Translation of core terms of chemical risk assessment into the language of systematic review: research protocol

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Disclaimer

The author Ingrid Druwe is employed at the U.S. Environmental Protection Agency. The views expressed in this manuscript are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

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Abstract

The focus on implementation of systematic review (SR) principles in chemical risk assessments (CRAs) is growing as it has the potential to advance the rigour and transparency of the CRAs. However, the SR and CRA communities use their own specific terminologies. Understanding the meaning of core SR and CRA terms and where they overlap is critical for application of SR methods and principles in CRAs. Moreover, it will increase the possibility for cross-sectorial collaboration, avoid misunderstandings, and improve communication among risk assessors, researchers, and policy makers.

We present a process for the translation of core CRA terms into the SR language. Core terms for study appraisal, evidence synthesis and integration used in the SR and CRA communities will be included. The outcome will be an overview of how core SR terms map

onto core CRA terms and a description of the relationship and conceptual overlap between the terms.

The cross-mapping is divided in four phases, where in the first phase the core SR and CRA terms will be identified. In the second phase, existing CRA definitions will be mapped. Authoritative definitions for core SR terms will be derived in the third phase. In the fourth phase descriptions of the relationship and conceptual overlap between the terms will be derived. The third and fourth phase will include weekly one-hour online meetings for SR and CRA experts.

Key words

Conceptual overlap, cross-mapping, definitions, interoperability, terminology.

1. Introduction

Chemical risk assessments (CRAs) should be evidence-based, which means that they are grounded in a comprehensive and rigorous, transparent and objective analysis of all evidence relating to the assessment task. Applying systematic review (SR) principles in CRAs has become an established methodology for achieving this goal, from its first practical introduction in 2013-14 (NTP OHAT, 2015; Woodruff and Sutton, 2014), its popularisation in the following few years (Hoffmann et al., 2017; Whaley et al., 2016), and its wider uptake by national and international risk assessment agencies including US EPA (EPA, 2022; EPA, 2023), EFSA (EFSA, 2010; EFSA et al., 2017a), and WHO (WHO, 2021).

Because SR and CRA methodologies were developed independently of each other, the SR and CRA communities use their own specific terminologies and language. Numerous SRs performed as part of CRAs have shown that these terminologies often are analogous to each other or overlapping, but rarely the same or directly translatable. It can therefore be difficult to understand which SR method (or to what level/extent) is applied in the CRAs (i.e., whether a given framework or application is sufficiently rigorous to be described as "systematic") and may be impeding the understanding and therefore potentially slowing the uptake of SR methods in the CRA community.

In this project, we will analyse conceptual overlap and differences between the core CRA terms of SR and CRA. This way, we aim to increase the interoperability of SR and CRA terminologies by improving the understanding of the meaning of and the relationships between the core terms of the respective domains.

1.1 Project governance

This project is a part of the "Next generation risk assessment in practice" project (VKM, 2023) which is included in the European Partnership for the Assessment of Risks from Chemicals (PARC; Project 101057014)". The participants in this project include the members of the research team and the members of the scientific advisory group (SAG). A project group (PG) has been established with the responsibility for drafting the protocol and performing the study.

2 Methods

2.1 Study design

A cross-mapping of core SR and CRA terms will be performed to explore the relationship between the terms, to identify conceptual overlaps, and to identify how SR terms map onto CRA terms. By "core" we mean terms denoting key concepts in the study appraisal, evidence synthesis, and evidence integration steps of systematic reviews. The project is divided into four phases as shown in Figure 1.

