neurologically intact patients with blunt trauma after a negative cervical spine CT result compared to no follow-up
a) Wu et al. b) 2018 c) JAMA	Cost-utility analysis	Model-based	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after normal CT b) no follow-up after CT	a) $14,185 b) 24.02 Qaly	a) $1,059 b) 24.11 Qaly	No follow-up dominates MRI follow-up after normal CT.	MRI had a lower health benefit and a higher cost compared with no follow-up after a normal CT finding in patients with obtunded blunt trauma to the cervical spine
a) Garcia et al. b) 2013 c) J Trauma Acute Care Surg	Cost-utility analysis	Model-based	a) hypothetical cohort of 20-year-old males b) penetrating trauma (All) c)N/A	Societal	a) routine prehospital spine immobilization b) no PHSI	a) $930,446 b) 25.44 Qaly	a) $929,883 b) 25.44 Qaly	N/A No PHSI dominates routine PHSI	PHSI was not cost-effective for patients with torso or extremity penetrating trauma
a) Oudenaarde et al. b) 2018 c) Skeletal radiology	Cost-utility analysis	RCT	a) 18-45 years b) traumatic knee complaints c) 356 patients	Societal and healthcare	a) MRI within 2 weeks b) no MRI, but referral to an orthopedic surgeon when conservative treatment was unsatisfactory	a) $1,109 b) 0.888 Qaly	a) $837 b) 0.899 Qaly	MRI within 2 weeks is dominated	MR scan referral by the general practitioner was not cost-effective in patients with traumatic knee complaints, MRI led to more healthcare costs without improving health outcomes.
a) Cotton et al. b) 2011 c) J Trauma	Cost-utility analysis	RCT	a) N/A b) Early posttraumatic Brain injury seizure prophylaxis c) N/A	Healthcare (trauma center Level I)	a) levetiracetam b) phenytoin	a) $480 b) 23.2 Qaly	a) $37.50 b) 23.6 Qaly	Levetiracetam was dominated	Phenytoin is more cost-effective than levetiracetam at all reasonable prices and at all clinically plausible reductions in post-TBI seizure potential.

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
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
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
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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)
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
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	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)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.**

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

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Secondary Subject Heading:	Epidemiology, Diagnostics, Evidence based practice, Intensive care
Keywords:	Injury, value-based care, low-value clinical practices, HEALTH ECONOMICS

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

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Running head: ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

ABSTRACT

Introduction:

Underuse of high-value clinical practices and overuse of low-value practices are major sources of inefficiencies in modern healthcare systems. Injuries are second only to cardiovascular disease in terms of acute care costs but data on the economic impact of clinical practices for injury admissions is lacking. This study aims to summarize evidence on the economic value of intra-hospital clinical practices for injury care.

Methods and analysis:

We will perform a systematic review to identify research articles in economic evaluation of intra-hospital clinical practices in acute injury care. We will search Medline and databases such as Embase, Web of Science, NHS Economic Evaluation Database, Cochrane CENTRAL, BIOSIS, and CINAHL for randomized or non-randomized controlled trials and observational studies using a combination of keywords and controlled vocabulary. We will consider the following outcomes relative to economic evaluations: Incremental Cost-Effectiveness Ratio, Incremental Cost-Utility Ratio, incremental Net Health Benefit, incremental Net Monetary Benefit (iNMB) and incremental Cost-Benefit Ratio. Pairs of independent reviewers will evaluate studies that meet eligibility criteria and extract data from included articles using an electronic data extraction form. All outcomes will be converted into iNMB. We will report iNMB for practices classified by type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-other). Results obtained with a ceiling ratio of $50,000 per QALY gained for identified clinical practices will be summarized by charting forest plots. In line with Cochrane recommendations for systematic reviews of economic evaluations, meta-analyses will not be conducted.

Ethics and dissemination:

Ethics approval is not required as original data will not be collected. This study will summarize existing evidence on the economic value of clinical practices in injury care. Results will be used to advance knowledge on value-based care for injury admissions and will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations.

Strengths and limitations of this study

- Fill a major knowledge gap on the economic value of intra-hospital clinical practices for acute injury care.
- Advance the agenda on value-based healthcare for injury admissions.
- Inform research priorities.
- Represents a crucial step towards the de-adoption of low-value clinical practices in acute injury care.
- For feasibility reasons, restricted to studies published in English since 2009.

INTRODUCTION

In Canada, injuries represent the leading cause of potential years of life lost and cost more than heart and stroke diseases combined[1]. In 2035, the direct costs of injury are expected to reach $CAN 75 billion while they were estimated at $CAN 27 billion in 2007[1], representing an increase of almost 200% [2]. Injuries represent the third leading cause of potential years of life lost in the United States [3]. The estimated total lifetime medical and work loss costs associated with fatal and non-fatal injuries in the US were $671 billion in 2013 [4].

