Title: The Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE).
Journal: Drug Safety
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Supplementary File 4. Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies (RIMES)-StaRI Extension (RIMES-SE): Explanation and Elaboration Document

Title

RIMES-SE item 1. Identification as a risk minimization evaluation study and description of the targeted safety risk, medicinal product, target population, geographical location, and description of study methodology in title or keywords.	
Explanation	Risk minimization programs are typically (although not exclusively) imposed as a condition of marketing authorization of the product, thus requiring that the program be implemented across the entire geographic region under the regulator's jurisdiction at the time of initial market launch. As a result, certain types of study designs (e.g., experimental randomized control design; pre-post) are often not feasible to use in evaluating the program's effectiveness. In addition to specifying the type of study design used (e.g., mixed-methods, observational, time-series, etc.), it is important to identify the work explicitly as a risk minimization evaluation study, so that relevant studies can be easily identified and indexed. The study design and 'risk minimization evaluation study' should both be included as key words and in the abstract.
Example	A mixed methods evaluation of the HIV PrEP risk minimization program to reduce the risk of HIV infection in adolescent girls and young women in Nairobi, Kenya

Abstract

RIMES-SE item 2. Identification as a risk minimization evaluation study, description of risk minimization program including its goal(s) and theoretical basis (if known), how it as implemented and by whom, the target population, evaluation methods, and the key process and health outcomes.	
Explanation	For ease of identification and indexing, the abstract should state the study design, and identify the study as a risk minimization program evaluation. It should also describe the risk minimization program, how it was implemented, and both the implementation process outcomes and program outcomes.
Example	Background: Accutane®, approved by the Food and Drug Administration (FDA) for the treatment of severe, recalcitrant cystic acne, is only available in the United States (US) through a Risk Evaluation and Mitigation Strategy (REMS) program due to its high potential for teratogenicity. The REMS program consists of prescriber certification, patient educational materials on the need to use birth control, a monthly pregnancy test prior to prescription renewal, and patient attestation that they will use two forms of contraception while on drug. The program was implemented by a third party vendor who conducted a 20 minute training certification session with eligible dermatologists who applied to participate in the REMS. Objective: We report findings from a mixed methods evaluation of the Accutane® REMS program involving surveys, qualitative interviews and healthcare site audits. Patients and Methods: Cross-sectional, online, multiple-choice surveys were distributed to randomly selected healthcare professionals (HCPs) and patients from healthcare settings across the US (April 2016–May 2016). Eligibility criteria: current/potential

	Accutane prescriber and/or dermatologists and for patients, current Accutane use. In-depth interviews were conducted with a 20% subset of HCPs and patients surveyed. Site audits were conducted with a randomly selected set of dermatologist offices. Primary implementation outcomes were program 'reach' (proportion of Accutane patients who reported receiving the Accutane REMS patient education materials), adoption (proportion of HCPs who reported committing to follow the REMS program; and implementation (degree to which participating sites had implemented all elements of the REMS). Primary effectiveness outcome was incidence of pregnancy among females who were using the drug.

Introduction

RIMES-SE item 3. Description of the problem, challenge, or deficiency in healthcare or public health that the intervention being implemented aims to address.	
Explanation	Characterizing the public health issue for which the risk minimization program was designed to address may include epidemiologic data on its prevalence and incidence, how it affects patients, and the challenges to implementing it within the healthcare delivery system.
Example[[1]]	"Following a centralized authorization within the European Union, on 1 August 2011, dabigatran was marketed in two doses (either 150 or 110 mg bid) for stroke prevention in patients with NVAF [non-valvular atrial fibrillation] and having one or more stroke risk factors….Following early post-marketing reports of bleedings, cautionary recommendations were issued by regulatory authorities. In the safety update from the European Medicines Agency (EMA) (18 November 2011), it was recommended that low doses should be prescribed for elderly patients. Also, this update emphasized the importance of monitoring of renal function, in particular in patients over 75 years. The impact of this [risk minimization] safety update …. is assessed …. below" [1].

