APPENDIX A: Protocol submitted to CDC

Change in condom use in high-risk populations newly aware of HIV diagnosis in the United States and Canada: A systematic review and meta-analysis

The impact of HIV serostatus knowledge on HIV transmission risk in adults and adolescents with HIV infection in North America: Protocol for a systematic review and meta-analysis

Project: HIV-RAMP Model Input Assessment Project

Consortium for the Assessment of Prevention Economics (CAPE)

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ABBREVIATIONS

AIDS	International AIDS conference
ART	Antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CROI	Conference on Retroviruses and Opportunistic Infections
HIV	Human immunodeficiency virus
IAS Pathogenesis	International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention
MeSH	National Library of Medicine Medical Subject Heading
MSM	Men who have sex with men
MSMW	Men who have sex with men and women
Non-RCT	Non-randomized controlled trial
PICO	Population, Intervention, Comparator, Outcomes
PWID	People who inject drugs
RCT	Randomized controlled trial
TSM	Transgender women who have sex with men
US	United States
WSM	Women who have sex with men

BACKGROUND

Systematic reviews have found decreased sexual and drug injection risk behavior in patients receiving human immunodeficiency virus (HIV) seropositive diagnoses after testing (Marks 2005, Zakher 2014) and no difference in the risk of such behavior in patients on antiretroviral therapy (ART; Crepaz 2004, Zakher 2014). However, high-risk behaviors may still be widespread in populations with HIV infection (Weinhardt 2004, Crepaz 2009, Laisaar 2015). In patients receiving HIV seropositive diagnoses in the United States (US), the degree to which this knowledge of HIV status actually reduces and sustains the reduction of sexual and drug injecting risk behavior – and thus reduces HIV transmission – is currently unclear.

More than 168,000 people, about one in seven of the 1.2 million people living with HIV in the US, do not know that they have the infection (CDC 2014). Undiagnosed HIV infection is an important driver of the HIV epidemic in the US and other countries (CDC 2014), with close to 50,000 people in the US newly infected each year (CDC 2015) through unprotected sex (i.e., vaginal or anal sex without correct use of a condom) or sharing of drug injection equipment. Compared to the US population as a whole, African-Americans are disproportionately over-represented in new HIV infections, as are people of Latino heritage (CDC 2015). Adolescents are also disproportionately over-represented, as are groups such as men who have sex with men (MSM), people who inject drugs (PWID; CDC 2015) and other high-risk groups. New HIV infections in the US in general and in high-risk populations could be dramatically reduced by optimizing strategies for testing and diagnosing people with HIV, linking them to care and getting them stable on ART with a suppressed viral load. With viral load suppressed, people with HIV are at much lower risk of transmitting HIV to sexual partners (Anglemyer 2013). Widespread population level use of ART is also associated with reduced new infection rates in PWID (Wood 2012).

However, even if all people with HIV in the US were linked to care and started on ART, it would still be a tremendous challenge not only addressing their HIV risk behavior but also keeping them adherent to ART, a key factor in viral load suppression. In the US, only around three quarters of patients on ART in the US have suppressed viral loads, with even lower rates in African-Americans, PWID and other high-risk populations (Yehia 2012). High-risk populations may face continuing obstacles in maintaining the high level of ART adherence necessary to suppress viral load and keep it suppressed (Benator 2015). Major depression and other chronic psychiatric conditions are extremely common in people at risk of HIV, along with intimate partner violence, substance abuse, alcohol dependence and other conditions (Safren 2015). Indeed, these psychiatric and psychosocial conditions may be so prevalent in high-risk populations that they rise to the level of syndemics, or co-occurring epidemics (González-Guarda 2011, Di Paola 2014, Wilson 2014, Mimiaga 2015, Gilbert 2015, Safren 2015).

