Original Research

Making science computable: Developing code systems for statistics, study design, and risk of bias

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ABSTRACT

The COVID-19 crisis led a group of scientific and informatics experts to accelerate development of an infrastructure for electronic data exchange for the identification, processing, and reporting of scientific findings. The Fast Healthcare Interoperability Resources (FHIR®) standard which is overcoming the interoperability problems in health information exchange was extended to evidence-based medicine (EBM) knowledge with the EBMonFHIR project. A 13-step Code System Development Protocol was created in September 2020 to support global development of terminologies for exchange of scientific evidence. For Step 1, we assembled expert working groups with 55 people from 26 countries by October 2020. For Step 2, we identified 23 commonly used tools and systems for which the first version of code systems will be developed. For Step 3, a total of 368 non-redundant concepts were drafted to become display terms for four code systems (Statistic Type, Statistic Model, Study Design, Risk of Bias). Steps 4 through 13 will guide ongoing development and maintenance of these terminologies for scientific exchange. When completed, the code systems will facilitate identifying, processing, and reporting research results and the reliability of those results. More efficient and detailed scientific communication will reduce cost and burden and improve health outcomes, quality of life, and patient, caregiver, and healthcare professional satisfaction. We hope the achievements reached thus far will outlive COVID-19 and provide an infrastructure to make science computable for future generations. Anyone may join the effort at https://www.gps.health/covid19_knowledge_accelerator.html.

1. Introduction

Crisis leads to innovations. The COVID-19 crisis stimulated collaborative efforts resulting in a breakthrough in the communication of evidence in scientific literature. Today the evidence is not reported in a form that computers can understand. Evidence is not yet expressed in precise, unambiguous format (i.e., computable formats). The near-infinite variations in how evidence can be expressed using natural language means that it requires substantial expertise and contextual awareness for people to determine if the evidence matters, to interpret what the evidence means, and to determine the certainty of these interpretations. To make scientific evidence shareable, interoperable, and computable, it is essential to use standardized concepts from controlled terminologies and vocabularies. This article introduces early efforts to develop an infrastructure for electronic data exchange for the identification, processing, and reporting of scientific findings, and presents a 13-step Code System Development Protocol created to support global development of terminologies for exchange of scientific evidence

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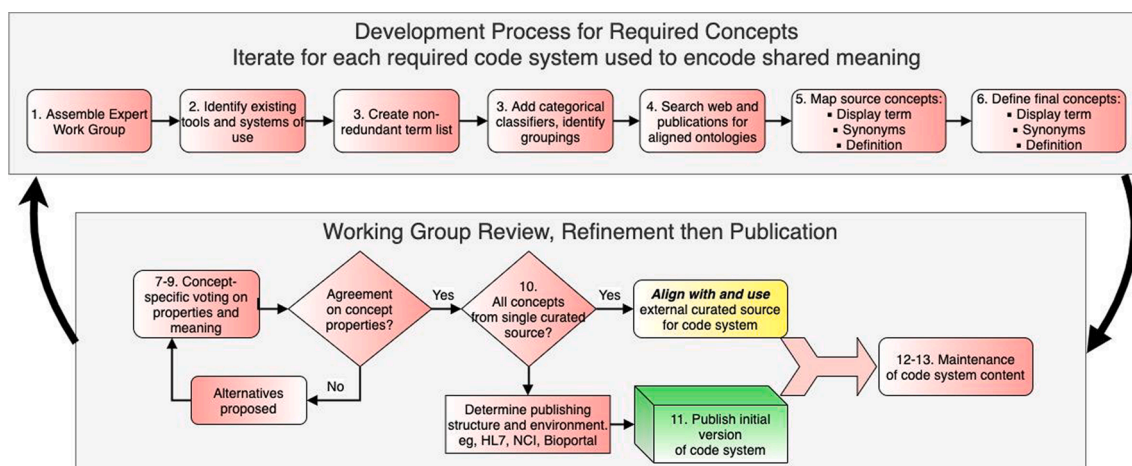
Fig. 1. Code System Development Protocol Flow Diagram.

2. Background

2.1. Introduction to Fast Healthcare Interoperability Resources

Fast Healthcare Interoperability Resources (FHIR®) is rapidly overcoming the seemingly intractable interoperability problem in the sharing and exchange of health information [1]. FHIR solves the interoperability problems by breaking down key units of data exchange into resources. Each FHIR resource instance describes a distinct identifiable entity, and each FHIR resource has a FHIR *StructureDefinition* Resource instance that describes the set of data element definitions and their rules of use that define the FHIR specification itself. Rather than forcing all health-related knowledge to fit one organizational pattern for a common structural model, FHIR enables resource-specific structure definitions to enable the most efficient and flexible approach. Health Level 7 International (HL7®), the standards developing organization that created and maintains FHIR, addresses the human problem in universal agreement to a technical standard by supporting open, transparent, logical processes and systems for people from all perspectives to participate [2].

2.2. Extension of FHIR to evidence-based medicine

There is currently no widely implemented standard that overcomes the seemingly intractable interoperability problem of sharing and exchange of computable representations of scientific knowledge. Facing such challenges with the communication of scientific knowledge to inform healthcare decision making, communities within and across researchers, systematic reviewers, guideline developers, and healthcare professionals have advanced human-interpretable expectations for trustworthy interpretation and application of scientific knowledge [3]. This area is often labeled evidence-based medicine (EBM), evidence-based practice, or evidence-based healthcare [4,5].

HL7 approved a project in 2018 to develop FHIR Resources for Evidence-Based Medicine Knowledge Assets (EBMonFHIR) [6]. In the following 18 months via weekly web meetings and five Connectathons, the EBMonFHIR project created FHIR *StructureDefinition* Resources for *Evidence*, *EvidenceVariable*, *Statistic*, and *OrderedDistribution* FHIR resources.

- The *EvidenceVariable* Resource is used to describe a variable used in statistical expressions, with one or more of defining characteristics expressed using standardized concept codes (i.e., codable concepts [7]).
- The *Statistic* Resource supports the expression of a statistic, including the numerical values, the related attributes which are also statistics, and the type of statistic as a codable concept [8].

- The *OrderedDistribution* Resource supports expression of a statistical array [9].
- The *Evidence* Resource supports expression of the statistics for a distinct combination of variables and the certainty of the interpretation of the statistics [10].

2.3. Extension of EBMonFHIR to COVID-19 Knowledge Accelerator

Multiple groups in the EBM community sought to use EBMonFHIR resources to support efforts related to global collaboration, cooperation and coordination for identification, evaluation, and reporting of COVID-19 evidence. Participating and related efforts include Agency for Healthcare Research and Quality (AHRQ) evidence-based Care Transformation Support initiative (ACTS) [11], ACTS COVID-19 Guidance-to-Action Collaborative [12], Australian National Clinical Evidence Taskforce [13], Centers for Disease Control and Prevention's Adapting Clinical Guidelines for the Digital Age [14], COVID-19 Advanced Literature Classifier (CALC) [15], COVID-19 DistillerSR Access [16], COVID-19 Evidence Alerts from McMaster Plus [17], COVID-19 Evidence Network to support Decision making (COVID-END) [18], COVID-19 Open Research Dataset (CORD-19) [19], HL7 Biomedical and Research Regulation (BRR) Work Group [20], HL7 Clinical Decision Support Work (CDS) Group [21], Librarian Reserve Corps [22], the LIVING Project [23], Mobilizing Computable Biomedical Knowledge (MCBK) [24], and Systematic Review Data Repository (SRDR) [25].