RIMES-SE item 4a. The scientific background and rationale for the risk minimization program being implemented (including any theory, model or framework used, any evidence about its effectiveness (e.g., pilot studies) and how it is expected to achieve its effects). Report "None used" if no theory, model or framework used or report "Information not available" if any of the above information is unknown.	
Explanation	Authors of risk minimization evaluation studies should explain the rationale for the selection of the risk minimization program ("intervention") and any theoretical or empirical basis for its selection. The strength of the supportive evidence for the program (e.g., pilot study data) should be indicated.
Example	The eculizamab risk minimization program featured education for healthcare professionals on the risk of meningococcal infection, the different types of anti-meningitis vaccines available, and the importance of ensuring that patients were vaccinated prior to use of eculizamab. The program was based on the Theory of Reasoned Action which posits that knowledge is a necessary pre-condition for taking action (i.e., achieving the desired risk minimization behavior change). The risk minimization program was piloted in the phase 3 clinical trial program.

RIMES-SE item 4b. The scientific rationale for the implementation strategy (including any underpinning theory, model or framework, how it is expected to achieve its effects, and any pilot work). Report "None used "if no theory, model or framework used or report "Information not available" if any of the above information is not known. (Note: "Implementation strategy" refers to, for example, site training on how to implement the risk minimization program and how to implement it; or the requirement for local country sponsor affiliate offices to develop 'local implementation plans' and to monitor the implementation process.)	
Explanation	Authors should describe the rationale for selecting the implementation strategy, any supporting evidence for its effectiveness and any supportive pilot work (or examples from other clinical areas or contexts).
Example	A train-the-trainer (TTT) model was used to implement the risk minimization program across all regions in the United States (US). This model was selected because it has been empirically demonstrated as an efficient and effective way to train healthcare professionals. The TTT model was pilot tested in 4 sites in 2 different states during phase 3 trials and minor modifications were made as a result.

Aims and Objectives

RIMES-SE item 5. The aims of the evaluation study, differentiating between the risk minimization ("intervention") objectives and the program implementation ("process") objectives.	
Explanation	The overall aims and specific objectives of the evaluation study should be clearly stated. The Specific, Measurable, Achievable, Relevant and Time-bound (SMART) mnemonic is a useful tool for crafting objectives. A clear statement of aims and objectives is essential in order to understand whether the program has been implemented fully and is (or is not) effective.
Example	The aim of the evaluation was to determine if the HIV PrEP risk minimization program had been successful in preventing HIV incidence among PrEP patients (i.e., those at high risk for HIV infection). Study evaluation objectives were to determine whether: 1) >90% of targeted specialists received the risk minimization educational materials ('reach'); 2) >90% of all targeted healthcare settings implemented the program fully ('adoption'); 3) >90% of patients prescribed PrEP were screened monthly for HIV infection; 4) the monthly incidence of HIV infection among PrEP patients was less than 5%.

Methods (Description)

RIMES-SE item 6. The broader context in which the risk minimization program (the "intervention") was implemented. (Consider healthcare regulations, other relevant policies, social, economic or political factors that might influence implementation).	
Explanation	Authors should describe the larger context in which the risk minimization program was implemented in order to allow assessment of the external validity of the study, and to highlight important ecological factors that may have impeded the implementation of the risk minimization program.

Example	The revised REMS program for Mifeprex was implemented following the US Supreme Court decision to reverse Roe v. Wade. Mifeprex is predominantly prescribed in family planning clinics; many of these clinics were experiencing physician staffing shortages.

RIMES-SE item 7a. The population(s) targeted by the risk minimization program and any eligibility criteria.	
Explanation	Authors should describe the population(s) for whom the risk minimization program is appropriate (e.g., patients, specific types of healthcare professionals, family or informal care providers), including specific eligibility criteria. For patients, this may mean specific clinical criteria as set forth in the product label; for health care professionals, this may mean specific professional training or practice characteristics (e.g., specialty, years in practice, number of patients seen in practice on a monthly basis).
Example	The risk minimization program targeted 1) US adults (aged 18 years+) who have been prescribed clozapine for treatment-resistant schizophrenia, and 2) psychiatrists who prescribe clozapine for treatment-resistant schizophrenia.

RIMES-SE item 7b. The characteristics of the targeted healthcare sites for the evaluation (type, location, and eligibility criteria).	
Explanation	Authors should describe the *targeted* settings where the risk minimization program is intended to be implemented, including the different types of sites (e.g., public clinic, private medical office, teaching hospital outpatient clinic), geographic location, resources, and any specific eligibility criteria. This information is important for determining the external validity of the study.
Example	Infusion centers and pharmacies associated with infusion centers where natalizumab is infused and dispensed and which had completed the mandated training and registration were eligible for participation in the risk minimization program.

