Drug Safety (2023) 46:243–255
https://doi.org/10.1007/s40264-022-01270-4

ORIGINAL RESEARCH ARTICLE

What Factors Make EU Regulators Want to Communicate Drug Safety Issues Related to SGLT2 Inhibitors? An Online Survey Study

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Accepted: 14 November 2022 / Published online: 15 February 2023

Abstract

Introduction Previous studies have found differences in the communication of safety issues among medicines regulatory agencies.

Objectives To explore (1) to what extent regulators' opinions regarding the need to communicate safety issues related to sodium-glucose cotransporter-2 (SGLT2) inhibitors might be influenced by their concern about the safety issue, and (2) whether regulators' concerns might be influenced by certain characteristics of the safety issue or by the demographic and professional characteristics and attitudes of the regulators.

Methods An online cross-sectional survey study with a rating-based conjoint analysis among clinical and pharmacovigilance assessors from the EU regulatory network was performed between April and June 2021. Regulators were invited by email, and participants were asked about their level of concern and their opinion regarding the need to communicate about 12 scenarios defined by four characteristics: adverse drug reaction, source of information, causality, and frequency. The outcomes for the first objective were to update the summary of product characteristics (SmPC; yes/no) and to send direct healthcare professional communications (DHPC; yes/no). The determinant was regulators' level of concern (range 0–100%). The outcome of the second objective was regulators' level of concern, and the determinants were the characteristics of the safety issue, demographic and professional characteristics, and attitudes of the regulators (beliefs about medicines and risk perception).

Results A total of 222 regulators completed the survey (64% women; mean age 46 ± 10 years). Depending on the scenario, 54–94% and 25–74% of the participants would update the SmPC or send a DHPC, respectively. The participants' level of concern influenced their opinions regarding the need to update the SmPC and send a DHPC (odds ratio (OR) 13.0; 95% confidence interval (CI) 7.8–21.7 and OR 13.6; 95% CI 9.5–19.2, respectively, for every 10% increase in the level of concern). All characteristics of the safety issue influenced the level of concern. Younger participants, women, and those working for Eastern European agencies had a higher level of concern than older participants, men, and those working in other regions. Beliefs about medicines and general risk perception also influenced their concern.

Conclusions The opinion regarding the need to communicate safety issues was influenced by the concern of regulators. Regulators' concern was influenced by the characteristics of the safety issue, demographic characteristics, and attitudes. Diverse groups of experts regarding such factors would ensure that various views are incorporated in risk communication decisions.

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1 Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a relatively new class of medicines for the treatment of type 2 diabetes (T2DM); dapagliflozin, the first medicine in this class, was approved in the EU in 2012 [1]. SGLT2 inhibitors lower glycated haemoglobin (HbA1c) levels and body weight, are generally not associated with hypoglycaemia, and have demonstrated cardiovascular and renal benefits [2, 3]. Nonetheless, several rare but serious safety issues have emerged for this class of medicines after marketing

Key Points

Previous studies have shown differences in the communication of safety issues related to SGLT2 inhibitors across medicines regulatory agencies.

In this study, regulators' opinions regarding the need to communicate about safety issues was partly influenced by their level of concern, which varied according to the characteristics of the safety issue as well as the regulator's gender, region, age, beliefs about medicines, and general risk perception.

The results of this study provide a better understanding of factors that may influence risk communication decisions in the highly regulated European system.

authorisation, including diabetic ketoacidosis (DKA), bone fractures, and lower limb amputations [4]. Medicines regulatory authorities around the world, however, have communicated differently about these safety issues. For example, whereas the US Food and Drug Administration (FDA) issued urgent safety advisories regarding the increased risk of bone fractures, the European Medicines Agency (EMA) and the Australian Government Therapeutic Goods Administration (TGA) did not [5]. Such differences may have been due to variations among regulatory agencies, for example in internal guidelines and legal frameworks [5, 6].

The regulatory system in the EU is based on guidelines for good regulatory practices, and assessments and decisions are made by groups of experts who are part of so-called committees or working parties at the EMA [7]. These groups consist of representatives of the entire EU regulatory network who are made available by the national regulatory agencies. Specifically during the post-marketing phase, the Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for the detection, assessment, minimisation, and communication of the risks of adverse drug reactions (ADRs) [8]. There are multiple forms of risk minimisation and communication, for example updates of the summary of product characteristics (SmPC) and dissemination of direct healthcare professional communications (DHPCs). The SmPC is a document that contains information for healthcare professionals regarding the officially approved conditions for which to use a medicine. If new information is identified during the medicines life-cycle, SmPCs may be updated when it is considered necessary [9]. DHPCs are documents that are sent to individual healthcare professionals to inform them about important new (safety) information related to a medicine or group of medicines.