Such complex problems don't just go away when a person receives his or her HIV diagnosis. The same experienced difficulties of daily life that contributed to heightened HIV risk behavior before diagnosis may continue to increase patient risk for ART non-adherence with a resulting unsuppressed viral load (Mimiaga 2013, Mizuno 2015, Robinson 2015, Wawrzyniak 2015) and the potential for new infections. There are few, if any, efficacious behavioral interventions shown to have reduced HIV risk behavior over the long term in people receiving HIV diagnoses (Wang 2013, Jiwatram-Negron 2014, Yin 2014). Concomitant to the increased risk for unsuppressed viral load, there will likely continue to be many new HIV infections in the US unless complex and multifaceted but effective interventions addressing lifelong HIV risk reduction and ART adherence are developed and implemented.

With the goal of assessing the degree to which sexual and drug use risk behavior may be reduced when people are aware they have HIV infection, it is first crucial to identify and quantify in a nuanced way the correlates of decreased HIV risk behavior in populations and subpopulations testing positive for HIV

infection. This analysis is also necessary for determining the factors associated with unchanged risk behavior and with increased risk behavior in people with HIV infection who know their serostatus.

Rationale for systematic review

This systematic review and meta-analysis is urgently needed in order to provide the US Centers for Disease Control and Prevention (CDC) with updated quantitative effect estimates of HIV testing interventions on HIV transmission risk among adult and adolescent population in the US. It will expand on the scope and findings of two previous reviews in this subject area.

Marks and colleagues (2005) reviewed studies that compared the prevalence of high-risk sexual behaviors in HIV-positive populations who were aware of their status to those that were not. Their review included 11 independent comparisons (six between-group comparisons and five within-subject comparisons) identified in studies published between 1987-2004. An update to these findings including more recent studies will provide valuable information, especially given the context of increasing availability and use of ART.

A more recent review examining high-risk HIV transmission behaviors identified studies published between January 2004 and February 2012, assessing the effects of both awareness of HIV-positive status and use of ART (Chou 2014, Zakher 2014). However, the current review will expand on the findings of Chou and colleagues in several important ways: (1) our search process will be more comprehensive (including searches of several additional databases, as well as grey literature) and will capture studies published from January 1996 through our search date (late 2015); (2) in addition to quantitative assessment of effect sizes, we will attempt to conduct meta-analyses of study data, where appropriate; and (3) in addition to assessing bias risk in individual studies, we will use the GRADE methodology to assess the quality of evidence for each outcome across the body of literature (Guyatt 2011).

OBJECTIVES

To systematically review the scientific literature and quantitatively assess the short- and long-term effect of HIV testing interventions in the US on HIV sexual and drug injection risk behavior in patients testing HIV-seropositive.

METHODS: Inclusion and Exclusion criteria

Our search, screening, study selection, analysis and other methods will be based on those of the Cochrane Collaboration, as presented in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We use the Population, Intervention, Comparator, Outcomes (PICO) schema to outline our review's scope and inclusion criteria.

PICO framework

Population

Studies with the following populations will be eligible for inclusion

- Adults and adolescents in the United States and Canada who have been tested for HIV infection and received HIV-positive results, including:
    - General populations (or participants who are not specified to be members of sub-populations)
    - Populations at high risk of transmitting or acquiring HIV infection:
        - MSM including men who have sex with transgender women

    - Young MSM (as defined by investigators)
- Transgender women who have sex with men (TSM)
    - Young TSM (as defined by investigators)
- Men who have sex with men and women (MSMW)
- Women who have sex with men (WSM)
    - Adolescent WSM (age <20)
- Men who have sex with women (MSW)
    - Adolescent MSW (age <20)
- PWID
- People who use non-injection drugs (e.g. methamphetamine users, crack cocaine users)

A note about Canada

Although the focus of our review is the effect of these interventions in the US, we will include relevant studies from Canada. There are two reasons for this stipulation. The first is that while there are important differences between the countries, the US and Canada share many cultural commonalities. Travel between the countries has historically been quite easy to do and is frequently done. The second is that we are aware of potentially relevant HIV prevention research by investigators in Vancouver (especially at the British Columbia Centre for Excellence in HIV/AIDS, University of British Colombia) and in other Canadian cities. We anticipate that most if not all Canadian studies meeting our review's inclusion criteria would be highly relevant to HIV testing in the US. Should we determine that evidence from an included Canadian study is not directly applicable to US concerns, we will consider providing a detailed reason for excluding it or only include it with detailed caveats.

