The Reporting Recommendations Intended for Pharmaceutical Risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE)

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ORIGINAL RESEARCH ARTICLE

The Reporting Recommendations Intended for Pharmaceutical Risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE)

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Abstract

Introduction The Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies (RIMES) was developed to improve the quality of reporting of risk minimization program evaluations. In light of continued inadequacies in study reporting, and high-profile program implementation failures, we updated the RIMES Checklist to incorporate additional concepts from the Standards for Reporting of Implementation studies (StaRI).

Methods The development of the updated checklist, the RIMES-StaRI Extension (RIMES-SE), entailed developing a study protocol and drafting an initial pool of items based on a mapping of the RIMES against the StaRI checklist. A modified e-Delphi exercise was then conducted to determine the importance and understandability of items for checklist inclusion. An expert workshop and an online commentary period for additional feedback followed.

Results The RIMES-SE contains 27 items. It includes two signature features of the StaRI Checklist: 1) a dual strand of items (represented in two columns) describing the risk minimization program (the 'intervention') and the corresponding implementation strategy; and 2) applicable to an array of different research methodologies.

Conclusions The RIMES-SE Statement and Checklist extends the reporting guidelines set forth in the original RIMES Checklist via inclusion of key implementation science concepts. It is intended to improve the quality and transparency of reporting of risk minimization evaluation studies so as to advance drug safety science.

1 Introduction

The effectiveness of pharmaceutical risk minimization programs in protecting public health has been the subject of intense regulatory scrutiny over the past decade. These programs, which represent a population-based type of drug safety measure, are mandated by regulators for products with serious risks, either as a condition of marketing authorization or to investigate safety information newly identified in the post-market period [1, 2]. Under the terms of the regulatory commitment, these programs must be evaluated to determine whether they have been implemented as intended and are effective and sustainable in the context of real-world clinical care.

Risk minimization programs can be defined as 'complex interventions' [3, 4]. Characteristic features of complex interventions are that they have several interacting components, require numerous behaviors by those delivering or receiving the intervention (e.g., healthcare professionals [HCPs], patients), target different groups or organizational levels (e.g., individual, healthcare setting, healthcare system), involve a range of outcomes, and may require some flexibility or tailoring of the intervention to optimally fit within different healthcare settings [4].

When designing and evaluating complex interventions, it is essential to specify the theoretical (or empirical) basis for

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Key Points

The Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies (RIMES) was published in 2018 to improve the quality of reporting of risk minimization evaluation studies.

Evidence that the reporting of these studies continued to be inadequate, and that risk minimization programs were being poorly implemented, prompted us to update and harmonize the RIMES with constructs from the Standards for Reporting of Implementation studies (StaRI) Checklist, a best practice standard for reporting implementation science studies in public health.

The 27-item RIMES-StaRI Extension (RIMES-SE) was derived by the use of rigorous methodology. It has a dual strand of items that focus on both the risk minimization program ('the intervention') and the strategy used to implement it and it is applicable for studies using a heterogeneous range of designs.

Adoption of the RIMES-SE Checklist by researchers and endorsement by journal editors should improve the reporting of risk minimization studies, enhance transparency, facilitate researchers' ability to identify these studies, and promote synthesis of the available evidence base.

how the program is expected to achieve the desired effects. Similarly, it is important to conduct both a formative evaluation (to determine intervention feasibility and acceptability) and a comprehensive process evaluation (to determine the quality and fidelity of program implementation, and whether any adaptations occurred). A process evaluation is especially valuable when program evaluation results show lack of effect as it can clarify whether this was due to problems in program implementation or to the ineffectiveness of the program itself [4]. Lastly, a range of measures are needed to fully understand program effects, including measures of reach, adoption, impact, and ongoing maintenance, as well as whether the program was successful in reducing the incidence of the targeted risk(s), imposed undue burden on the healthcare system, impeded patient access to the drug, or had other unintended consequences [2, 4].

In recent years, three high-profile assessments of risk minimization programs—one in Europe for valproate products, and two in the United States (US) (one generally, and a second for opioid analgesics specifically)—revealed that program implementation had been incomplete and evaluation data insufficient [5–7]. Similarly, published reviews have shown that both the quality and comprehensiveness of risk minimization evaluation studies are highly variable, assessment of program implementation and context often inadequate, and findings regarding program effects limited or uncertain [8–11].

In an effort to build the evidence base in this area, a group of researchers under the auspices of the International Society for Pharmacoepidemiology (ISPE) developed a quality reporting checklist called the Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies (RIMES) [12]. The RIMES Checklist consists of 43 items and was designed to guide standardized, comprehensive, and transparent reporting of risk minimization evaluation study results. The RIMES was intended to be reviewed and updated periodically to remain abreast of the evolving science and regulatory guidance in this area.

Since its publication in 2018, the RIMES Checklist has had a significant impact on the field of drug safety. First, it engendered two comprehensive reviews of risk minimization evaluation studies, one focusing on studies published in the peer-reviewed literature, and a second focusing on risk minimization evaluation study reports submitted to the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) [13, 14]. These reviews highlighted numerous shortcomings in risk minimization reporting, including that evaluations rarely referenced the use of theories, models, or frameworks to guide program design and evaluation, and descriptions of program implementation, adaptations, and context were inadequate or missing.

Second, prominent pharmacovigilance organizations in Europe, including the EMA and the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [1, 15], cited the RIMES Checklist in relevant guidance documents and recommended that it be used when reporting the results of risk minimization evaluation studies. A translated version of the RIMES Checklist along with guidance on how it should be applied were also published in a Chinese pharmacovigilance journal [16].

Globally, healthcare delivery organizations, including pharmacovigilance bodies, have been facing mounting pressures to transform into learning healthcare systems [17, 18]. Implementation science, defined as "the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice," is instrumental to such a transformation [19]. Consistent with this, and contemporaneously with the development of the RIMES, a new checklist, the Standards for Reporting of Implementation studies (StaRI), was published. The StaRI Statement and Checklist were intended to guide standardized, transparent, and complete reporting of IS research [20].

The application of implementation science for drug safety and risk minimization has been gaining increasing recognition [3, 19, 21–26]. Recently, pharmacovigilance regulatory

guidance documents have begun incorporating concepts, constructs, and terminology from implementation science that are consistent with recommendations for evaluating complex interventions [1, 2, 4].