On March 30, 2020, we started the COVID-19 Knowledge Accelerator (COKA) and by July had more than 150 working meetings with more than 40 active participants from more than 25 organizations from academia, industry, government, and nonprofits in 7 countries [26]. The COKA developed 10 active working groups meeting virtually 12 times per week. COKA efforts revised the FHIR *Statistic* Resource to include expressions of the statistical model. COKA efforts also created two more FHIR *StructureDefinition* resources: *Citation* Resource to support exchange of about 100 elements used to identify articles referenced for scientific reporting [27], and *EvidenceReport* Resource to support compositions of all the other resources in many combinations [28].

Across the six FHIR resources maintained by the EBMonFHIR/COKA efforts, there were more than 30 elements that would benefit from the use of standardized encoded concepts. Some concepts can be expressed with commonly used code systems such as SNOMED CT® [29], RxNorm [30], and LOINC® [31]. However, we discovered many situations where we could not find a comprehensive code system that was functionally applicable for the concepts commonly communicated.

3. Methods

3.1. Development of code system development protocol

We initially developed code systems [32] with pragmatic approaches by using codable concepts found in other code systems where available (such as the STATistics Ontology [STATO] [33] and National Cancer Institute thesaurus [NCIt] [34]) and developing mnemonic codes for terms commonly used by the EBMonFHIR and COKA participants. Though functional for the growing but small community, the desire for interoperability with many related communities included those represented in the HL7 CDS, Clinical Quality Information, BRR, and Vocabulary Work Groups. This demanded development of methods to support open, multinational, multidisciplinary input; comprehensive attention to existing ontologies; global consensus development; and sustainability planning.

Through multiple open virtual web meetings and shared documents, we developed a Code System Development Protocol (full protocol in Appendix A, related image in Fig. 1) which includes 13 steps [35]:

1) Assemble an expert working group.
2) Identify tools or systems commonly used today to express relevant concepts.
3) Map out a single list of non-redundant concepts to support common uses.
4) Identify existing ontologies that are openly available without restrictions.
5) Map related terms and definitions across the ontologies.
6) Define preferred terms, alternative terms, and definitions for the new code system.
7) Identify code system entries with universal agreement by the expert working group.
8) Deliberate suggested changes and reach universal agreement for code system entries where possible.
9) Deliberate unresolved disagreements and reach at least 80% agreement for code system entries where possible.
10) Determine the relative contribution of ontologies to the code system and seek further collaboration for heavily used ontologies.
11) Publish the initial version of the new code system.
12) Evaluate implementation of the code system and refine the system as needed.
13) Maintain continued support to adjust the code system based on changes in the prior 12 steps.

3.2. Scope setting

We selected four domains for initial application of the Code System Development Protocol and defined them as [35]:

- "**The Statistic Type Code System** will be used to precisely classify univariate statistics (such as mean, median, and proportion), comparative statistics (such as relative risk, mean difference, and odds ratio), and statistic attribute estimates (such as confidence interval, p value, and measures of heterogeneity). Consistent reporting across systems will facilitate interoperability for science communication.
- **The Statistic Model Code System** will precisely communicate characteristics that define the model used for a statistic. Science reports often do not convey complete information about statistical models. Model characteristics may include concepts such as fixed-effects analysis, linear regression, and Mantel-Haenszel method for pooling. Consistent reporting of statistical models will facilitate interoperability for science communication.
- **The Study Design Code System** will be used to precisely describe methodology characteristics of scientific observations including exposure introduction (such as interventional or observational),

cohort definition (such as parallel, crossover or case-control), and group assignments (such as block randomization, every-other quasi-randomization, or non-randomized). Consistent reporting of research study design across systems will facilitate interoperability for science communication.
- **The Risk of Bias Code System** will be used to precisely describe concerns with methods or reporting of scientific observations including selection bias (such as gaps in randomization or allocation concealment), performance bias (such as gaps in blinding), and analysis bias (such as gaps in intention to treat analysis or selective analysis reporting). Consistent reporting of risk of bias across systems will facilitate interoperability for science communication."

3.3. Step 1: Assemble an expert working group

For Step 1, we developed an Invitation to Join an Expert Working Group for any of the four code systems (Statistic Type, Statistic Model, Study Design, Risk of Bias). Joining the group was open to anyone and group members could self-identify their expertise. Relevant expertise for a code system could include without limitation experience evaluating or expressing the concepts to be included in the code system, either for human interpretation or for machine interpretation.

We shared the invitations through multiple communities (mostly via email distribution lists) including the COKA Initiative, COVID-END, the evidence-based healthcare (EBH) listserv, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group, the Developing and Evaluation Communication strategies to support Informed Decisions and practice based on Evidence (DECIDE) project participants, the AHRQ evidence-based practice centers (EPCs), the HL7 CDS and BRR work groups, the Society for Clinical Trials, the Society for Participatory Medicine, International Society for Clinical Biostatistics, and Patient-Centered Outcomes Research Institute (PCORI).

3.4. Step 2: Identify commonly used tools and systems

For Step 2, we asked Expert Working Group members to identify sources to signal the scope of (or common need for) a code system, namely tools or systems in common current use for reporting concepts relevant to the code system.

3.5. Step 3: Create lists of non-redundant concepts

For Step 3, we started with one of the common tools or systems, identified a series of non-redundant concepts for expression to support it, and provided a categorical classification. We then mapped the next identified tool or system, matched concepts where possible, added more concepts where needed, and adjusted the categorical classification. The process was shared openly during weekly Steering Group web meetings and summarized for the Expert Working Group by email distribution lists with open links to the Step 3 mapping spreadsheets.

3.6. Time course for initial development

The COVID-19 Knowledge Accelerator consists of 10 active working groups meeting a total of 12 times weekly in open web meetings. Several working groups were developing code systems and the discussions about a common approach started on August 24, 2020. The first draft of a Code System Development Protocol with 11 steps was created on August 28. The protocol was finalized on September 17. Initial efforts were started ahead of wider dissemination of invitations. Invitations to join the expert working groups were sent widely during the week of September 21. All participants were asked to comment by an October 14 cutoff date for communicating the degree of contribution to Step 3 for version 1.0.0 of the code systems.

We report here the results of Steps 1–3 of this effort as of October 14,

```
"coding": [{"system": "http://build.fhir.org/codesystem-study-
type.html","version": "4.2.0","code": "RCT","display": "randomized
trial","userSelected": true}]
```

2020. These results are not complete in terms of code system development as they do not include definitions or codes and may change through the remaining steps. These remaining steps, and the overall protocol, share and build upon principles and practices in existing ontology development methods [36,37,38]. Key aspects such as reusing existing ontologies, enumerating important terms (ie, concepts) across ontologies, and the overall iterative and agile nature of ontology development are well represented in our code system development protocol. We presented our protocol and preliminary findings in an October 30 Workshop on COVID-19 Ontologies (https://github.com/CIDO-ontology/WCO). In November of 2020, we met with ontology developers of the STATO and Ontology of Biological and Clinical Statistics (OBCS), both of which are Open Biological and Biomedical Ontologies (OBO) Foundry recognized ontologies. The ontology developers found our work valuable for identifying gaps, alignments, new terms, and other improvements for existing ontologies and potentially for creating an application ontology.