Regional variations in injury outcomes between healthcare providers have been observed in Canada, the United States and the United Kingdom that are not explained by patient case mix [5-7]. This evidence of suboptimal injury outcomes suggests that efforts must be made to optimise clinical practices in injury care[8]. Value-based health care is defined as "care that is tailored for optimising health and wellbeing by delivering what is needed, wanted, clinically effective, affordable, equitable, and responsible in its use of resources"[9, 10]. When patients do not receive tests and treatments that have been shown to be effective for their condition, we refer to *underuse[11]*. Up to 50% of patients admitted for injury do not receive recommended care[12]. The economic impact of the *underuse of recommended care* implies missed opportunities of healthcare cost savings, averted productivity losses, and the monetized value of potential reductions in morbidity and mortality. When patients undergo tests and treatments that are not supported by evidence and/or could expose them to unnecessary harm, they receive low-value care, widely referred to as *overuse[13]*. Overuse is driven by low-value clinical practices, which consume up to 30% of healthcare resources and threaten the sustainability of affordable and accessible health care [14-17]. From an economic evaluation standpoint, the overuse of low-value practices implies inefficiency in resources use that results in a waste of resources. More importantly, low-value practices expose patients to adverse events and delays to effective treatment [18]. The estimated overuse of healthcare services in the US amounts to $780 billion annually[19].

To achieve value-based care, guidelines and recommendations should target both underuse and overuse and be supported by data provided from economic evaluations[20]. However, current guidelines on clinical practices in injury care focus almost exclusively on underuse and are rarely supported by evidence of cost-effectiveness [21-24]. This systematic review aims to review evidence of the economic value of intra-hospital clinical practices in acute injury care to advance knowledge on value-based care in this patient population.

METHODS AND ANALYSIS

The structure of the protocol follows PRISMA-P guidelines for systematic reviews[25]. Any changes to the protocol will be documented in the final published report.

Patient and Public Involvement
No patient involved

Relevant studies
Inclusion criteria
We will include research articles, systematic reviews, reports and guidelines on cost-effectiveness analyses (e.g. cost per life year gained), cost-utility analyses (e.g. cost per quality-adjusted life year gained or cost per disability-adjusted life year averted), cost-benefit and cost-minimization analyses of intra-hospital clinical practices for patients treated in hospital for injury. Clinical practices could include admissions, transfers, consultations, as well as diagnostic or therapeutic procedures. A "do nothing" strategy, standard care or any other strategy will be considered as potential comparators.

The following outcomes of economic evaluation will be considered: Incremental Cost-Effectiveness Ratio "ICER", Incremental Cost-Utility Ratio "ICUR", incremental Net Monetary Benefit "iNMB", incremental Net Health Benefit "iNHB" and the incremental Cost-Benefit ratio. Studies identifying the results of the economic evaluation as one clinical practice being dominant or dominated will be included. Such results would indicate that one comparator is less costly and more effective than the other. We will restrict the review to studies published in English in the last ten years (from January 2009) to ensure feasibility of the review and results that are current.

Exclusion criteria
We will not include cost-consequences analyses, budget impact studies, narrative reviews, research protocols or conference abstracts. Studies providing incremental costs without incremental effectiveness or vice versa will not be included. Studies on experimental interventions, military injuries, cadavers or animals will be excluded. Studies in which there is no comparator group will be excluded. Our systematic review will be limited to evidence from high-income countries.

Information sources
We will search MEDLINE (via PubMed), EMBASE, Web of Science, NHS Economic Evaluation Database, Health Technology Assessment Database, EconLit, Tufts CEA Registry, Cochrane CENTRAL, BIOSIS, and CINAHL to identify research articles on economic evaluation of clinical practices specific to intrahospital acute injury care. The grey literature will be searched through thesis repositories, injury association websites, healthcare quality websites and the Web of Knowledge. Thesis repositories include Thesis portal Canada, Electronic Thesis Online Service (EThOS), Digital Access to Research Theses (DART)-Europe E-Theses Portal, the National Library of Australia's Trove and ProQuest Dissertations & Theses Global. Healthcare quality websites include the World

Health Organization, National Institute for Health and Care Excellence, National Association for Healthcare Quality, National Quality Forum, Lown Institute, Agency for Healthcare Research and Quality, Choosing Wisely, Canadian Institutes for Health Information, Australasian Association for Quality in Healthcare. Injury organisations include the American College of Surgeons, Trauma Association of Canada, International Association for Trauma Surgery and Intensive Care, Australasian Trauma Society, Trauma Audit Research Network, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, American Trauma Society, British Trauma Society, Orthopaedic Trauma Association, Western Trauma Association, Trauma.org, The Society of Trauma Nurses, International Trauma Anaesthesia and Critical Care Society, the BrainTrauma Foundation and patient advocacy organisations including Safer Healthcare Now!