The purpose of the current work was to further refine and harmonize the RIMES with updated frameworks from implementation science, namely, by reviewing and including relevant items from StaRI to create a RIMES StaRI extension (RIMES-SE).

1.1 Scope and Relationship with Other Reporting Standards

The RIMES-SE fills a niche in the growing array of quality checklists developed for the reporting of healthcare research [27]. The field of therapeutic risk minimization seeks to implement, scale up, and maintain effective interventions (e.g., behavioral, educational, healthcare process improvements) in the context of real-world clinical care to minimize the harmful effects of exposure to product-related risks. The programs are mandated to be implemented in full according to the terms of the marketing authorization commitment at the time of product launch. As a result, randomized experimental designs are not feasible and evaluators must employ non-experimental study designs (e.g., observational, time series, and/or mixed methods approaches) for program evaluation purposes. Given the variety of drug-related risks that may be targeted for minimization and the diversity of HCPs, healthcare settings, and patients involved, a heterogeneous array of data sources and data collection methods are appropriate and relevant to use.

Existing checklists for observational research in healthcare (i.e., STROBE [28]), or for research using routinely collected health data (RECORD [29]; RECORD-PE [30]) focus on a limited set of study designs, methods, and data sources. Other checklists developed for reporting quality improvements in healthcare (SQUIRE [31]) or for reporting behavioral and public health evaluations using non-randomized designs (TREND [32]) are not fully applicable due to their lack of emphasis on program implementation and maintenance.

2 Methods

Extending the original RIMES Checklist involved a five-stage process (Fig. 1) guided by the methodology described in the Development Health Research Reporting Guidelines [33].

2.1 Initial Steps

In 2023, a team of experts in risk minimization and/or implementation science (MYS, EHM, HP, and AW) convened to review the RIMES Checklist and guide the e-Delphi review process. Two experts (MYS and EHM) were members of the original RIMES authoring team; a third member (HP) was the lead author of the StaRI Statement; and a fourth member (AW) had chaired the FDA's Drug Safety and Risk Management Advisory Committee. We developed a protocol to describe the development process and publicly posted it on the EQUATOR website [27].

2.2 Pre-e-Delphi Activities

We mapped the items from the RIMES ($n = 47$) and StaRI ($n = 27$) against each other to converge on similarities and determine gaps in the RIMES (Table 1). We then developed a pool of items for potential inclusion in the RIMES-SE . In doing so, we eliminated the StaRI item (#20) on resource costs and economic outcomes as not being applicable as financial measures are not regulatory considerations and drug manufacturers view this information as proprietary and hence do not make it publicly available.

2.3 Defining Concepts

The RIMES-SE shares two signature features with the StaRI Checklist. The first feature is the dual strand of items (represented in two columns) describing the intervention (i.e., the risk minimization program) and the corresponding implementation strategy [20]. In contrast to the StaRI Checklist, however, which places primary emphasis on the implementation strategy, the first strand of the RIMES-SE refers to the risk minimization program and the second strand refers to the supporting implementation strategy [20]. Items in both columns should be populated; however, if any information is unknown to the evaluator (as can often be the case for third-party evaluators such as academically based research groups), there is an option to report 'information unknown.'

In the RIMES-SE Checklist, the term 'implementation strategy' is meant to encompass the collective set of activities that the product manufacturer and local HCPs, healthcare site staff, and third-party program administrators might use to implement the risk minimization program across different geographic regions and different levels (e.g., individual, healthcare setting, healthcare system, national regulatory policy). For example, common risk minimization

