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Electronic Health Records, Interoperability, and Patient Safety in Health Systems of High-Income Countries: A Systematic Review Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-044941
Article Type:	Protocol
Date Submitted by the Author:	19-Sep-2020
Complete List of Authors:	<p>Li, Edmond; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; London School of Hygiene and Tropical Medicine Faculty of Infectious and Tropical Diseases, Clinical Research Department</p> <p>Neves, Ana Luisa; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; University of Porto, Center for Health Technology and Services Research / Department of Community Medicine, Health Information and Decision</p> <p>Clarke, Jonathan; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; Imperial College London, Centre for Mathematics of Precision Healthcare</p> <p>Ashrafian, Hutan; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer</p> <p>Darzi, Ara; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer</p>
Keywords:	<p>Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT</p>

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Electronic Health Records, Interoperability, and Patient Safety in Health Systems of High-Income Countries: A Systematic Review Protocol

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Keywords [MeSH terms]: electronic health records, electronic medical records, computerised patient records, health information technology, health information exchanges, interoperability, patient safety, patient harm, adverse events, health outcomes

Word count: 1821

Target journal: BMJ Open

Abstract

Introduction

The availability and routine use of electronic health records (EHRs) have become commonplace in healthcare systems of many high-income countries. While there is an ever-growing body of literature pertaining to EHR use, evidence surrounding the importance of EHR interoperability and its impact on patient safety remains less clear. There is therefore a need and opportunity to evaluate the evidence available regarding this relationship so as to better inform health informatics development and policies in the years to come.

Objective

This systematic review aims to evaluate the impact of EHR interoperability on patient safety in health systems of high-income countries.

Methods and analysis

A systematic literature review will be conducted via a computerised search through three databases: PubMed, Embase, and HMIC for relevant articles published between March 2010 and March 2020. Outcomes of interest will include: impact on patient safety, and the broader effects on health systems. Quality of the randomised quantitative studies will be assessed using Cochrane Risk of Bias Tool. Non-randomised papers will be evaluated with the Risk of Bias In Non-Randomised Studies - of Interventions (ROBINS-I) tool. Drummond's Checklist will be utilised for publications pertaining to economic evaluation. The National Institute for Health and Care Excellence (NICE) quality appraisal checklist will be used to assess qualitative studies. A narrative synthesis will be conducted for included studies, and the body of evidence will be summarised in a summary of findings table.

Ethics and dissemination

This review will summarise published studies with non-identifiable data and therefore does not require ethical approval. This protocol complies with the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols guidelines. Findings will be disseminated through preprints, open access peer-reviewed publication, and conference presentations. Patients or members of the public were not involved in the design of this study.

Strengths and limitations of this study

Strengths	Limitations
<ul style="list-style-type: none"> • Comprehensive characterisation of interventions using interoperable EHRs • Summary and quality appraisal of existing evidence on the potential impact on patient safety • Inclusion of both quantitative and qualitative methods can provide a comprehensive overview of the multitude of ways in which interoperable EHRs may affect patient safety and health systems. 	<ul style="list-style-type: none"> • The heterogeneity of methods and outcomes assessed may obscure the true effect interoperable EHRs have had on patient safety in the clinical setting • Potential small sample size in subgroup analyses, may negatively impact the statistical power in quantitative data synthesis.

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| <ul style="list-style-type: none">• The proposed review attempts to answer a pragmatic question which is integral to influencing future health informatics development and policies. | |
|--|--|

PROSPERO registration number [CRD42020209285]

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Introduction

Electronic health records (EHRs) have become an integral part of modern healthcare since their initial mainstream implementation in the mid-late 2000s through the passing of the Health Information Technology for Economic and Clinical Health Act (HITECH) in the United States and the NHS National Programme for IT initiative (NPfIT) in England (1–4). From the documentation & retrieval of patient records and the prescription of medications, to coordinating complex care plans between different healthcare providers and electronic billing, EHRs fulfil a multitude of roles for both clinicians and patients alike (5–9).

In order to achieve EHR's full potential, it is critical to improve interoperability - i.e. “*the ability of health information systems to work together within and across organisation boundaries in order to advance effective delivery of healthcare for individuals and communities*” (10). The lack of universal interoperability is often cited as one of the many significant shortcomings of EHRs currently in use, resulting in duplication in healthcare costs, increased clinician workload fatigue, and poses a potential risk to patient safety (2). This is especially problematic for patient populations with chronic conditions, polypharmacy, and multiple comorbidities who are reliant upon effective patient information sharing via EHRs to facilitate their care (11).

In the fragmented EHR landscape of the United Kingdom, understanding this poor interoperability and accurately measuring its cost both to patient safety and the health system as a whole, remain challenging (12). Although there is a growing body of literature investigating areas such as the facilitators and barriers to EHR greater adoption, technical capabilities, and usability (13,14), no systematic review has been conducted exploring specifically the problem of interoperability amongst the assortment of EHRs in use, how it affects patient safety, and ultimately the financial cost savings lost to health systems.

In a recent systematic review by Dobrow *et al.* assessing the effects of EHR and HIT interoperability on health systems, 130 publications were included, with the majority being studies conducted in the United States, utilised quantitative methods, and focussed primarily in acute healthcare settings. The authors noted the use of interoperable EHRs had a positive impact on outcomes measures such as quality of care and productivity (13). However, in domains such as stakeholder engagement, performance & reliability, security & privacy, information quality, and ease of use, the benefits of interoperable EHRs was less clear (13). Amongst the 130 publications, 17 were reviews with the majority directed at exploring facilitators & barriers to EHR implementation, and the general benefits and impact of EHR use. While this review did focus on studies pertaining to the topic of interoperable EHRs, this was done so only from a broad perspective and included studies exploring a wide range of outcomes related to the effects of EHR on healthcare rather than specifically on their implications to patient safety.

In another review by Hersh *et al.*, the authors explored how health information exchange (HIE) affected health systems on a variety of domains, including costs, healthcare utilisation, health outcomes, healthcare worker attitudes, and sustainability. Despite the widespread routinely use of HIE, the authors described a general lack of robust evidence on the quality, costs, efficiency, usage, and sustainability (15). However, there was some evidence demonstrating HIEs being

associated with reduced utilisation and costs in emergency care settings despite methodological issues being present in many of the included publications (15). Although this review was ambitious in the wide scope of interest regarding the effects of HIE use, patient safety was not a primary topic of focus. Another limitation of this study was that it only contained US-based publications, and thus findings lack generalisability internationally to other health systems in high-income countries (HIC) which are both organised, financed differently.

Research aim

The overall aim of this literature review is to explore how EHR interoperability impacts patient safety, in the context of health systems in HICs. The results generated will aim to inform healthcare policymakers and help shape more effective EHR system implementation and modernisation efforts in the coming years.

Methods and analysis

Search strategy

A computerised search of the literature published in the last 10 years (March 2010 to March 2020) search will be performed on PubMed, Embase and Health Management Information Consortium (HMIC). The list of search strings used will include both free text and controlled terms, whenever supported (Table 1) and will be iteratively refined in consultation with the Imperial College St. Mary's campus medical librarian.

Grey literature sources will also be searched, including registrations in the International Prospective Register of Systematic Reviews, reports of relevant stakeholder organisations (NHS England, American Medical Informatics Association (AMIA), eHealth at WHO, and conference proceedings (last 5 years) of several related conferences (AMIA, MedInfo, Medicine 2.0, Medicine X)), in order to identify possible additional studies that meet the inclusion criteria.

The search has also been restricted to HIC and articles published in English only.

Table 1: Concepts and database search terms

Electronic health records		Interoperability		Patient safety
<ul style="list-style-type: none"> ● Electronic health record* / EHR ● Electronic medical record* / EMR ● Health information exchange / HIE ● Health information technology / HIT ● EHR-based interventions 	AND	<ul style="list-style-type: none"> ● Interoperabl* ● Interoperability ● Standards of information 	AND	<ul style="list-style-type: none"> ● Patient safety ● Patient adj1 incident* ● Adverse adj1 event* ● Patient adj1 outcome* ● Patient adj1 harm ● Risk management

• Computerised patient record* / CPR				
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Study selection criteria

A summary of the population, intervention, comparison, outcomes, and type of studies being considered is provided in **Table 2**. This systematic review will focus on studies performed in high-income countries and published in English only. Studies assessing the impact of EHR interoperability will be included. Interventions will include EHR systems interoperable with other health information technology systems both within and across healthcare facilities, as well as those used in tertiary and community settings. The primary outcomes to be considered in this review will be safety outcomes, including adverse events/incidents, safety-related patient experiences, and health outcomes. In addition, secondary outcomes would include studies exploring the broader impact of interoperable EHRs on health systems such as cost effectiveness and clinical culture amongst healthcare providers on the topic. Both qualitative and quantitative studies will be included. Reference lists of the selected articles will also be screened for papers which may have been missed by the initial database search but still meet the eligibility criteria.