Search strategy

A rigorous strategy will be designed using a combination of Boolean terms with relevant keywords and subject headings covering 'injury', 'trauma' and 'economic evaluation' for EMBASE (EMBASE tree; EMTREE) and PubMed (Medical Subject Headings; MeSH), and then adapted to the remaining databases (see Appendix 1 in supplementary file for the preliminary search strategy of December 28, 2019). Clinicians in the project steering committee and information specialists will be consulted to refine the search strategy using the Peer Review of Electronic Search Strategies checklist[26]. The sensitivity of our search strategy will be evaluated by identifying between five and ten sentinel articles and checking whether they are detected.

Select studies

Data management

Citations will be managed using EndNote software (version X7.0.1, New York City: Thomson Reuters, 2011). Duplicates will be identified and removed via electronic and manual screening. If multiple publications based on the same dataset are identified, we will select the most recent study or the one with the largest sample size.

Selection process

Pairs of independent reviewers (LM, BC, PAT, IF, TM, KS, SB) will screen all titles, abstracts, and full texts to identify eligible studies. Prior to selection, we will evaluate inter-reviewer agreement on eligibility using the first 500 citations. Discrepancies between reviewers will be resolved by consensus. We will re-specify eligibility criteria if necessary and repeat the selection process until an acceptable inter-rater agreement is attained. A third reviewer will adjudicate if necessary (JRG). The level of agreement between reviewers will be assessed with Kappa coefficients[27] and agreement will be considered acceptable if kappa > 0.9. If information on eligibility is unavailable or unclear, study authors will be contacted.

Chart material

Data collection

An electronic data abstraction form will be developed with a detailed instruction manual and piloted on a representative sample of 10 publications. An example of the extraction grid is presented in Appendix 2 (in supplementary file). Pairs of reviewers with methodological and content expertise (BC, IF, PAT, MAG) will extract the following information from eligible articles: study design (systematic review, randomized controlled trial (RCT), observational study, simulation study), setting (country, year, hospital), type of economic evaluation (cost-effectiveness, cost-minimization, cost-utility, cost-benefit), perspective of economic evaluation (patient, hospital/clinic, healthcare system or societal), population (age, type of injury, injury severity, sample size), treatment and comparator, primary outcomes of the economic evaluation as stated above and authors' conclusions. Any discrepancies between reviewers will be resolved by consensus and a third reviewer will adjudicate if necessary (JRG). If important information is missing or requires clarification, we will contact study authors using up to three email attempts over 1 month to all listed authors.

Collate, summarise and report on results

Two reviewers (BC, MAG) will independently classify clinical practices according to the type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-device, therapeutic-other). Any disagreements will be adjudicated by a third reviewer (LM). Evidence of cost-effectiveness, cost-utility, cost-benefit or cost-minimization (or lack of cost-effectiveness, cost-utility or cost-benefit) for clinical practices will be presented by the type and number of studies as well as measures of economic value. All measures will be converted into iNMB using a ceiling ratio (i.e., the maximum acceptable willingness to pay per unit of health gain) of $50,000 per QALY gained. We will use a threshold of $50,000 per QALY gained because it is a widely used threshold in the literature for developed countries and using a single threshold will facilitate the comparison between studies. Results obtained with this ceiling ratio for identified clinical practices will be summarized by charting forest plots or league tables. We anticipate that meta-analyses will be inappropriate due to the heterogeneity of cost estimates both within and between settings[28].

Methodological quality of included studies

Two content experts will independently assess methodological quality using the Consensus on Health Economic Criteria[29].

ETHICS AND DISSEMINATION

The results of this systematic review will fill a major knowledge gap on the economic value of clinical practices in acute injury care. They will be used to advance knowledge on value-

based healthcare in this population. Results will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations. Ethics approval is not required as original data will not be collected.

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Blanchard Conombo led the development of the protocol and drafted the manuscript.

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Pier-Alexandre Tardif contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Imen Farhat contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Thomas Moore contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Samy Bouderba contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Kahina Soltana contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Patrick Archambault contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Simon Berthelot contributed to the development of research objectives and inclusion criteria, elaborated keywords, critically revised the manuscript and approved the final version.

François Lauzier contributed to developing keywords, validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Alexis F. Turgeon elaborated inclusion criteria and clinically significant outcomes, validated the search strategy, elaborated keywords, revised the manuscript and approved the final version.

Henry Thomas Stelfox contributed to the development of research objectives, inclusion criteria, the search strategy and the extraction form, developed keywords, revised the manuscript and approved the final version.

Michael Chassé validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Jeffrey Hoch contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Lynne Moore led the development of the protocol and drafted the manuscript. She acts as guarantor for the review.

