Research Protocol
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Implementation of blockchains in healthcare: A Systematic Review Protocol
ABSTRACT

Background
A blockchain is a digitised, decentralised, public ledger; a shared and synchronised database that records cryptocurrency transactions. Despite the shift towards digital platforms enabled by Electronic Medical Records (EMRs), demonstrating a will to reform the healthcare sector, health systems face issues including security, interoperability, data fragmentation, timely access to patient data and siloes. Application of healthcare blockchains could enable data interoperability, enhancement of precision medicine and reduction in prescription frauds. The proposed systematic review will summarise the evidence on the strategies and frameworks utilised to implement blockchains in healthcare.

Objective
To summarise the evidence on the strategies and frameworks utilised to implement blockchains for patient data in healthcare to ensure privacy and improve interoperability and scalability.

Methods
A systematic search of MEDLINE/PubMed, Embase, Scopus, ProQuest Technology Collection and Engineering Index (Compendex) will be conducted. Two experienced independent reviewers will undergo titles and abstract screening followed by full-text reading to determine study eligibility. Data will then be extracted onto data extraction forms before using the Cochrane Collaboration Risk of Bias Tool (CCROBT) to appraise the quality of included randomised studies and the Risk of Bias in Non-Randomised Studies - of Interventions (ROBINS-I) to assess the quality of non-randomised studies. Data will then be analysed and synthesised.

Results
Database searches will be initiated in May 2018. We expect to complete the review in August 2018.

Conclusions
This review will summarize the strategies and frameworks used to implement blockchains in healthcare to increase data privacy, interoperability and scalability. This review will also help clarify if the strategies and frameworks required for the operationalisation of blockchains in healthcare ensure privacy of patient data whilst enabling efficiency, interoperability and scalability when compared to other healthcare approaches.

Trial registration
This protocol will be registered on PROSPERO.

Keywords
Blockchain, interoperability, distributed ledger technology, scalability, health information exchange
Introduction

While blockchains are essentially decentralised databases, there is no primary ownership of data [1,2]. Through collaboration, users decide which data is added to the blockchain while ensuring that identical copies of data are received and automatically updated [2]. Healthcare, in any setting, generates abundant complex and rich data, ranging from sensitive patient identifiable data to operational analytics and the dissemination and essential actions of exchanging this health-related data means that it remains at risk of privacy breaches [3]. Blockchain technologies have been proposed to respond to this challenge [3]. Once granted permission, verified users gain access to blockchain systems. This allows them to share relevant data with other verified users, guaranteeing accountability, scalability and efficiency [3]. While this innovation has shown promise in various sectors, in order to ensure successful implementation in healthcare, various challenges need to be addressed first [2]. Because health-related data is numerous and sourced from many areas, the integration and linkage of data has the potential to generate valuable population-level insight [4]. A key consideration with greater integration of health data sources is the need for strategies that safeguard access control to sensitive patient data. Additionally, as there is an expansion of health and lifestyle related data resulting from, for example, mobile applications and wearable devices, blockchain technologies may be exploited by patients, providers and researchers through access of health data in a timely manner through “all or nothing” access permissions [5].

As blockchains utilise cryptographic techniques to authenticate and verify users, their application may be used to control access to sensitive data [3]. While adoption of Electronic Medical Records (EMRs) has become the defacto standard, most data within EMRs cannot be shared and exchanged between users appropriately [5]. Blockchain technologies, therefore, have the potential to increase interoperability between patients, carers, healthcare professionals and researchers [5]. As data can be sourced from one location, blockchains have the potential to tackle storage issues. By recording patient consent, blockchains could be a patient-empowering platform [6]. Information flow and exchange between users may only take place once the patient has consented [6]. Consent also allows healthcare providers to trust the data they access, thereby enabling them to treat their patients accordingly [6].