Even in this coordinated European regulatory system, differences in general risk communication strategies across national authorities have been observed. A previous study, for instance, assessed the distribution of DHPCs in four European countries for centrally authorised products and showed that although at least one DHPC had been issued for 53 medicines in the studied time period, a DHPC had been issued in all four countries for only 32% of these medicines [10]. A possible explanation for these differences may be variation in the interpretation of guideline recommendations or regulatory assessment reports. As regulatory decisions are made at the group level, the views and opinions of the individuals composing the group contribute to the final outcome [9].

Previous research in the medical field has shown that the interpretation of clinical guidelines varies broadly among individuals [11–13]. According to a comprehensive model based on the general risk communication process, factors such as age, gender, prior beliefs and risk perception might have an impact on assessing the risk, on the decision of whether to take any actions, and on the actual actions taken [14]. In addition, previous research regarding regulatory decision-making has shown that in addition to scientific evidence, regulators' demographic and professional characteristics, such as gender and work experience, and their attitudes, such as general risk perception and personal preferences, influence regulatory outcomes [15–17]. It is of interest, therefore, to examine factors that might influence the medicines safety communication process.

The first aim of this study was to explore to what extent regulators' opinions regarding the need to communicate safety issues related to SGLT2 inhibitors might be influenced by their concern about the safety issue. We focused on two forms of communication, namely updating the SmPC and sending a DHPC. The second aim was to assess whether regulators' concerns might be influenced by certain characteristics of the safety issue or by the demographic and professional characteristics and attitudes of the regulators.

2 Methods

2.1 Study Design and Participants

We conducted an online cross-sectional survey study among medicines regulators of the EU regulatory network [18]. For recruitment, we first presented the study to the members of various committees and working parties at EMA, namely the PRAC, the Committee for Medicinal Products for Human Use (CHMP), and the Scientific Advice Working Party (SAWP). Committee members subsequently received an email including an information

letter, a unique survey link, and a request to provide up to five further email addresses of clinical and pharmacovigilance assessors from their national regulatory agencies, whom we then also invited to participate in the study. There was no financial compensation for participation, and regulators who did not complete the survey received a maximum of three reminder emails in a 6-week period. To ensure that the included participants were only clinical and pharmacovigilance assessors, we used the response to the survey question "Do you have experience as an assessor of human medicinal products?" as a check. The survey was open from 19 April 2021 to 21 June 2021; responses were collected anonymously. The information letter provided to the participants, the survey, and the Checklist for Reporting Results of Internet E-Surveys (CHERRIES checklist) [19] are available in the Electronic Supplementary Material (ESM) 1.

2.2 Survey

The survey consisted of three parts: questions regarding demographic and professional characteristics, a rating-based conjoint analysis experiment containing various safety issues, and questions regarding regulators' attitudes (ESM 1). The questions were asked in English, and the online format of the survey was created using the Research Electronic Data Capture 10.0.23 web application (REDCap—http://www.projectredcap.org) [20, 21]. The survey was piloted for ease of use, functionality, and content by 18 individuals, who were researchers at the University Medical Center, Groningen, the Netherlands, and medicines regulators at the Dutch Medicines Evaluation Board. These participants were excluded from participating in the study, and minor adaptations to the survey were made according to their feedback.

2.2.1 Demographic and Professional Characteristics

The survey assessed the following information regarding demographic and professional characteristics: age (continuous), gender (woman or man), country (listed as per the EMA website, grouped for the analyses in Northern, Southern, Eastern, and Western Europe as per United Nations division [22, 23]), experience in pharmacovigilance (yes or no), and experience in endocrinology (yes or no). Given the focus of the study on post-marketing safety issues of a medicine for T2DM, experience in pharmacovigilance and endocrinology were considered relevant for the study.