4. Results

4.1. Expert working groups

As of October 10, 2020, a total of 55 people from 26 countries in 6 continents joined an Expert Working Group for up to four code system development efforts (see Table 1 and Appendix B).

4.2. Initial results (Step 2 and Step 3)

Twenty-three commonly used tools and systems were applied across the four code systems, ranging from 2 to 12 per code system (Table 2). There were 368 non-redundant concepts (draft display terms for a code system) identified across the four code systems, ranging from 53 to 170 per code system (Table 2, Appendices C, D, E and F).

Table 1
Demographics of 55 Members of Expert Working Groups.

Country (total 26)	Australia (1), Bangladesh (2), Brazil (2), Canada (5), Costa Rica (1), Czech Republic (1), Egypt (1), Finland (2), France (1), Ghana (1), Greece (2), India (2), Ireland (1), Italy (2), Japan (1), Lebanon (1), Malaysia (1), Nigeria (4), Peru (1), Romania (2), South Africa (1), South Korea (1), Sri Lanka (1), Switzerland (2), United Kingdom (2), United States (14)
Type of expertise*, n (%)	
Researcher	42 (76%)
Evaluate scientific concepts	34 (62%)
Systematic Reviewer	32 (58%)
Statistician	23 (42%)
Guideline developer	14 (25%)
Developer of reporting systems	12 (22%)
Learner	10 (18%)
Software engineer/ Informatics specialist	10 (18%)
Write-in responses	Librarian (3), Teacher of medical literature evaluation (2), Clinician/health professional, Terminologist, Standards developer, Qualitative researcher, Book author
Age, n (%)	
18–25 years	2 (4%)
26–40 years	16 (29%)
41–55 years	21 (38%)
56–69 years	13 (24%)
70+ years	1 (2%)
Not shared	2 (4%)
Sex, n (%)	
Female	18 (33%)
Male	36 (65%)
Not shared	2 (2%)
Race/ethnicity*, n (%)	
Asian	11 (20%)
Black	6 (11%)
Hispanic/Latino	6 (7%)
Indigenous	2 (4%)
White	27 (49%)
Not stated	7 (13%)

*More than one selection may apply to each person.

Table 2
Step 2 and Step 3 Results to Inform Code System Development.

Code System	Tools and Systems Considered	# draft codable concepts
Statistic Type	– StatisticType code system defined by the FHIR project [39] – StatisticAttributeEstimateType code system defined by the FHIR project [40] – ObservationMethodAggregate value set from HL7 V3 ObservationMethod code system [41] – Cochrane Review Manager (RevMan) [42]	88
Statistic Model	– StatisticModelCode code system defined by the FHIR project [43] – StatisticModelMethod code system defined by the FHIR project [44]	53
Study Design	– StudyType code system defined by the FHIR project [45] – ResearchStudyPhase code system defined by the FHIR project [46] – MEDLINE MeSH Headings for Study Characteristics [Publication Type][47] – ClinicalTrials.gov study type classifiers [48] – ResearchStudy-StudyDesign code system used in the database of Genotypes and Phenotypes (dbGaP) [49]	57
Risk of Bias	– StatisticCertaintySubcomponentType code system defined by the FHIR project [50] – StatisticCertaintySubcomponentRating code system defined by the FHIR project [51] – Cochrane Collaboration's Risk of Bias tool (ROB-1) [52] – Revised Risk of Bias Tool (ROB-2) [53] – Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) [54] – Newcastle-Ottawa Scale for non-randomized studies [55] – Risk of Bias in Systematic Reviews (ROBIS) [56] – Prediction Model Risk of Bias Assessment Tool (PROBAST) [57] – Quality in Prognosis Studies (QUIPS) [58] – Quality Assessment of Diagnostic Accuracy Studies (QUADAS) [59] – Mixed Methods Assessment Tool (MMAT) [60] – Cochrane Handbook Chapter 9 (reporting styles for risk of bias tables) [61]	170

Table 3
Example of coding element.

Element name	Value
System	http://build.fhir.org/codesystem-study-type.html
Code	RCT
Display	randomized trial

5. Discussion

5.1. Progress toward code system development

Coordinating 55 experts from 26 countries to identify 198 concepts for the development of code systems for scientific methodology (statistics and study design) and 170 concepts for the assessment of quality of evidence (risk of bias) is an early step in what is needed to support interoperable data exchange for scientific communication.

Next steps include mapping concepts across ontologies, reaching universal or near-universal agreement for common code systems for data exchange, and continuous adaptation to meet needs discovered in implementation.

The COKA effort will benefit from the newly crafted HL7 Unified Terminology Governance (UTG) process wherein terminology artifacts, such as the code systems and mappings we are creating, are published by HL7 [62]. The UTG approach aligns with our protocol by subjecting the artifacts created to an open comment and review process. The UTG process starts with transforming the code system and concept map terminology content into FHIR code system and concept map artifacts, typically represented in FHIR JSON or XML [63]. Once the content is entered into the UTG environment, it exists as a set of proposed changes to the core HL7 terminology. Those proposals are made available for review and comment within the UTG environment, consistent with steps 12 and 13 of our protocol. Once comments on the proposed artifacts are resolved and voting requirements are met, if approved, the terminology additions are merged into the HL7 terminology environment at terminology.hl7.org, which is updated and made available through a continuous integration process [63]. In this way, updates and improvements for any content can be developed, proposed, reviewed, improved, voted on and released within a documented environment aligned with the American National Standards Institute (ANSI)-sectioned HL7 ballot process, and ultimately published as part of the official HL7 terminology content.

Our protocol (step 6) includes entering data into an ontology web editor which by design would include top-level ontology concepts (classes, hierarchy, attributes) such as those represented in the Basic Formal Ontology [64] to help refine the classes and hierarchy. The consideration of the FHIR CodeSystem Resource StructureDefinition [65] in preparation for the UTG approach helped us realize we can represent these top-level ontology concepts as property elements within the CodeSystem Resource and we are currently considering modifying step 6c of our protocol to use FHIR tooling directly instead of a web ontology editor.

5.2. Strengths and limitations

Strengths of our approach include a substantial spirit of comradery across many diverse people facing a common challenge, multidisciplinary engagement, and coordination with global systems for standards development. In addition, use of FHIR as the underlying standard provides support from a method demonstrated to meet the interoperability needs for a similarly complex global community.

Limitations include the rapid timeline for development, having processed the initial listing of hundreds of concepts in just a month or so. There will undoubtedly be multiple revisions. The current list does not include outcome-specific statistic types (such as mortality for observed proportion or incidence related to death) or application-specific statistic types (such as recall instead of sensitivity for the application to information retrieval). This approach was purposefully taken to maximize simplicity and flexibility. Also, it is not yet established what resources will be needed to complete and maintain the code systems. For the initial effort, the degree of volunteerism and availability was influenced substantially by COVID-19 and we hope the spirit will continue for application across other domains.