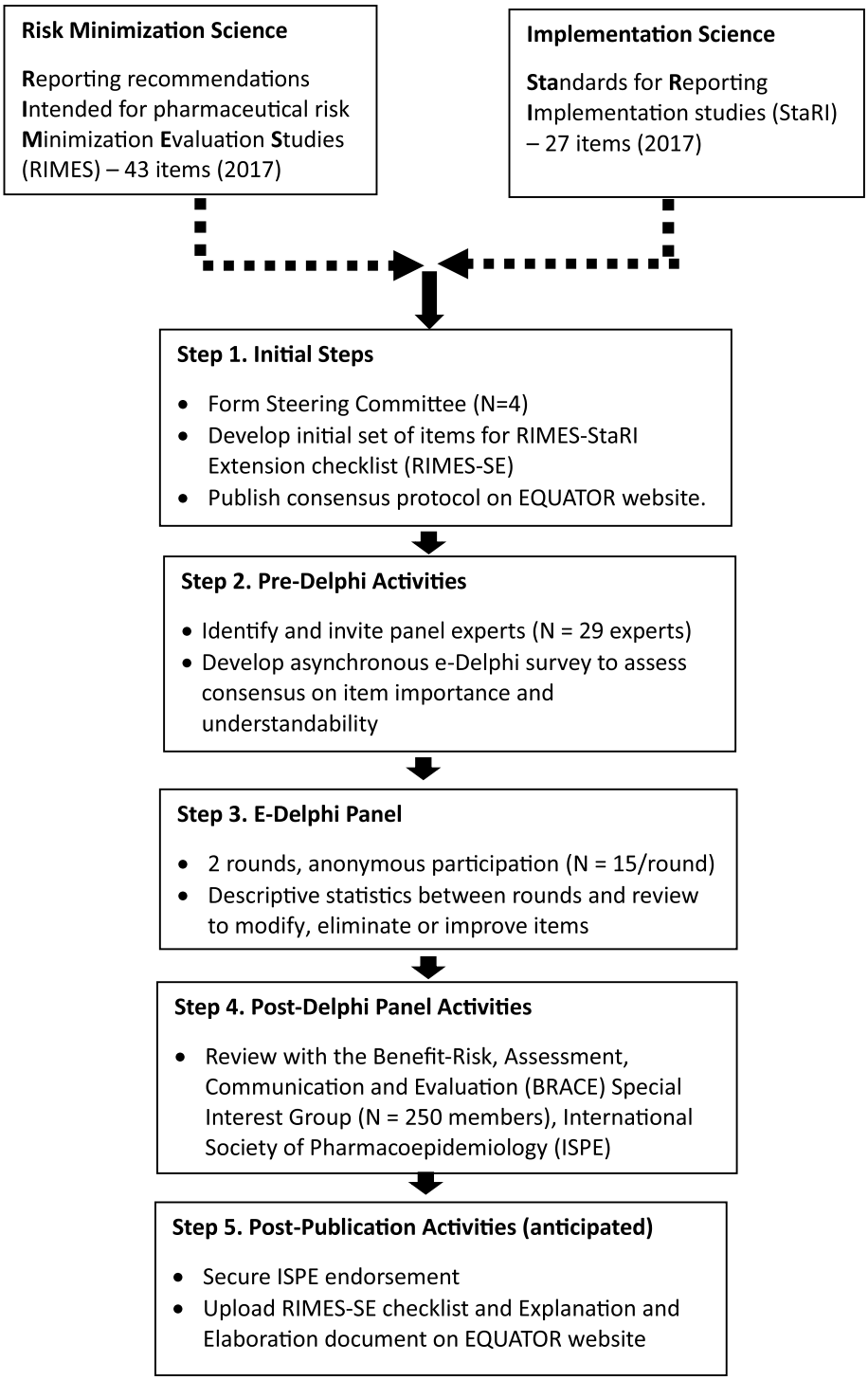

Fig. 1 RIMES-SE: consensus process diagram

program implementation activities include training of company staff at local country affiliate offices, establishing centralized hubs for verifying HCP program certification status, and requiring local affiliates to develop a detailed implementation plan outlining the steps to be completed as well as the process metrics to capture.

The second signature feature is that RIMES-SE is designed to be applicable to the heterogeneous array of research methodologies used in risk minimization program evaluation [1, 2]. It is recommended that researchers consult other reporting checklists for guidance as to how to report specific types of evaluation.

Table 1 Mapping of items from the Recommendations for reporting of rIsk Minimization Evaluation **S**tudies (RIMES) Checklist against those included in the Standards for Reporting of Implementation Studies (StaRI) Checklt

StaRI domain	StaRI items	RIMES topic	RIMES items
	NA	Declarations	1. Name(s) and affiliation(s) of the study sponsor(s) in the Conflicts of Interest statement and/or Acknowledgments statement
Title	1. Identification as an implementation study, and description of the methodology in the title	Title and abstract	2a. Title mentioning type of evaluation study design, name of medicinal product(s), and target population/healthcare setting (all three required)
Abstract	2. Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes or keywords		2b. Structured abstract describing the purpose of the intervention and target recipient(s), evaluation methods, results, and conclusions
Discussion	25. Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications	Discussion	3a. Summary of key results with reference to study objectives
Discussion	NA		3b. Internal validity. Evaluation limitations, degree to which sources of potential bias were addressed, including both the direction and magnitude of any potential bias
Discussion	NA		3c. External validity and generalizability (e.g. Will the intervention work across diverse populations and settings?)
Discussion	26. Discussion of policy, practice and/or research implications of the *implementation strategy* (specifically including scalability)		NO CORRESPONDING ITEM
Discussion	26. Discussion of policy, practice and/or research implications of the *intervention* (specifically including sustainability)		3d. Likelihood of sustainability. Discussion of the degree to which the intervention was integrated into the delivery setting (e.g. policies or incentives put in place to support ongoing intervention maintenance)
General	27. Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial or study registration (availability of protocol), funding, and conflicts of interest	Funding	4. Sources of evaluation study funding and other support, role of funders
Introduction	3. Description of the problem, challenge, or deficiency in healthcare or public health that the intervention being implemented aims to address	Design	5a. Goals and objectives of the risk minimization intervention
	NA		5b. Implementation date of the risk minimization intervention
Introduction	4. The scientific background and rationale for the implementation strategy (*including any underpinning theory, framework, or model, how it is expected to achieve its effects, and any pilot work)*		NO CORRESPONDING ITEM
	4. The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects		5c. Theory or theories used to design intervention and/or risk minimization tools, including the expected causal pathway for intervention impact
	17. Proportion recruited and characteristics of the recipient population for the *implementation strategy*		NO CORRESPONDING ITEM
Results	17. Proportion recruited and characteristics (if appropriate) of the recipient population for the *intervention*	Target population	6. Description of the key characteristics of geography and population targeted for intervention (i.e. age, sex, race/ethnicity, disease condition, socioeconomic status), enabling the reviewer/reader to determine if the evaluation study sample adequately reflected the targeted population
		Risk minimization tool selection and development	7a. Risk minimization tool(s) [e.g. managed distribution program; Medication Guide]
			7b. Pilot testing and formative evaluation of tools
			7c. Cultural sensitivity (i.e. reporting regarding whether local language, sociocultural values and traditions were considered when designing tools)

Table 1 (continued)

StaRI domain	StaRI items	RIMES topic	RIMES items
			7d. Stakeholder engagement, (i.e. patient and other stakeholder input considered/obtained in design of tools
			7e. Risk minimization tool message content (could be included in an online supplement or appendix) *Example: Information on [drug name] risks, symptoms to watch for, and actions to take if symptoms presented themselves*
			7f. Intervention distribution modality, including rationale for why a specific modality/ies were selected (the latter is recommended but not essential) *Example: The tool was intended for distribution via Medscape email to physicians, journal advertisements, and a website posting*
		Success metrics	8. A priori specification of measures and threshold for determination of intervention success
Methods: description	8. The characteristics of the targeted 'site(s)' (locations, personnel, resources, etc.) for implementation and any eligibility criteria	Setting	9a. Organizations responsible for implementing the intervention
	9. A description of the implementation strategy		NO CORRESPONDING ITEM
Results			9b. Implementers of risk minimization intervention, including, for example, how they were selected and their qualifications
			9c. Training (i.e., did implementers receive training in the intervention and how to implement it?)
Methods: description	7. The context in which the intervention was implemented (consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere)		9d. Ecological context (i.e., healthcare settings where the intervention was implemented (number, type and location[s])
Results	22. Fidelity to implementation strategy as planned and adaptation to suit context and preferences	Fidelity	10a. Use of a formal protocol for implementing the intervention
	22. …. Adaptation of intervention to suit context and preferences		10b. Important intentional modifications made to risk minimization intervention after commencement (including at local level)
Aims and objectives	5. The aims of the study, differentiating between implementation objectives and any intervention objectives	Hypotheses	12. Specific goals/objectives of the risk minimization evaluation study, including any hypotheses *Example: We hypothesized that, as a result of distributing a brochure, 80% of physicians who prescribed [drug name] would correctly identify the three key steps involved in screening patients for low blood pressure prior to initiating [drug name] therapy*
Methods: description	6. The design and key features of the evaluation (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		NO CORRESPONDING ITEM
	8. The population targeted by the intervention and any eligibility criteria	Participants	13a. Eligibility requirements (i.e. inclusion and exclusion criteria) for participating in the evaluation study *Example: Physicians were eligible to participate in the evaluation if they had prescribed [drug name] to 10 patients within the last 6 months*
			13b. Method of participant recruitment into evaluation study, including whether financial reimbursement was provided (code as zero for exceptions, e.g. secondary data analysis)
Methods: description	10. Any subgroups recruited for additional research tasks, and/or nested studies are described		NO CORRESPONDING ITEM