Interventions

The following types of interventions will be eligible for inclusion

Any modality of HIV testing, including:

- voluntary counseling and testing (VCT)
- provider-initiated counseling and testing (PITC)
- couples HIV counseling and testing (CHTC)
- community- and outreach-based testing
- other modalities as identified

If the data allow, we will separately present and pool results for participants receiving post-test counseling vs. those not receiving such counseling. We may further stratify results in the event there are important differences in the duration or intensity of post-test counseling.

Comparator

- No HIV testing (outcomes from participants unaware of HIV status)
- Pre-HIV testing (outcomes from HIV-tested participants, measured before testing)

Outcomes

If the data allow, we will separately present and pool results for participants on ART vs. those not on ART; and those with suppressed vs. unsuppressed viral load.

Primary 1:

- HIV sexual transmission (to participants' primary sexual partners)
- HIV parenteral transmission (to participants' primary injecting drug use partners, through sharing injection materials)
- HIV sexual or parenteral transmission (to participants' primary sexual partners who also share injection materials)
- Newly diagnosed syphilis, gonorrhea or chlamydia (in participants)

Primary 2 (with adjustments, if feasible, when partners were believed by participants to be HIV-infected):

- Any variation of unprotected (no condom) anal or vaginal sex during follow-up period (self-report).
- Share, lend, or borrow needles/syringes or other drug paraphernalia with drug-using partners (self-report)
- Two or more sexual partners during follow-up period (self-report)
- HIV serosorting and seroadaptive behavior (i.e., attempting to minimize transmission risk to sexual partners of unknown HIV serostatus)
- In couples, level of agreement about condom use during follow-up period (self-report)

Time-points

With a view to addressing the duration of HIV risk behavior change in patients after they become aware of their HIV-seropositivity, we will capture outcomes from all reported time-points during follow-up period, e.g., at one month, three months, six months, 12 months, or as reported by investigators.

Study Design

The following study designs will be eligible for inclusion

- Randomized controlled trials (RCTs)
- Prospective cohort studies (minimum two study arms)
- Retrospective cohort studies (minimum two study arms)
- Before & after study (pre- and post-intervention assessment in same participants)
- Time series study (pre- and post-intervention assessment in same participants, at several post-intervention time-points)

Criteria for exclusion

- Studies reporting only HIV testing uptake (without post-testing outcomes)
- Studies only reporting outcomes of HIV tested participants without baseline
- Studies only reporting outcomes of participants not tested for HIV

- Studies reporting post-testing HIV risk behavior with less than one month follow-up
- Studies examining the effects of multifaceted behavioral interventions, unless it is possible to separately evaluate the unique effect of HIV testing
- Studies not conducted in the US or Canada

Search methods for identifying studies

Journal and trial databases

We will search multiple bibliographic databases for primary studies. We will examine other systematic reviews (including those described above) through which we may identify primary studies. Studies published in any language will be eligible for inclusion. We will include all eligible studies regardless of publication status (published, unpublished, in press and in progress).

We will search the following databases for the period from January 1, 1996 to the search date:

- Cochrane Central Register of Controlled Trials
- PubMed
- SCOPUS (includes EMBASE)
- PsycINFO

We selected 1996 as the beginning of the search frame to correspond to the availability of Highly Active Antiretroviral Therapy (HAART)

We will use appropriate Medical Subject Heading (MeSH) terms and keywords to identify relevant studies. The search strategy will be iterative, in that references of included studies will be searched for additional references. Studies published in any language languages will be eligible for inclusion. Our PubMed search strategy will be modified and adapted as needed for use in the other databases. We will improve the sensitivity of our search strategies and build upon them as needed by iteratively updating them with text and key words from relevant studies that were not detected in initial searches.

Conference databases

We will search available abstracts from the International AIDS Conference (AIDS), the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS Pathogenesis), and the Conference on Retroviruses and Opportunistic Infections (CROI).

Searching other resources

In addition to searching electronic databases, we will contact individual researchers, experts working in the field and colleagues at CDC to learn of any relevant studies that may exist in the "grey literature," or that may be in preparation or in press. We will also conduct searches in the "grey literature," including academic and scientific studies published by government agencies, non-profit organizations and universities, and not published in the peer-reviewed literature.