In addition to ensuring access security, scalability and data privacy [5], blockchains also have the potential to enhance medical research through various use cases. Via implementation of health record blockchains, data sourced from medical records, health applications and wearable devices could be stored and made accessible to users throughout their lives [5], thereby facilitating the conduct of longitudinal studies and pharmacovigilance applications. Each time a patient obtains a new prescription or test results, a patient could be notified that new data has been encrypted, sent for storage and added to an automated system [5]. Moreover, patients would be able to add data sourced from wearable devices and health applications into this system [5]. Once data is encrypted and stored, researchers can trust the data will not be altered [7]. Patients and participants may consent and revoke access, remaining in control of their information [7]. In addition to facilitating the collection of longitudinal data such as heart rate, diet and exercise frequency, blockchains may store genomic data [7]. Blockchain technology may also be used to counter prescription drug fraud [7]. For example, Nuco, a blockchain company addresses prescription duplication and “doctor shopping”, whereby individuals visit numerous physicians to obtain as many prescriptions as they can [7].
According to Nuco, the problem lies in the inadequate communication between physicians and pharmacists and blockchains have the capacity to tackle this issue through the verification of prescription authenticity [7]. These implementation scenarios show the strengths of implementation of a secure distributed data technology and the benefits they could make for individual and population data analysis.

Before adopting blockchains to empower patients, advance personalised medicine, accelerate Research & Development (R&D) and engage with populations that are considered “hard-to-reach” [5], challenges restricting their implementation need to be addressed. While broader access to health records may be achieved through blockchains, a challenge includes limited information on costs required to establish and operationalise this decentralised framework [8]. However, health systems spend large monetary sums on designing and maintaining traditional information system frameworks [8]. Various resources are required when dealing with troubleshooting issues, updating parameters and extracting data [8]. As blockchains do not undergo frequent troubleshooting nor do they require frequent updates, it is predicted that these costs may be reduced through the implementation of blockchain technologies in healthcare [8]. Additionally, to ensure adequate performance, organisations and institutions adopting blockchain technologies need to select specific frameworks to establish the size and format of the data that may be added to the system [8]. Another challenge consists of incentivising those in the healthcare sector to adopt novel blockchain technologies [8], expanding networks and scalability. In addition to allowing clinicians access real-time data, thereby enabling nationwide interoperability and the delivery of more coordinated patient care, researchers will be able to access and monitor nationwide data that could potentially aid in national surveillance and public health. Using national programs to encourage digital data adoption have been successful [9], it is envisaged that if similar approaches are applied, uptake of blockchains may also be achieved.

To the best of our knowledge, there are currently no systematic reviews on the strategies and frameworks utilised to implement blockchains in healthcare. Nevertheless, few reviews have been published focusing on specific aspects of blockchains in healthcare, such as its applications in healthcare [1], its potential to finance universal health coverage [10] and its potential to tackle fake medicine trade [11]. Despite its potential to improve healthcare financing, the right systems must be put in place and “appropriate regulatory guidelines" must be followed before blockhains can be used in healthcare [10]. This is also true for the use of blockchain for tracking medication trade, which was described to be in its "infancy" and in need for further research [11].

Blockchains have the potential to address various challenges pertaining to data in healthcare. By requiring patient consent and user verification, privacy and security measures are enforced. interoperability is facilitated as data is securely shared amongst those with permission. Storage issues are also addressed through blockchains as all the data is found in one location. By engaging various users, implementation of this novel approach may, in the long-run, lead to disease prevention and the promotion of health. This aim of this review is to summarise the evidence on the strategies and frameworks utilised to implement blockchains for patient data in healthcare to ensure privacy and improve interoperability and scalability.
Methods

The Cochrane protocol guide will be used to guide the development of the systematic review protocol [12]. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 Checklist [13] will be used to report this systematic review (Appendix 1). A research question will be defined and a Population, Intervention, Comparator and Outcome (PICO) framework will be established in order to develop and combine Medical Subject Headings (MeSH), subject headings and keywords. The review will undergo the following six stages:

1. Literature search
2. Selection of articles
3. Extraction of data
4. Appraisal of quality
5. Analysis of data
6. Synthesis of data

Identification of a research question:
Do the strategies and frameworks required for the operationalisation of blockchains in healthcare ensure privacy of patient data whilst enabling efficiency, interoperability and scalability when compared to other healthcare approaches?

Criteria for considering studies for the review

Types of studies
As blockchains applied to the healthcare sector remains a novel approach, we will not place restrictions on study type. All types of studies will be included as long as other eligibility criteria are met; for example, randomised controlled trials (RCTs) and observational studies will be considered. We will only include studies published in English.

Types of participants
The population will consist of adult patients who have their data incorporated within healthcare blockchains.