Table 1 (continued)

StaRI domain	StaRI items	RIMES topic	RIMES items
Methods: evaluation	12. Process evaluation objectives and outcomes related to the mechanism(s) through which the strategy is expected to work	Measures	14a. Process evaluation measures prespecified as a goal of the evaluation (e.g., reach, adoption, dose delivered, fidelity of implementation)
Methods: evaluation	11. Defined pre-specified primary and other outcome(s) of the *intervention* (if assessed), and how they were assessed. Document any pre-determined targets		14b. Primary and secondary outcome measures
			14c. Explicit link between evaluation study goals and methods in particular, and selection of processes and outcome measures
			14d. Sources of data and methods of measurement for each variable of interest
Methods: evaluation	13. Methods for resource use, costs, economic outcomes, and analysis for the *implementation strategy*		NO CORRESPONDING ITEM
Methods: evaluation	13. Methods for resource use, costs, economic outcomes, and analysis for the *intervention*		NO CORRESPONDING ITEM
Methods: evaluation	14. Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)	Statistical analysis	15a. Study size calculation and power analysis (as applicable, depending on whether the study is qualitative or quantitative)
Methods: evaluation	11. Defined pre-specified primary and other outcome(s) of the *implementation strategy*, and how they were assessed. Document any pre-determined targets		NO CORRESPONDING ITEM
Methods: evaluation	11. Defined pre-specified primary and other outcome(s) of the *intervention* (if assessed), and how they were assessed. Document any pre-determined targets		NO CORRESPONDING ITEM
Methods: evaluation	15. Methods of analysis (with reasons for that choice)		15b. Statistical methods for analysis of primary and secondary outcomes
Methods: evaluation	16. Any a priori subgroup analyses (such as between different sites in a multi-centre study, different clinical or demographic populations) and subgroups recruited to specific nested research tasks		NO CORRESPONDING ITEM
			15c. Explanation of missing data handling
Results	18. Primary and other outcome(s) of the *implementation strategy*	Results: process measures	16a. Results for each process evaluation measure
Results	19. Process data related to the *implementation strategy* mapped to the mechanism by which the strategy is expected to work		NO CORRESPONDING ITEM
		Results: process measures	16b. Description of factors that served to impede or facilitate intervention adoption and implementation
		Results: main outcomes	17a. A table showing baseline characteristics of the evaluation participants and evaluation settings (e.g., demographic, clinical, social, setting type, number, and locations)
			17b. Results of participant recruitment (for human subjects research only), including dates and reasons for non-response or attrition rates (a participant flow diagram is strongly recommended but not required, not applicable for analysis of secondary dataset)
Results	18. Primary and other outcome(s) of the *intervention* (if assessed)		17c. Description of primary and secondary outcome results
			17d. Precision of reporting of outcomes (e.g. 95% confidence interval) [as applicable, see above]
			17e. Description of whether primary outcome(s) exceeded a specified success threshold (as applicable, see above)

Table 1 (continued)

StaRI domain	StaRI items	RIMES topic	RIMES items
Results	21. Representativeness and outcomes of subgroups including those recruited to specific research tasks		17*i*. Results of any other analyses performed, including subgroup analyses, interactions and sensitivity analyses, distinguishing pre-specified from exploratory, identification of unintended impact of the risk minimization intervention or the evaluation study
Results	20. Resource use, costs, economic outcomes, and analysis for the *implementation strategy*	NO CORRESPONDING ITEM	
Results	20. Resource use, costs, economic outcomes, and analysis for the *intervention*	NO CORRESPONDING ITEM	
Results	23. Contextual changes (if any) which may have affected outcome	NO CORRESPONDING ITEM	
Results	24. All important harms or unintended effects in each group	NO CORRESPONDING ITEM	

A key concept of the StaRI is the dual strands of describing (a) the implementation strategy and (b) the clinical, healthcare, or public health intervention that is being implemented (Pinnock et al. 2018 [20]). These strands are represented as two columns in the checklist. The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed. The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations. While all items are worthy of consideration, not all items will be applicable to or feasible within every study

NA Not applicable; no corresponding item existed in the StARI Checklist, *RIMES-SE* RIMES-StaRI Extension checklist

2.4 E-Delphi Panel

An e-Delphi process [34] was used to select items for inclusion in the RIMES-SE and reach scientific consensus with experts engaging asynchronously in an anonymous manner.

2.4.1 Selection of Experts

We identified an international, cross-disciplinary group of scientific experts ($n = 29$) knowledgeable in risk minimization or implementation science with a focus in the healthcare setting.

First, we directly contacted eligible individuals within our collective professional networks. We then used a snowball sampling approach in which we asked invited participants to identify others. As risk minimization program evaluation is a specialized area within drug safety science, the pool of eligible scientific experts is relatively limited.

2.4.2 Survey Administration

Invitation to participate in the e-Delphi panel and links to the online surveys were emailed to the experts ($n = 28$, 96.6% intention to participate) with a deadline of 2 weeks for responding. Reminders emails were sent out 1 week before the deadline.

The experts were asked to rate the importance and understandability of each checklist item using an 11-point rating scale that ranged from 0 (not at all important/understandable) to 10 (extremely important/understandable). Open-ended, free-text responses were invited to allow for further input regarding item meaning and rationale. See Supplementary Files 1 and 2 for the e-Delphi survey instruments (Round 1 and Round 2, respectively) in the electronic supplementary material (ESM).

Surveys were administered using Qualtrics (Qualtrics.com; Provo, UT, USA) and ethical review was conducted by the Advarra Institutional Review Board (IRB), Columbia, MD, USA. For the US and Western Europe, the project was deemed to be exempt from IRB review (May 18, 2023; Pro00071189); for Canada, ethics approval was granted on May 24, 2023 (Pro00071646).