We will also search ClinicalTrials.gov at the National Institutes of Health to identify any ongoing trials.

Screening and data collection

The methodology for data collection and analysis will be based on the guidance of the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008). Two authors working independently

will examine abstracts of all studies identified by electronic or bibliographic scanning. Where necessary, we will obtain the full text to determine the eligibility of studies for inclusion.

Methods for selection of studies:

After removing duplicate records, one author will perform a broad first cut of all downloaded material from the electronic searches to exclude citations that are plainly irrelevant. Two authors working independently will read the titles, abstracts and descriptor terms of the remaining downloaded citations to identify potentially eligible studies. We will obtain full text copies for all citations identified as potentially eligible, and two authors will independently inspect these to establish the relevance of the study according to the pre-specified inclusion criteria. The two authors will examine studies for relevance based on intervention, design, types of participants, and outcome measures, and will then decide which studies meet inclusion criteria. Where there is disagreement between the two authors, eligibility will be established by discussion with a neutral arbiter.

Data extraction and management

From all studies meeting inclusion criteria, two authors will independently extract data into a standardized, pre-piloted data extraction form. The following characteristics will be extracted from each included study:

- **Study details:** Complete citation, study location, study design characteristics and other relevant details.
- **Details of participants:** Risk group or groups, socioeconomic status, psychosocial factors (e.g., substance abuse), psychiatric (e.g., depression) or other comorbidities (e.g., hepatitis C), other relevant details.
- **Details of intervention:** Modality of testing (e.g., clinic-based, community-based etc.), specific intervention characteristics and other relevant details.
- **Outcome details:** Numerators and denominators associated with each outcome, definitions and descriptions of outcomes provided in papers, details of how outcomes were assessed.
- **Methodological details:** Recruitment methods, method of randomization if an RCT, numbers of participants entering the study, comparability of groups, study inclusion and exclusion criteria, length of follow-up, losses to follow-up, withdrawals or drop-outs.
- **Bias assessment data:** Other details necessary to perform a bias risk assessment using the Cochrane tool described below, or the criteria for observational studies described below.

Risk of bias assessment

Two review authors will independently assess risk of bias for each included study (see Appendix for further details). For RCTs, we will use the bias assessment tool described in the Cochrane Handbook (Higgins 2011). For non-RCTs, we will apply four criteria described below under “Observational studies.” We will resolve any disagreement by discussion or by involving a neutral third party to adjudicate. We will generate summary figures to illustrate risk of bias in each study and across all included studies.

The Cochrane approach assesses risk of bias in individual studies across six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and “other” potential biases.

Sequence generation (checking for selection bias)

- Low risk: investigators described a random component in the sequence generation process, such as the use of random number table, coin tossing, card or envelope shuffling.
- High risk: investigators described a non-random component in the sequence generation process, such as the use of odd or even date of birth, algorithm based on the day or date of birth, hospital or clinic record number. Or: Not randomized at all.
- Unclear risk: insufficient information to permit judgment about the sequence generation process.

Allocation concealment (checking for selection bias)

- Low risk: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; or sequentially numbered, opaque, sealed envelopes).
- High risk: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule, a list of random numbers), or envelopes were unsealed, non-opaque or not sequentially numbered. Or: Allocation not concealed at all.
- Unclear risk: insufficient information to permit judgment of the allocation concealment or the method not described.

Blinding (checking for performance bias and detection bias)

- Low risk: blinding of the participants, key study personnel and outcome assessor and unlikely that the blinding could have been broken. Not blinding in the situation where non-blinding is unlikely to introduce bias.
- High risk: no blinding or incomplete blinding when the outcome is likely to be influenced by lack of blinding.
- Unclear risk: insufficient information to permit judgment of adequacy or otherwise of the blinding.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Low risk: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome or missing outcome data balanced in number across groups.
- High risk: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data.
- Unclear risk: insufficient reporting of attrition or exclusions.