Intervention and comparator
Included studies will assess blockchain technologies in healthcare systems to improve issues revolving around access, interoperability and scalability. Dates of publication and study location will not be restricted. Comparators may consist of other traditional frameworks or technological
advances adopted in health systems to improve access, interoperability and scalability, thereby providing more coordinated healthcare. For example, learning health systems, systems which utilise data to provide evidence, thereby allowing continuous learning and improvement of healthcare, may represent a comparator. Studies that have not identified a comparator may also be included if the remaining criteria required for study inclusion are met.

Types of outcomes

Review outcomes are outlined in Table 1. Primary outcomes will include extent of access, interoperability and scalability of healthcare blockchains following the implementation of various strategies and frameworks required for their operationalisation. Health outcomes will be considered as a secondary outcome and will be assessed to determine whether blockchains can improve the health of individuals and populations when compared to more traditional platforms and/or other technological advances.

<table>
<thead>
<tr>
<th>Primary Outcomes</th>
<th>Secondary Outcomes</th>
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<tr>
<td>● Extent of interoperability</td>
<td>● Health outcomes</td>
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<td>● Extent of scalability</td>
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<td>● Privacy</td>
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</table>

Levels of Information Systems Interoperability (LISI), a reference model [14], will be used to measure the level of interoperability. Details of how this model will be discussed under the ‘data analysis and synthesis’ section. Scalability of the blockchain will be assessed by measuring blockchain adoption across study or survey implementation contexts. To assess privacy, we will identify whether the blockchains abide to legal and regulatory frameworks. As regulatory frameworks may vary according to study setting, relevant frameworks and legislations will be identified once studies are selected and settings identified.

Search Methods

We will systematically search the following electronic databases: MEDLINE/Pubmed, Embase, Scopus, ProQuest Technology Collection and Engineering Index (Compendex). MeSH, subject headings and keywords will be developed following exploratory research around the review research question. No restrictions will be placed on dates of publication, study types and geographic locations. However, only studies published in English will be included. We intend to search MEDLINE/Pubmed first by implementing a search strategy for preliminary research (Appendix 2). Based on the finding of this search, we will develop our search strategy and will adapt the strategy for Embase and Scopus databases. The search will not be restricted by date. Results of our searches will be imported EndNote X8.2 (Clarivate Analytics, USA), where duplicates will be removed. Bibliographic citations of included studies will also be manually searched to identify other studies that fill the review's inclusion criteria. We will also use similar search terms when utilising search engines such as Google to systematically search the grey literature; conference proceedings and reports will also be
considered if review criteria are met. Additionally, bibliographic citations of studies that have been included will be reviewed to not miss any potentially relevant studies.

Selection of studies
Two independent reviewers will screen titles and abstracts of studies identified following database searches. Upon completion of titles and abstract screening, the remaining studies will be assessed through full-text reading. Where the two reviewers cannot agree on study inclusion, a third reviewer will be asked to assist them. The review's selection process will be demonstrated using a PRISMA flow diagram.

Data extraction and management
Data will be extracted by two independent reviewers onto predetermined data extraction forms. Where reviewers cannot agree following discussion, a third reviewer will be asked to assist in the decision-making process. Data obtained will be assembled in an individual form. Data extraction forms will be tested by the review team prior to utilisation to ensure the data is collected appropriately. The following data will be extracted onto the review's data extraction forms:

1. Date of publication, author
2. Characteristics of the study: location, duration, sample size, control
3. Characteristics of the intervention: departments/facilities adopting the blockchain, blockchain enablers, challenges, costs, implementation strategies/frameworks
4. Characteristics of comparator: departments/facilities adopting the comparator, comparator enablers, challenges, costs, implementation strategies/frameworks
5. Outcomes: Extent of access (primary outcome), interoperability (primary outcome), scalability (primary outcome), health outcomes (secondary outcome).

Assessment of risk of bias of included studies
Two independent reviewers will assess the risk of bias of included studies. A third reviewer will assist in the decision-making if the two reviewers disagree on their assessments regarding the methodological quality of included studies.

The Cochrane Collaboration Risk of Bias Tool will be used to assess the following [13]:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding (performance bias and detection bias)
4. Incomplete outcome data (attrition bias)
5. Selective reporting (reporting bias)
6. Other bias

Subsequent to the determination of selection, performance, detection, attrition, reporting and other bias assessments, included studies will be categorised as ‘high risk’, ‘low risk’ or ‘unclear risk’. A Risk
of Bias Graph and a Risk of Bias Summary will then be developed to illustrate the methodological quality of included studies.