5.3. Example for computable evidence

We demonstrate a computable expression of evidence [66] with the results (summary effect estimate) of a meta-analysis of three randomized trials [67,68,69] for the effect of remdesivir on 14-day mortality in patients with COVID-19 pneumonia. This example includes 43 instances of a "coding" element to express codable concepts with a "system" element to denote the code system, a "code" element to denote the specific code, and a "display" element for human-readable interpretation of the code. For example, the JSON includes (see Table 3):

This example of computable evidence uses existing codes in published code systems where available, and these may differ from the code systems in development. Where not available, we use "system": "not yet published" and "code": "not yet defined" and this shows the need for creation or extension of code systems. One can search the JSON in this example to find 1 code related to study design ("display": "randomized trial"), 8 codes related to statistic type ("display" values of "Relative Risk", "Confidence Interval", "Z-score", "P-value", "I-squared", "Cochran's Q statistic", "degrees of freedom", and "Tau squared"), 4 codes related to statistic model ("display" values of "Meta-analysis", "Fixed-effects", "Random-effects", and "Dersimonian-Laird method"), and 1 code related to risk of bias ("display": "Lack of blinding"). In this example, the effect estimate is statistically significant using a fixed-effect model and not statistically significant using a random-effects model for the meta-analysis, a situation for which explicit representation of the statistic model is necessary for proper interpretation.

5.4. Benefits of code system development

When completed, the code systems will make finding knowledge easier. For example, systematic reviewers may specify study design concepts to facilitate identification of articles meeting their inclusion criteria. The code systems will facilitate re-use of scientific results. For example, clinical trial reporters who express their results for regulatory purposes could re-use the data to express their results for publication, and the systematic reviewers could directly re-use these results without the need for manual data extraction. All of these code systems will expedite recognition of the trustability of scientific knowledge whether seeking the data parameters (as expressed with statistic type codes), the methods for data creation (as expressed with study design and statistic model codes), or the assessments of others (as expressed with risk of bias codes). Someday, via explicit encoded study results, data within published papers can integrate with clinical decision support systems, particularly when reporting meta-analysis results.

We hope the processes, systems, and accomplishments we have produced so far in response to the COVID-19 crisis are sufficient to provide an infrastructure that will endure to make scientific communication accessible for a long time.

6. Conclusion

We started with efforts to support each other to accelerate knowledge transfer for COVID-19, and then developed solutions with expansive potential. We identified non-redundant concepts to support computable expression of scientific methods. Mapping these concepts to existing ontologies, selecting preferred terms and definitions by the global community, evaluating the implementation of the code systems,

and supporting continued development of the systems will support an extensive ecosystem for communicating scientific evidence. More efficient scientific communication will reduce cost and burden and improve health outcomes, quality of life, and patient, caregiver and healthcare professional satisfaction. Anyone who is communicating these concepts may join the effort at https://www.gps.health/covid19_knowledge_accelerator.html [70].

CRediT authorship contribution statement

Brian S. Alper: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Joanne Dehnbostel:** Methodology, Investigation, Data curation, Writing - review & editing, Writing - original draft, Project administration. **Muhammad Afzal:** Methodology, Investigation, Data curation, Writing - review & editing, Writing - original draft. **Vignesh Subbian:** Methodology, Data curation, Writing - review & editing. **Andrey Soares:** Methodology, Data curation, Writing - review & editing, Writing - original draft. **Ilkka Kunnamo:** Methodology, Investigation, Data curation, Writing - review & editing. **Khalid Shahin:** Methodology, Data curation. **Robert C. McClure:** Methodology, Writing - review & editing, Visualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors are members of the COVID-19 Knowledge Accelerator (COKA) Initiative. The COKA Initiative is a volunteer virtual organization with no funding or contractual relations. The non-software content created by the COKA Initiative (including the data shared in this manuscript) is openly and freely available by Creative Commons Attribution-ShareAlike 4.0 International (CC BY-SA 4.0) license. BSA is the owner of Computable Publishing LLC which may commercialize software services related to this content. JD and KS are employed by Computable Publishing LLC. MA, VS, AS, IK, and RCM have no conflicts to report.

Appendix A. Code system development protocol

For the COVID-19 Knowledge Accelerator (COKA) Initiative
Protocol as of September 17, 2020
This protocol will be applied to the development of Risk of Bias Code System, Statistic Type Code System, Statistic Model Code System, and Study Design Code System.

Code System Descriptions

The Statistic Type Code System will be used to precisely classify univariate statistics (such as mean, median, and proportion), comparative statistics (such as relative risk, mean difference, and odds ratio), and statistic attribute estimates (such as confidence interval, p value, and measures of heterogeneity). Consistent reporting across systems will facilitate interoperability for science communication.

The Statistic Model Code System will precisely communicate characteristics that define the model used for a statistic. Science reports often do not convey complete information about statistical models. Model characteristics may include concepts such as fixed-effects analysis, linear regression, and Mantel-Haenszel method for pooling. Consistent reporting of statistical models will facilitate interoperability for science communication.

The Study Design Code System will be used to precisely describe methodology characteristics of scientific observations including exposure introduction (such as interventional or observational), cohort definition (such as parallel, crossover or case-control), and group assignments (such as block randomization, every-other quasi-randomization, or non-randomized). Consistent reporting of research study design across systems will facilitate interoperability for science communication.

The Risk of Bias Code System will be used to precisely describe concerns with methods or reporting of scientific observations including selection bias (such as gaps in randomization or allocation concealment), performance bias (such as gaps in blinding), and analysis bias (such as gaps in intention to treat analysis or selective analysis reporting). Consistent reporting of risk of bias across systems will facilitate interoperability for science communication.

Protocol Steps:

1. Assemble an expert working group for each code system.
   a. Expert working group membership will be open to any individual who self-identifies as a relevant expert for the code system. Relevant expertise for a code system may include but is not limited to experience evaluating or expressing the concepts to be included in the code system, either for human interpretation or for machine interpretation.
   b. We will post open invitations as email messages to the distribution lists for the COKA Initiative, COVID-END, EBH listserv, GRADE Working Group, DECIDE project participants, AHRQ EPC listserv, HL7 CDS and BRR work groups, the Society for Clinical Trials, the Society for Participatory Medicine, International Society for Clinical Biostatistics, and PCORI.
   c. With the invitation we will share an introduction to what is a code system, why we are doing this, a link to the protocol, and a link to a data entry form to sign up. Sign up at Code System Development Intake Form.
   d. The data entry form will include optional demographic questions (age, gender, race/ethnicity) for the sole purpose of reporting demographic distribution of the expert working group in submitted publications of the code system.
   e. Set up a code system steering group from the most actively engaged participants, specifically those who join open weekly work group meetings.
2. For each code system, identify sources to signal the scope of (or common need for) a code system, namely tools or systems in common current use for reporting the concepts relevant to the code system. Expert working group members will be asked to identify such sources.
3. Create a list of non-redundant concepts that convey the concepts in commonly used tools and systems.
   a. Categorical classifiers (names of code sets) may be added. (A concept may be a member of a code set.)
   b. A concept may be marked as "also serves as a categorical classifier" in which case the concept may be a "parent" in one or more IS-A relationships with other concepts. (A name of a code set may be a member of another code set.)

    c. A concept may be marked as being a "child" in an IS-A relationship with another concept by listing the "parent" concept as a categorical classifier.

    d. This list will be reviewed in the open work group meetings.

4. Identify ontologies likely to include concepts on the lists created in step 3. Expert working group members will be asked to identify such ontologies. We will limit the effort to ontologies available for use without restrictions (or limited to Category 0 or 1 Restrictions per UMLS Restriction Levels described at https://uts.nlm.nih.gov/help/license/licensecategoryhelp.html).

5. For each concept, from each ontology, extract the display (or preferred term), synonym list (or alternative terms), and definition(s) that best match the concept, and note closely related variations.