RIMES-SE item 8a. A description of the risk minimization program ("the intervention"), including the risk minimization tool(s) and including whether any stakeholders were involved in program and or tool development. (Key content/messages in any educational material recommended to be included in online supplementary materials or appendix.)	
Explanation	To enable the program to be replicated, it is important for authors to describe the risk minimization program components, including the type of risk minimization tools, their dose and duration (e.g., 30 minutes patient selection and counseling training session), and whether they were developed with input from end-users. Involvement of end-users

	increases the likelihood that the risk minimization tools or activities will be feasible within the specified clinical care context and hence adopted into practice.
Example	The risk minimization program consisted of educating healthcare professionals. The specific risk minimization tools, which were developed based on focus group input from healthcare professionals, included a Dear Healthcare Professional letter and a Benefit-Risk Counseling tool for physicians.

RIMES-SE item 8b. A description of the risk minimization program implementation and dissemination strategies. If the implementation and/or dissemination strategies are unknown, report "Unknown."	
Explanation	Implementation strategies refer to activities undertaken expressly to promote the uptake, and integration of the risk minimization program into clinical care. In the context of risk minimization programs, implementation strategies may be multi-faceted and consist of a set of different implementation activities aimed at addressing determinants of implementation at multiple levels; these should be considered collectively as the 'implementation strategy.' To enable replication of implementation strategies, it is important that authors describe these strategies, including the responsible actors, the types of activities included in the implementation strategy, how frequently and at what intensity they were delivered and over what period of time. Any theoretical or empirical justification for their selection should be specified, including whether relevant implementation frameworks were used [2, 3]. Compendium of implementation strategies for use in public health have been developed [4, 5].
Example	The implementation strategy for the risk minimization program involved healthcare site-specific training programs for healthcare professionals (HCPs) regarding how to use the risk minimization tools. A letter was sent to all HCPs describing the risk minimization program and informing the HCPs about how to access a dedicated website where electronic versions of the tools were available for downloading.

Methods (Evaluation)

RIMES-SE item 9a. Describe the outcome measures of the risk minimization program evaluation study, (including knowledge-, behavior- and patient health-related), how they were selected and assessed, and the sources of data and methods of measurement, and what were the pre-determined thresholds of success. If not assessed or not pre-specified, report such (e.g., "Not assessed").	
Explanation	Authors should report the intended clinical care outcomes of the risk minimization program, including when assessed in relation to program implementation (e.g., 18 months post-program implementation). These may include proximal outcomes such as knowledge about the product risk(s), and the performance of specified safe use behaviors (e.g., selection of appropriate patients to be prescribed the drug; providing patient counseling concerning the risks of using the medication), as well as more distal

	clinical or patient health impacts (e.g., reduction in number of patients becoming pregnant while using a teratogenic medicinal product). It is good practice to include an a priori specification of the success thresholds for the program outcomes.
Example	The primary effectiveness outcome of the risk minimization evaluation study was the cumulative annual incidence of patients using clozapine who developed agranulocytosis. The (pre-determined) acceptable threshold was set at .05% or lower based on clinician input and discussions with the regulatory authority.

RIMES-SE item 9b. Describe the implementation outcomes ("process measures") prespecified as a goal of the evaluation study (Note: these include, for example, degree of program reach, adoption, and the fidelity with which the program was implemented) and how they were selected and assessed. If not assessed or unknown, report such (e.g., "Not assessed', or "Unknown").	
Explanation	A taxonomy of implementation outcomes has been specified [2]. Implementation outcomes measure the success of the implementation strategy; at minimum, the reach, adoption and implementation of the risk minimization program should be reported. Risk minimization programs that include a formative evaluation may report on other implementation outcomes, including acceptability, appropriateness, and feasibility of the intervention and the implementation strategy. It is good practice to include an a priori specification of the success thresholds for the program implementation outcomes.
Example[6]	The implementation process outcomes reported in this evaluation included reach, adoption, and implementation [6]. Reach was defined as 80%+ of participating patients reporting that they had received the risk minimization educational brochure. Adoption was defined as 80% of participating healthcare providers reporting that the specified risk minimization program steps were being followed in their healthcare facility. Program implementation was defined as completion of a 1 hour training on the purpose and components of the risk minimization program by 100% of participating sites.