Other non-randomised studies will be assessed using the Risk of Bias in Non-Randomised Studies - of Interventions (ROBINS-I) [15]. This tool will be used to assess the following seven domains [16]:

1. Bias due to confounding (pre-intervention)
2. Bias in selection of participants onto the study (pre-intervention)
3. Bias in classification of interventions (at intervention)
4. Bias due to deviations from intended interventions (post-intervention)
5. Bias due to missing data (post-intervention)
6. Bias in measurement of outcomes (post-intervention)
7. Bias in selection of the reported result (post-intervention)

Data analysis and synthesis

We intend to summarise our data (i) numerically - by describing the number and type of studies incorporated within the review and (ii) narratively - by synthesising all included studies. As the application of blockchains in health systems remains in progress, we do not expect to identify numerous studies, thereby preventing us from conducting a meta-analysis. As no restrictions will be placed on study type, we anticipate that conduction of a meta-analysis will not be feasible due to study heterogeneity. Through review results, we aim to map the strategies and frameworks enabling the operationalisation of blockchains within health systems in a clear format. We intend to measure the extent of interoperability using the LISI Model [14]. The level of interoperability will therefore be classified into the following:

1. Enterprise (universal): data is fully shared and distributed across the health system.
2. Domain (integrated): data is exchanged through shared domain-based models.
3. Functional (distributed): where logical data models (for example, relational tables) are shared across a health system.
5. Isolated (manual): integration of data from various systems conducted manually.

To assess scalability, we will determine whether studies measured adoption/uptake across the healthcare sector, thereby enabling us to assess whether nation-wide uptake of the automated system is feasible.

In order to assess whether the blockchain addresses privacy and security issues adequately, whether legislations including the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Regulations have been considered will be evaluated [17]. Legislations considered by the review will depend on study settings and will be, therefore, identified upon study selection. Where HIPAA is used, this will include:

1. Data encryption: whether the system has encrypted information, allowing only those with a ‘key’ to access.
2. ‘Audit trail’: whether the system stores information on who accessed the information, what modifications have been applied and when access was granted and modifications applied.
3. ‘Access control’: whether passwords and PIN numbers are used in the system, limiting access only to those authorised.

Results

Database search is planned to be completed by May 2018. Title and abstract screening will follow data search and will be completed by two reviewers. The review is expected to be completed by August 2018.

Discussion

By means of the proposed systematic review, we intend to provide evidence on the strategies and frameworks utilised in the implementation of healthcare blockchains. Through development of recommendations that will assist key stakeholders in healthcare blockchain implementation, we predict that the evidence generated will challenge the healthcare status quo, moving away from more traditional approaches and facilitating decision-making of patients, healthcare providers and researchers. As the current traditional system applied in health systems does not fully support interoperability, it is predicted that healthcare blockchains will enable the delivery of team-based healthcare by means of nationwide interoperability while optimising precision medicine research and ensuring prescription authenticity. However, prior to large scale implementation of these automated systems, it is crucial that research and trials ensure that they are cost-effective and secure systems that maintain the privacy and security of patients and comply with regulatory frameworks.

We intend to consult blockchain experts from Imperial College London and the University of Oxford as well as Infrastructure Technology (IT) professionals during the various stages of this systematic review. This will allow the review authors to gain insight beyond what was gathered from the searched literature. Additionally, we will ask them to provide us with advice regarding the protocol and the final manuscript.

Strengths

1. The proposed systematic review will provide evidence on the strategies and frameworks required for the operationalisation of efficient healthcare blockchains.
2. A systematic search of various medicine and health databases will be conducted to identify relevant literature.
3. The potential of healthcare blockchains in enhancing user access, interoperability, scalability and health outcomes will be assessed.
4. We predict that unmet needs of patients, healthcare providers and researchers regarding data sharing will be identified through conduction of this systematic review.
5. We predict that areas around the architecture of healthcare blockchains which require further research will be identified upon completion of the systematic review.

Limitations
1. Studies published in languages other than English will be excluded.
2. The costs associated with operating such systems in healthcare (for example, the cost required for computing) will not be evaluated.