Table 2: PICO inclusion criteria

<i>Population</i>	High-income countries utilising electronic health records
<i>Intervention</i>	EHRs with interoperability
<i>Comparison</i>	Usual care (i.e. existing baseline of interoperability)
<i>Outcome</i>	Impact on patient safety and quality of care

Screening

Articles to be included will be screened by two independent reviewers, following the process described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (16). The initial screening will be done by the first reviewer based on the publication titles, followed by a second screening based on the abstracts. Included abstracts will then be fully reviewed by two independent researchers to produce a unified selection of articles to be included in this review. Cohen's kappa will be calculated to ensure inter-rater agreement and consistency in the selection of studies to be included (17,18). Any disagreements will be resolved by consensus; if a Cohen's kappa value of less than 0.6 is reported, the discrepancies will be addressed through discussions with a more experienced third investigator.

Data extraction & analysis

Data extraction will be performed using a standardised extraction table for each of the two investigators to summarise the characteristics and findings of each included study, including name of the first author, year of publication, study design, number of participants, retention rates, setting characteristics, outcome measures, and main results. The content of the two summary tables will then be aggregated and reviewed once more by both investigators, with any disagreements being solved by the third senior investigator.

Quality assessment

The quality of randomised controlled trials and cluster randomised trials will be assessed using the Cochrane Risk of Bias Tool (19), and the quality of non-randomised intervention studies (i.e., case control, cohort, quasi-experimental) will be appraised using the 'Risk of Bias In Non-

1
2
3 Randomised Studies - of Interventions' (ROBINS-I) tool (20). For cost-effectiveness studies, the
4 Drummond's checklist for assessing economic evaluations will be used (21). The National
5 Institute for Health and Care Excellence (NICE) quality appraisal checklist will be utilised to
6 assess the selected qualitative studies (22). Two independent reviewers will score the selected
7 studies and any disagreements will be resolved by a third person. A risk of bias table along with
8 an overall, collective bias narrative will be produced to summarise the biases of outcomes
9 observed amongst the evaluated studies.
10

11 Descriptive analysis

12 A narrative synthesis will be conducted for all the included studies.

13 Quantitative studies with comparable outcome measures will be aggregated to allow for
14 comparative analyses whenever possible. However, no meta-analysis will be done for this
15 systematic review as the likely heterogeneity of the outcomes would make this impractical.
16 Qualitative studies will be thematically analysed. Those that demonstrate related, prominent
17 themes in their findings will be grouped together and collectively summarised via a thematic
18 narrative. The body of evidence will be summarised in two separate Summary of Findings tables
19 (for both qualitative and quantitative studies) in accordance to the 'Grading of Recommendations
20 Assessment, Development and Evaluation' (GRADE) criteria where possible (23).
21

22 Patient and public involvement

23 This systematic literature review saw no direct participation by patients or the public during the
24 design of this study. However, this study was designed following a series of structured
25 interviews with patients regarding their experience of attending multiple institutions for hospital
26 care (24). As this literature review will be used to form the basis for subsequent studies exploring
27 the topic including ones involving patients, findings from this review will be shared with patient
28 research groups to gain feedback and encourage further discourse surrounding the topic of EHR
29 interoperability and patient safety.
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32 Amendments

33 Any amendments to this protocol will be documented with reference to saved searches and
34 analysis methods, which will be recorded in bibliographic databases, Mendeley and Excel
35 templates for data collection and synthesis.
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39 Discussion

40 One of the primary strengths stemming from the almost exploratory nature of this systematic
41 review is the ability to generate a succinct, comprehensive appraisal of the best evidence
42 currently available regarding how EHR interoperability impacts patient care and safety. By
43 publishing this review protocol beforehand, we demonstrate a clear, robust, and transparent
44 approach to aggregating the anticipated assortment of literature on the subject in question.
45 There are also some potential limitations to be acknowledged. A potential challenge would be
46 the likely anticipated heterogeneity in methodology of the included articles. With such diverse
47 means of measuring and assessing the effects of EHR interoperability, this will likely make
48 comparisons between studies difficult and may obscure the true measure of effect EHR
49 interoperability has had in the clinical setting. To mitigate this risk, outcomes will be grouped
50 whenever possible, and summarised as a narrative synthesis. However, this can also represent a
51 strength as it will provide a comprehensive overview on the subject, capitalising on various
52 research methodologies, and providing novel insights on the impact of interoperable EHR
53 systems on patient safety.
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Acknowledgments

We would like to thank Michael Gainsford (Library Manager and Liaison Librarian at Imperial College London) for his support and guidance provided to improve the composition of the search terms and procedural aspects of the overall search strategy. JC acknowledges support from the Wellcome Trust [215938/Z/19/Z].

Funding

This research was supported through the Imperial College National Institute for Health Research (NIHR) Patient Safety Translational Research Centre (PSTRC) and the Imperial College Biomedical Research Centre (BRC). However, the funder/sponsor has had no role in development and drafting of this protocol.

For peer review only

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

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
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	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	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)	7
	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	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

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

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

BMJ Open

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Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-044941.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Feb-2021
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Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health policy, Public health, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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1 **Electronic Health Records, Interoperability, and Patient Safety in** 2 **Health Systems of High-Income Countries: A Systematic Review** 3 **Protocol**

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36 **Keywords [MeSH terms]:** electronic health records, electronic medical records, computerised
37 patient records, health information technology, health information exchanges, interoperability,
38 patient safety, patient harm, adverse events, health outcomes

39 **Word count:** 2723

41 Abstract

42 Introduction

43 The availability and routine use of electronic health records (EHRs) have become commonplace
44 in healthcare systems of many high-income countries. While there is an ever-growing body of
45 literature pertaining to EHR use, evidence surrounding the importance of EHR interoperability
46 and its impact on patient safety remains less clear. There is therefore a need and opportunity to
47 evaluate the evidence available regarding this relationship so as to better inform health
48 informatics development and policies in the years to come.

50 Objective

51 This systematic review aims to evaluate the impact of EHR interoperability on patient safety in
52 health systems of high-income countries.

54 Methods and analysis

55 A systematic literature review will be conducted via a computerised search through four
56 databases: PubMed, Embase, HMIC, and PsycInfo for relevant articles published between 2010
57 and 2020. Outcomes of interest will include: impact on patient safety, and the broader effects on
58 health systems. Quality of the randomised quantitative studies will be assessed using Cochrane
59 Risk of Bias Tool. Non-randomised papers will be evaluated with the Risk of Bias In Non-
60 Randomised Studies - of Interventions (ROBINS-I) tool. Drummond's Checklist will be utilised
61 for publications pertaining to economic evaluation. The National Institute for Health and Care
62 Excellence (NICE) quality appraisal checklist will be used to assess qualitative studies. A
63 narrative synthesis will be conducted for included studies, and the body of evidence will be
64 summarised in a summary of findings table.

66 Ethics and dissemination

67 This review will summarise published studies with non-identifiable data and therefore does not
68 require ethical approval. This protocol complies with the Preferred Reporting Items for
69 Systematic Review and Meta-Analyses Protocols guidelines. Findings will be disseminated
70 through preprints, open access peer-reviewed publication, and conference presentations. Patients
71 or members of the public were not involved in the design of this study.

73 Article Summary

74 Strengths and limitations of this study

75 Strengths

- 76 • Inclusion of quantitative, qualitative, and mixed-methods studies can provide a
77 comprehensive overview of the multitude of ways in which interoperable EHRs may
78 affect patient safety and health systems.
- 79 • The proposed review attempts to answer a pragmatic question which is integral to
80 influencing future health informatics development and policies.

82 Limitations

- 83 • The heterogeneity of methods and outcomes assessed may obscure the true effect
84 interoperable EHRs have had on patient safety in the clinical setting.