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Patient consent: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Appendix 1. Search strategy within Pubmed (28-12-2019)

Concepts	keywords	Research	# Results
Trauma (injuries) (free text)	"injure"[TIAB] OR "injured"[TIAB] OR "injures"[TIAB] OR "injuries"[TIAB] OR "injury"[TIAB] OR "Injuries and Wounds"[TIAB] OR "Wounds and Injury"[TIAB] OR "Injury and Wounds"[TIAB] OR "Wounds, Injury"[TIAB] OR "Injuries, Wounds"[TIAB] OR "Wounds"[TIAB] OR "Wound"[TIAB] OR "Research-Related Injuries"[TIAB] OR "Injuries, Research-Related"[TIAB] OR "Injury, Research-Related"[TIAB] OR "Research Related Injuries"[TIAB] OR "Research-Related Injury"[TIAB] OR Trauma*[TIAB]	#1	1,147,497
Trauma (controlled vocabulary)	"Wounds and Injuries"[Mesh]	#2	884,715
Total trauma	#1 OR #2	#3	1,631,620*
Economic evaluation (controlled vocabulary)	"Cost-Benefit Analysis"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Resource Allocation"[Mesh] OR "Health Care Costs"[Mesh]	#4	172,964
Economic evaluation (free text)	Cost[TIAB] OR costs[TIAB] OR economic*[TIAB] OR marginal analys*[TIAB] OR budget*[TIAB] OR fee[TIAB] OR fees[TIAB] OR finance*[TIAB] OR price*[TIAB] OR pricing[TIAB] OR resource allocat*[TIAB] OR monetary value[TIAB] OR (value[TIAB] AND money*[TIAB])	#5	796,642
Total economic evaluation	#4 OR #5	#6	860,748*
Total trauma and economic evaluation	#3 AND #6	#7	42,684
Filter for humans	"animals"[Mesh] NOT "Humans"[Mesh]	#8	4,653,747
Total in humans	#7 NOT #8	#9	41,025
Filter for studies	Epidemiologic studies[MeSH:noexp] OR case control studies[MeSH] OR cohort studies[MeSH] OR Cross-sectional studies[MeSH:noexp] OR "Observational Study"[Publication Type] OR (Case control[TIAB] OR (cohort[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Cohort analy*[TIAB] OR (Follow up[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (observational[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Longitudinal[TIAB] OR Retrospective[TIAB] OR Cross sectional[TIAB] OR prospective[TIAB] OR (epidemiologic*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (correlational*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (clinical*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (famil*[TIAB] AND (study[TIAB] OR studies[TIAB]))) OR ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]))	#10	7,919,395
Total studies	#9 AND #10	#11	22,781
Date of publication	2009[DP] OR 2010[DP] OR 2011[DP] OR 2012[DP] OR 2013[DP] OR 2014[DP] OR 2015[DP] OR 2016[DP] OR 2017[DP] OR 2018[DP] OR 2019[DP]	#12	11,331,791
Total since 2009	#11 AND #12 Limits English	#13	13,892

* indicates that there are duplicate records

Appendix 2. Example of extraction grid

1. Study a) Author b) Year of publication c) Journal	**2. Type of economic evaluation**	**3. Design**	**4. Population** a) Mean age, b) Type of injury c) Sample size	**5. Perspective of economic evaluation**	**6. Treatments** a) New treatment b) Comparator	**7. New Intervention** a) cost b) outcome of Effectiveness	**8. Comparator** a) cost b) outcome of Effectiveness	**9. ICER / iNMB / iNHB / C/B**	**10. Authors' conclusion***
a) Wu et al. b) 2017 c) Annals of Emergency Medicine	Cost-utility analysis	Model-based	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after a negative CT b) No follow-up after CT	$11,477 24.03 QALY	$6,432 24.08 QALY	No follow-up dominates MRI	MRI follow-up is not cost-effective for further evaluation of unstable injury in neurologically intact patients with blunt trauma after a negative cervical spine CT result compared to no follow-up
a) Wu et al. b) 2018 c) JAMA	Cost-utility analysis	Model-based	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after normal CT b) No follow-up after CT	$14,185 24.02 QALY	$1,059 24.11 QALY	No follow-up dominates MRI follow-up after normal CT	MRI had a lower health benefit and a higher cost compared with no follow-up after a normal CT finding in patients with obtunded blunt trauma to the cervical spine
a) Calori et al. b) 2013 c) Injury, Int. J. Care Injured	Cost-utility analysis	Retrospective cohort	a) 42 years b) Tibial non-union treatment c) 54 patients	Public health care providers	a) Autologous bone graft b) Recombinant human bone morphogenetic protein 7 (rhBMP-7)	€7,665.7 0.79 QALY	€8,461.12 0.768 QALY	Autologous bone graft is a dominant strategy	Considering patients' perceived health, the costs of 1 QALY gained, using rhBMP-7, is below the $50,000 threshold (€40,751), and it can therefore be considered cost-effective
a) Oudenaarde et al. b) 2018 c) Skeletal radiology	Cost-utility analysis	RCT	a) 18-45 years b) Traumatic knee complaints c) 356 patients	Societal and healthcare	a) MRI within 2 weeks b) No MRI, but referral to an orthopedic surgeon when conservative treatment was unsatisfactory	$1,109 0.888 QALY	$837 0.899 QALY	MRI within 2 weeks is dominated	MR scan referral by the general practitioner was not cost-effective in patients with traumatic knee complaints, MRI led to more healthcare costs without improving health outcomes.
a) Cotton et al. b) 2011 c) J Trauma	Cost-utility analysis	RCT	a) N/A b) Early posttraumatic Brain injury seizure prophylaxis c) N/A	Healthcare (trauma center Level I)	a) Levetiracetam b) Phenytoin	$480 23.2 QALY	$37.50 23.6 QALY	Levetiracetam was dominated	Phenytoin is more cost-effective than levetiracetam at all reasonable prices and at all clinically plausible reductions in post-TBI seizure potential.