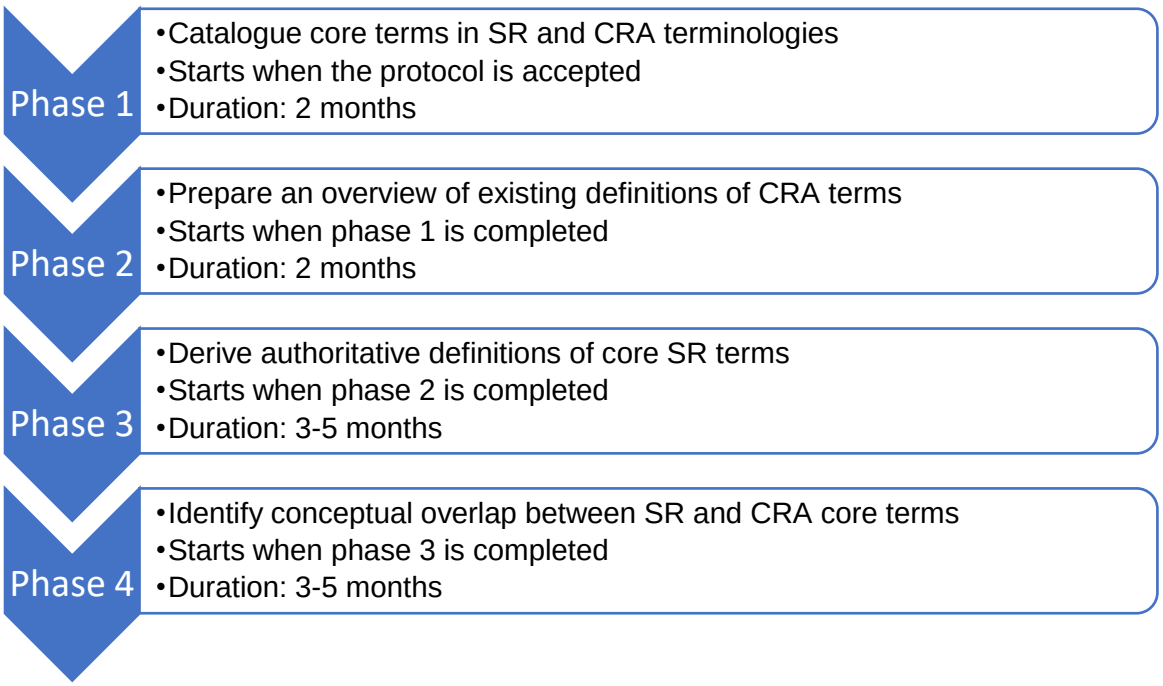

Figure 1. Overview of the four phases and the timeline for the translation of core terms of systematic review into the language of chemical risk assessment. Abbreviations: CRA, chemical risk assessment; SR, systematic review.

The timeline for the project and estimated duration for each phase are shown in Figure 1. Phases 3 and 4 will include weekly one-hour online meetings for the discussion and

derivation of authoritative SR definitions and the descriptions of SR and CRA term relationships, and the anticipated duration of these phases is 3 to 5 months each.

2.2 Phase 1: Cataloguing core terms in SR and CRA terminologies

The objective is to catalogue core SR and CRA terms that are used for study appraisal, evidence synthesis and integration.

Creating longlists of SR and CRA terms

We will create a list of 400 SR terms and a list of 400 CRA terms as potential candidates for inclusion in this terminology cross-mapping, assuming that the core terms will be included in such extensive lists. The lists will be machine-generated using the Term Frequency - Inverse Document Frequency (TF-IDF) method. TF-IDF compares the relative importance of a term between two topic domains (in this case, SR or CRA compared with everyday general communication) by assuming that terms that are more important in the first domain will occur relatively infrequently in the second domain (Nettleton, 2014). For example, the term “bias” is a central term in SRs and can therefore be expected to occur with higher relative frequency in a corpus of SR documents than it will in a general language corpus. The terms that occur least frequently in the general corpus have a higher probability of being core terms in the domain of interest.

The TF-IDF method is an efficient way of generating a longlist of key terms as it does not require extensive interviewing of domain experts or the creation of a comprehensive corpus of the domain of interest. The only requirement is that the target domain terms occur at least once in the domain corpus, and the comparator corpus is representative of a different community of language users. In our case, the comparator corpus will be the English Web corpus enTenTen21 (Sketch Engine, 2023). enTenTen21 is an English language corpus made up of texts collected from the Internet. The target domain corpora will be (1) a selection of SR manuscripts, tools, and current guidelines from governmental and international agencies as well as SR professional organisations (Table 1), and (2) a selection of CRA manuscripts and current guidelines from governmental and international agencies as well as CRA professional organisations (Table 2). To maximise differences between the two long-lists, the systematic review documents should not be from the CRA or adjacent domains, and the CRA documents should not apply SR specific terms. In addition, the documents should include the concepts study appraisal, evidence integration and synthesis.