6. For each concept:

    a. Review the displays, synonym lists, and definitions available from ontologies.

    b. Draft a preferred display, synonym list, and definition, and note matches to the ontologies to measure relative contributions.

    c. Enter the draft preferred display, synonym list, and definition into an ontology web editor (such as WebProtege). If approved, the dataset can be shared with National Cancer Institute (NCI) Enterprise Vocabulary Services (EVS) for entry in the NCI Thesaurus and exported for use with WebProtege.

7. Each member of the expert working group will, for each concept that will be a code system entry, note agreement (with the draft preferred display, synonym list and definition) or suggest changes.

    a. For concepts that are "parents" in IS-A relationships, agreement will also be sought that the concept is useful functionally without subordinate coding.

    b. For concepts that are "children" in IS-A relationships, agreement will also be sought that if the child concept applies then the parent concept must apply AND the parent concept can apply while the child concept does not apply.

    c. This process will be online and asynchronous.

8. For any concepts without universal agreement we will discuss the suggested changes in open meetings, revise as appropriate, then resend for voting as noted in step #7.

9. If a concept does not achieve universal agreement (cycling through steps 7 and 8 with conflicting suggestions):

    a. Each person recommending changes will write a rationale.

    b. The rationales will be shared with the expert working group prior to a group meeting.

    c. The group meeting will discuss and prepare the preferred version. The preferred version and meeting discussion will be shared with the group.

    d. Group members will have 48 h to vote for the presented version.

    e. The preferred version will become the included version if it achieves at least 80% agreement with at least 5 people voting.

    f. If unable to achieve at least 80% agreement with at least 5 people voting, options may include extending the voting period, dropping the item, or preparing for another group discussion.

10. For the first complete version of the code system with agreement reached for all entries, we will determine the percent contribution from the different ontologies. If an ontology provides >50%

contribution across the series of code systems or >75% contribution to a single code system, we may consider deeper collaboration rather than continued maintenance of a new code system.

11. We will publish the code system at terminology.hl7.org and seek publication of introductory articles to the code system in the biomedical literature.

12. For implementation and initial evaluation of the code system:

    a. Identify tools and systems that could use the code system.

    b. Offer support for implementation. Measure proportion of systems that get engaged.

    c. Evaluate ease of use.

    d. Generate code system change requests as needed.

    e. Track systems that implement the code system and set a regular review interval to inquire about usefulness and change requests.

13. For ongoing maintenance and development of the code system:

    a. Maintain an open invitation for code system users to join the expert working group for continued feedback.

    b. Maintain a method for expert working group members to suggest additional tools or systems with common current use of concepts matching the code system.

    c. Code system changes may be initiated by change requests from the community.

    d. The code system steering group will validate that change requests are appropriate for group deliberation (eg, fits the purpose of the code system, has sufficient rationale, avoids duplication).

    e. Valid change requests will lead to drafting a preferred display, synonym list, and definition.

    f. Each member of the expert working group will, for each valid change request, note agreement (with the draft preferred display, synonym list and definition) or suggest changes. This process will be online and asynchronous. (step #7)

    g. For any concepts without universal agreement we will discuss the suggested changes in open meetings, then resend for voting as noted in steps #7 and #8. If not reaching universal agreement, manage as step #9.

    h. Changes to the code system will be published at terminology.hl7.org and released as needed.

Cite as:

Alper BS, Dehnbostel J, Robinson K, Subbian V, Afzal M, Soares A, Kunnamo I, Shahin K, Lehmann H, Fedorowicz Z, McClure R, Thabane L. For the COVID-19 Knowledge Accelerator (COKA) Initiative. Code System Development Protocol. Created September 1, 2020. Last revised September 17, 2020. Available at: https://tinyurl.com/CodeSystemDevelopmentProtocol

Also available at OSF:

https://osf.io/3akjv/?view_only=65c2ab5809c1484895d4fb03a2a9ee84

Appendix B. Participants in the COVID-19 Knowledge Accelerator (COKA) Initiative

See Tables B1 and B2.

Table B1

Expert Working Group Contributors to the Code System Development Concept Lists.

Name	Country	Code System Development Expert Working Group (number of participants) 1 = signed up for continued participation 2 = AND approved Step 3 results 3 = AND actively contributed to Step 3 results			
		Study Design (44)	Statistic Type (34)	Statistic Model (32)	Risk of Bias (31)
Gaelen P. Adam	United States	1			1
Muhammad Afzal	South Korea		3	3	
Tanvir Ahammed	Bangladesh	1	1	1	1
Brian S. Alper	United States	3	3	3	3
Eric H. Au	Australia	1	1	1	1
Phillip O. Awodutire	Nigeria		2	2	
Sébastien Bailly	France	1	1	1	1
Yusentha Balakrishna	South Africa	1	1	1	
Sorana D. Bolboacă	Romania	1	3	3	
Marek Brabec	Czech Republic		1	1	
Stacy B. Brody	United States	3			
Comes Calin-Adrian	Romania		1	1	
Rachel Couban	Canada	2			
Keitty Regina C. de Andrade	Brazil	1	1	1	1
Joanne Dehnbostel	United States	3	3	3	3
Sandra Dimitri	Egypt	1			
Marc L. Duteau	Canada		2		2
Zbys Fedorowicz	United Kingdom	1			1
Emilia J. Flores	United States	1		1	
Isaac Fwemba	Ghana	1	1	1	1
Abhay M. Gaidhane	India	1			
Eric M. Harvey	United States	3			2
Danielle Johnson	United Kingdom	1	1		
Samer A. Kharroubi	Lebanon		1	1	
Bhagvan Kommadi	India	3	3	3	3
Polychronis Kostoulas	Greece			1	
Evangelos Kritsotakis	Greece	3	3		
Ilkka Kunnamo	Finland	1			1
Louis E. Leff	United States		2	2	
Harold Lehmann	United States	1	1	1	1
Jesus Lopez-Alcalde	Switzerland	1			1
Robert C. McClure	United States	2	2	2	2
Matthew D. Mitchell	United States	1			1
Tamara Navarro-Ruan	Canada	3			1
Pentti Nieminen	Finland		1	1	
Akaninyene Patrick Obot	Nigeria	1	1	1	
Aloysius Odii	Nigeria	1	1	1	
Cheow Peng Ooi	Malaysia	1			
Alejandro Piscoya	Peru	1	1		1
Vivek Podder	Bangladesh	1			1
K.M. Saif-UR- Rahman	Japan	1			1
Karen A. Robinson	United States	1	1	1	1
Paola Rosati	Italy	1			1
Carolyn M. Rutter	United States	1	1	1	1
Khalid S. Shahin	United States	3	3	3	3
Roshini Sooriyarachchi	Sri Lanka	1	1		
Vignesh Subbian	United States	3	2	1	1
Lehana Thabane	Canada	3	3	3	3
Mario Tristan	Costa Rica	1	1	1	1
Chidi Ugwu	Nigeria	1			1
Linlu Zhao	Canada				1
Name Withheld	Brazil	1			1
Name Withheld	Ireland	1		1	
Name Withheld	Italy	1	1	1	1
Name Withheld	Switzerland		1	1	

Table B2

Participants in the COVID-19 Knowledge Accelerator (COKA) Initiative.