* Conclusions reported by the authors in these articles.

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
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
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
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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)
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
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	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)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.**

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

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ECONOMIC EVALUATION OF INTRA-HOSPITAL CLINICAL PRACTICES IN INJURY CARE: PROTOCOL FOR A 10-YEAR SYSTEMATIC REVIEW

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ABSTRACT

Introduction:

Underuse of high-value clinical practices and overuse of low-value practices are major sources of inefficiencies in modern healthcare systems. Injuries are second only to cardiovascular disease in terms of acute care costs but data on the economic impact of clinical practices for injury admissions is lacking. This study aims to summarize evidence on the economic value of intra-hospital clinical practices for injury care.

Methods and analysis:

We will perform a systematic review to identify research articles in economic evaluation of intra-hospital clinical practices in acute injury care. We will search Medline and databases such as Embase, Web of Science, NHS Economic Evaluation Database, Cochrane CENTRAL, BIOSIS, and CINAHL for randomized or non-randomized controlled trials and observational studies using a combination of keywords and controlled vocabulary. We will consider the following outcomes relative to economic evaluations: Incremental Cost-Effectiveness Ratio, Incremental Cost-Utility Ratio, incremental Net Health Benefit, incremental Net Monetary Benefit (iNMB) and incremental Cost-Benefit Ratio. Pairs of independent reviewers will evaluate studies that meet eligibility criteria and extract data from included articles using an electronic data extraction form. All outcomes will be converted into iNMB. We will report iNMB for practices classified by type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-other). Results obtained with a ceiling ratio of $50,000 per QALY gained for identified clinical practices will be summarized by charting forest plots. In line with Cochrane recommendations for systematic reviews of economic evaluations, meta-analyses will not be conducted.

Ethics and dissemination:

Ethics approval is not required as original data will not be collected. This study will summarize existing evidence on the economic value of clinical practices in injury care. Results will be used to advance knowledge on value-based care for injury admissions and will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations.

Strengths and limitations of this study

- Fill a major knowledge gap on the economic value of intra-hospital clinical practices for acute injury care.
- Advance the agenda on value-based healthcare for injury admissions.
- Inform research priorities.
- Represents a crucial step towards the de-adoption of low-value clinical practices in acute injury care.
- For feasibility reasons, restricted to studies published in English since 2009.

INTRODUCTION

In Canada, injuries represent the leading cause of potential years of life lost and cost more than heart and stroke diseases combined[1]. In 2035, the direct costs of injury are expected to reach $CAN 75 billion while they were estimated at $CAN 27 billion in 2007[1], representing an increase of almost 200% [2]. Injuries represent the third leading cause of potential years of life lost in the United States [3]. The estimated total lifetime medical and work loss costs associated with fatal and non-fatal injuries in the US were $671 billion in 2013 [4].

Regional variations in injury outcomes between healthcare providers have been observed in Canada, the United States and the United Kingdom that are not explained by patient case mix [5-7]. This evidence of suboptimal injury outcomes suggests that efforts must be made to optimise clinical practices in injury care[8]. Value-based health care is defined as "care that is tailored for optimising health and wellbeing by delivering what is needed, wanted, clinically effective, affordable, equitable, and responsible in its use of resources"[9, 10]. When patients do not receive tests and treatments that have been shown to be effective for their condition, we refer to *underuse[11]*. Up to 50% of patients admitted for injury do not receive recommended care[12]. The economic impact of the *underuse of recommended care* implies missed opportunities of healthcare cost savings, averted productivity losses, and the monetized value of potential reductions in morbidity and mortality. When patients undergo tests and treatments that are not supported by evidence and/or could expose them to unnecessary harm, they receive low-value care, widely referred to as *overuse[13]*. Overuse is driven by low-value clinical practices, which consume up to 30% of healthcare resources and threaten the sustainability of affordable and accessible health care [14-17]. From an economic evaluation standpoint, the overuse of low-value practices implies inefficiency in resources use that results in a waste of resources. More importantly, low-value practices expose patients to adverse events and delays to effective treatment [18]. The estimated overuse of healthcare services in the US amounts to $780 billion annually[19].

To achieve value-based care, guidelines and recommendations should target both underuse and overuse and be supported by data provided from economic evaluations[20]. However, current guidelines on clinical practices in injury care focus almost exclusively on underuse and are rarely supported by evidence of cost-effectiveness [21-24]. This systematic review aims to review evidence of the economic value of intra-hospital clinical practices in acute injury care to advance knowledge on value-based care in this patient population.