2.2.2 Rating-Based Conjoint Analysis Experiment

The rating-based conjoint analysis experiment was introduced by providing some basic information about a medicine for the treatment of T2DM. The medicine was presented as a hypothetical drug, without mentioning a specific medicine or class of medicines. However, the provided information regarding the medicine was based on real information regarding SGLT2 inhibitors and included a short summary of selected favourable and unfavourable effects. To obtain an indication of the responders' benefit-risk evaluation of the drug, they were asked the question "How would you rate the benefit-risk balance of this drug?" (using a visual analogue scale (VAS) from 0 to 100).

Next, we presented various scenarios of safety issues described in terms of four characteristics, termed attributes. Each attribute had two or three alternatives, termed levels. The first attribute was the ADR, which could have three levels, namely DKA, amputation, or bone fracture. These ADRs have been associated with SGLT2 inhibitors and were described according to the definitions available in the EMA assessment reports of this drug class [24–26]. We selected these ADRs because of the previously reported discrepancies in safety advisories among regulatory agencies worldwide [5]. The other three attributes were hypothetical for each scenario and had two levels each (Table 1): (1) source of information (i.e., spontaneous reports/epidemiological studies or clinical trials), (2) level of causality (possible or probable), and (3) frequency of the ADR (two times higher or three times higher than the risk with the standard of care, which was specified for each ADR). These attributes were selected because of their possible relevance at the time of assessing a safety issue, based on input from pharmacovigilance experts and information from regulatory guidelines [24–29].

To obtain the minimum number of scenarios necessary to estimate all main effects and all possible interaction effects between the ADRs and the other attributes, we generated an orthogonal fractional factorial design for each ADR. This process resulted in a total of 12 scenarios, four per ADR, with differences in the level of at least one of the attributes. We created three blocks of scenarios based on the ADRs, and the order of the scenarios within each block was randomised. The order in which the blocks were presented in the survey was also randomised, and all participants were asked to assess the 12 scenarios.

For each scenario, the participants were asked three questions. The first question assessed their concern for the safety issue: "With this additional hypothetical information available, how concerned are you about this safety issue?" (VAS from 0 to 100). The next questions addressed their opinion on the need to communicate about the safety issue: "In your opinion, should the summary of product characteristics (SmPC) of the drug be updated?" (yes or no) and "In your opinion, should a direct healthcare professional communication (DHPC) be sent out?" (yes or no).

Table 1 Attributes and attribute levels used in the rating-based conjoint experiment

Attributes	Levels
ADRs	Diabetic ketoacidosis—Serious complication caused by low insulin levels that leads to the accumulation of acidic ketone bodies in the blood. Patients may require hospitalization or treatment in an emergency department*
	Amputations—Lower limb amputation (mostly affecting the toes)
	Bone fracture—Bone fracture and decrease in bone mineral density. Bone fracture may occur when minor trauma. For example, when falling from standing height
Source of information	Spontaneous reports and/or epidemiological studies*
	Clinical trials
Level of causality	Possible—the ADR happened within a reasonable time sequence to drug administration, but it could also be explained by concurrent disease or other drugs or chemicals*
	Probable—the ADR happened within a reasonable time sequence to drug administration, and it is unlikely to be attributed to concurrent disease or other drugs or chemicals
Frequency of the ADR	Two times higher than with the standard of care *(this was specified for each ADR)**
	Three times higher than with the standard of care *(this was specified for each ADR)*

ADR adverse drug reaction

*Reference level

2.2.3 Regulators' Attitudes

For the regulators' attitudes, we assessed the influence of their beliefs about medicines and general risk perception, which were measured using the Beliefs about Medicines Questionnaire (BMQ) and the Domain-Specific Risk-Taking (DOSPERT) Scale, respectively. For the BMQ, we included the subscales of benefits (e.g., "Medicines help many people to live better lives"), harm (e.g., "People who take medicines should stop their treatment for a while every now and again"), and overuse (e.g., "Doctors use too many medicines"), each of which contains four items. Each item is scored on a 5-point Likert scale; therefore, the score of each subscale can range from 4 (strongly disagree) to 20 (strongly agree) [30]. The Cronbach alpha values for each subscale were 0.55, 0.50 and 0.66, respectively. For the DOSPERT scale, we included the domains of ethical (e.g., "Taking some questionable deductions on your income tax return"), financial (e.g., "Betting a day's income at the horse races"), health and safety (e.g., "Drinking heavily at a social function"), recreational (e.g., "Going camping in the wilderness"), and social (e.g., "Admitting that your tastes are different from those of a friend"), each of which contain six items. The items are scored on a 7-point Likert scale, and the scores can range from 6 (not at all risky) to 42 (extremely risky) per domain [31]. The Cronbach alpha values for each domain, following the above order, were 0.63, 0.81, 0.66, 0.72, and 0.70, respectively.