2.4.3 Analysis

Descriptive statistics were calculated for each item (median, inter-quartile range). A pre-specified threshold level of 80% agreement was used as defined by importance and understandability scores of 7, 8, 9, or 10 [35]. In round one, the experts were asked to rate all items ($n = 34$). In round two, the experts rated only the items that did not achieve the threshold level of agreement in round one and that had been subsequently revised to improve meaning and/or clarity.

Items from both survey rounds were analyzed using Stata, version 12 (stata.com; College Station, TX, USA). Qualitative comments and suggestions were imported into a Word document for review by authoring team members (MYS, VN, and EHM).

2.5 Post-e-Delphi Panel Activities

To further evaluate understandability of the consensus items among risk minimization practitioners who will apply the standards for their evaluations, we convened a face-to-face, 1-hour workshop at the International Conference for Pharmacoepidemiology in Halifax, Nova Scotia, Canada, on August 25, 2023. Attendees were members of ISPE's Benefit–Risk Assessment, Communication, and Evaluation Special Interest Group (BRACE SIG) [36], and possessed training and professional experience in drug safety and/or pharmacoepidemiology ($n = 8$), were drug regulators ($n = 2$), or had combined expertise in implementation science, public health, drug safety, and pharmacoepidemiology ($n = 2$). The group reviewed the results of the e-Delphi exercise. Workshop attendees recommended some additional, minor editorial changes to item wording and provided suggestions regarding examples to include in an accompanying explanation and elaboration document to the RIMES-SE Checklist.

Following the workshop, the proposed RIMES-SE Checklist was posted on the BRACE SIG message board hosted by ISPE. The full BRACE membership, consisting of 250 professionals working in the field of drug safety in the pharmaceutical industry, academia, or in regulatory authorities globally, was invited to review and comment for a 2-week period. The final version of the RIMES-SE Checklist was developed based on a distillation of the feedback received and iterative discussions among the authors (MYS and EHM).

2.6 Post-Publication Activities

While this is outside the scope of the present paper, the intention is to upload the reporting standard and accompanying explanation and elaboration document (see ESM File 4) onto the EQUATOR Network website to facilitate guideline translation to practice.

3 Results

Table 2 presents summary descriptive statistics for the e-Delphi process. Of the 29 experts initially approached, all but one accepted the invitation to participate. During the first e-Delphi round, 15 of the 28 experts (53.6% response rate) provided ratings on the importance of each item. Of the 34 items listed, 29 (85.3%) reached the a priori level of consensus for inclusion. In terms of understandability, 18 items (52.9%) reached the a priori level of consensus for inclusion.

Based on the results of Round 1, items with either importance or understandability scores <80% agreement were reviewed, and their wording was revised in response to comments from the e-Delphi panelists. Qualitative comments from Round 1 are summarized by theme and domain in Table 3. Exemplar quotes included "More tangible examples may be helpful."; and "I had to read this a few times. There are a lot of concepts (all important) rolled into one" (Table 3).

In summarizing the received feedback, seven items were deemed to be redundant or irrelevant to risk minimization programs and removed altogether, leaving an item pool of 27 items.

Among the 27 retained items, only those which had importance or understandability ratings of < 80% from Round 1 were included in Round 2 ($n = 19$ items). The response rate in Round 2 was 53.6% (15/28). Fifteen of the invited experts also rated the items in Round 2; however, because responses were anonymous, we are unable to determine the round-to-round response rate.

Of the 19 items assessed, 18 reached the a priori level of consensus for importance (94.7% consensus). Fifteen of the 19 items reached the a priori level of consensus for inclusion in terms of understandability (78.9% consensus). The single item (item 7) which failed to reach 80% consensus on importance referred to the context in which the program was delivered, including healthcare regulations, other relevant policies, social, economic or political factors that might influence implementation. Given that context can strongly affect program implementation and external generalizability, a decision was made to retain that item.

The other four items were reworded to improve their understandability, including item 4b (the scientific rationale for the implementation strategy/ies); item 6 (the goals/objectives of the risk minimization evaluation study, design and key features of the evaluation, date of implementation of risk minimization program, and any changes to evaluation plan, with reasons); item 17a (primary and other outcome(s) of the Intervention, including precision of assessment and whether the primary outcome met a pre-specified success threshold); and item 20a (degree of fidelity involved in delivering the risk minimization program intervention elements). Qualitative comments from Round 2 are summarized by theme and domain in Table 4. Exemplar quotes regarding understandability included "It may be beneficial to distinguish RM objectives and RMP implementation objectives in the example using (A) and (B) in the first sentence and then categorize the example accordingly;" and, "As an implementation scientist, the fidelity Q[uestions]s are clear and

understandable, but I think others will need more explanation." (items 6 and 20a, respectively; see Table 4).

3.1 The RIMES-SE

The updated, 27-item RIMES-SE Checklist is presented in Supplementary File 3 (see ESM); Table 5 describes key terms used in the Checklist. Items fall into nine sections consistent with the organization of scientific manuscripts and with the reporting conventions set forth in the StaRI [20]. A detailed description of all RIMES-SE items along with a supporting rationale and illustrative examples are provided in the Explanation and Elaboration document in Supplementary File 4 (see ESM), and in the StaRI Statement's Explanation and Elaboration document [20].

Twelve of the RIMES-SE Checklist items entail consideration of the risk minimization program and its implementation strategy together. In particular, authors are asked to specify (a) the hypothesized mechanism(s) by which both the intervention and the implementation strategy are expected to work, (b) the characteristics of the intervention recipients (e.g., HCPs, patients) as well as the implementing sites and site staff, (c) a description of the intervention components (including any stakeholder involvement in their development) as well as the implementation strategies deployed, and d) the intervention and implementation outcome measures and corresponding results.

Areas where the RIMES-SE Checklist differs significantly from its predecessor include its clear demarcation between the intervention and the implementation strategy, its focus on implementation planning, execution, and assessment as a cohesive longitudinal process, and its emphasis on describing program implementation context, including barriers and facilitators that may have affected implementation. These approaches are consistent with the emerging emphasis on designing for dissemination and sustainability from the outset [37], and on understanding contextual factors when comparing effectiveness of interventions between programs and within programs over time [38, 39].