The longlists will be available as supplementary materials.

Table 1. The systematic review document collection.

Document	Reference
Cochrane Handbook for Systematic Reviews of Interventions version 6.3	Higgins et al. (2022)
Finding What Works in Health Care: Standards for Systematic Reviews	Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness (2011)
JBI Manual for Evidence Synthesis	Aromataris et al. (2020)
Methodological Expectations of Cochrane Interventions Reviews (MECIR)	Higgins et al. (2023)
Handbook for Conducting a Literature Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration	NTP OHAT (2019)
Systematic reviews (n=5)	*To be selected by the project group*

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145 **Table 2.** The chemical risk assessment document collection.

Document	Reference
Framework for the use of systematic review in chemical risk assessment	WHO (2021)
Guidance on the assessment of the biological relevance of data in scientific assessments	EFSA et al. (2017b)
Guidance on information requirements and chemical safety assessment. Part B: Hazard assessment.	ECHA (2011)
Guidance on the use of the weight of evidence approach in scientific assessments	EFSA et al. (2017a)
Guiding Principles and Key Elements for Establishing a Weight of Evidence for Chemical Assessment	OECD (2019)

ORD Staff Handbook for Developing IRIS Assessments	EPA (2022)
Weight of Evidence: General Principles and Current Applications at Health Canada	Tao et al. (2018)
Risk Assessment in the Federal Government: Managing the Process	National Research Council Committee on the Institutional Means for Assessment of Risks to Public (1983)
Science and Decisions: Advancing Risk Assessment	National Research Council (2009)
Chemical risk assessments (n=5)	*To be selected by the project group*

Creating shortlists and final shortlists of essential SR and CRA terms

The essential SR and CRA terms will be selected from the extended lists of 400 terms by an expert group consisting of PG and SAG members.

A minimum of four expert group members will individually screen each extended list in Excel, with the terms presented in the TF-IDF rank order. CRA experts screen the longlist with CRA terms and SR experts screen the longlist of SR terms. The expert group members will i) highlight all terms perceived as relevant for study appraisal, evidence synthesis and integration, and ii) add additional terms they believe should be included but are not on the extended list. There will be no upper or lower limit on the number of terms that can be highlighted as relevant. The possibility for the experts to include additional terms is considered to take care of a possible problem that may be introduced if core terms are abbreviated in the documents. An overview of all terms perceived as relevant will be created and the experts will then be requested to i) categorise the terms according to importance using the categories: “important”, “neither important or unimportant” and “unimportant”, and ii) to indicate for each term for which of the three steps study appraisal, evidence integration and synthesis the term is applied. The categorisation according to importance will be based on the judgement of each individual expert.

In the next step, shortlists of SR and CRA terms categorised as “important” by one or more members of the expert group with information on the number of experts that categorised the term as “important”, will be created by the PG.

The shortlists will be presented and discussed in PG and SAG meetings to identify i) terms on the shortlist that are not related to study appraisal, evidence synthesis and integration process, and ii) additional terms that should be included. The final shortlists will be prepared by the PG and be available as supplementary materials.

Cataloguing core SR and CRA terms

To be included as a core term in the process of study appraisal, evidence synthesis and/or integration, the term must be i) perceived to be relevant AND ii) categorised as “important” by ≥50% of the expert group participating in the creation of the short lists.

PG will prepare the overview of SR and CRA terms fulfilling the core term criteria.

2.3 Phase 2: Preparing a list of existing definitions of CRA terms

The objective of this phase is to prepare a list of a representative range of definitions of the core CRA terms. Note that whereas we will derive definitions of the core SR terms in phase 3, we will not reconcile varying definitions of the core CRA terms.

The definitions for the CRA terms will be collected from glossaries, guidance’s and/or assessments from the European Chemicals Agency (ECHA), the European Food Safety Authority (EFSA), the National Toxicology Program (NTP), the Organisation for Economic Co-operation and Development (OECD), and the U.S. Environmental Protection Agency (EPA). The definitions of the core CRA terms will be extracted by one PG member and checked by another PG member. The table will be made available as supplementary materials.