2.2.4 Outcome Variables and Determinants

For the first study aim, the outcomes were the regulators' opinions regarding the need to update the SmPC and to send a DHPC, and the determinant was the level of concern. For the second study aim, the outcome was the concern regarding the safety issues, and the determinants were the attributes of the safety issue, the demographic and professional characteristics, and the regulators' attitudes (Fig. 1).

2.3 Data Analyses

We used descriptive statistics for the analysis of the demographic and professional characteristics, the regulators' attitudes, the benefit-risk evaluation, and the level of concern per scenario, as well as for the calculation of the proportion of participants who considered it necessary to communicate the risk per scenario. Only those participants who completed at least one question regarding their level of concern towards the safety issue, their opinion on the need to update the SmPC, or the need to send a DHPC were included in the study.

To determine the influence of the level of concern on the need to update the SmPC or to send a DHPC, we fitted generalised linear mixed-effects models (GLMMs) with a binomial distribution and a logit link function. In these models, the level of concern was included as a fixed effect and by-subject random intercepts and slopes for the level of concern were included as random effects. Results regarding the effect of the level of concern on the need to communicate are presented as the odds ratios of updating the SmPC or sending a DHPC for a 10 percentage-point increase in the level of concern and graphically by plotting the estimated population-level probabilities of updating the SmPC or sending a DHPC against the level of concern.

To assess the effects of the attributes of the safety issue, demographic and professional characteristics, and regulators' attitudes on the level of concern, we fitted multiple linear mixed effects models. We began by fitting a crude model in which the attributes of the safety issue were included as

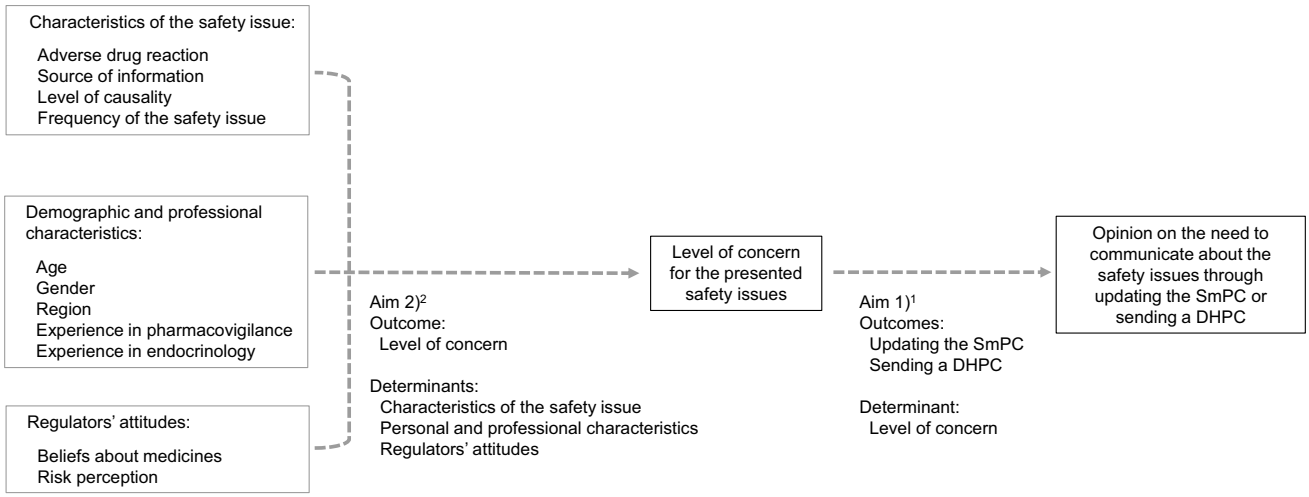

Fig. 1 Overview of the study aims, outcomes, and determinants. [1]Aim A, to explore to what extent regulators' opinions regarding the need to communicate through updating the SmPC or sending a DHPC is influenced by regulators' concern about the safety issue. [2]Aim B, to assess whether regulators' concerns are influenced by certain characteristics of the safety issue, demographic and professional characteristics of the regulators, and regulators' attitudes. *SmPC* summary of product characteristics, *DHPC* direct healthcare professional communication