Selective reporting

- Low risk: a protocol is available, and the primary outcomes in the final trial report correspond closely to those presented in the protocol
- High risk: the primary outcomes differ between the protocol and final trial report.
- Unclear risk: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.

Other forms of bias

- Low risk: no evidence of bias from other sources.

- High risk: potential bias from other sources (e.g., early stopping of trial for benefit, fraudulent activity, baseline imbalance between study groups, loss to follow-up ≥20%, no analyses to control for potential confounders).
- Unclear risk: insufficient information to permit judgment of other forms of bias.

For blinding and incomplete outcome data, multiple entries can be made if more than one outcome (or time point) is involved.

Observational studies

During our bias assessment with the Cochrane instrument (and particularly during our assessment of "other forms of bias") we will make note of any additional methodological issues that would likely increase bias risk. We will look in particular for four considerations recommended by the GRADE Working Group (Schünemann 2013):

- Failure to develop and apply appropriate eligibility criteria (comparability of groups)
- Flawed measurement of both exposure and outcome
- Failure to adequately control confounding
- Incomplete or inadequately short follow-up

Quality of evidence

We will assess the quality of evidence across the body of literature using the GRADE approach (Guyatt 2011), which defines evidence quality as "the extent of our confidence that an estimate of effect is correct" (Higgins 2011). Evidence quality for a given outcome across all studies contributing data for that specific outcome may be rated as "high," "moderate," "low" or "very low."

Data from randomized trials are initially considered to be of high quality but could be downgraded for any of five reasons; similarly, data from observational studies are considered to be of low quality but could be upgraded for any of three reasons. The five factors that could decrease the quality of evidence are as follows:

1) high risk of bias
2) indirectness of evidence
3) unexplained heterogeneity or inconsistency of results
4) imprecision of results
5) publication bias

The three factors that could increase the quality level of a body of evidence are as follows:

1) large magnitude of effect
2) plausible confounding that would increase confidence in an estimated effect (e.g., better outcomes in intervention group despite worse baseline status than controls)
3) the presence of a dose-response gradient

We will assess the quality of evidence separately for the RCT-based literature and other literature (i.e. non-RCT experiments and observational studies). We will generate GRADE evidence profiles for all outcomes of interest for which data are available.

Analysis

We will calculate and present summary statistics for the risk ratio (RR) for dichotomous outcomes and the weighted-mean difference for continuous outcomes, using the 95% confidence interval (CI).

We will use the Review Manager 5 software (RevMan 2013) provided by the Cochrane Collaboration for statistical analysis and GRADEpro software (GRADEpro 2008) provided by the GRADE Working Group to produce GRADE evidence profiles.

If possible, we will calculate summary statistics using meta-analytic methods. Where meta-analysis is infeasible or inappropriate, we will perform a narrative synthesis of results. To summarize evidence quality by outcome across the body of literature, we will present findings in GRADE evidence profiles for all outcomes of interest.

Unit of analysis issues

The unit of analysis will be the individual study participant.

Dealing with missing data

We will contact study authors if it is necessary to obtain data missing from published reports. If necessary and appropriate, we may impute data.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 >45%) in pooled data for primary outcomes, we will explore it by pre-specified subgroup analysis. If heterogeneity persists, we will perform sensitivity analyses, present results separately and propose explanations for the observed heterogeneity.

Assessment of reporting biases

Where we suspect reporting bias we will attempt to contact study authors and ask them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If any meta-analysis in our review includes 10 more studies, we will assess the potential for publication bias for the studies using a funnel plot (Egger 1997, Higgins 2011). We will attempt to minimize the potential for publication bias through rigorous review methods and by using comprehensive search strategies, including evaluating published and unpublished literature in all languages.

Data synthesis

We will conduct meta-analysis, if appropriate, using Cochrane's Review Manager software (RevMan 2015). If heterogeneity between or among studies is low to moderate (I^2 ≤45%), we will generally use a fixed effects model. If heterogeneity is substantial (I^2 >45%) we will generally use a random effects model. However, choice of meta-analysis model is subject to both quantitative and qualitative assessment of heterogeneity. For example, even if heterogeneity is low in pooled data (I^2<45%), we may still use a random effects model because included interventions and populations may still be quite different. If heterogeneity is extremely high (I^2 ≥85%), we may consider not pooling data.