RIMES-SE item 10. Describe the rationale for the study sample size (including effect size estimate, budgetary constraints, practical considerations, data saturation, as appropriate).	
Explanation	Authors should report the method used to determine the risk minimization evaluation study sample size needs (along with the confidence intervals) so that readers can assess whether sufficient statistical precision was achieved. Many risk minimization programs are required for ultra rare medical conditions treated by specialists; hence, it may be difficult to recruit large samples of patients or prescribers to participate in the evaluation. Consult other relevant reporting standards for additional study design-specific guidance [7-9].

Example[10]	"A survey was administered to assess the effectiveness of the communication of the key [risk minimization] information in approximately 2% of enrolled patients. At least 20% of the sample were patients who had been enrolled [in the risk minimization program] for greater than 1 year…. The recommended sample size was selected to establish a confidence interval of 8 percentage points at the 98% confidence level if 80% of the questions were answered correctly" [10].

RIMES-SE item 11. State the methods used for analysis (with reasons for that choice), including explanation of how missing data were handled.	
Explanation	Guidance regarding the reporting of methods can be found in study design-specific reporting standards, including for mixed-methods research [7-9, 11].
Example[12]	"We considered 3 pairwise contrasts to compare prenatal exposure and safe-use measure outcomes: phentermine– topiramate versus topiramate, phentermine–topiramate versus AOM, [anti-obesity medications] and topiramate versus AOM. We used a propensity score weighting method to balance cohorts on measured confounders. Propensity scores for exposure (the index drug) in each pairwise comparison were estimated given the covariates using a logistic regression model (29, 30). Our statistical models accounted for cohort reentry and multiple treatment episodes per patient and were constructed in the full cohort, the 20- to 39-year-old subgroup, and the 40- to 55-year-old subgroup (31–33). In the prenatal exposure analysis, we estimated the prevalence, prevalence ratio, and prevalence difference for treatment initiation during pregnancy (33). We also estimated the incidence rate per 1000 years of follow-up, rate ratio, and rate difference for conception during treatment (31, 32). A more detailed description of the analytic methods is available in the Supplement (Study Methods, Statistical Analysis)" [12].

RIMES-SE item 12. Describe any planned sub-group analyses (e.g., between different sites, or difference clinical or demographic populations).	
Explanation	Any subgroup analyses should be specified a priori and the method of analysis stated. Further guidance can be found in design-specific reporting standards [8, 9].
Example	We planned to assess level of self-reported adherence to using 2 forms of birth control among 3 subgroups of patients using isotretinoin: 1) adolescent females of child-bearing potential (FCBP); 2) FCBP aged 20-30; and 3) FCBP aged 31+).

Results

RIMES-SE item 13. Report proportion recruited and characteristics of the targeted population for the risk minimization evaluation study, including a table showing baseline characteristics of study sample and settings.	
Explanation	Authors should report the proportion of eligible patients who were recruited for inclusion in the evaluation (including key characteristics e.g., sex, age, race/ethnicity, clinical status) and how many actually participated and their representativeness. A table presenting baseline characteristics of those participating in the study - either alone or in comparison to the characteristics of the population eligible to receive the intervention (if such data are available) - is useful to include as well. The latter comparison is especially valuable for gauging the extent to which program results are generalizable.
Example[13]	"A total of 23,282 initial invitations to participate in the survey were issued to HCPs. The response rate to the survey during the first data collection period was considerably lower (1.4%) than that assumed in the study protocol (30%) ….. In total, 118 HCPs responded to the survey. The HCPs most commonly treated patients with BPI at community teaching hospitals (32/118 [27%]) and university teaching hospitals (25/118 [21%]). Most of the HCPs were from Spain (42/118 [36%]) and were general psychiatrists (74/ 118 [63%]) and child/adolescent psychiatrists (40/118 [34%]). Table 1 shows the overall recruitment of HCPs across ten countries in the EU" [13].

RIMES-SE item 14a. Report primary and other outcome(s) of the program evaluation, including whether primary outcome met a pre-specified success threshold, and statistic(s) for the precision of result estimate(s). (Report "Unknown" if pre-specified success threshold is unknown.)	
Explanation	Guidance regarding the reporting of the primary and other outcomes can be found in study design-specific reporting standards, including for mixed-methods research [7-9, 11].
Example	The majority (95/100) (95.0%; 95% CI 87.0–98.7) of healthcare professional respondents correctly identified all of the contraindications for prescribing [drug X]…. Additionally, 77/100 (77.0%; 95% CI 61.5–90.9) respondents identified correctly that patients should be counselled not to drive or operate machinery for at least 12 hours after taking [drug X] and 77/100 (77.4%; 95% CI 61.3–90.9) correctly identified the key symptoms that would require the patient to be de-prescribed [drug X].