the only fixed effects and by-subject random intercepts and slopes for the attributes of the safety issue were included as the random effects. Subsequently, we fitted separate follow-up models in which, while maintaining the fixed and random effects of the crude model, we added the other determinants (i.e., demographic and professional characteristics and regulators' attitudes) one by one as fixed effects. We tested for the determinants' main effect as well as all possible two-way interactions between each determinant and the attributes of the safety issue. We performed backward elimination to stepwise remove all non-significant interaction terms. Results are presented as estimated marginal means (also known as least-squares means), which reflect the predicted outcome for each level of a factor averaged over all possible combinations of the levels of the other factors in the model. They were unstratified for the crude model and stratified by demographic and professional characteristics, and by regulators' attitudes for the follow-up models. The groups of categorical variables were pre-defined by definition (e.g., women vs. men), and groups of the continuous variables were created using the score of the variable at the 25th, 50th and 75th percentiles. Further details regarding the estimated marginal means as well as the regression coefficients of each model are presented in ESM 2.

Because the sampling scheme per country could have resulted in data clusters per country, we generated a multilevel model with observations grouped by individuals nested in country. These results showed no indication of clusters (ESM 2); therefore, no adjustments for the sampling scheme were made in the statistical analysis.

The analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria; URL https://www.R-project.org/) with the packages lme4, emmeans and lmerTest [32–34]. Statistical significance was indicated by p-values less than 0.05. Figures were generated in R and Microsoft Excel® 2010 (Microsoft Corp., Redmond, WA, USA).

3 Results

The survey was sent to 327 potential participants, 255 (78%) of whom responded to at least one question in the survey, and 222 (68%) fulfilled the inclusion criteria (ESM 2). The 222 included participants were on average 46 (SD 10.8) years old, 141 (64%) were women, 88 (40%) were working for a regulatory agency in Western Europe, 92 (41%) had experience in pharmacovigilance, and 94 (42%) had experience in endocrinology (Table 2). The median score for the benefit-risk evaluation of the medicine was 80 (interquartile range (IQR) 70–90). For the beliefs about medicines, the highest median scores were reported for the belief of benefits (16; IQR 15–18) and the lowest for the belief of harm (7; IQR 5–8). The highest and lowest risk perception scores were reported for the health and safety domain (32; IQR 29–35) and for the social domain (32; IQR 11–18), respectively (Table 2).

3.1 Association Between the Opinion Regarding the Need to Communicate About the Safety Issues and the Level of Concern

The proportion of participants who considered it necessary to update the SmPC or send a DHPC ranged from 54 to

Table 2 Regulators' demographic and professional characteristics and attitudes included in the analyses

	N = 222
Demographic and professional characteristics	
Age in years, mean (SD)	46 (10.8)
Women, *n* (%)	141 (64)
Region, *n* (%)*	
Northern Europe	57 (26)
Southern Europe	48 (22)
Eastern Europe	25 (11)
Western Europe	88 (40)
Areas of expertise, *n* (%)	
Experience in pharmacovigilance	92 (41)
Experience in endocrinology	94 (42)
Regulators' attitudes, median (IQR)	
Beliefs about medicines[$]	
Benefits	16 (15–18)
Harm	7 (5–8)
Overuse	11 (9–13)
Risk perception[^]	
Ethical	30 (26–33)
Financial	29 (24–34)
Health and safety	32 (29–35)
Recreational	27 (24–32)
Social	15 (11–18)

IQR interquartile range

*Country indicates where the participant worked as a regulator. Regions were formed as follows (number of respondents per country): Northern Europe includes the countries Finland (10), Denmark (8), Ireland (8), Norway (8), Sweden (8), Latvia (7), Estonia (4), Lithuania (3), and Iceland (1). Southern Europe includes the countries Croatia (16), Italy (12), Spain (8), Portugal (6), Malta (5), Cyprus (1), Greece (0), and Slovenia (0). Eastern Europe includes the countries Slovakia (7), Bulgaria (5), Czechia (5), Hungary (4), Poland (2), and Romania (2). Western Europe includes the countries Germany (29), Austria (20), France (17), Netherlands (12), Belgium (10), Liechtenstein (0), and Luxembourg (0)