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3 85 • Potential small sample size in subgroup analyses, may negatively impact the statistical
4 86 power in quantitative data synthesis.
5 87 • Limiting the search strategy to English-only publications may not capture studies
6 88 exploring the EHR interoperability experiences of health systems in non-English
7 89 speaking countries.
8 90

9 91 [PROSPERO registration number \[CRD42020209285\]](#)

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97 Introduction

98 Electronic health records (EHRs) have become an integral part of modern healthcare since their
99 initial mainstream implementation in the mid-late 2000s through the passing of the Health
100 Information Technology for Economic and Clinical Health Act (HITECH) in the United States
101 and the NHS National Programme for IT initiative (NPfIT) in England (1–4). From the
102 documentation & retrieval of patient records and the prescription of medications, to coordinating
103 complex care plans between different healthcare providers and electronic billing, EHRs fulfil a
104 multitude of roles for both clinicians and patients alike (5–9).

105
106 In order to achieve EHR's full potential, it is critical to improve interoperability - i.e., “*the ability*
107 *of health information systems to work together within and across organisation boundaries in*
108 *order to advance effective delivery of healthcare for individuals and communities*” (10). The lack
109 of universal interoperability is often cited as one of the many significant shortcomings of EHRs
110 currently in use, resulting in duplication in healthcare costs, increased clinician workload fatigue,
111 and poses a potential risk to patient safety (2). This is especially problematic for patient
112 populations with chronic conditions, polypharmacy, and multiple comorbidities who are reliant
113 upon effective patient information sharing via EHRs to facilitate their care (11).

114
115 Poor EHR interoperability is detrimental to patient safety and costly for health systems. Its
116 consequences range from increased risks of medication errors, fragmentation of patient data, to
117 iatrogenic harm resulting from redundant testing, and additional healthcare expenditure (12–17).
118 In the fragmented EHR landscape of the United Kingdom, measuring the effect poor EHR
119 interoperability has in the National Health Service (NHS), remain challenging (18). Although
120 there is a growing body of literature investigating areas such as the facilitators and barriers to
121 EHR greater adoption, technical capabilities, and usability (19,20), no systematic review has
122 been conducted exploring specifically the problem of interoperability amongst the assortment of
123 EHRs in use, how it affects patient safety, and ultimately the financial cost savings lost to health
124 systems.

125
126 In a recent systematic review by Dobrow *et al.* assessing the effects of EHR and HIT
127 interoperability on health systems, 130 publications were included, with the majority being
128 studies conducted in the United States, utilised quantitative methods, and focussed primarily in
129 acute healthcare settings. The authors noted the use of interoperable EHRs had a positive impact
130 on outcomes measures such as quality of care and productivity (19). However, in domains such
131 as stakeholder engagement, performance & reliability, security & privacy, information quality,
132 and ease of use, the benefits of interoperable EHRs was less clear (19). Amongst the 130
133 publications, 17 were reviews with the majority directed at exploring facilitators & barriers to
134 EHR implementation, and the general benefits and impact of EHR use. While this review did
135 focus on studies pertaining to the topic of interoperable EHRs, this was done so only from a
136 broad perspective and included studies exploring a wide range of outcomes related to the effects
137 of EHR on healthcare rather than specifically on their implications to patient safety.

138
139 In another review by Hersh *et al.*, the authors explored how health information exchange (HIE)
140 affected health systems on a variety of domains, including costs, healthcare utilisation, health

141 outcomes, healthcare worker attitudes, and sustainability. Despite the widespread routinely use
 142 of HIE, the authors described a general lack of robust evidence on the quality, costs, efficiency,
 143 usage, and sustainability (21). However, there was some evidence demonstrating HIEs being
 144 associated with reduced utilisation and costs in emergency care settings despite methodological
 145 issues being present in many of the included publications (21). Although this review was
 146 ambitious in the wide scope of interest regarding the effects of HIE use, patient safety was not a
 147 primary topic of focus. Another limitation of this study was that it only contained US-based
 148 publications, and thus findings lack generalisability internationally to other health systems in
 149 high-income countries (HIC) which are both organised, financed differently.

150 Research aim

151 The overall aim of this literature review is to explore how EHR interoperability impacts patient
 152 safety, in the context of health systems in HICs. The results generated will aim to inform
 153 healthcare policymakers and help shape more effective EHR system implementation and
 154 modernisation efforts in the coming years.

155 Methods and analysis

156 Search strategy

157 A computerised search of the literature published in the last 10 years (2010 to 2020) search will
 158 be performed on PubMed/Medline, Embase, Cumulative Index to Nursing and Allied Health
 159 Literature (CINAHL), Health Management Information Consortium (HMIC), and PsycInfo. This
 160 publication timeframe was chosen as it coincides with the mainstream implementation of EHRs
 161 in several HIC healthcare systems such as Kaiser Permanente in the US, and thus would select
 162 for the most up to date, relevant evidence concerning EHR interoperability and patient safety
 163 challenges faced by healthcare systems today to be included (22,23). The list of search strings
 164 used will include both free text and controlled terms, whenever supported (Table 1) and will be
 165 iteratively refined in consultation with the Imperial College St. Mary's campus medical librarian.

166 Grey literature sources will also be searched, including registrations in the International
 167 Prospective Register of Systematic Reviews, reports of relevant stakeholder organisations (NHS
 168 England, American Medical Informatics Association (AMIA), eHealth at WHO, and conference
 169 proceedings (last 5 years) of several related conferences (AMIA, MedInfo, Medicine 2.0,
 170 Medicine X)), in order to identify possible additional studies that meet the inclusion criteria.

171 The search has also been restricted to HIC and articles published in English only.

172 *Table 1: Concepts and database search terms*

Electronic health records		Interoperability		Patient safety
<ul style="list-style-type: none"> ● Electronic health records ● Electronic medical records ● Computerised medical records systems 	AND	<ul style="list-style-type: none"> ● Interoperability ● Health information interoperability ● Systems integration 	AND	<ul style="list-style-type: none"> ● Patient safety ● Patient adj1 incident* ● Adverse adj1 event* ● Patient adj1 outcome*

<ul style="list-style-type: none"> ● Health information exchange / HIE ● Health information technology / HIT ● Hospital information systems ● Medical informatics ● Medical records linkage 				<ul style="list-style-type: none"> ● Patient adjl harm ● Risk management
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174 Study selection criteria

175 A summary of the population, intervention, comparison, outcomes, and type of studies being
 176 considered is provided in **Table 2**. This systematic review will focus on studies performed in
 177 high-income countries and published in English only. Studies assessing the impact of EHR
 178 interoperability will be included. Interventions will include EHR systems interoperable with
 179 other health information technology systems both within and across healthcare facilities, as well
 180 as those used in tertiary and community settings. The primary outcomes to be considered in this
 181 review will be safety outcomes, including adverse events/incidents, safety-related patient
 182 experiences, and health outcomes. In addition, secondary outcomes would include studies
 183 exploring the broader impact of interoperable EHRs on health systems such as cost effectiveness
 184 and clinical culture amongst healthcare providers on the topic Quantitative, qualitative, and
 185 mixed methods studies will be included. Reference lists of the selected articles will also be
 186 screened for papers which may have been missed by the initial database search but still meet the
 187 eligibility criteria.

188

189 *Table 2: PICO inclusion criteria*

<i>Population</i>	High-income countries utilising electronic health records
<i>Intervention</i>	EHRs with interoperability
<i>Comparison</i>	Usual care (i.e., existing baseline of interoperability)
<i>Outcome</i>	Impact on patient safety and quality of care

190 Screening

191 Articles to be included will be screened by two independent reviewers, following the process
 192 described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 193 (PRISMA) flow diagram (24). The initial screening will be done by the first reviewer based on
 194 the publication titles, followed by a second screening based on the abstracts. Included abstracts
 195 will then be fully reviewed by two independent researchers to produce a unified selection of
 196 articles to be included in this review. Cohen's kappa will be calculated to ensure inter-rater
 197 agreement and consistency in the selection of studies to be included (25,26). Any disagreements
 198 will be resolved by consensus; if a Cohen's kappa value of less than 0.6 is reported, the
 199 discrepancies will be addressed through discussions with a more experienced third investigator.

200 Data extraction

201 Data extraction will be performed using a standardised extraction table for each of the two
202 investigators to summarise the characteristics and findings of each included study, including
203 name of the first author, year of publication, study design, number of participants, retention rates,
204 setting characteristics, outcome measures, and main results. The content of the two summary
205 tables will then be aggregated and reviewed once more by both investigators, with any
206 disagreements being solved by the third senior investigator.