2.4 Phase 3 Deriving definitions of core SR terms

The objective of Phase 3 is to provide definitions of the core SR terms that are as accurate and unambiguous as possible. This will be done via a consensus process involving an SR expert group with PG and SAG members and additional experts self-identifying as having relevant SR expertise (see Section 2.6). The authoritative definitions will be derived according to a modified version of the SEVCO protocol for developing an ontology (Alper et al., 2021a; Alper et al., 2021b). The main steps for defining terms are shown in Table 3. A more detailed overview is included in the Supplementary materials (Table S-1).

195 **Table 3.** The process for defining a core SR term. PG, project group; SAG, scientific
196 advisory group; SEVCO, Scientific Evidence Code System; SR, systematic review.

Step	What
1. Definitions of core SR terms available in SEVCO are identified.	Relevant SEVCO definitions will be collected. These definitions will be the draft definitions used as the basis for discussions in step 4.
2. Commonly used definitions of the core SR terms are identified. *This step is only performed for terms without a SEVCO definition*.	Definitions will be collected from the documents in Table 1. If definitions are not available in these documents, glossaries from the institutions preparing the manuals/handbooks will be used. Based on the collected definitions, a draft term definition will be suggested by the PG.
3. Assembling of an expert group with PG members, SAG members, and additional experts, all self-identifying as having relevant SR expertise.	
4. Identification of agreement on discussed definitions.	The expert group discusses the draft definitions, to develop a refined draft that can be put to vote for approval. For approval of definitions, the expert group members vote in an asynchronous, blinded, online ballot “agree” or “not agree” on each discussed statement. A definition is approved if at least 5 experts vote, and unanimously vote “yes”. “No” votes have to be accompanied by comments suggesting changes that could lead to agreement. If a definition is approved, stop here.

	If a definition is not approved, proceed to step 5.
5. Suggestion of changes to the descriptions where no agreement was reached.	The result of the vote and any accompanying comments are discussed in the expert group and the definition will be redrafted. The definition is put back out to vote. The criteria for agreement for definitions for terms that are discussed for the second time are: i) At least 5 members voted AND ii) at least 80% votes were for “agree”. If an agreement is reached, stop here. If no agreement is reached, proceed to step 4. Steps 4 and 5 are repeated a maximum of two times. If agreement is not reached, a definition of the term will not be derived, and the term will not be included in the next phase.

We will work down the list of terms ranked in terms of importance (most categorisations as “important” at the top). If we cannot complete the full list in the planned time (5 months) we will stop, prioritising timely completion over comprehensiveness.

Synonymous SR terms will be identified by the expert group during this phase. For synonymous SR terms, only one of the terms will be included in the cross-mapping in phase 4. However, the synonyms will be mapped onto the preferred term in phase 4.

2.5 Phase 4: Identifying conceptual overlap between CRA and SR terms

The objective is to identify areas of conceptual overlap and difference between CRA terms and SR terms (as illustrated in Figure 2). The cross-mapping will be done via a consensus process involving an expert group with PG and SAG members and additional experts (see section 2.6) self-identifying as having relevant CRA and/or SR expertise. The main steps in the cross-mapping are shown in Table 4. A more detailed overview of the steps is included in the Supplementary materials (Table S-2).