[$]Beliefs about medicines were measured with the Beliefs about Medicines Questionnaire General (BMQ-General). The BMQ-General is copyrighted (©Professor Robert Horne). Each item is scored on a 5-point Likert scale with total scores ranging from 4 (strongly disagree) to 20 (strongly agree)

[^]Risk perception was measured using the Domain-Specific Risk-Taking (DOSPERT) scale. Each item is scored on a seven-point Likert scale with total scores ranging from 6 (not at all risky) to 42 (extremely risky) per domain

Missing responses: Age = 6 (3%); Gender = 2 (1%); Country = 4 (2%); Beliefs about medicines—benefits = 15 (7%); harm = 18 (8%); overuse = 15 (7%); Risk perception—ethical = 21 (9%); financial = 17 (8%); health and safety = 21 (9%); recreational = 19 (9%); social = 16 (7%)

94% and from 25 to 74%, respectively (Fig. 2, points). More than one-third of the participants ($n = 83$; 37%) would have updated the SmPC for each of the 12 safety issues, while this was the case for 9% ($n = 20$) of the participants with respect to sending a DHPC. In the GLMM analyses, a statistically significant association between the level of concern and the probability of communicating about the safety issues was found (Fig. 2, solid lines); the odds ratios (ORs) of updating the SmPC and sending a DHPC were 13.0 (95% confidence interval (CI) 7.8–21.7) and 13.6 (95% CI 9.5–19.2), respectively, for every 10 percentage-point increase in the level of concern.

3.2 Aspects Influencing the Level of Concern

Overall, the mean level of concern was 70.6% (SD 6.0), ranging from 58.9 to 76.2% across the scenarios. The crude model showed that all attributes significantly contributed to the level of concern. With regard to the ADR, the level of concern was highest for amputations (72.2%; 95% CI 69.4–74.9), followed by DKA (70.2%; 95% CI 67.2–73.2) and bone fracture (68.0%; 95% CI 65.5–70.4). Regarding the other attributes, the level of concern was higher when information had come from clinical trials rather than from spontaneous reports or epidemiological studies (73.3%; 95% CI 71.0–75.6 vs. 67.0%; 95% CI 64.3–69.6, respectively), had a probable causality instead of a possible causality (73.8%; 95% CI 71.3–76.3 vs. 66.5%; 95% CI 64.0–68.9, respectively), and had a three times increased frequency compared to a two times increased frequency (72.9%; 95% CI 70.5–75.2 vs. 67.4%; 95% CI 65.0–69.8, respectively; Fig. 3 and ESM 2).

In the follow-up models in which the effects of the demographic and professional characteristics were assessed (Fig. 4), gender, age and region influenced the level of concern. Women, younger participants and participants working for Eastern European regulatory agencies had a higher level of concern than men, older participants and participants working for regulatory agencies in other regions. In addition, these three demographic characteristics interacted with the attribute source of information, resulting in smaller differences between genders ($p = 0.009$), age ($p = 0.015$) and regions ($p = 0.008$) if the information had come from clinical trials rather than from spontaneous reports or epidemiological studies. Furthermore, gender also interacted with the ADRs ($p < 0.001$), resulting in smaller differences between women and men when the ADRs were fractures or amputations compared to DKA. Professional characteristics, i.e., experience in pharmacovigilance and endocrinology, did not have any effect on regulators' concern or any interaction with the attributes of the safety issue.

With regard to regulators' attitudes (Fig. 5), their beliefs about the benefits of medicines interacted with the frequency of the ADR ($p = 0.007$); those with higher benefit beliefs were more concerned when the frequency of the safety issue was three times higher than the risk with the standard of