4 Discussion

Reporting guidelines are intended to facilitate study replication and synthesis of the evidence base by stipulating a common set of items that should be reported in all study manuscripts [40]. In the context of risk minimization, there is a public health imperative to improve the transparency of reporting of evaluation studies so as to build the evidence base regarding what types of programs and implementation strategies work to reduce drug-related risks, under what types of conditions and for what types of patient and healthcare provider populations.

The RIMES-SE Checklist was developed specifically to address this gap in the reporting of risk minimization evaluation studies. It represents an advance over the original RIMES Checklist in several ways. First, it enhances ease of use by reducing the number of Checklist items from 43 to 27. In doing so, several items were deleted altogether from the original RIMES Checklist (e.g., details regarding risk minimization tool content and distribution modalities, training of implementers, and specific discussion of internal and external validity). The remainder were reworded and incorporated into new, more broadly defined items in the Methods, Results, and Discussion sections.

Second, the RIMES-SE updates the content of the original RIMES Checklist to reflect evolving best practices in the design and evaluation of risk minimization programs as set forth in regulatory guidance. Third, it emphasizes the essential inter-connection between the development of a risk minimization program and its implementation by the use of a dual strand reporting format. Fourth, it explicitly links pharmaceutical risk minimization evaluation to the field of implementation science, a positioning which may foster greater inter-disciplinary collaboration in this area, encourage increased scientific rigor in the design and reporting of risk minimization program implementation processes, strategies and outcomes, and facilitate interpretation of evaluation study results. Lastly, by virtue of the extensive consensus process we undertook, uptake of the RIMES-SE among key stakeholders (e.g., pharmacovigilance professionals, regulators, and pharmacoepidemiologist researchers) should be strong. Whether this proves to be the case, however, should be assessed in a future study.

We recognize that some RIMES-SE items may reflect approaches not yet in wide use among risk minimization program evaluators (e.g., application of theories, models, and frameworks to guide design and/or piloting of the intervention; the assessment of barriers and facilitators to program uptake; description of context of program implementation and contextual changes). In particular, in instances where the evaluators were not involved in the program's design or implementation planning, they may not know or have access to such information. In such cases, researchers can report 'not known.' In other instances, where it has been determined that the approach was not used or not examined, 'none used' or 'not assessed', respectively, are the appropriate response options. Moving forward, however, we hope that risk minimization program planners will collaborate with program evaluators during the design phase (as has been recommended by regulators [2]), and that the RIMES-SE will be consulted throughout the process to promote adoption of the good practices which this checklist embodies.

Our study had several notable strengths. First, we used an e-Delphi method to obtain input on the RIMES-SE items from a group of leading experts in drug safety, risk

Table 2 RIMES-SE: results from Rounds 1 and 2 of the e-Delphi exercise

Domain/checklist item		Round 1						Round 2					
		Section I. Importance			Section II. Understandability			Section I. Importance			Section II. Understandability		
		Obs	Median (IQR)	80% Consensus[a]	Obs	Median (IQR)	80% Consensus[a]	Obs	Median (IQR)	80% Consensus[a]	Obs	Median (IQR)	80% Consensus[a]
Title	*1*	15	9 (7–10)	93.3	13	9 (6–9)	69.2	15	9 (8–10)	93.3	15	9 (8–10)	100.0%
Abstract	*2*	15	9 (8–10)	100.0	12	7 (6–9.5)	66.7	15	9 (8–10)	100.0	15	8 (7–9)	86.7%
Introduction	*3*	15	10 (9–10)	100.0	12	9.5 (8–10)	91.7	NA	NA		NA	NA	
	4a	15	8 (7–10)	80.0	12	8.5 (6–10)	66.7	15	8 (7–9)	93.3	15	8 (7–10)	80.0%
	4b	15	7 (5–10)	60.0	12	8 (6–10)	66.7	15	8 (7–10)	80.0	15	7 (6–10)	66.7%
Aims and objectives	*5*	15	9 (6–10)	73.3	12	9 (5.5–10)	66.7	15	9 (7–10)	86.7	15	8 (7–9)	80.0%
Methods: description	*6*	15	9 (8–10)	93.3	12	7 (6–9)	66.7	15	9 (8–10)	86.7	15	8 (6–8)	73.3%
	7	15	9 (8–10)	93.3	12	8.5 (8–10)	91.7	15	9 (6–9)	73.3	15	8 (7–9)	100.0%
	8a	15	8 (6–10)	73.3	11	9 (7–10)	81.8	15	9 (8–10)	93.3	15	9 (8–10)	100.0%
	8b	15	9 (8–10)	93.3	11	9 (9–10)	100.0	NA	NA		NA	NA	
	9a	15	9 (6–10)	73.3	11	8 (7–10)	81.8	15	9 (9–9)	93.3	15	9 (8–9)	93.3%
	9b	15	9 (9–10)	86.7	11	9 (7–10)	90.1	15	9 (8–9)	93.3	15	9 (8–10)	100.0%
Methods: evaluation	*10a*	15	10 (8–10)	100.0	12	8 (7–10)	83.3	15	10 (9–10)	100.0	15	8 (7–10)	93.3%
	10b	15	10 (9–10)	100.0	11	8 (8–10)	90.9	NA	NA		NA	NA	
	11a	15	9 (8–10)	100.0	12	8 (6.5–9)	75.0	15	9 (8–10)	93.3	15	8 (7–9)	80.0%
	11b	15	9 (8–10)	93.3	12	8 (6–8.5)	66.7	NA	NA		NA	NA	
	12	15	8 (6–8)	66.7	12	7.5 (6–10)	66.7	15	8 (7–9)	80.0	15	9 (7–10)	86.7%
	13	15	8 (7–10)	80.0	12	9 (8.5–10)	91.7	NA	NA		NA	NA	
	14	15	10 (7–10)	86.7	12	9.5 (8.5–10)	91.7	NA	NA		NA	NA	
	15	15	8 (7–10)	80.0	12	8.5 (6.5–10)	75.0	15	9 (7–10)	93.3	15	9 (8–10)	86.7%
	16a	15	9 (8–10)	100.0	12	8 (7–10)	75.0	15	9 (8–10)	93.3	15	9 (8–10)	100.0%
	16b	15	8 (8–10)	100.0	12	8.5 (8–10)	91.7	NA	NA		NA	NA	
Results	*17a*	15	9 (8–10)	93.3	12	8 (8–10)	83.3	15	9 (9–10)	93.3	15	8 (6–10)	73.3%
	17b	15	9 (8–10)	93.3	12	7.5 (6–10)	66.7	15	9 (9–10)	93.3	15	8 (7–9)	100.0%
	18	15	8 (7–8)	80.0	11	8 (8–10)	90.9	NA	NA		NA	NA	
	19	15	8 (7–9)	93.3	12	8 (6.5–10)	75.0	NA	NA		NA	NA	
	20a	15	8 (8–9)	100.0	12	7 (5–8.5)	50.0	15	8 (7–9)	93.3	15	6 (6–9)	46.7%
	20b	15	8 (7–8)	80.0	12	7 (5–9)	50.0	NA	NA		NA	NA	
	21	15	8 (8–9)	86.7	12	8.5 (7–10)	91.7	NA	NA		NA	NA	
	22a	15	10 (8–10)	93.3	12	8 (7–9)	83.3	15	9 (7–10)	93.3	15	9 (7–10)	93.3
	22b	14	8 (7–10)	100.0	12	8 (6–10)	66.7	NA	NA		NA	NA	
Discussion	*23*	15	9 (9–10)	100.0	12	9 (8–10)	91.7	NA	NA		NA	NA	
	24	15	9 (7–10)	86.7	12	9 (8–10)	83.3	NA	NA		NA	NA	
	25	15	10 (9–10)	93.3	12	9.5 (8.5–10)	100.0	NA	NA		NA	NA	