METHODS AND ANALYSIS

The structure of the protocol follows PRISMA-P guidelines for systematic reviews[25]. Any changes to the protocol will be documented in the final published report.

Patient and Public Involvement
No patient involved

Relevant studies
Inclusion criteria
We will include research articles, systematic reviews, reports and guidelines on cost-effectiveness analyses (e.g. cost per life year gained), cost-utility analyses (e.g. cost per quality-adjusted life year gained or cost per disability-adjusted life year averted), cost-benefit and cost-minimization analyses of intra-hospital clinical practices for patients treated in hospital for injury. Clinical practices could include admissions, transfers, consultations, as well as diagnostic or therapeutic procedures. A "do nothing" strategy, standard care or any other strategy will be considered as potential comparators.

The following outcomes of economic evaluation will be considered: Incremental Cost-Effectiveness Ratio "ICER", Incremental Cost-Utility Ratio "ICUR", incremental Net Monetary Benefit "iNMB", incremental Net Health Benefit "iNHB" and the incremental Cost-Benefit ratio. Studies identifying the results of the economic evaluation as one clinical practice being dominant or dominated will be included. Such results would indicate that one comparator is less costly and more effective than the other. We will restrict the review to studies published in English in the last ten years (from January 2009) to ensure feasibility of the review and results that are current.

Exclusion criteria
We will not include cost-consequences analyses, budget impact studies, narrative reviews, research protocols or conference abstracts. Studies providing incremental costs without incremental effectiveness or vice versa will not be included. Studies on experimental interventions, military injuries, cadavers or animals will be excluded. Studies in which there is no comparator group will be excluded. Our systematic review will be limited to evidence from high-income countries.

Information sources
We will search MEDLINE (via PubMed), EMBASE, Web of Science, NHS Economic Evaluation Database, Health Technology Assessment Database, EconLit, Tufts CEA Registry, Cochrane CENTRAL, BIOSIS, and CINAHL to identify research articles on economic evaluation of clinical practices specific to intrahospital acute injury care. The grey literature will be searched through thesis repositories, injury association websites, healthcare quality websites and the Web of Knowledge. Thesis repositories include Thesis portal Canada, Electronic Thesis Online Service (EThOS), Digital Access to Research Theses (DART)-Europe E-Theses Portal, the National Library of Australia's Trove and ProQuest Dissertations & Theses Global. Healthcare quality websites include the World

Health Organization, National Institute for Health and Care Excellence, National Association for Healthcare Quality, National Quality Forum, Lown Institute, Agency for Healthcare Research and Quality, Choosing Wisely, Canadian Institutes for Health Information, Australasian Association for Quality in Healthcare. Injury organisations include the American College of Surgeons, Trauma Association of Canada, International Association for Trauma Surgery and Intensive Care, Australasian Trauma Society, Trauma Audit Research Network, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, American Trauma Society, British Trauma Society, Orthopaedic Trauma Association, Western Trauma Association, Trauma.org, The Society of Trauma Nurses, International Trauma Anaesthesia and Critical Care Society, the BrainTrauma Foundation and patient advocacy organisations including Safer Healthcare Now!

Search strategy

A rigorous strategy will be designed using a combination of Boolean terms with relevant keywords and subject headings covering 'injury', 'trauma' and 'economic evaluation' for EMBASE (EMBASE tree; EMTREE) and PubMed (Medical Subject Headings; MeSH), and then adapted to the remaining databases (see Appendix 1 in supplementary file for the preliminary search strategy of December 28, 2019). Clinicians in the project steering committee and information specialists will be consulted to refine the search strategy using the Peer Review of Electronic Search Strategies checklist[26]. The sensitivity of our search strategy will be evaluated by identifying between five and ten sentinel articles and checking whether they are detected.

Select studies

Data management

Citations will be managed using EndNote software (version X7.0.1, New York City: Thomson Reuters, 2011). Duplicates will be identified and removed via electronic and manual screening. If multiple publications based on the same dataset are identified, we will select the most recent study or the one with the largest sample size.

Selection process

Pairs of independent reviewers (LM, BC, PAT, IF, TM, KS, SB) will screen all titles, abstracts, and full texts to identify eligible studies. Prior to selection, we will evaluate inter-reviewer agreement on eligibility using the first 500 citations. Discrepancies between reviewers will be resolved by consensus. We will re-specify eligibility criteria if necessary and repeat the selection process until an acceptable inter-rater agreement is attained. A third reviewer will adjudicate if necessary (JRG). The level of agreement between reviewers will be assessed with Kappa coefficients[27] and agreement will be considered acceptable if kappa > 0.9. If information on eligibility is unavailable or unclear, study authors will be contacted.