RIMES-SE item 14b. State results of the analysis of the program implementation measures ("implementation outcomes") associated with program implementation. (Report "No assessed" if not assessed.)	
Explanation	The authors should report the impact of the implementation strategy on pre-specified implementation outcomes (e.g., reach, adoption, maintenance) [2]. The logic model is one useful tool for specifying the specific mechanism(s) by which a strategy would be expected to work [14].
Example	The percentage of patients who reported having received the risk minimization materials was 80% (160/200); of the 30 participating healthcare facilities, 20 of them (66.6%) adopted the program into the clinic workflow via updating their internal care delivery protocols.

RIMES-SE item 15. Describe any added time/procedures/processes incurred as a result of implementing the risk minimization program as compared to usual care (i.e., program 'burden').	
Explanation	Understanding whether a risk minimization program poses significant burdens (e.g., procedural complexities, documentation requirements) on the healthcare delivery process is important as this can affect its' long-term viability and sustainability. Regulators require that marketing authorization holders (MAHs) assess and report on the issue of burden when evaluating risk minimization programs [15, 16].
Example	Results of the time and motion study conducted in 5 of the 20 participating healthcare sites showed that the risk minimization program added 8 additional steps to the clinical care workflow as compared to pre-program implementation (8/20 steps in total). Interviews with prescribers in each of the 20 sites showed that these extra steps caused an extra 7 minutes on average per patient which the prescribers considered posed a medium level of additional burden on the care process in those facilities.

RIMES-SE item 16. Report the degree to which the risk minimization program measures were delivered completely and as intended to all participants (i.e., degree of 'fidelity') and whether and what types of program adaptations occurred. (Report "Unknown" or "Not measured" if not measured.)	
Explanation	Program fidelity refers to the degree to which the program was delivered as specified in the original program plan. Degree of fidelity affects the potential effect size of the risk minimization program. However, adaptations to 'non-core' components of the risk minimization program may be needed to allow it to be implemented in different contexts and should be documented. Distinguishing 'core' program elements (i.e., those that are viewed as essential for effectiveness) from those which are non-core is important to do prior to program implementation. There are several fidelity frameworks for reference [17-19].
Example[20]	"[REMS] Education for prescribers of ER/LA opioid analgesics is provided through accredited CE [Continuing Education] training courses supported by unrestricted educational grants from the RPC [REMS Program companies]. The

	CE training courses must include the full content of the FDA Blueprint, as well as a knowledge assessment covering all sections of the FDA Blueprint, in order to be considered "REMS-compliant." ….. Over 500 RPC-funded REMS-compliant CE training courses were conducted by CE providers in 2013 and 2014. A performance goal of 80,000 ER/LA opioid prescribers having completed training within 2 years of the first training becoming available (March 1, 2013) was established by the FDA….. There are approximately 320,000 active ER/LA opioid prescribers in the United States (unpublished data from IMS). To count towards the goal, FDA required that a prescriber had to take a REMS-compliant CE activity, complete the post-training evaluation, and endorse that they had prescribed an ER/LA opioid in the past year…….. As of February 28, 2015, approximately 143,126 participants participated in a REMS-compliant CE [continuing education] activity, of which approximately 82,131 completed the post-test evaluation, of which 37,512 endorsed that they had prescribed an ER/LA opioid in the past year. Therefore 37,512 trained prescribers count toward the REMS performance goals" [20].

RIMES-SE item 17. Report any contextual changes which may have affected program outcomes, including description of any factors that may have served to impede or facilitate program adoption.	
Explanation	A whole host of contextual factors may affect the extent to which the risk minimization program is implemented, adopted and continuous to operates over time and hence, implementation and program outcomes. Contextual factors can be diverse, dynamic and multi-level [21]. Given this, researchers should consult relevant dissemination and implementation theories, models and frameworks to guide them in assessing contextual factors [22].
Example	Shortly after the risk minimization program for [drug X] was launched in the United Kingdom, the SARS-CoV-2 pandemic occurred and widespread lock-downs were implemented across the country. Many of the clinician prescribers of [drug X] were re-assigned to assist in emergency care for COVID-infected patients; thus, ongoing counseling and monitoring of patients (a key component of the risk minimization program) was not conducted in many instances.