If relevant data from one or more studies cannot be pooled with data from other studies, we will undertake a narrative synthesis of these data. We will also synthesize data using the GRADEpro software (GRADEpro 2008) to summarize the quality of evidence across the body of literature. We will generate GRADE evidence profiles for all outcomes of interest for which data are available.

Subgroup-analyses (contingent on stratification and reporting in final included studies)

In pooled results with substantial heterogeneity (I^2 >45%), and as the data may allow, we will explore heterogeneity through subgroup analyses of the following:

- Ethnicity:
  - African-American
  - Native American/First Nations (indigenous peoples of North America)
  - Latino
  - Other non-Euro-American ethnicities (as reported by investigators)
- High-risk populations:
  - Individual high-risk populations (and appropriate combinations of high-risk populations) as listed above.
- Biomedical:
  - Participants on ART, studies 1996-present. (Triple ART regimens became widely available in the United States in 1996.)
  - Participants virally suppressed (as defined by investigators) on ART, studies 1996-present.
- Other:
  - Urban or rural setting
  - Canadian studies
  - Region of the US or Canada. For example, studies from the Northeastern US, conducted in New York, Massachusetts and Pennsylvania might be pooled in subgroup analysis; studies from the US west coast, conducted in California, Oregon and Washington might be pooled in subgroup analysis; etc.

Sensitivity analysis

Where relevant, we will conduct sensitivity analysis to investigate the effect of excluding studies with high overall risk of bias, studies with arbitrary inclusion criteria, and studies with other methodological issues.

Declarations of interest

None known.

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Appendix – Risk of Bias Assessment

General notes

- Below, see tables for discussion of criteria for high and low risk of bias for each domain by study design. "Unclear" risk of bias is essentially when there is insufficient reported information to make a judgment of high or low risk.
- Do not assess RCT risk of bias domains for observational studies, or vice versa. Enter N/A in the data extraction sheet. However, keep in mind other kinds of bias risk listed under the four observational domains recommended in the GRADE methodology (comparability of groups, inadequate follow-up, problems with assessment of exposures or outcomes, failure to adequately control for confounding) as "other" sources of biases.

Special notes on observational studies

- Observational studies are inherently at high risk of bias.
- For observational study domains, only assign "high" risk if risk of bias is beyond the normal risks associated with observational study designs. For example, most non-randomized studies have some risk of residual confounding, but they should not be assigned a "high" risk of bias for confounding unless there are additional situations which indicate an exceptionally high probability of confounding.
    - Example: A cohort study in which socioeconomic status is a risk factor for the outcome, and the intervention group had significantly higher socioeconomic status than those not receiving the intervention.
- If there is a high risk of bias **toward null**, rate risk as "high" but note in explanation that bias will likely be towards null. (Later, in GRADE-ing evidence quality, this could potentially increase the quality of evidence, if there are no other "downgrades" in evidence quality for that outcome.)
- We do not want to double-"penalize" studies for the same bias in multiple domains.
- The Cochrane Handbook recommends a four step process to assess risk of bias due to confounders in observational studies:
    1. Write a list of potential predictors of outcome (Cochrane says to do this at the protocol stage)
    2. Identify the confounding factors that the study has identified and those that have been omitted. Note how the potential confounders have been measured.
    3. Assess the balance between comparator groups at baseline with regard to potential confounders
    4. Identify adjustments made for potential confounders such as restriction, matching, stratification, multivariable regression, or propensity scores

Cochrane recommends that step one occurs at the time the protocol is written. For projects where the protocol has already been written and data collection has begun, we should still make a list of important potential confounders to be used in assessing risk of confounding for all studies across a project, and perhaps amend the protocol.

Notes about your judgments

Briefly provide a rationale for your judgments about bias risk in each domain for each study. For most items, say what was done, as the authors describe it. It is OK to copy-paste (in quotes) what they actually say.