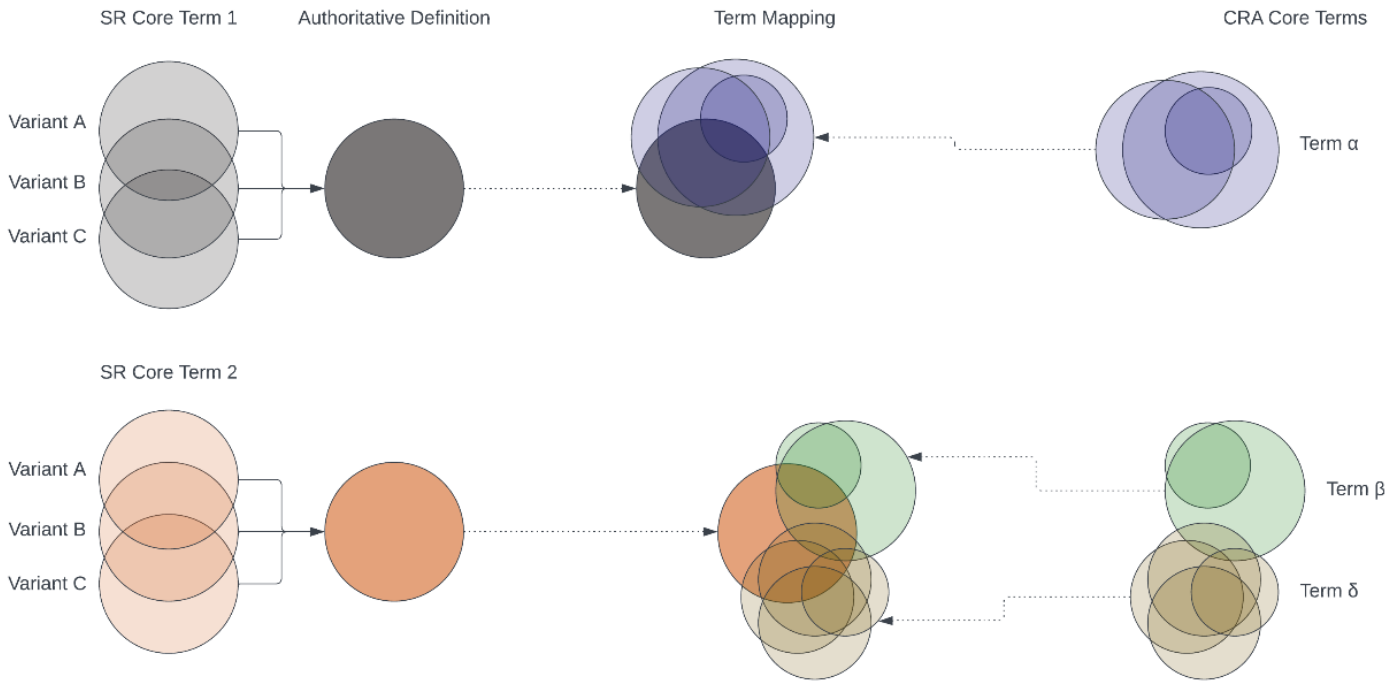

Figure 2. Visual representation of the mapping of core concepts used in systematic review (SR) onto core concepts used in chemical risk assessment (CRA). Circles represent the conceptual space denoted by a term. Variants of SR term definitions are identified and normalised into an authoritative definition. Variants of CRA term definitions and how they relate to each other are described. Relations between SR concepts and CRA concepts are then mapped onto each other, with potential for multiple relationships between individual SR and CRA concepts.

The cross-mapping will be performed in decreasing rank order of the importance of CRA terms, as determined by the number of times a term is classified as “important” by the expert group.

Table 4. The four main steps in the cross-mapping process.

Step	**What**
1. Identification of relationships between core CRA terms and core SR terms.	PG will draft statements of how CRA and SR terms are related.

2. Assembling an expert group with PG members, SAG members, and additional experts, all self-identifying as having relevant SR and/or CRA expertise.	The draft statements are discussed in the expert group and revised according to the discussion.
3. Identification of agreement on discussed descriptions (approval of the draft statements from step 2).	The experts vote (online) “agree” or “not agree” on approval of the draft statement from step 2. The criteria for agreement are: i) at least 5 members voted AND ii) all votes were for “agree”. If an agreement is reached, stop here. If no agreement is reached, proceed to step 4.
4. Suggestion of changes to the descriptions where no agreement was reached.	The result of the vote is discussed in the expert group and redrafted when needed. Participants will vote (online) “agree” or “not agree” on each discussed statement. The criteria for agreement for definitions for terms that are discussed for the second time are: i) at least 5 members voted AND ii) at least 80% of the votes were for “agree”. If an agreement is reached, stop here. If no agreement is reached, proceed to step 3. Steps 3 and 4 are repeated a maximum of two times. If agreement is not reached, no statement of the relationship between the CRA and the SR terms will be created.

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2.6 The expert groups participating in phases 3 and 4

The experts participating in the online meetings will be PG and SAG members and additional experts self-identifying as having relevant SR expertise (phase 3 expert group) and SR or CRA expertise (phase 4 expert group).