Name	Organization	A	B	C	D	E	F	G	H	I	J
Gaelen P. Adam	Brown University				o						
Muhammad Afzal	Sejong University	o	o							o	o
Eitan Agai	**PICO Portal**						o				
Brian S. Alper	**Computable Publishing LLC**	o	o	o	o	o	o	o	o	o	o
Ray Alsheikh	Johns Hopkins University		o	o							
Stacy B. Brody	George Washington University, Librarian Reserve Corps				o						
Mary Butler	University of Minnesota									o	
Comes Calin-Adrian	**George Emil Palade University of Medicine, Pharmacy, Science and Technology of Targu Mures**										o
Rachel Couban	McMaster University				o						
Joanne Dehnbostel	**Computable Publishing LLC**	o	o	o	o	o	o	o	o	o	o
Marc L. Duteau	**Duteau Design**	o	o						o		
Zbys Fedorowicz	**Veritas Health Sciences**										o
Gilbert, Mike	**Evidence Partners Inc.**	o					o				
Eric M. Harvey	Swedish Health Services, University of Washington				o						
Sharon Hibay	**Advanced Health Outcomes**							o			
Alfonso Iorio	McMaster University				o						
Jens Jap	**SRDR,** Brown University							o			
Bhagvan Kommadi	**Value Momentum**		o	o	o	o					o
Ilkka Kunnamo	**Duodecim Medical Publications Ltd.**	o					o	o			
Pawel Kunstman	**Evidence Prime Inc.**							o			
Eddy Lang	**Alberta Health Services**				o	o					o
Harold Lehmann	Johns Hopkins University	o	o	o	o				o		
Sara Loree	**Librarian Reserve Corps**								o	o	
Martin Mayer	EBSCO		o	o	o	o					
Robert C. McClure	**MD Partners**	o							o		o
Tamara Navarro-Ruan	McMaster University				o						
Jerry Osheroff	**TMIT Consulting**									o	
Amy Price	Stanford University				o			o			
Joshua Richardson	**RTI International**										o
Karen A. Robinson	Johns Hopkins University	o	o	o	o	o	o	o	o	o	o
Lisa Schilling	University of Colorado							o			
Birol Senturk	**Brown University EPC, SRDR**							o			
Khalid S. Shahin	**Computable Publishing LLC**	o	o	o	o	o	o	o	o	o	o
Andrey Soares	University of Colorado				o			o			o
Ian Saldanha	**Brown University EPC, SRDR**							o			
Vignesh Subbian	University of Arizona				o						o
Jennifer Tetzlaff	**Evidence Partners Inc.**		o	o	o	o					o
Lehana Thabane	McMaster University				o	o					
Mario Tristan	**IHCAI Institute-Cochrane Centroamerica and DIME**				o			o			
Danny van Leeuwen	**Health Hats**				o	o					
Jody Wachs	Vizient		o	o							

Bold type used for organization-level participation.

A Project Management Group
B Statistic Type Code System Development Steering Group
C Statistic Model Code System Development Steering Group
D Study Design Code System Development Steering Group
E Risk of Bias Code System Development Steering Group
F Content Citation and Classification Tools Development Work Group
G Evidence Evaluation and Reporting Tools Development Work Group
H Systematic Meta-Review Project Group
I Knowledge Ecosystem Liaison Work Group
J Communications Work Group

Appendix C. Draft term list for statistic type code system version 1.0.0

This list has 88 non-redundant codable concepts for the Statistic Type Code System (items bolded if they are both a classifier and a codable concept):

1. Univariate (CATEGORY ONLY)
   a. Count
   b. Sum
   c. Maximum Observed Value
   d. Maximum Possible Value
   e. Minimum Observed Value
   f. Minimum Possible Value
   g. Cutoff value
   h. Central Tendency (CATEGORY ONLY)
      i. Mean
      ii. Median
      iii. Mode
2. Difference (CATEGORY ONLY)
   a. Count Difference
   b. Mean Difference
   c. Standardized Mean Difference
   d. Median Difference
   e. Risk Difference
3. Ratio (CATEGORY ONLY)
   a. Observed (CATEGORY ONLY)
      i. Observed Proportion
      ii. Incidence
      iii. Cumulative Incidence

    iv. Incidence Rate (Incidence Density)
    v. Period Prevalence
    vi. Point Prevalence
  f. Effect (CATEGORY ONLY)
    i. Hazard Ratio
    ii. Incidence Rate Ratio
    iii. Odds Ratio
    iv. Prevalence Ratio
    v. Risk Ratio
    vi. Number Needed to Treat (NNT)
    vii. Number Needed to Screen (NNS)
    viii. Number Need to Diagnose (NND)
    ix. Relative Risk Difference
  g. Agreement (CATEGORY ONLY)
    i. Diagnostic Accuracy
    ii. Diagnostic Odds Ratio
    iii. **Kappa**
      1. Bennett's Kappa
      2. Cohen's Kappa
      3. Scott's Kappa
    iv. Misclassification Rate
    v. F1-score
  h. Conditional Probability (CATEGORY ONLY)
    i. Predicted Risk
    ii. Sensitivity
    iii. Specificity
    iv. Positive Predictive Value
    v. Negative Predictive Value
    vi. Likelihood Ratio Positive
    vii. Likelihood Ratio Negative
    viii. Positive Clinical Utility Index
    ix. Negative Clinical Utility Index
4. Correlation (CATEGORY ONLY)
  a. Covariance
  b. Pearson Correlation Coefficient
  c. Regression Coefficient
  d. Spearman Rank-Order Correlation Coefficient
  e. Matthews Correlation Coefficient
  f. Kendall Correlation Coefficient
  g. Calibration (CATEGORY ONLY)
    i. Mean calibration
    ii. Calibration-in-the-large
    iii. Calibration intercept
    iv. Calibration slope
5. Dispersion (CATEGORY ONLY)
  a. Range
  b. Interquartile range
  c. **Standard deviation**
    i. Standard deviation for population
    ii. Standard deviation for sample
    iii. Sampling standard deviation
  d. Variance
    i. Variance for population
    ii. Variance for sample
    iii. Sampling variance
  e. Gini Index
6. Statistical Distribution Measure (CATEGORY ONLY)
  a. Dispersion (CATEGORY ONLY)
    i. **Standard error**
      i. Standard error of the mean
      ii. Standard error of the median
      iii. Standard error of the proportion
      iv. Standard error of the difference between means
      v. Standard error of the difference between proportions
    x. Credible interval
    xi. Confidence interval

  b. Discrimination (CATEGORY ONLY)
    i. Area Under the ROC Curve (AUC)
      1. C-statistic
  c. Heterogeneity (CATEGORY ONLY)
    i. Chi square for homogeneity
    ii. Cochran's Q statistic
    iii. I-squared
    iv. Tau squared
  d. Hypothesis Testing (CATEGORY ONLY)
    i. Chi square for independence
    ii. Chi square for trend
    iii. P-value
    iv. Z-score
    v. T-score
7. Descriptive

The list above was the current list as of October 15, 2020. The list continues to evolve and the current list can be found at https://confluence.hl7.org/display/CDS/COKA+Code+System+Development+Working+Groups.