208 Quality assessment

209 The quality of randomised controlled trials and cluster randomised trials will be assessed using
210 the Cochrane Risk of Bias Tool (27), and the quality of non-randomised intervention studies (i.e.,
211 case control, cohort, quasi-experimental) will be appraised using the 'Risk of Bias In Non-
212 Randomised Studies - of Interventions' (ROBINS-I) tool (28). For cost-effectiveness studies, the
213 Drummond's checklist for assessing economic evaluations will be used (29). The National
214 Institute for Health and Care Excellence (NICE) quality appraisal checklist will be utilised to
215 assess the selected qualitative studies (30). Two independent reviewers will score the selected
216 studies and any disagreements will be resolved by a third person. A risk of bias table along with
217 an overall, collective bias narrative will be produced to summarise the biases of outcomes
218 observed amongst the evaluated studies.

220 Narrative synthesis, subgroup analysis, and meta-analysis

221 A narrative synthesis will be performed for all studies included in this systematic review to
222 summarise any salient findings observed (31).

224 In quantitative studies with homogenous or comparable outcome measures, whenever possible,
225 continuous and dichotomous outcomes will be pooled together in a meta-analysis. If possible,
226 effect sizes will be transformed in a common metric (Hedges' g – the bias-corrected standardised
227 difference in means) and classified as positive when in favour of the intervention. Heterogeneity
228 will be assessed using I^2 and the presence of publication bias will be evaluated using a funnel
229 plot and the Duval and Tweedie's trim and fill method (32).

231 For both qualitative and quantitative studies that report comparable outcomes, a subgroup
232 analysis based on clinical settings (e.g., primary vs. secondary healthcare settings) will be
233 conducted to explore any patterns or relationships ascertained from the data. Through a
234 standardised spreadsheet shared amongst the reviewers, the body of evidence will be organised
235 in two separate Summary of Findings tables (for both qualitative and quantitative studies) in
236 accordance to the 'Grading of Recommendations Assessment, Development and Evaluation'
237 (GRADE) criteria (33).

239 Patient and public involvement

240 This systematic literature review saw no direct participation by patients or the public during the
241 design of this study. However, this study was designed following a series of structured
242 interviews with patients regarding their experience of attending multiple institutions for hospital
243 care (34). As this literature review will be used to form the basis for subsequent studies exploring
244 the topic including ones involving patients, findings from this review will be shared with patient

245 research groups to gain feedback and encourage further discourse surrounding the topic of EHR
246 interoperability and patient safety.

248 Amendments

249 Any amendments to this protocol will be documented with reference to saved searches and
250 analysis methods, which will be recorded in bibliographic databases, Mendeley and Excel
251 templates for data collection and synthesis.

252 Discussion

253 One of the primary strengths stemming from the almost exploratory nature of this systematic
254 review is the ability to generate a succinct, comprehensive appraisal of the best evidence
255 currently available regarding how EHR interoperability impacts patient care and safety. By
256 publishing this review protocol beforehand, we demonstrate a clear, robust, and transparent
257 approach to aggregating the anticipated assortment of literature on the subject in question.

258
259 There are also some limitations to be acknowledged. By restricting the inclusion criteria to
260 publications made English only, this could potentially exclude relevant papers pertaining to
261 interoperable EHR systems in non-English healthcare settings. However, this is expected to be
262 minimal as the majority of the papers concerning this topic published from the United States and
263 European countries and are primarily done so in English journals. It must also be noted that both
264 the heterogeneity of measures and outcomes evaluated, as well as the potentially reduced number
265 of studies in subgroup analyses, may negatively influence the statistical power in data synthesis,
266 and may preclude pooling of data as a meta-analysis. With such diverse means of measuring and
267 assessing the effects of EHR interoperability, this will likely make comparisons between studies
268 difficult and may obscure the true measure of effect EHR interoperability has had in the clinical
269 setting. To mitigate this risk, outcomes will be grouped whenever possible, and summarised as a
270 narrative synthesis. However, this can also represent a strength, as it will provide a
271 comprehensive overview on the subject, capitalising on various research methodologies and
272 providing novel insights on the impact of interoperable EHR systems on patient safety.

273 Acknowledgments

274 We would like to thank Michael Gainsford (Library Manager and Liaison Librarian at Imperial
275 College London) for his support and guidance provided to improve the composition of the search
276 terms and procedural aspects of the overall search strategy.

277 Authors' contributions

278 Conception and design of the work: ECL, ALN, and JC wrote the manuscript. HA, and AD
279 provided critical revision of drafts for important intellectual content. All authors provided input
280 into drafts of the manuscript and agree on the contents of the final version.

281 Funding statement

282 This research was supported through the Imperial College National Institute for Health Research
283 (NIHR) Patient Safety Translational Research Centre (PSTRC) and the Imperial College
284 Biomedical Research Centre (BRC). JC acknowledges support from the Wellcome Trust

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3 285 [215938/Z/19/Z]. However, the funder/sponsor has had no role in development and drafting of
4 286 this protocol.
5

6 287 **Competing Interests**

8 288 The authors declare that there are no competing interests.
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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	Reported on Page No.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5
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	5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
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	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	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)	7
	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	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

*** 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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BMJ Open

Electronic Health Records, Interoperability, and Patient Safety in Health Systems of High-Income Countries: A Systematic Review Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-044941.R2
Article Type:	Protocol
Date Submitted by the Author:	27-May-2021
Complete List of Authors:	<p>Li, Edmond; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; London School of Hygiene and Tropical Medicine Faculty of Infectious and Tropical Diseases, Clinical Research Department</p> <p>Clarke, Jonathan; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; Imperial College London, Centre for Mathematics of Precision Healthcare</p> <p>Neves, Ana Luisa; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; University of Porto, Center for Health Technology and Services Research / Department of Community Medicine, Health Information and Decision</p> <p>Ashrafian, Hutan; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer</p> <p>Darzi, Ara; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer</p>
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health policy, Public health, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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1 **Electronic Health Records, Interoperability, and Patient Safety in** 2 **Health Systems of High-Income Countries: A Systematic Review** 3 **Protocol**

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36 **Keywords [MeSH terms]:** electronic health records, electronic medical records, computerised
37 patient records, health information technology, health information exchanges, interoperability,
38 patient safety, patient harm, adverse events, health outcomes

39 **Word count:** 2752

41 Abstract

42 Introduction

43 The availability and routine use of electronic health records (EHRs) have become commonplace
44 in healthcare systems of many high-income countries. While there is an ever-growing body of
45 literature pertaining to EHR use, evidence surrounding the importance of EHR interoperability
46 and its impact on patient safety remains less clear. There is therefore a need and opportunity to
47 evaluate the evidence available regarding this relationship so as to better inform health
48 informatics development and policies in the years to come.

50 Objective

51 This systematic review aims to evaluate the impact of EHR interoperability on patient safety in
52 health systems of high-income countries.

54 Methods and analysis

55 A systematic literature review will be conducted via a computerised search through four
56 databases: PubMed, Embase, HMIC, and PsycInfo for relevant articles published between 2010
57 and 2020. Outcomes of interest will include: impact on patient safety, and the broader effects on
58 health systems. Quality of the randomised quantitative studies will be assessed using Cochrane
59 Risk of Bias Tool. Non-randomised papers will be evaluated with the Risk of Bias In Non-
60 Randomised Studies - of Interventions (ROBINS-I) tool. Drummond's Checklist will be utilised
61 for publications pertaining to economic evaluation. The National Institute for Health and Care
62 Excellence (NICE) quality appraisal checklist will be used to assess qualitative studies. A
63 narrative synthesis will be conducted for included studies, and the body of evidence will be
64 summarised in a summary of findings table.

66 Ethics and dissemination

67 This review will summarise published studies with non-identifiable data and therefore does not
68 require ethical approval. This protocol complies with the Preferred Reporting Items for
69 Systematic Review and Meta-Analyses Protocols guidelines. Findings will be disseminated
70 through preprints, open access peer-reviewed publication, and conference presentations. Patients
71 or members of the public were not involved in the design of this study.

73 Article Summary

74 Strengths and limitations of this study

75 Strengths

- 76 • Inclusion of quantitative, qualitative, and mixed-methods studies can provide a
77 comprehensive overview of the multitude of ways in which interoperable EHRs may
78 affect patient safety and health systems.
- 79 • The proposed review attempts to answer a pragmatic question which is integral to
80 influencing future health informatics development and policies.

82 Limitations

- 83 • The heterogeneity of methods and outcomes assessed may obscure the true effect
84 interoperable EHRs have had on patient safety in the clinical setting.