Recruitment of additional experts will be done by via PG and SAG networks. Anyone self-identifying as having the relevant expertise can sign up at any time. Expert group participants will be sent project updates, in particular notifications of when terms are open for vote, by email. Votes will be cast by email to the PG member tasked with facilitating the discussion and voting process. The facilitator will anonyme the votes to the rest of the PG and expert group.

Following the additional experts first participation, they will be asked to fill out a short questionnaire with questions about their affiliation, country of residence, gender, and number of years of experience with SRs (phase 3) or SRs and CRAs (phase 4).

Everyone on the mailing list will receive meeting documents in front of the meetings. Everyone that participated in a meeting will be asked to participate in the voting after the meeting. The votes will not be anonymous for the PG but will be anonymised in the manuscript.

Expert Group members are eligible to be co-authors if they i) vote and/or comment on at least ten terms or cross-mappings in total, and ii) reviews the manuscript. Expert group members not eligible to be co-authors will be listed in the acknowledgements. No financial compensation or other incentives are offered for the participation as additional expert.

3 Anticipated results

In this section we describe how the result of the study will be presented in the results section of the finalised manuscript. All other results will be made available as supplementary materials.

3.1 Core SR and CRA terms

A list of core terms in the SR and CRA terminologies, and the categorisation of each term according to importance, will be presented. A table illustrating a proposed way to present the results is included in the Supplementary materials (Table S-3).

3.2 SR and CRA term definitions

The authoritative definitions of SR core terms and their synonyms will be presented. In addition, the catalogue of CRA terms will be presented. Tables illustrating the presentation of the catalogues definitions of CRA terms and the collected and the derived authoritative definitions for the SR Terms are included in the Supplementary materials. Tables illustrating the presentation of the catalogued definitions of the core CRA terms, the authoritative definitions of SR terms and an overview of the synonymous SR terms are included in the Supplementary materials (Tables S-4 and S-5). The presentation of participant characteristics for the expert group participating in phase 3 is illustrated in the Supplementary materials (Table S-6).

3.4 Conceptual overlap between core SR and core CRA terms

Descriptions of the relationship between CRA terms and SR terms will be presented. Tables illustrating how this information will be presented are included in the Supplementary materials. The proposed presentation of the cross-mapping of CRA terms on the SR terms is shown in the Supplementary materials (Table S-7). The proposed presentation of the SR terms and the related CRA terms and the conceptual overlap is shown in the Supplementary materials (Table S-8). The proposed presentation of participant characteristics for the expert group participating in phase 4 is shown in the Supplementary materials (Table S-9).

4 Limitations

The methods described in this protocol are considered to provide a grounded process towards a common understanding for the meaning of these terms without being too time-consuming. A consequence may be that not all terms perceived as essential in all SR and CRA communities will be included. Not all versions of definitions of the CRA terms will be identified. If it turns out that additional terms need clarification, these can be included in a follow-up project.

While we attempt to involve a broad and diverse group of experts from several institutions in this project, it is possible that we will not be able to recruit participants from all relevant institutions within the SR and CRA communities. However, being able to distribute information through the networks of both the PG and the SAG, we expect to recruit participants from several relevant institutions.

Dissemination

The outcome of this project will be published in a scientific journal.

Abbreviations

CRA: chemical risk assessment

PG: project group

SAG: scientific advisory group

SEVCO: Scientific Evidence Code System

SR: systematic review

Definition

Core terms are in this project defined as terms denoting key concepts in the study appraisal, evidence synthesis, and evidence integration steps of systematic reviews.

Funding

Camilla Svendsen, Gro H. Mathisen, Gunn E. Vist, Trine Husøy, Heather M.R. Ames, Emma Di Consiglio, Kyriaki Machera, Eliana Spilioti, Anastasia Spyropoulou, Olga Tcheremenskaia, Emanuela Testai, and Paul Whaley were supported by HORIZON-HLTH-2021-ENVHLTH-03, Grant [101057014]; Nicolas Roth was supported by The Swiss State Secretariat for Education, Research and Innovation (SERI) under contract no. 22.00230.

Ethical considerations

Application for ethical approval will be submitted to the Norwegian Institute of Public Health.

Declaration of interests

Completed declaration of interest forms for each author are available as supplementary materials. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this protocol.

Authors contribution

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