Appendix D. Draft term list for statistic model code system version 1.0.0

This list has 53 non-redundant codable concepts for the Statistic Model Code System (items bolded if they are both a classifier and a codable concept):

1. Determination of Relationship codes (CATEGORY ONLY)
  a. Threshold framing (CATEGORY ONLY)
    i. one-tailed test (one threshold)
    ii. two-tailed test (two thresholds)
  b. Parametric tests (CATEGORY ONLY)
    i. Z-test
    ii. 1-sample *t*-test
    iii. 2-sample *t*-test
    iv. paired *t*-test
    v. chi-squared test
    vi. chi-squared test for trend
    vii. Pearson correlation
    viii. **ANOVA** (ANalysis Of VAriance)
      1. One-way ANOVA
      2. 2-way ANOVA without replication
      3. 2-way ANOVA with replication
      4. 3-way ANOVA
      5. multivariate ANOVA (MANOVA)
  c. Nonparametric tests (CATEGORY ONLY)
    i. sign test
    ii. Wilcoxon signed-rank test
    iii. Wilcoxon rank-sum test
    iv. Mann-Whitney *U* test
    v. Fisher's exact test
    vi. McNemar's test
    vii. Kruskal Wallis test
    viii. Spearman correlation
    ix. Kendall correlation
    x. Friedman test
    xi. Goodman Kruska's Gamma
  d. Regression model (CATEGORY ONLY)
    i. Linear Regression
    ii. Logistic Regression
    iii. Poisson Regression
    iv. Negative Binomial Regression
    v. GLM (Generalized Linear Model)
2. Adjustment of Variables codes (CATEGORY ONLY)
  a. Adjusted analysis

b. Zero-cell adjustment with constant
c. Zero-cell adjustment with continuity correction
3. Pooling codes (CATEGORY ONLY)
    a. **Pooling with Meta-analysis**
        i. Mantel-Haenszel method
        ii. Inverse variance method
        iii. Peto method
        iv. Generalized linear mixed model (GLMM)
4. Variance codes (CATEGORY ONLY)
    a. Adjustment of variance codes (CATEGORY ONLY)
        i. Hartung-Knapp adjustment
        ii. Modified Hartung-Knapp adjustment
    b. Effects codes (CATEGORY ONLY)
        i. Fixed-effects
        ii. Random-effects
    c. Heterogeneity codes (CATEGORY ONLY)
        i. Chi-squared test for homogeneity
        ii. **Tau estimation**
            1. Dersimonian-Laird method
            2. Paule-Mandel method
            3. Restricted Maximum Likelihood method
            4. Maximum Likelihood method
            5. Empirical Bayes method
            6. Hunter-Schmidt method
            7. Sidik-Jonkman method
            8. Hedges method

The list above was the current list as of October 15, 2020. The list continues to evolve and the current list can be found at https://confluence.hl7.org/display/CDS/COKA+Code+System+Development+Working+Groups.

Appendix E. Draft term list for study design code system version 1.0.0

This list has 57 non-redundant codable concepts for the Study Design Code System (items bolded if they are both a classifier and a codable concept):

1. Method of exposure introduction (CATEGORY ONLY)
    a. Interventional method of exposure introduction
    b. Observational method of exposure introduction
    c. Indirect method of exposure introduction
2. Assignment (CATEGORY ONLY)
    a. **Randomized Assignment**
        i. Simple randomization for assignment
        ii. Stratified randomization for assignment
        iii. Block randomization for assignment
    b. **Quasi-Randomized Assignment**
        i. Minimization method of quasi-randomization for assignment
        ii. Every-other method of quasi-randomization for assignment
    c. Non-Randomized Assignment
    d. Cluster Assignment
    e. Matched Assignment
    f. Adaptive Assignment
3. Comparator Design Definition (CATEGORY ONLY)
    a. Parallel cohort definition
    b. Crossover cohort definition
    c. **Time series** (multiple time point comparison)
        i. Before-after comparison
    d. Case-Control design approach
    e. **Uncontrolled cohort**
        i. Case Report
        ii. Case Set
    f. Twin Study
    g. Ecological/Population-based

h. Tumor vs. Matched-Normal
4. Context (CATEGORY ONLY)
    a. Clinical Trial
    b. Pragmatic Clinical Trial
    c. Clinical Testing
    d. Clinical Care Records
    e. Healthcare Financing Records
    f. Patient Registry
    g. Multicenter Study
    h. Clinical Conference
    i. Collection
    j. Control Set
    k. Mendelian
    l. Metagenomics
    m. Xenograft
5. Data Collection Timing (CATEGORY ONLY)
    a. Cross-sectional data collection
    b. Longitudinal data collection
6. Analysis Approach (CATEGORY ONLY)
    a. Quantitative analysis approach
    b. Qualitative analysis approach
    c. Critique analysis approach
    d. Nonsystematic analysis approach
7. Clinical Research Regulatory Subsets (CATEGORY ONLY)
    a. Expanded Access Studies
    b. Early Phase 1 trial
    c. Phase 1 trial
    d. Phase 1/Phase 2 trial
    e. Phase 2 trial
    f. Phase 2/Phase 3 trial
    g. Phase 3 trial
    h. Post-marketing Study
    i. Post-marketing Surveillance Study
8. Study Goal (CATEGORY ONLY)
    a. Equivalence Trial
    b. Evaluation Study
    c. Validation Study
    d. Scientific Integrity Review

The list above was the current list as of October 15, 2020. The list continues to evolve and the current list can be found at https://confluence.hl7.org/display/CDS/COKA+Code+System+Development+Working+Groups.

Appendix F. Draft term list for risk of bias code system version 1.0.0

This list has 170 non-redundant codable concepts for the Risk of Bias Code System (items bolded if they are both a classifier and a codable concept):

Type Classifiers

1. **Participant Selection Bias** (for overall sample, not for comparator group)
    1a. Inappropriate selection criteria
    1b. Biased sampling strategy
    1c. Non-representative sample
    1d. Inadequate participation by eligible persons
    1e. Post-intervention factors bias selection
    1f. Intervention associated with post-intervention factors that bias selection
    1g. Outcome associated with post-intervention factors that bias selection
    1h. Mismatch in start of intervention and start of follow-up
2. **Comparator Selection Bias**
    2a. Inadequate Random sequence generation

2b. Inadequate Allocation concealment

2c. Biased selection of the non-exposed cohort

2d. Case-control design

    2d1. Case-control design without appropriate definition of controls

    2d2. Case-control design without appropriate selection of controls

    2d3. Case-control design without description of selection of controls

    2d4. Case-control design with factor-specific concern for comparability of cases and controls

2e. **Potential for Confounding**

    2e1. Baseline differences

    2e2. Confounding by follow-up time

    2e3. Prognostic factors influencing intervention

    2e4. Post-intervention confounding

3. **Performance Bias**

    3a. Performance Bias - Blinding of Participants

    3b. Performance Bias - Blinding of Intervention Deliverers

    3c. Performance Bias - Deviations from intended Intervention

    3d. Performance Bias - Imbalance in Deviations from Intended Interventions

    3e. **Performance Adherence Bias**

        3e1. Performance Adherence Bias - Blinding of Participants

        3e2. Performance Adherence Bias - Blinding of Intervention Deliverers

        3e3. Performance Adherence Bias - Imbalance in Deviations from intended Intervention