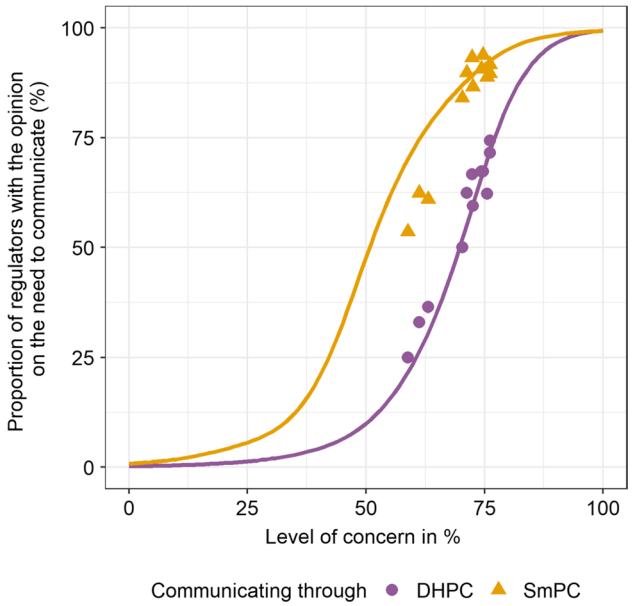

Fig. 2 Proportion of regulators communicating about various safety issues as a function of the level of concern. In the single points, proportion of regulators communicating through updating the SmPC or sending a DHPC at the mean level of concern of each scenario. In solid lines, population-level predicted probability of updating the SmPC and sending a DHPC as a function of the level of concern. *SmPC* summary of product characteristics, *DHPC* direct healthcare professional communication

care. The beliefs about the overuse of medicines ($p = 0.041$) and the financial risk perception ($p = 0.028$) were associated with a higher level of concern. The health and safety risk perceptions were associated with a higher level of concern and interacted with the source of information ($p = 0.025$); differences between participants with higher and lower health and safety risk perceptions were smaller if the information had come from clinical trials. The same interaction was shown for the social risk perception ($p = 0.020$), which also interacted with the ADR of amputations ($p = 0.027$). This interaction showed that for the amputation ADR, the higher the social risk perception, the steeper the increase in concern. The ethical risk perception interacted with the ADRs of amputations ($p = 0.013$) and bone fractures ($p = 0.046$). The level of concern of participants with higher ethical risk perception differed less across the three ADRs. The beliefs about the harm of medicines and the recreational risk perception did not have any effect on the level of concern and did not interact with any of the attributes of the safety issue. The raw models and the values of the estimated marginal means are shown in ESM 2.

4 Discussion

This study has shown that regulators' opinions regarding the need to communicate about safety issues related to a medicine for T2DM were influenced by their concern about the safety issue. The concern of regulators was influenced by the attributes of the safety issue, demographic characteristics, and their attitudes. Regulators were most concerned when the ADR was amputation, when data had come from clinical trials, when causality was assessed as probable, and when the frequency of the ADR was three times higher than with the standard of care. With regard to demographic characteristics, gender, age, and region had an effect on the level of concern. Finally, beliefs about benefits and overuse of medicines, as well as all risk-perception domains with the exception of recreational risk perception, influenced the regulators' level of concern.

The majority of the regulators considered it necessary to update the SmPC for all the presented scenarios, whereas there was more variation in regulators' opinions regarding issuing a DHPC. The high probability of

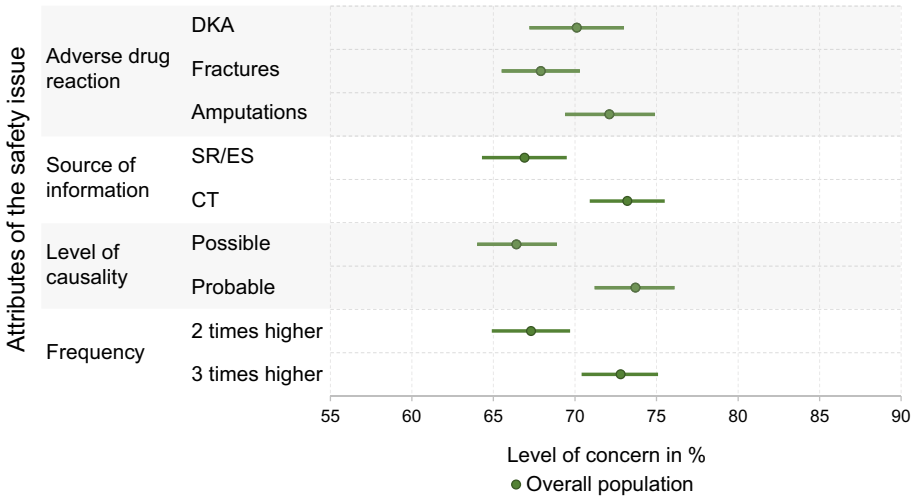

Fig. 3 Estimated marginal means of the regulators' concern with 95% CI for each attribute level for the overall population. The estimated marginal means reflect the predicted outcome for each level of a factor averaged over all possible combinations of the levels of the other factors in the model. *DKA* diabetic ketoacidosis, *SR* spontaneous reports, *ES* epidemiological studies, *CT* clinical trials, *CI* confidence interval. The complete *x*-axes ranged from 0 to 100%