- 1
2
3 85 • Potential small sample size in subgroup analyses, may negatively impact the statistical
4 86 power in quantitative data synthesis.
5 87 • Limiting the search strategy to English-only publications may not capture studies
6 88 exploring the EHR interoperability experiences of health systems in non-English
7 89 speaking countries.
8 90

9 91 [PROSPERO registration number \[CRD42020209285\]](#)

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97 Introduction

98 Electronic health records (EHRs) have become an integral part of modern healthcare since their
99 initial mainstream implementation in the mid-late 2000s through the passing of the Health
100 Information Technology for Economic and Clinical Health Act (HITECH) in the United States
101 and the NHS National Programme for IT initiative (NPfIT) in England (1–4). From the
102 documentation & retrieval of patient records and the prescription of medications, to coordinating
103 complex care plans between different healthcare providers and electronic billing, EHRs fulfil a
104 multitude of roles for both clinicians and patients alike (5–9).

105
106 In order to achieve EHR's full potential, it is critical to improve interoperability - i.e., “*the ability*
107 *of health information systems to work together within and across organisation boundaries in*
108 *order to advance effective delivery of healthcare for individuals and communities*” (10). The lack
109 of universal interoperability is often cited as one of the many significant shortcomings of EHRs
110 currently in use, resulting in duplication in healthcare costs, increased clinician workload fatigue,
111 and poses a potential risk to patient safety (2). This is especially problematic for patient
112 populations with chronic conditions, polypharmacy, and multiple comorbidities who are reliant
113 upon effective patient information sharing via EHRs to facilitate their care (11).

114
115 Poor EHR interoperability is detrimental to patient safety and costly for health systems. Its
116 consequences range from increased risks of medication errors, fragmentation of patient data, to
117 iatrogenic harm resulting from redundant testing, and additional healthcare expenditure (12–17).
118 In the fragmented EHR landscape of the United Kingdom, measuring the effect poor EHR
119 interoperability has in the National Health Service (NHS), remain challenging (18). Although
120 there is a growing body of literature investigating areas such as the facilitators and barriers to
121 EHR greater adoption, technical capabilities, and usability (19,20), no systematic review has
122 been conducted exploring specifically the problem of interoperability amongst the assortment of
123 EHRs in use, how it affects patient safety, and ultimately the financial cost savings lost to health
124 systems.

125
126 In a recent systematic review by Dobrow *et al.* assessing the effects of EHR and HIT
127 interoperability on health systems, 130 publications were included, with the majority being
128 studies conducted in the United States, utilised quantitative methods, and focussed primarily on
129 acute healthcare settings. The authors noted the use of interoperable EHRs had a positive impact
130 on outcomes measures such as quality of care and productivity (19). However, in domains such
131 as stakeholder engagement, performance & reliability, security & privacy, information quality,
132 and ease of use, the benefits of interoperable EHRs was less clear (19). Amongst the 130
133 publications, 17 were reviews with the majority directed at exploring facilitators & barriers to
134 EHR implementation, and the general benefits and impact of EHR use. While this review did
135 focus on studies pertaining to the topic of interoperable EHRs, this was done so only from a
136 broad perspective and included studies exploring a wide range of outcomes related to the effects
137 of EHR on healthcare rather than specifically on their implications to patient safety.

138
139 In another review by Hersh *et al.*, the authors explored how health information exchange (HIE)
140 affected health systems on a variety of domains, including costs, healthcare utilisation, health

141 outcomes, healthcare worker attitudes, and sustainability. Despite the widespread routinely use
 142 of HIE, the authors described a general lack of robust evidence on the quality, costs, efficiency,
 143 usage, and sustainability (21). However, there was some evidence demonstrating HIEs being
 144 associated with reduced utilisation and costs in emergency care settings despite methodological
 145 issues being present in many of the included publications (21). Although this review was
 146 ambitious in the wide scope of interest regarding the effects of HIE use, patient safety was not a
 147 primary topic of focus. Another limitation of this study was that it only contained US-based
 148 publications, and thus findings lack generalisability internationally to other health systems in
 149 high-income countries (HIC) which are both organised, financed differently.

150 Research aim

151 The overall aim of this literature review is to explore how EHR interoperability impacts patient
 152 safety, in the context of health systems in HICs. The results generated will aim to inform
 153 healthcare policymakers and help shape more effective EHR system implementation and
 154 modernisation efforts in the coming years.

155 Methods and analysis

156 Search strategy

157 A computerised search of the literature published in the last 10 years (2010 to 2020) search will
 158 be performed on PubMed/Medline, Embase, Cumulative Index to Nursing and Allied Health
 159 Literature (CINAHL), Health Management Information Consortium (HMIC), and PsycInfo. This
 160 publication timeframe was chosen as it coincides with the mainstream implementation of EHRs
 161 in several HIC healthcare systems such as Kaiser Permanente in the US, and thus would select
 162 for the most up to date, relevant evidence concerning EHR interoperability and patient safety
 163 challenges faced by healthcare systems today to be included (22,23). The list of search strings
 164 used will include both free text and controlled terms, whenever supported (Table 1) and will be
 165 iteratively refined in consultation with the Imperial College St. Mary's campus medical librarian.

166 Grey literature sources will also be searched, including registrations in the International
 167 Prospective Register of Systematic Reviews, reports of relevant stakeholder organisations (NHS
 168 England, American Medical Informatics Association (AMIA), eHealth at WHO, and conference
 169 proceedings (last 5 years) of several related conferences (AMIA, MedInfo, Medicine 2.0,
 170 Medicine X)), in order to identify possible additional studies that meet the inclusion criteria.

171 The search has also been restricted to HIC and articles published in English only.

172 *Table 1: Concepts and database search terms*

Electronic health records		Interoperability		Patient safety
<ul style="list-style-type: none"> ● Electronic health records ● Electronic medical records ● Computerised medical records systems 	AND	<ul style="list-style-type: none"> ● Interoperability ● Health information interoperability ● Systems integration 	AND	<ul style="list-style-type: none"> ● Patient safety ● Patient adj1 incident* ● Adverse adj1 event* ● Patient adj1 outcome*

<ul style="list-style-type: none"> ● Health information exchange / HIE ● Health information technology / HIT ● Hospital information systems ● Medical informatics ● Medical records linkage 				<ul style="list-style-type: none"> ● Patient adj1 harm ● Risk management
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173

174 Study selection criteria

175 A summary of the population, intervention, comparison, outcomes, and type of studies being
 176 considered is provided in **Table 2**. This systematic review will focus on studies performed in
 177 high-income countries and published in English only. High-income countries will be defined in
 178 accordance with the World Bank's definition of "*countries where the gross national income*
 179 *(GNI) per capita is higher than \$12,536 USD*" (24). Studies assessing the impact of EHR
 180 interoperability will be included. Interventions will include EHR systems interoperable with
 181 other health information technology systems both within and across healthcare facilities, as well
 182 as those used in tertiary and community settings. The primary outcomes to be considered in this
 183 review will be safety outcomes, including adverse events/incidents, safety-related patient
 184 experiences, and health outcomes. In addition, secondary outcomes would include studies
 185 exploring the broader impact of interoperable EHRs on health systems such as cost effectiveness
 186 and clinical culture amongst healthcare providers on the topic Quantitative, qualitative, and
 187 mixed methods studies will be included. Reference lists of the selected articles will also be
 188 screened for papers which may have been missed by the initial database search but still meet the
 189 eligibility criteria.

190

191 *Table 2: PICO inclusion criteria*

<i>Population</i>	High-income countries utilising electronic health records
<i>Intervention</i>	EHRs with interoperability
<i>Comparison</i>	Usual care (i.e., existing baseline of interoperability)
<i>Outcome</i>	Impact on patient safety and quality of care

192 Screening

193 Articles to be included will be screened by two independent reviewers, following the process
 194 described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 195 (PRISMA) flow diagram (25). The initial screening will be done by the first reviewer based on
 196 the publication titles, followed by a second screening based on the abstracts. Included abstracts
 197 will then be fully reviewed by two independent researchers to produce a unified selection of
 198 articles to be included in this review. Cohen's kappa will be calculated to ensure inter-rater
 199 agreement and consistency in the selection of studies to be included (26,27). Any disagreements

1
2
3 200 will be resolved by consensus; if a Cohen's kappa value of less than 0.6 is reported, the
4 201 discrepancies will be addressed through discussions with a more experienced third investigator.