Chart material

Data collection

An electronic data abstraction form will be developed with a detailed instruction manual and piloted on a representative sample of 10 publications. An example of the extraction grid is presented in Appendix 2 (in supplementary file). Pairs of reviewers with methodological and content expertise (BC, IF, PAT, MAG) will extract the following information from eligible articles: study design (systematic review, randomized controlled trial (RCT), observational study, simulation study), setting (country, year, hospital), type of economic evaluation (cost-effectiveness, cost-minimization, cost-utility, cost-benefit), perspective of economic evaluation (patient, hospital/clinic, healthcare system or societal), population (age, type of injury, injury severity, sample size), treatment and comparator, primary outcomes of the economic evaluation as stated above and authors' conclusions. Any discrepancies between reviewers will be resolved by consensus and a third reviewer will adjudicate if necessary (JRG). If important information is missing or requires clarification, we will contact study authors using up to three email attempts over 1 month to all listed authors.

Collate, summarise and report on results

Two reviewers (BC, MAG) will independently classify clinical practices according to the type of practice (hospitalisation, consultation, diagnostic, therapeutic-surgical, therapeutic-drugs, therapeutic-device, therapeutic-other). Any disagreements will be adjudicated by a third reviewer (LM). Evidence of cost-effectiveness, cost-utility, cost-benefit or cost-minimization (or lack of cost-effectiveness, cost-utility or cost-benefit) for clinical practices will be presented by the type and number of studies as well as measures of economic value. All measures will be converted into iNMB using a ceiling ratio (i.e., the maximum acceptable willingness to pay per unit of health gain) of $50,000 per QALY gained. We will use a conservative threshold of $50,000 per QALY gained because it is a widely used threshold in the literature for developed countries and using a single threshold will facilitate the comparison between studies. Measures of iNMB based on this threshold will represent a conservative estimate of incremental net monetary benefits. Results obtained with this ceiling ratio for identified clinical practices will be summarized by charting forest plots or league tables. We anticipate that meta-analyses will be inappropriate due to the heterogeneity of cost estimates both within and between settings[28].

Methodological quality of included studies

Two content experts will independently assess methodological quality using the Consensus on Health Economic Criteria[29].

ETHICS AND DISSEMINATION

The results of this systematic review will fill a major knowledge gap on the economic value of clinical practices in acute injury care. They will be used to advance knowledge on value-based healthcare in this population. Results will be disseminated through a peer-reviewed article, international scientific meetings and clinical and healthcare quality associations. Ethics approval is not required as original data will not be collected.

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Jason Robert Guertin contributed to the development of research objectives and inclusion criteria, elaborated keywords, validated the data extraction form, critically revised the manuscript and approved the final version.

Pier-Alexandre Tardif contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Imen Farhat contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Thomas Moore contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Samy Bouderba contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Kahina Soltana contributed to the elaboration of keywords, developed and tested the search strategy, critically revised and approved the final version of the manuscript.

Patrick Archambault contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Simon Berthelot contributed to the development of research objectives and inclusion criteria, elaborated keywords, critically revised the manuscript and approved the final version.

François Lauzier contributed to developing keywords, validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Alexis F. Turgeon elaborated inclusion criteria and clinically significant outcomes, validated the search strategy, elaborated keywords, revised the manuscript and approved the final version.

Henry Thomas Stelfox contributed to the development of research objectives, inclusion criteria, the search strategy and the extraction form, developed keywords, revised the manuscript and approved the final version.

Michael Chassé validated the search strategy and the data extraction form, revised the manuscript and approved the final version.

Jeffrey Hoch contributed to working definitions, developed keywords, revised the manuscript and approved the final version.

Lynne Moore led the development of the protocol and drafted the manuscript. She acts as guarantor for the review.

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Appendix 1. Search strategy within Pubmed (28-12-2019)