NA not applicable. In Round 2, only items which emerged from Round 1 with importance or understandability scores below 80% were included. *RIMES-SE* RIMES-StaRI Extension checklist

[a]80% consensus is defined as scores of 7, 8, 9, or 10

Table 3 Open text field results: themes by domain with exemplar quotes from eDelphi Round 1

Domain	Importance		Understandability	
	Themes	Exemplary quote	Themes	Exemplary quote
Title	Add geography Change the example in question	*"Specific Geography- Should also be mentioned in the Title, if study was limited to specific Geography."*	Clarify the example	*"I had to read this a few times. There are a lot of concepts (all important) rolled into one."*
Abstract	Content and structure depend on the journal for publication Review language around evidence-based, implementation strategy	*"Reasonable but different journals will want different things in an abstract."* *"Implementation strategy/ies to be tested, the evidence-based intervention being implemented,"*	Review language around implementation science	*"Terminology confusing as seems to be a lot expected related to the design and implementation which evaluator may not know."*
Introduction	Change the example in question	*"More tangible examples may be helpful."*	Define better terminology around implementation science	*"People still unfamiliar with implementation strategies."*
Aims and objectives	Review language about objectives, indicators, and outcomes The request for too much detail regarding differentiating between implementation and intervention outcomes	*"Aims and objectives are extremely important, but the distinction between implementation and intervention objectives not necessary, also this terminology is confusing."* *"I don't think categorizing the two types of outcomes is critical, but requiring both types to be reported is."*	Revise objectives and outcomes in the sentence	*"This item is focused on the objectives and the first sentence states implementation outcomes - not objectives."*
Methods: description section	Differentiate between implementation, adaptation, dissemination, and evaluation strategies	*"What's described above in item 9a sounds more like a dissemination strategy than an implementation strategy. An implementation strategy would refer to something like guidance or training on screening procedures."*	Revise language: stakeholder, implementation science terms	*"Doubt understandability of yet unfamiliar implementation science concepts in concerned researchers."*
Methods: evaluation section	Revise terminology	*"It may be helpful to consider whether these terms are most universal or if others may be more widely understood."*	Clarify type of outcomes to be measured Revise language	*"These Qs are understandable, but depending on the reader, the labeling of the different outcome types may not resonate quickly."* *"Would benefit to have examples of process and outcome measures."*
Results	Clarify concepts about representativeness, fidelity, adaptation measures, and meaningfulness	*"Some of this may not be "knowable" to the evaluation team versus the design team for the RMM."*	Define terms related to implementation science	*"As an implementation scientist, the fidelity Qs are clear and understandable, but I think others will need more explanation."*

Table 3 (continued)

Domain	Importance		Understandability	
	Themes	Exemplary quote	Themes	Exemplary quote
Discussion	Clarify the threshold concept Sustainability and scalability should not be required for all projects	*"Was there a recommendation to specify a success threshold?; these items are generally common to any discussion section."* *"Not all interventions are scalable, nor should all interventions be scaled. As for discussion of policy, practice, and/or research implications... recommend keeping it simple and focus on sustainability. But again, should it be sustained?"*	NA	NA

NA not applicable as there were no data reported

minimization, and implementation science. E-Delphi is a technique for achieving consensus among subject matter experts in an iterative, anonymous, and asynchronous manner, and it is a recommended approach for developing reporting guidelines [29, 33]. A key advantage of an e-Delphi approach, as compared with group discussions or other in-person consensus techniques, is that it minimizes known biases associated with face-to-face group processes [41]. It is also a more feasible, convenient, and cost-effective way to bring together a group of experts, thus helping to maximize representativeness. An additional strength of our study is that we pre-specified the e-Delphi level of consensus, a documented shortcoming of some e-Delphi research to date [42]. Lastly, we succeeded in recruiting a heterogeneous panel of experts both in terms of content expertise (i.e., drug safety, regulatory science, implementation science, pharmacoepidemiology) and sector affiliation (i.e., regulatory agency, academia, pharmaceutical industry, pharmacovigilance consulting).

Two study limitations are worth noting. First, the size of our e-Delphi panel was relatively small. However, given that pharmaceutical risk minimization is a highly specialized topic, this was not unexpected. Individuals with expertise at the intersection of public health, implementation science, pharmacovigilance, and pharmacoepidemiology constitute a singular group.

Second, e-Delphi participants were drawn from Western Europe, the United Kingdom, and North America exclusively. Lack of input from other regions, including countries in the Asia-Pacific area, may potentially have caused us to overlook some cultural and/or healthcare system factors germane to risk minimization programs and their evaluation. The authors used their collective (and extensive) professional networks to identify eDelphi panelists who had deep subject matter expertise in their respective disciplines. In recruiting known professional connections, we hoped to increase the panelists' commitment to completing the eDelphi questionnaires.