6 202 Data extraction

7 203 Data extraction will be performed using a standardised extraction table for each of the two
8 204 investigators to summarise the characteristics and findings of each included study, including
9 205 name of the first author, year of publication, study design, number of participants, retention rates,
10 206 setting characteristics, outcome measures, and main results. The content of the two summary
11 207 tables will then be aggregated and reviewed once more by both investigators, with any
12 208 disagreements being solved by the third senior investigator.
13 209

15 210 Quality assessment

16 211 The quality of randomised controlled trials and cluster randomised trials will be assessed using
17 212 the Cochrane Risk of Bias Tool (28), and the quality of non-randomised intervention studies (i.e.,
18 213 case control, cohort, quasi-experimental) will be appraised using the 'Risk of Bias In Non-
19 214 Randomised Studies - of Interventions' (ROBINS-I) tool (29). For cost-effectiveness studies, the
20 215 Drummond's checklist for assessing economic evaluations will be used (30). The National
21 216 Institute for Health and Care Excellence (NICE) quality appraisal checklist will be utilised to
22 217 assess the selected qualitative studies (31). Two independent reviewers will score the selected
23 218 studies and any disagreements will be resolved by a third person. A risk of bias table along with
24 219 an overall, collective bias narrative will be produced to summarise the biases of outcomes
25 220 observed amongst the evaluated studies.
26 221

29 222 Narrative synthesis, subgroup analysis, and meta-analysis

30 223 A narrative synthesis will be performed for all studies included in this systematic review to
31 224 summarise any salient findings observed (32).
32 225

33 226 In quantitative studies with homogenous or comparable outcome measures, whenever possible,
34 227 continuous and dichotomous outcomes will be pooled together in a meta-analysis. If possible,
35 228 effect sizes will be transformed in a common metric (Hedges' g – the bias-corrected standardised
36 229 difference in means) and classified as positive when in favour of the intervention. Heterogeneity
37 230 will be assessed using I^2 and the presence of publication bias will be evaluated using a funnel
38 231 plot and the Duval and Tweedie's trim and fill method (33).
39 232

40 233 For both qualitative and quantitative studies that report comparable outcomes, a subgroup
41 234 analysis based on clinical settings (e.g., primary vs. secondary healthcare settings) will be
42 235 conducted to explore any patterns or relationships ascertained from the data. Through a
43 236 standardised spreadsheet shared amongst the reviewers, the body of evidence will be organised
44 237 in two separate Summary of Findings tables (for both qualitative and quantitative studies) in
45 238 accordance to the 'Grading of Recommendations Assessment, Development and Evaluation'
46 239 (GRADE) criteria (34).
47 240

51 241 Patient and public involvement

52 242 This systematic literature review saw no direct participation by patients or the public during the
53 243 design of this study. However, this study was designed following a series of structured
54 244 interviews with patients regarding their experience of attending multiple institutions for hospital
55
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59

245 care (35). As this literature review will be used to form the basis for subsequent studies exploring
246 the topic including ones involving patients, findings from this review will be shared with patient
247 research groups to gain feedback and encourage further discourse surrounding the topic of EHR
248 interoperability and patient safety.

250 Amendments

251 Any amendments to this protocol will be documented with reference to saved searches and
252 analysis methods, which will be recorded in bibliographic databases, Mendeley and Excel
253 templates for data collection and synthesis.

254 Discussion

255 One of the primary strengths stemming from the almost exploratory nature of this systematic
256 review is the ability to generate a succinct, comprehensive appraisal of the best evidence
257 currently available regarding how EHR interoperability impacts patient care and safety. By
258 publishing this review protocol beforehand, we demonstrate a clear, robust, and transparent
259 approach to aggregating the anticipated assortment of literature on the subject in question.

260
261 There are also some limitations to be acknowledged. By restricting the inclusion criteria to
262 publications made in English only, this could potentially exclude relevant papers pertaining to
263 interoperable EHR systems in non-English healthcare settings. However, this is expected to be
264 minimal as the majority of the papers concerning this topic published from the United States and
265 European countries and are primarily done so in English journals. It must also be noted that both
266 the heterogeneity of measures and outcomes evaluated, as well as the potentially reduced number
267 of studies in subgroup analyses, may negatively influence the statistical power in data synthesis,
268 and may preclude pooling of data as a meta-analysis. With such diverse means of measuring and
269 assessing the effects of EHR interoperability, this will likely make comparisons between studies
270 difficult and may obscure the true measure of effect EHR interoperability has had in the clinical
271 setting. To mitigate this risk, outcomes will be grouped whenever possible, and summarised as a
272 narrative synthesis. However, this can also represent a strength, as it will provide a
273 comprehensive overview on the subject, capitalising on various research methodologies and
274 providing novel insights on the impact of interoperable EHR systems on patient safety.

275 Acknowledgments

276 We would like to thank Michael Gainsford (Library Manager and Liaison Librarian at Imperial
277 College London) for his support and guidance provided to improve the composition of the search
278 terms and procedural aspects of the overall search strategy.

279 Authors' contributions

280 Conception and design of the work: EL, ALN, and JC wrote the manuscript. HA, and AD
281 provided critical revision of drafts for important intellectual content. All authors provided input
282 into drafts of the manuscript and agree on the contents of the final version.

283 Funding statement

284 This research was supported through the Imperial College National Institute for Health Research
285 (NIHR) Patient Safety Translational Research Centre (PSTRC) and the Imperial College

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2
3 286 Biomedical Research Centre (BRC). JC acknowledges support from the Wellcome Trust
4 287 [215938/Z/19/Z]. However, the funder/sponsor has had no role in development and drafting of
5 288 this protocol.
6

7 289 **Competing Interests**

8 290 The authors declare that there are no competing interests.
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For peer review only

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

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
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	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	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)	7
	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	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

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

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

BMJ Open

Electronic Health Records, Interoperability, and Patient Safety in Health Systems of High-Income Countries: A Systematic Review Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-044941.R3
Article Type:	Protocol
Date Submitted by the Author:	05-Jun-2021
Complete List of Authors:	<p>Li, Edmond; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; London School of Hygiene and Tropical Medicine Faculty of Infectious and Tropical Diseases, Clinical Research Department</p> <p>Clarke, Jonathan; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; Imperial College London, Centre for Mathematics of Precision Healthcare</p> <p>Neves, Ana Luisa; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer; University of Porto, Center for Health Technology and Services Research / Department of Community Medicine, Health Information and Decision</p> <p>Ashrafian, Hutan; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer</p> <p>Darzi, Ara; Imperial College London, Patient Safety Translational Research Centre, Institute of Global Health Innovation, Department of Surgery & Cancer</p>
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health policy, Public health, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Information technology < BIOTECHNOLOGY & BIOINFORMATICS, Information management < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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1 **Electronic Health Records, Interoperability, and Patient Safety in** 2 **Health Systems of High-Income Countries: A Systematic Review** 3 **Protocol**

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36
37 **Keywords [MeSH terms]:** electronic health records, electronic medical records, computerised
38 patient records, health information technology, health information exchanges, interoperability,
39 patient safety, patient harm, adverse events, health outcomes
40

41 Abstract

42 Introduction

43 The availability and routine use of electronic health records (EHRs) have become commonplace
44 in healthcare systems of many high-income countries. While there is an ever-growing body of
45 literature pertaining to EHR use, evidence surrounding the importance of EHR interoperability
46 and its impact on patient safety remains less clear. There is therefore a need and opportunity to
47 evaluate the evidence available regarding this relationship so as to better inform health
48 informatics development and policies in the years to come. This systematic review aims to
49 evaluate the impact of EHR interoperability on patient safety in health systems of high-income
50 countries.

52 Methods and analysis

53 A systematic literature review will be conducted via a computerised search through four
54 databases: PubMed, Embase, HMIC, and PsycInfo for relevant articles published between 2010
55 and 2020. Outcomes of interest will include: impact on patient safety, and the broader effects on
56 health systems. Quality of the randomised quantitative studies will be assessed using Cochrane
57 Risk of Bias Tool. Non-randomised papers will be evaluated with the Risk of Bias In Non-
58 Randomised Studies - of Interventions (ROBINS-I) tool. Drummond's Checklist will be utilised
59 for publications pertaining to economic evaluation. The National Institute for Health and Care
60 Excellence (NICE) quality appraisal checklist will be used to assess qualitative studies. A
61 narrative synthesis will be conducted for included studies, and the body of evidence will be
62 summarised in a summary of findings table.