RIMES-SE item 18. Report results of other analyses performed (e.g., important, pre-defined sub-group analyses, sensitivity analyses) and any evaluation of important harms and unintended effect(s) of the risk minimization program (e.g., lack of patient access to the drug).	
Explanation	Subgroup analyses are important to conduct in risk minimization programs in order to determine whether the program produced differential impacts for certain groups versus others. These analyses should be pre-specified and based on a priori hypotheses about how the risk minimization program was expected to work overall and within specific subgroups. The representativeness of the subgroups should be assessed as well.
Example[ref]	A subgroup analysis of the isotretinoin pregnancy prevention program showed that among females prescribed the drug, those aged 19-25 years had lower rates of pregnancy than those aged 12-18.

Discussion

RIMES-SE item 19. Summarize evaluation study findings, strengths and limitations, comparisons with other studies, conclusions and implications.	
Explanation	The discussion should provide an interpretation of findings, taking into account the causal mechanism(s) whereby the program was intended to work, any pre-specified hypotheses), strengths and limitations (including sources of bias) of the study, and the extent to which results are generalizable (external validity) based on the location, and characteristics of the study population (e.g., patients, healthcare professionals) and healthcare settings. The discussion should also situate this evaluation in comparison with other risk minimization program evaluations of similar medicinal products and/or patient populations.
Example	This was a cross-sectional web-based survey to evaluate the impact of a risk minimization program for an atypical psychotic [drug name] in the European Union (EU) in patients with bipolar 1 condition. The risk minimization program, which was designed based on the Theory of Reasoned Action, aimed to inform healthcare professionals (HCPs) about the risk of extrapyramidal symptoms (EPS) in adolescents exposed to the product and the need to counsel and monitor them for symptoms of EPS via a set of HCP Frequently Asked Questions (FAQs) …. This was the first evaluation of a risk minimization program for a drug in this class of atypical antipsychotics and indication. Results supported the hypothesis that HCPs who had higher levels of awareness about the risk of EPS would be more like to self-report counseling and monitoring adolescent patients for this risk… Limitations of the study included a low response rate in all five countries where the survey was conducted; hence results may not be generalizable to the population of adolescent psychiatrists in active practice in those countries…

RIMES-SE item 20a. Discuss policy, practice and/or research implications of the risk minimization program (specifically including program sustainability).	
Explanation	The authors should discuss the implications of the success (or lack thereof) of the risk minimization evaluation results for the design and conduct of other risk minimization programs and evaluations, clinical practice and public health. The discussion should address the issue of program sustainability and its' integration into healthcare delivery in the long-term.
Example	In future risk minimization programs for risk X, efforts should be made to partner with the affected HCP population in designing the risk minimization tools and the evaluation study to increase the likelihood of tool uptake and higher survey response rates. Implications for psychiatric practice are….. Given the lack of effect seen in patient outcomes, more effective risk minimization tools are needed.

RIMES-SE item 20b. Discuss policy, practice and/or research implications of the implementation strategy (specifically including scalability).	
Explanation	Risk minimization programs need to be fully implemented in order to work optimally. Because such programs are mandated to the implemented across entire regulatory jurisdictions (involving multiple geographic regions, healthcare settings, systems, and provider types) for long time periods, the degree to which the program is scalable (i.e., can be expanded into either new populations or new settings or health systems or both while retaining effectiveness) is a critical consideration [23]. The authors should discuss the implications of the success (or lack thereof) of the risk minimization program implementation strategy in order to inform the design and conduct of future risk minimization research, clinical practice and public health. The discussion should address the issue of the scalability of the implementation strategy into other geographic locales, and different types of healthcare settings and systems in the longer-term.
Example	Given that uptake of the risk minimization program was low in all but the Northeast region of the United States suggests that the implementation strategy requires further tailoring to improve scalability.

General

RIMES-SE item 21. Include statement(s) on regulatory approvals (e.g., as appropriate, ethical approval, confidential use of routine data, governance approval, study registration (availability of protocol), funding and conflicts of interest.	
Explanation	Authors should report any conflicts of interest (including involvement of the product manufacturer in the evaluation or implementation), any other ethical considerations, regulatory approvals of the study, study registration (e.g., on the European Union Post-Authorization Study (PAS) Registrar), and funding sources

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