Concepts	keywords	Research	# Results
Trauma (injuries) (free text)	"injure"[TIAB] OR "injured"[TIAB] OR "injures"[TIAB] OR "injuries"[TIAB] OR "injury"[TIAB] OR "Injuries and Wounds"[TIAB] OR "Wounds and Injury"[TIAB] OR "Injury and Wounds"[TIAB] OR "Wounds, Injury"[TIAB] OR "Injuries, Wounds"[TIAB] OR "Wounds"[TIAB] OR "Wound"[TIAB] OR "Research-Related Injuries"[TIAB] OR "Injuries, Research-Related"[TIAB] OR "Injury, Research-Related"[TIAB] OR "Research Related Injuries"[TIAB] OR "Research-Related Injury"[TIAB] OR Trauma*[TIAB]	#1	1,147,497
Trauma (controlled vocabulary)	"Wounds and Injuries"[Mesh]	#2	884,715
Total trauma	#1 OR #2	#3	1,631,620*
Economic evaluation (controlled vocabulary)	"Cost-Benefit Analysis"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Resource Allocation"[Mesh] OR "Health Care Costs"[Mesh]	#4	172,964
Economic evaluation (free text)	Cost[TIAB] OR costs[TIAB] OR economic*[TIAB] OR marginal analys*[TIAB] OR budget*[TIAB] OR fee[TIAB] OR fees[TIAB] OR finance*[TIAB] OR price*[TIAB] OR pricing[TIAB] OR resource allocat*[TIAB] OR monetary value[TIAB] OR (value[TIAB] AND money*[TIAB])	#5	796,642
Total economic evaluation	#4 OR #5	#6	860,748*
Total trauma and economic evaluation	#3 AND #6	#7	42,684
Filter for humans	"animals"[Mesh] NOT "Humans"[Mesh]	#8	4,653,747
Total in humans	#7 NOT #8	#9	41,025
Filter for studies	Epidemiologic studies[MeSH:noexp] OR case control studies[MeSH] OR cohort studies[MeSH] OR Cross-sectional studies[MeSH:noexp] OR "Observational Study"[Publication Type] OR (Case control[TIAB] OR (cohort[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Cohort analy*[TIAB] OR (Follow up[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (observational[TIAB] AND (study[TIAB] OR studies[TIAB])) OR Longitudinal[TIAB] OR Retrospective[TIAB] OR Cross sectional[TIAB] OR prospective[TIAB] OR (epidemiologic*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (correlational*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (clinical*[TIAB] AND (study[TIAB] OR studies[TIAB])) OR (famil*[TIAB] AND (study[TIAB] OR studies[TIAB]))) OR ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]))	#10	7,919,395
Total studies	#9 AND #10	#11	22,781
Date of publication	2009[DP] OR 2010[DP] OR 2011[DP] OR 2012[DP] OR 2013[DP] OR 2014[DP] OR 2015[DP] OR 2016[DP] OR 2017[DP] OR 2018[DP] OR 2019[DP]	#12	11,331,791
Total since 2009	#11 AND #12 Limits English	#13	13,892

* indicates that there are duplicate records

Appendix 2. Example of extraction grid

1. Study a) Author b) Year of publication c) Journal	2. Type of economic evaluation	3. Design	4. Population a) Mean age, b) Type of injury c) Sample size	5. Perspective of economic evaluation	6. Treatments a) New treatment b) Comparator	7. New Intervention	8. Comparator	9. ICER / iNMB / iNHB / C/B	10. Authors' conclusion*
a) Wu et al. b) 2017 c) Annals of Emergency Medicine	Cost-utility analysis	Model-based	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after a negative CT b) No follow-up after CT	$11,477 24.03 QALY	$6,432 24.08 QALY	No follow-up dominates MRI	MRI follow-up is not cost-effective for further evaluation of unstable injury in neurologically intact patients with blunt trauma after a negative cervical spine CT result compared to no follow-up
a) Wu et al. b) 2018 c) JAMA	Cost-utility analysis	Model-based	a) 40 years b) blunt Cervical Spine trauma c)N/A	Societal	a) MRI follow-up after normal CT b) No follow-up after CT	$14,185 24.02 QALY	$1,059 24.11 QALY	No follow-up dominates MRI follow-up after normal CT	MRI had a lower health benefit and a higher cost compared with no follow-up after a normal CT finding in patients with obtunded blunt trauma to the cervical spine
a) Calori et al. b) 2013 c) Injury, Int. J. Care Injured	Cost-utility analysis	Retrospective cohort	a) 42 years b) Tibial non-union treatment c) 54 patients	Public health care providers	a) Autologous bone graft b) Recombinant human bone morphogenetic protein 7 (rhBMP-7)	€7,665.7 0.79 QALY	€8,461.12 0.768 QALY	Autologous bone graft is a dominant strategy	Considering patients' perceived health, the costs of 1 QALY gained, using rhBMP-7, is below the $50,000 threshold (€40,751), and it can therefore be considered cost-effective
a) Oudenaarde et al. b) 2018 c) Skeletal radiology	Cost-utility analysis	RCT	a) 18-45 years b) Traumatic knee complaints c) 356 patients	Societal and healthcare	a) MRI within 2 weeks b) No MRI, but referral to an orthopedic surgeon when conservative treatment was unsatisfactory	$1,109 0.888 QALY	$837 0.899 QALY	MRI within 2 weeks is dominated	MR scan referral by the general practitioner was not cost-effective in patients with traumatic knee complaints, MRI led to more healthcare costs without improving health outcomes.
a) Cotton et al. b) 2011 c) J Trauma	Cost-utility analysis	RCT	a) N/A b) Early posttraumatic Brain injury seizure prophylaxis c) N/A	Healthcare (trauma center Level I)	a) Levetiracetam b) Phenytoin	$480 23.2 QALY	$37.50 23.6 QALY	Levetiracetam was dominated	Phenytoin is more cost-effective than levetiracetam at all reasonable prices and at all clinically plausible reductions in post-TBI seizure potential.

* Conclusions reported by the authors in these articles.

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
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
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
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
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
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
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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)
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
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
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
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
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	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)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** 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.**

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