64 Ethics and dissemination

65 This review will summarise published studies with non-identifiable data and thus does not
66 require ethical approval. Findings will be disseminated through preprints, open access peer-
67 reviewed publication, and conference presentations.

69 PROSPERO registration number [CRD42020209285]

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73 the licence is given, and indication of whether changes were made. See:
74 <https://creativecommons.org/licenses/by/4.0/>.

75 Article Summary

76 Strengths and limitations of this study

77 Strengths

- 78 • Inclusion of quantitative, qualitative, and mixed-methods studies can provide a
79 comprehensive overview of the multitude of ways in which interoperable EHRs may
80 affect patient safety and health systems.
- 81 • Using robust methodology to examine the wealth of existing literature, the proposed
82 systematic review attempts to answer a pragmatic question which is integral to future
83 health informatics development and policies.

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Limitations

- The heterogeneity of methods and outcomes assessed may obscure the true effect interoperable EHRs have had on patient safety.
- Potential small sample size in subgroup analyses, may negatively impact the statistical power in quantitative data synthesis.
- Limiting the search strategy to English-only publications may not capture studies exploring EHR experiences in non-English speaking countries.

For peer review only

94 Introduction

95 Electronic health records (EHRs) have become an integral part of modern healthcare since their
96 initial mainstream implementation in the mid-late 2000s through the passing of the Health
97 Information Technology for Economic and Clinical Health Act (HITECH) in the United States
98 and the NHS National Programme for IT initiative (NPfIT) in England (1–4). From the
99 documentation & retrieval of patient records and the prescription of medications, to coordinating
100 complex care plans between different healthcare providers and electronic billing, EHRs fulfil a
101 multitude of roles for both clinicians and patients alike (5–9).

102
103 In order to achieve EHR's full potential, it is critical to improve interoperability - i.e., “*the ability*
104 *of health information systems to work together within and across organisation boundaries in*
105 *order to advance effective delivery of healthcare for individuals and communities*” (10). The lack
106 of universal interoperability is often cited as one of the many significant shortcomings of EHRs
107 currently in use, resulting in duplication in healthcare costs, increased clinician workload fatigue,
108 and poses a potential risk to patient safety (2). This is especially problematic for patient
109 populations with chronic conditions, polypharmacy, and multiple comorbidities who are reliant
110 upon effective patient information sharing via EHRs to facilitate their care (11).

111
112 Poor EHR interoperability is detrimental to patient safety and costly for health systems. Its
113 consequences range from increased risks of medication errors, fragmentation of patient data, to
114 iatrogenic harm resulting from redundant testing, and additional healthcare expenditure (12–17).
115 In the fragmented EHR landscape of the United Kingdom, measuring the effect poor EHR
116 interoperability has in the National Health Service (NHS), remain challenging (18). Although
117 there is a growing body of literature investigating areas such as the facilitators and barriers to
118 EHR greater adoption, technical capabilities, and usability (19,20), no systematic review has
119 been conducted exploring specifically the problem of interoperability amongst the assortment of
120 EHRs in use, how it affects patient safety, and ultimately the financial cost savings lost to health
121 systems.

122
123 In a recent systematic review by Dobrow *et al.* assessing the effects of EHR and HIT
124 interoperability on health systems, 130 publications were included, with the majority being
125 studies conducted in the United States, utilised quantitative methods, and focussed primarily on
126 acute healthcare settings. The authors noted the use of interoperable EHRs had a positive impact
127 on outcomes measures such as quality of care and productivity (19). However, in domains such
128 as stakeholder engagement, performance & reliability, security & privacy, information quality,
129 and ease of use, the benefits of interoperable EHRs was less clear (19). Amongst the 130
130 publications, 17 were reviews with the majority directed at exploring facilitators & barriers to
131 EHR implementation, and the general benefits and impact of EHR use. While this review did
132 focus on studies pertaining to the topic of interoperable EHRs, this was done so only from a
133 broad perspective and included studies exploring a wide range of outcomes related to the effects
134 of EHR on healthcare rather than specifically on their implications to patient safety.

135
136 In another review by Hersh *et al.*, the authors explored how health information exchange (HIE)
137 affected health systems on a variety of domains, including costs, healthcare utilisation, health

138 outcomes, healthcare worker attitudes, and sustainability. Despite the widespread routinely use
 139 of HIE, the authors described a general lack of robust evidence on the quality, costs, efficiency,
 140 usage, and sustainability (21). However, there was some evidence demonstrating HIEs being
 141 associated with reduced utilisation and costs in emergency care settings despite methodological
 142 issues being present in many of the included publications (21). Although this review was
 143 ambitious in the wide scope of interest regarding the effects of HIE use, patient safety was not a
 144 primary topic of focus. Another limitation of this study was that it only contained US-based
 145 publications, and thus findings lack generalisability internationally to other health systems in
 146 high-income countries (HIC) which are both organised, financed differently.

147 Research aim

148 The overall aim of this literature review is to explore how EHR interoperability impacts patient
 149 safety, in the context of health systems in HICs. The results generated will aim to inform
 150 healthcare policymakers and help shape more effective EHR system implementation and
 151 modernisation efforts in the coming years.

152 Methods and analysis

153 Search strategy

154 A computerised search of the literature published in the last 10 years (2010 to 2020) search will
 155 be performed on PubMed/Medline, Embase, Cumulative Index to Nursing and Allied Health
 156 Literature (CINAHL), Health Management Information Consortium (HMIC), and PsycInfo. This
 157 publication timeframe was chosen as it coincides with the mainstream implementation of EHRs
 158 in several HIC healthcare systems such as Kaiser Permanente in the US, and thus would select
 159 for the most up to date, relevant evidence concerning EHR interoperability and patient safety
 160 challenges faced by healthcare systems today to be included (22,23). The list of search strings
 161 used will include both free text and controlled terms, whenever supported (Table 1) and will be
 162 iteratively refined in consultation with the Imperial College St. Mary's campus medical librarian.
 163 For a sample of the search strategy, please see Supplement 1.

164 Grey literature sources will also be searched, including registrations in the International
 165 Prospective Register of Systematic Reviews, reports of relevant stakeholder organisations (NHS
 166 England, American Medical Informatics Association (AMIA), eHealth at WHO, and conference
 167 proceedings (last 5 years) of several related conferences (AMIA, MedInfo, Medicine 2.0,
 168 Medicine X)), in order to identify possible additional studies that meet the inclusion criteria.

169 The search has also been restricted to HIC and articles published in English only.

170 *Table 1: Concepts and database search terms*

Electronic health records		Interoperability		Patient safety
<ul style="list-style-type: none"> ● Electronic health records ● Electronic medical records 	AND	<ul style="list-style-type: none"> ● Interoperability ● Health information interoperability ● Systems integration 	AND	<ul style="list-style-type: none"> ● Patient safety ● Patient adj1 incident* ● Adverse adj1 event*

<ul style="list-style-type: none"> ● Computerised medical records systems ● Health information exchange / HIE ● Health information technology / HIT ● Hospital information systems ● Medical informatics ● Medical records linkage 				<ul style="list-style-type: none"> ● Patient adj1 outcome* ● Patient adj1 harm ● Risk management
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171

172 Study selection criteria

173 A summary of the population, intervention, comparison, outcomes, and type of studies being
 174 considered is provided in **Table 2**. This systematic review will focus on studies performed in
 175 high-income countries and published in English only. High-income countries will be defined in
 176 accordance with the World Bank's definition of "countries where the gross national income
 177 (GNI) per capita is higher than \$12,536 USD" (24). Studies assessing the impact of EHR
 178 interoperability will be included. Interventions will include EHR systems interoperable with
 179 other health information technology systems both within and across healthcare facilities, as well
 180 as those used in tertiary and community settings. The primary outcomes to be considered in this
 181 review will be safety outcomes, including adverse events/incidents, safety-related patient
 182 experiences, and health outcomes. In addition, secondary outcomes would include studies
 183 exploring the broader impact of interoperable EHRs on health systems such as cost effectiveness
 184 and clinical culture amongst healthcare providers on the topic Quantitative, qualitative, and
 185 mixed methods studies will be included. Reference lists of the selected articles will also be
 186 screened for papers which may have been missed by the initial database search but still meet the
 187 eligibility criteria.