Table 1: Risk of Bias domains for RCTs

Domain	Low Risk Criteria	High risk criteria
Randomization (Sequence generation)	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table • Using a computer random number generator • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).	The investigators describe a non-random component in the sequence generation process, for example: • Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number.
Allocation concealment	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (phone, web-based, pharmacy-controlled) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered) • Alternation or rotation

		• Date of birth • Case record number • Any other explicitly unconcealed procedure.
Blinding of participants and personnel	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessors (the person who is in charge of outcome measurement – if self-reported outcome using self-administrated survey, then participant is outcome assessor)	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Table 2: Risk of Bias for all studies

Domain	**Low Risk Criteria**	**High Risk Criteria**
Incomplete outcome data	Any one of the following: • No missing outcome data	Any one of the following: • Reason for missing outcome data likely to be related to true

	• Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size • Missing data have been imputed using appropriate methods. • Appropriate non-response weighting methods have been used	outcome, with either imbalance in numbers or reasons for missing data across intervention groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization • Potentially inappropriate application of simple imputation.
Selective outcome reporting*	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way • The study protocol is not available but it is clear that the published reports include all expected	Any one of the following: • Not all of the study's pre-specified (in protocol or methods) primary outcomes have been reported • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified • One or more reported primary

	outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).	outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis • The study report fails to include results for a key outcome that would be expected to have been reported for such a study. • Reporting of proximal outcomes if primary outcomes could have been measured
Other risk of bias	No other source of bias identified	Other problems with studies, for example: • Early stopping for benefit • Contamination • Changes to study protocol during study • Number of participants in each arm not reported • Randomized drop-outs replaced by non-randomized participants • Industry-funded authors apparently making “too strong a case” • Emphasis on significant secondary outcomes in the presence on non-significant primary outcomes • Secular trends in single arm pre-post studies • Inappropriate statistical techniques • Bias covered in “observational” domains, when rating an RCT

*Will often be “unclear” if no protocol exists or is available (common with observational studies)

Table #3: Risk of Bias for observational studies

Domain	**Low Risk Criteria**	**High Risk Criteria**
Comparability of groups	Major differences between baseline intervention and control (or case and control) groups are due to differences in the groups in the source population. • Same recruitment method and consenting process across groups • Control series is representative of the source population for the case series • Adjustment for baseline differences in groups	High probability of major differences in baseline intervention and control (or case and control) groups that are not present in the source population. May be due to: • Different eligibility criteria across groups • Different consenting methods across groups • Different recruitment settings (cohort or two multiple cross-sectional studies) • Different recruiting methods • Hospital or other institution based control series (case-control studies)* • Post-test only study with a single intervention or control "cluster" (city, state, school district, etc.)
Problems with assessment of exposures or outcomes	Low potential for misclassification of outcome or exposure in any group • Use of highly objective exposure or outcome assessments, like objective laboratory tests Or Dichotomous outcome and exposure are measured the same for all study participants and specificity is very high.	Any of the following: • Differences in measurement of exposure between outcome groups (e.g. potential for recall bias in case control studies) • Differential surveillance for outcome in exposed and unexposed • Test for outcome likely has different sensitivity and specificity in intervention and control groups • Low specificity, even if non-differential (bias toward null)

		• Low sensitivity or specificity of non-binary outcome, even if non-differential
Confounding	One of the following: • Major potential confounders are evenly balanced across intervention and control groups (or unlikely to be associated with intervention) • Studies include adjustment for baseline values of the outcome, and time between baseline and follow-up is short (can adjust for unmeasured confounders) • Appropriate methods are used to adjust for major potential confounders (restriction, stratification, instrumental variables, matching, propensity scores, multivariable regression	High probability that at least one potential confounder is associated with the intervention status, and any of the following: • Potential confounder is not measured • Lack of appropriate statistical adjustment for potential confounder • High potential of serious misclassification of potential confounder
Inadequate follow-up	Follow-up is adequate to observe outcomes, and follow-up is the same for all groups, including lead-time	One of the following: • Differential follow-up times between intervention and control groups • Inadequate follow-up time to observe outcome (bias toward null) • Failure to account for lead time in screening studies

* Where institution is not true source population for cases

** See section above on Cochrane recommended procedure to assess confounding. List of potential confounders should be pre-specified.