        3e4. Performance Adherence Bias - Nonadherence of Implementation

        3e5. Performance Adherence Bias - Nonadherence of Participants

4. **Attrition Bias**

    4a. Incomplete Outcome Data

    4b. Influence of Incomplete Outcome Data

    4c. Influence of Outcome on Missingness of Data

    4d. Exclusions due to missing data on intervention

    4e. Exclusions due to missing data on measured variables

    4f. Imbalance in missing data

    4g. Sensitivity to missing data

    4h. Inadequate response rate

    4i. Inadequate understanding of missing data

5. **Detection Bias**

    5a. **Detection Bias for Outcomes**

    5b. **Detection Bias for Exposures**

    5c. **Detection Bias for Reference Standard**

    5d. **Detection Bias for Index Test**

    5e. **Detection Bias for Classifiers**

    5f. **Detection Bias for Confounders**

    5g. Insufficient study characteristics available for proper results interpretation

    5h. Incomplete collection of relevant study results for synthesis

    5i. Methodologic quality assessment inadequate

    5j. Error in risk of bias assessment not minimized

    5x1. **Detection Bias for X - Classification Bias** (for x = X, substitute a = Outcomes, b = Exposures, c = Reference Standard, d = Index Test, e = Classifiers, or f = Confounders)

        5x1a. Nonrepresentative definition

        5x1b. Risk of misclassification

        5x1c. Definition not prespecified

        5x1d. Threshold not prespecified

        5x1e. Classification potentially influenced by risk of outcome

        5x1f. Definition unclear

    5x2. **Detection Bias for X - Assessment Method** (for x = X, substitute a = Outcomes, b = Exposures, c = Reference Standard, d = Index Test, e = Classifiers, or f = Confounders)

        5x2a. Inappropriate Measurement Method

        5x2b. Improper conduct of measurement assessment

        5x2c. Incomplete application of measurement assessment

        5x2d. Inadequate follow up period for outcome of interest

        5x2e. Assessment method unclear

        5x2f. Error in data collection not minimized

    5x3. **Detection Bias for X - Imbalance** (for x = X, substitute a = Outcomes, b = Exposures, c = Reference Standard, d = Index Test, e = Classifiers, or f = Confounders)

        5x3a. Imbalance in Application of Measurement Method

        5x3b. Differential data availability during tests

        5x3c. Inappropriate delay between index test and reference standard

    5x4. **Detection Bias for X - Confounding Influence** (for x = X, substitute a = Outcomes, b = Exposures, c = Reference Standard, d = Index Test, e = Classifiers, or f = Confounders)

        5x4a. Incorporation bias (eg non-independence of reference standard and index test)

        5x4b. Lack of blinding (eg blinding of index test result during reference test, blinding of outcome assessors)

        5x4c. Influence of Blinding on Measurement

6. **Analysis Bias**

    6a. **Bias controlling for confounding factors**

        6a1. Bias controlling for confounding factors and time-varying confounding

        6a2. Adjustment for selection bias

        6a3. Inadequate Intention-To-Treat Analysis

        6a4. Inadequate Adherence Effect Analysis

        6a5. Predictors included in outcome definition

    6b. Analysis Model Selection Bias - improper statistical model

    6c. Inadequate numbers for analysis

    6d. **Bias in Handling of Data**

        6d1. Incomplete data analysis

        6d2. No accounting for uninterpretable results

        6d3. Inappropriate handling of missing data

        6d4. Inappropriate handling of variables

        6d5. Inappropriate handling of complexities in the data

        6d6. Differential handling of confounder measurement

        6d7. Handling of confounders unclear

        6d8. Inappropriate handling of missing confounder data

    6e. **Analysis Selection Bias**

        6e1. Selective analysis reporting (from repeated analyses at multiple times)

        6e2. Selective analysis reporting (from multiple analytic models)

        6e3. Early trial termination

        6e4. Preliminary analysis

        6e5. Subgroup analysis

    6f. **Analysis bias in predictive model development**

        6f1. Selection of predictors based on univariable analysis

        6f2. Inappropriate evaluation of model performance measures

        6f3. Model overfitting and optimism

        6f4. Final model not corresponding to multivariable analysis

7. **Reporting Bias**

    7a. Reported Result Not Following Pre-Specified Analysis Plan

    7b. inadequate reporting to assess analytic strategy

    7c. Selective outcome measure reporting (within outcome domain)

    7d. Selective outcome measure reporting (across outcome domains)

    7e. Pre-final publication form

    7f. Subgroup analysis (reporting bias)

    7g. No explanation of withdrawals

    7h. Interpretation of findings not addressing risk of bias

    7i. Relevance of studies to research question not appropriately considered

7j. Results emphasized based on statistical significance

8. **Study Selection Bias**

    8a. **Bias in study eligibility criteria**

        8a1. Study eligibility criteria not prespecified

        8a2. Study eligibility criteria not appropriate for review question

        8a3. Study eligibility criteria ambiguous

        8a4. Study eligibility criteria limits for study characteristics not appropriate

        8a5. Study eligibility criteria limits for information sources not appropriate

    8b. Database search sources not appropriate

    8c. Nondatabase search sources inadequate

    8d. Search strategy not sensitive

    8e. Search strategy limits for information sources not appropriate

    8f. Study eligibility criteria not adhered to

    8g. Error in study selection not minimized

9. **Synthesis Bias**

    9a. Synthesis missing eligible studies

    9b. Study parameters not appropriate for synthesis

    9c. Heterogeneity not addressed

    9d. Sensitivity to factors

    9e. Biases in studies influence synthesis

L. Qualitative Research (CATEGORY ONLY)

    L1. Inappropriate qualitative approach

    L2. Inadequate qualitative data collection methods

    L3. Inappropriate qualitative analysis

    L4. Unsubstantiated interpretation of results

    L5. Incoherence between data, analysis and interpretation

M. Mixed Methods Research (CATEGORY ONLY)

    M1. Inadequate rationale for mixed methods design

    M2. Ineffective integration of study components

    M3. Inappropriate interpretation of integration of qualitative and quantitative findings

    M4. Inadequate handling of inconsistency

N. Predictive Model Subset (CATEGORY ONLY)

    N1. **Bias in Predictive Model Development** (used to subset classifiers noted elsewhere to be specific to predictive model development)

    N2. **Bias in Predictive Model Validation** (used to subset classifiers noted elsewhere to be specific to predictive model validation)

    N3. Absence of any validation

    N4. Absence of any external validation

Rating Classifiers

R. Rating of certainty (CATEGORY ONLY)

    R1. Low Risk of False Certainty

    R2. Moderate Risk of False Certainty

    R3. High Risk of False Certainty

    R4. Serious Risk of False Certainty

    R5. Critical Risk of False Certainty

    R6. Some Risk of False Certainty

S. Rating of factor presence (CATEGORY ONLY)

    S1. Factor Present

    S2. Factor Likely Present

    S3. Factor Likely Absent

    S4. Factor Absent

    S5. No Information

    S6. Factor Presence or Absence Unclear

T. Rating of bias direction (CATEGORY ONLY)

    T1. Risk of Bias Favoring Experimental

    T2. Risk of Bias Favoring Comparator

    T3. Risk of Bias Towards Null

    T4. Risk of Bias Away from Null

    T5. Risk of Bias Direction Unpredictable

U. Rating of influence (CATEGORY ONLY)

    U1. Factor has potential to impact results

    U2. Factor likely has potential to impact results

    U3. Factor likely does not have potential to impact results

    U4. Factor does not have potential to impact results

The list above was the current list as of October 15, 2020. The list continues to evolve and the current list can be found at https://confluence.hl7.org/display/CDS/COKA+Code+System+Development+Working+Groups.

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