188

189 *Table 2: PICO inclusion criteria*

<i>Population</i>	High-income countries utilising electronic health records
<i>Intervention</i>	EHRs with interoperability
<i>Comparison</i>	Usual care (i.e., existing baseline of interoperability)
<i>Outcome</i>	Impact on patient safety and quality of care

190 Screening

191 Articles to be included will be screened by two independent reviewers, following the process
 192 described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 193 (PRISMA) flow diagram (25). The initial screening will be done by the first reviewer based on

194 the publication titles, followed by a second screening based on the abstracts. Included abstracts
195 will then be fully reviewed by two independent researchers to produce a unified selection of
196 articles to be included in this review. Cohen's kappa will be calculated to ensure inter-rater
197 agreement and consistency in the selection of studies to be included (26,27). Any disagreements
198 will be resolved by consensus; if a Cohen's kappa value of less than 0.6 is reported, the
199 discrepancies will be addressed through discussions with a more experienced third investigator.

200 Data extraction

201 Data extraction will be performed using a standardised extraction table for each of the two
202 investigators to summarise the characteristics and findings of each included study, including
203 name of the first author, year of publication, study design, number of participants, retention rates,
204 setting characteristics, outcome measures, and main results. The content of the two summary
205 tables will then be aggregated and reviewed once more by both investigators, with any
206 disagreements being solved by the third senior investigator.

208 Quality assessment

209 The quality of randomised controlled trials and cluster randomised trials will be assessed using
210 the Cochrane Risk of Bias Tool (28), and the quality of non-randomised intervention studies (i.e.,
211 case control, cohort, quasi-experimental) will be appraised using the 'Risk of Bias In Non-
212 Randomised Studies - of Interventions' (ROBINS-I) tool (29). For cost-effectiveness studies, the
213 Drummond's checklist for assessing economic evaluations will be used (30). The National
214 Institute for Health and Care Excellence (NICE) quality appraisal checklist will be utilised to
215 assess the selected qualitative studies (31). Two independent reviewers will score the selected
216 studies and any disagreements will be resolved by a third person. A risk of bias table along with
217 an overall, collective bias narrative will be produced to summarise the biases of outcomes
218 observed amongst the evaluated studies.

220 Narrative synthesis, subgroup analysis, and meta-analysis

221 A narrative synthesis will be performed for all studies included in this systematic review to
222 summarise any salient findings observed (32).

224 In quantitative studies with homogenous or comparable outcome measures, whenever possible,
225 continuous and dichotomous outcomes will be pooled together in a meta-analysis. If possible,
226 effect sizes will be transformed in a common metric (Hedges' g – the bias-corrected standardised
227 difference in means) and classified as positive when in favour of the intervention. Heterogeneity
228 will be assessed using I^2 and the presence of publication bias will be evaluated using a funnel
229 plot and the Duval and Tweedie's trim and fill method (33).

231 For both qualitative and quantitative studies that report comparable outcomes, a subgroup
232 analysis based on clinical settings (e.g., primary vs. secondary healthcare settings) will be
233 conducted to explore any patterns or relationships ascertained from the data. Through a
234 standardised spreadsheet shared amongst the reviewers, the body of evidence will be organised
235 in two separate Summary of Findings tables (for both qualitative and quantitative studies) in
236 accordance to the 'Grading of Recommendations Assessment, Development and Evaluation'
237 (GRADE) criteria (34).

239 Patient and public involvement

240 This systematic literature review saw no direct participation by patients or the public during the
241 design of this study. However, this study was designed following a series of structured
242 interviews with patients regarding their experience of attending multiple institutions for hospital
243 care (35). As this literature review will be used to form the basis for subsequent studies exploring
244 the topic including ones involving patients, findings from this review will be shared with patient
245 research groups to gain feedback and encourage further discourse surrounding the topic of EHR
246 interoperability and patient safety.
247

248 Amendments

249 Any amendments to this protocol will be documented with reference to saved searches and
250 analysis methods, which will be recorded in bibliographic databases, Mendeley and Excel
251 templates for data collection and synthesis.

252 Discussion

253 One of the primary strengths stemming from the almost exploratory nature of this systematic
254 review is the ability to generate a succinct, comprehensive appraisal of the best evidence
255 currently available regarding how EHR interoperability impacts patient care and safety. By
256 publishing this review protocol beforehand, we demonstrate a clear, robust, and transparent
257 approach to aggregating the anticipated assortment of literature on the subject in question.
258

259 There are also some limitations to be acknowledged. By restricting the inclusion criteria to
260 publications made in English only, this could potentially exclude relevant papers pertaining to
261 interoperable EHR systems in non-English healthcare settings. However, this is expected to be
262 minimal as the majority of the papers concerning this topic published from the United States and
263 European countries and are primarily done so in English journals. It must also be noted that both
264 the heterogeneity of measures and outcomes evaluated, as well as the potentially reduced number
265 of studies in subgroup analyses, may negatively influence the statistical power in data synthesis,
266 and may preclude pooling of data as a meta-analysis. With such diverse means of measuring and
267 assessing the effects of EHR interoperability, this will likely make comparisons between studies
268 difficult and may obscure the true measure of effect EHR interoperability has had in the clinical
269 setting. To mitigate this risk, outcomes will be grouped whenever possible, and summarised as a
270 narrative synthesis. However, this can also represent a strength, as it will provide a
271 comprehensive overview on the subject, capitalising on various research methodologies and
272 providing novel insights on the impact of interoperable EHR systems on patient safety.
273

274 Ethics and Dissemination

275 This review will summarise published studies with non-identifiable data and therefore does not
276 require ethical approval. This protocol complies with the Preferred Reporting Items for
277 Systematic Review and Meta-Analyses Protocols guidelines. Findings will be disseminated
278 through preprints, open access peer-reviewed publication, and conference presentations.

279 Acknowledgments

280 We would like to thank Michael Gainsford (Library Manager and Liaison Librarian at Imperial
281 College London) for his support and guidance provided to improve the composition of the search
282 terms and procedural aspects of the overall search strategy.

For peer review only

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407 Authors' contributions

408 Conception and design of the work: EL, ALN, and JC wrote the manuscript. HA, and AD
409 provided critical revision of drafts for important intellectual content. All authors provided input
410 into drafts of the manuscript and agree on the contents of the final version.

411 Funding statement

412 This research was supported through the Imperial College National Institute for Health Research
413 (NIHR) Patient Safety Translational Research Centre (PSTRC) and the Imperial College
414 Biomedical Research Centre (BRC). JC acknowledges support from the Wellcome Trust
415 [215938/Z/19/Z]. However, the funder/sponsor has had no role in development and drafting of
416 this protocol.

417 Competing Interests

418 The authors declare that there are no competing interests.

419

420 **Word count:** 3886

421

Supplement 1: Search strategy exploring main themes, utilizing search terms and related terminology derivations for each theme (electronic health records, interoperability, and patient safety).

#	Searches
1	exp Medical Records Systems, Computerized/ or exp Electronic Health Records/ or exp Hospital Information Systems/
2	limit 1 to (english language and yr="2010 - 2020")
3	exp Electronic Health Records/
4	limit 3 to (english language and yr="2010 - 2020")
5	exp Health Information Exchange/ or exp Medical Informatics/ or exp Decision Support Systems, Clinical/ or exp Medical Records Systems, Computerized/ or exp Medical Record Linkage/
6	limit 5 to (english language and yr="2010 - 2020")
7	exp Medical Informatics/
8	limit 7 to (english language and yr="2010 - 2020")
9	exp Hospital Information Systems/
10	limit 9 to (english language and yr="2010 - 2020")
11	exp Medical Informatics/
12	limit 11 to (english language and yr="2010 - 2020")
13	exp Health Information Interoperability/
14	limit 13 to (english language and yr="2010 - 2020")
15	exp Systems Integration/
16	limit 15 to (english language and yr="2010 - 2020")
17	exp Patient Safety/
18	limit 17 to (english language and yr="2010 - 2020")
19	(Patient adj1 incident*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
20	limit 19 to (english language and yr="2010 - 2020")
21	(Adverse adj1 event*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary

	concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22	limit 21 to (english language and yr="2010 - 2020")
23	(Patient adj1 outcome*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
24	limit 23 to (english language and yr="2010 - 2020")
25	(Patient adj1 harm).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26	limit 25 to (english language and yr="2010 - 2020")
27	exp Risk Management/
28	limit 27 to (english language and yr="2010 - 2020")
29	2 or 4 or 6 or 8 or 10 or 12
30	14 or 16
31	18 or 20 or 22 or 24 or 26 or 28
32	29 and 30 and 31

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

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
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	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
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	6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6-7
	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)	7
	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	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7

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

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