Risk minimization program design, implementation, and evaluation is a dynamic area of pharmacovigilance and regulatory science. Innovative approaches to incorporating patient and provider perspectives, the use of digital risk minimization tools, and the use of mixed methods designs are all examples where the science is evolving. There is also a need for greater inter-disciplinary collaboration among scientists (e.g., in the fields of public health, implementation science, data science, behavioral medicine) to advance methods, improve the effectiveness of risk minimization program design, and to develop new, more effective risk minimization tools and strategies to enhance program adoption, impact, and sustained use.

Table 4 Open text field results: themes by domain with exemplar quotes from eDelphi Round 2

Domain	Importance and understandability	
	Themes	Exemplary quote
Title	Many items in the title	*"This proposes many details to be packed into a title or keywords, which can be a lot and get cumbersome."*
Abstract	Review language around "theoretical basis"	*"I am thrown by the 'theoretical basis' phrase."*
Introduction	Framework description Clarify implementation science terms	"I *think it is optimistic that authors will describe two theoretical frameworks in the introduction."* *"I think implementation strategies are too jargony and confusing to non-implementation scientists. Using other language to ask for this detail would be ideal. The basic premise is you need enough detail to be able to replicate the 'package.'"*
Aims and objectives	Clarification about the type of objectives: implementation, evaluation, program	*"It may be beneficial to distinguish RM objectives and RMP implementation objectives in the example using A) and B) in the first sentence and then categorize the example accordingly."*
Methods: description section	Redundancy with the objective section Include recruitment strategy	*"Objectives of the evaluation were mentioned in the previous question, would it be repeated here?"* "Details *on how the target population was contacted and when are very important."*
Methods: evaluation section	Revise terminology and a lot of information	*"Item 11 - still unclear."* *"There is a lot packed into item 10."*
Results	Create more items to clarify the question	*"Simplify message, e.g. split text, distinguish attributes for population and settings."* "*Item 17a perhaps should be split. Mixing the harms (an outcome) and the sensitivity analyses in one item seems unusual."*
Discussion	NA	NA

NA not applicable as there were no data reported

Table 5 Definitions of terminology used in the RIMES-StaRI Extension checklist (RIMES-SE)

Terminology	Definition
Adaptation	The degree to which an evidence-based intervention or implementation strategy is changed or modified by user before, during, and after adoption and implementation to suit the needs of the setting or to improve the fit to local conditions [43]
Context	A set of characteristics and circumstances that consist of active and unique factors within which the implementation of an intervention is embedded. Intervention effects are generated through interaction of new ways of working with existing contexts [44]
Dissemination	An active approach of spreading interventions to the target audience via determined channels using planned strategies [45]
Fidelity	The extent to which the core intervention elements (or implementation strategies) are successfully delivered as intended within a setting [46]
Implementation outcomes	The effects of deliberate and purposive actions to implement new treatments, practices, and services [46]
Implementation strategy	A method or technique used to enhance the adoption, implementation, and sustainability of an under-utilized intervention [46]
Scalability	The ability of a health intervention shown to be efficacious on a small scale and/or under controlled conditions to be expanded under real-world conditions to reach a greater proportion of the eligible population, while retaining effectiveness [47]

5 Conclusions

The RIMES-SE Statement and Checklist seeks to extend the risk minimization evaluation reporting guidelines set forth in the original RIMES Checklist via inclusion of key implementation science concepts incorporated in the StaRI Statement and Checklist. Our goal in doing so has been threefold. First, by specifying a standard, minimum set of items that should be reported in every risk minimization evaluation study, we aim to assist regulators,

researchers, and other readers in assessing the quality of the research. Specifically, standardized reporting on the goals and rationale of the program, how the program was implemented, and what implementation and intervention outcomes were achieved, makes it easier to interpret the risk minimization evaluation results, and to understand the study's strengths and limitations. Second, we seek to help researchers identify risk minimization evaluation studies in the published literature, thus facilitating their ability to critically appraise and synthesize this body of evaluation research. Third, we aim to increase awareness among regulators, researchers, and product manufacturers about good practices in risk minimization program design and evaluation. Such good practices include comprehensive implementation planning, the deployment of multiple, multi-level strategies to address identified barriers and facilitators to program uptake and maintenance, the use (and documentation) of program adaptations across different healthcare settings and geographies, and the assessment of program implementation outcomes as well as those relating to intervention effectiveness.

We recognize that these guidelines will need to be updated periodically in response to new developments in the field. We welcome input from pharmacovigilance practitioners, patients, regulators, researchers, and other interested stakeholders in the continuous updating of the RIMES-SE. Through the ongoing use of the RIMES-SE by researchers, regulators, and journal editors, we anticipate seeing improvements in the reporting of risk minimization evaluation studies in terms of both comprehensiveness and transparency. This, in turn, should lead to safer, more appropriate use of medicines and, ultimately, better outcomes for patients and public health more broadly.

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Conflict of interest MYS is a fulltime employee of Evidera, a consultancy that performs healthcare research for a wide range of biopharmaceutical and biotechnology companies, and is a shareholder in Thermo Fisher Scientific, which owns PPD. She is also an adjunct faculty member in the Department of Regulatory and Quality Sciences, School of Pharmacy, University of Southern California, Los Angeles, CA, USA. VN and NM have no conflicts of interest to report. EHM has received funding over the past three years for consulting services on issues of drug safety from Eli Lilly, Health Care Service Corporation, Inc., i2o, Humana Inc., Ipsen, Molina Healthcare, Inc., Reata Pharmaceuticals, Syneos Health, and United Healthcare Services. HP receives grant monies paid to her institution for applied and implementation research unrelated to risk minimization program evaluations. In the past three years she has received speaker fees from Teva and Sandoz for non-promotional talks unrelated to topics covered in this paper. AGW has received consulting fees from Bayer KG, Genentech Inc, Arbor Pharmaceuticals, and Ipsen, and has received research funding from Merck, Sharp and Dohme.

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Author contributions MYS designed the study, analysis, wrote the first draft of the manuscript, and prepared the final draft for submission. NM conducted statistical analysis of the e-Delphi data, prepared the e-Delphi results tables, and reviewed the final draft of the manuscript. VN prepared the tables and assisted in reviewing and revising the manuscript. HP, AGW, and EHM assisted in the study design, the conduct of the data analysis, and reviewed the final draft of the manuscript. All authors read and approved the final version. This manuscript has been endorsed by the International Society for Pharmacoepidemiology.

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