Conclusions
As systematic reviews provide the highest form of evidence, we anticipate that review findings will provide patients, researchers and healthcare providers with information on healthcare blockchains. Transparent and rigorous methods will be applied, thereby demonstrating replicability of the review. In addition to consulting blockchain experts and professionals, we anticipate that the review will guide the team in developing recommendations pertaining to blockchains that will enable decision-making of developers, patients, healthcare providers and researchers.

Acknowledgements
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Author's contributions
TO wrote the draft report. MVV provided feedback on methodology. EM reviewed and amended the report. DB and MVV reviewed the first draft. AA, JC, and AM reviewed the second draft. TO and AA reviewed BMC guidelines. TO incorporated feedback obtained from authors. The final report was agreed by all authors. EM conceived the study aims and objectives, contributed to draft and methodological review, revised both drafts, and provided oversight. EM is the guarantor.

Conflicts of Interest
The ICMJE uniform disclosure form at http://www.icmje.org/conflicts-of-interest/ was completed by all authors. The manuscript received financial support from the Sir David Cooksey Fellowship in Healthcare Translation. All authors declare that they have no relevant conflicts of interest, no financial relationships that could potentially influence the submitted manuscript. All authors do not have any patents that may be relevant to the manuscript or any relationship, circumstances or conditions that may lead to conflicts of interest. This article represents the authors’ individual opinions and may not necessarily represent the viewpoints of their employers. D.B. is a stockholder in Translation Ventures. Ltd. (Charlbury, Oxfordshire, UK) and IP Asset Ventures Ltd. (Oxford, Oxfordshire, UK), companies that, among other services, provide cell therapy biomanufacturing, regulatory, and financial advice to pharmaceutical clients. D.B. is also subject to the CFS institute's
codes, standards, and guidelines, so he must stress that this piece is provided for academic interest only and must not be seen in any way as an investment recommendation.

**Abbreviations**

- API: Application Programming Interface
- CMS: Center for Medicare and Medicaid Services
- EHR: Electronic Health Record
- EMR: Electronic Medical Record
- HIPAA: Health Insurance Portability and Accountability Act of 1996
- LISI: Levels of Information Systems Interoperability
- MeSH: Medical Subject Heading
- PCOR: Patient Centered Outcomes research
- PICO: Population, Intervention, Comparator, Outcome
- PMI: Precision Medicine Initiative
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
- R&D: Research & Development
References


Appendix 1: Table displaying the PRISMA-P 2015 Checklist

PRISMA-P 2015 Checklist
This checklist to be used for the Systematic Reviews protocol submission was adapted from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews 2015 4:1

<table>
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<th>Checklist Item</th>
<th>Information reported</th>
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<td>If the protocol is for an update of a previous systematic review, identify as such</td>
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<td>Authors</td>
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<tr>
<td>Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
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<td>Contributions</td>
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<td>Role of Sponsor or Funder</td>
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<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
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<td><strong>Methods</strong></td>
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<td>Eligibility criteria</td>
<td>8</td>
<td>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</td>
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<td>Information sources</td>
<td>9</td>
<td>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</td>
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<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated</td>
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<td>Data management</td>
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<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
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<td>Selection process</td>
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<td>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)</td>
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<td>Data collection process</td>
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<td>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</td>
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<td>Data items</td>
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<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
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<td>Outcomes and prioritization</td>
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<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
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<td>Risk of bias in individual studies</td>
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<td>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</td>
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<td>Describe criteria under which study data will be quantitatively synthesised</td>
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<td>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)</td>
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<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
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<td>Meta bias(es)</td>
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<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
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<td>Confidence in cumulative evidence</td>
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<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
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**Appendix 2: Table displaying the MEDLINE/Pubmed Search Strategy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Subject headings</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blockchain technology</td>
<td>_</td>
<td>blockchain technology OR blockchain$ OR bitcoin$ OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cryptocurrency$ OR cryptograph$ OR &quot;ledger technolog$&quot;</td>
</tr>
<tr>
<td>Healthcare access,</td>
<td>Health Information</td>
<td>Interoper$ OR Access$ OR Quality OR scalab$ OR data</td>
</tr>
<tr>
<td>interoperability and scalability</td>
<td>Interoperability</td>
<td>privacy</td>
</tr>
<tr>
<td></td>
<td>Health Services Accessibility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Health Care Quality, Access, and Evaluation</td>
<td></td>
</tr>
</tbody>
</table>