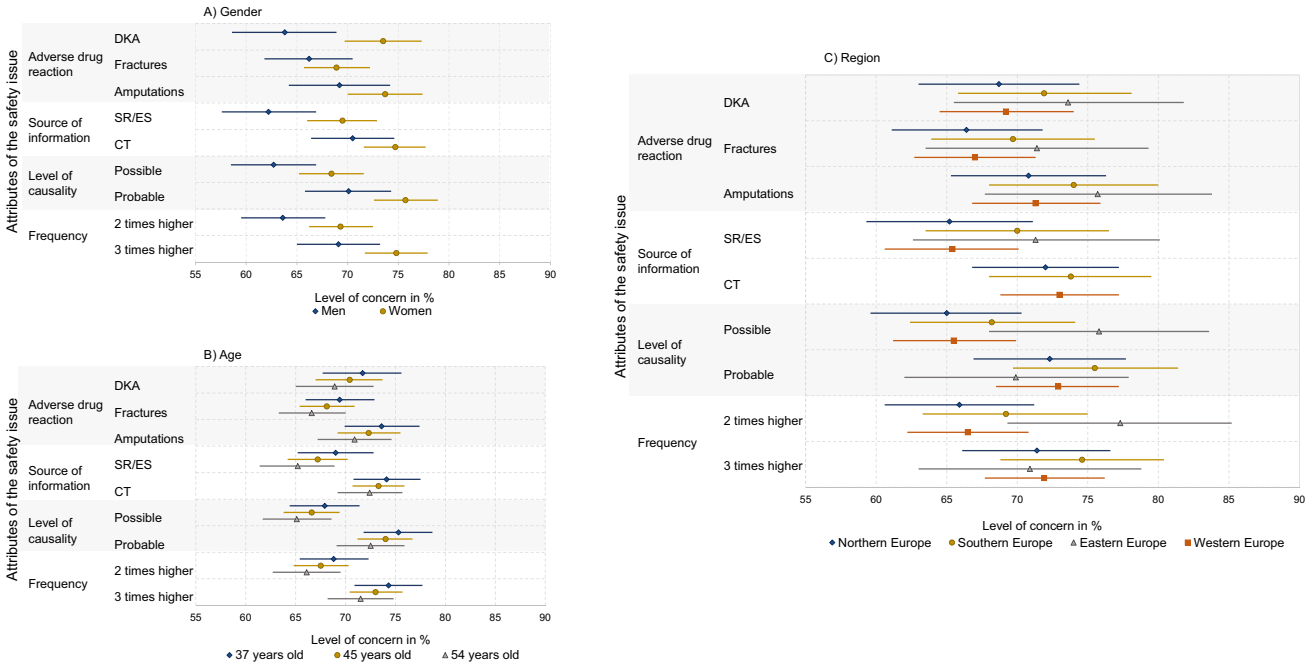

Fig. 4 Estimated marginal means of regulators' concern with 95% CI for each attribute level stratified by **A** gender, **B** age and **C** region. The estimated marginal means reflect the predicted outcome for each level of a factor averaged over all possible combinations of the levels of the other factors in the model. Regions were formed as follows: Northern Europe includes the countries Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway and Sweden. Southern Europe includes the countries Croatia, Cyprus, Greece, Italy, Malta, Portugal, Slovenia and Spain. Eastern Europe includes the countries Bulgaria, Czechia, Hungary, Poland, Romania and Slovakia. Western Europe includes the countries Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, and Netherlands. *DKA* diabetic ketoacidosis, *SR* spontaneous reports, *ES* epidemiological studies, *CT* clinical trials, *CI* confidence interval. To represent continuous variables, various groups were created using the value of the variable at the 25th, 50th and 75th percentiles. The complete *x*-axes ranged from 0 to 100%

updating the SmPC in our study is in line with the guidelines for SmPCs, which state that any ADR for which a reasonable possibility of causality can be established should be included in the SmPC [35]. The wider variation in the perceived need for sending a DHPC could be due to the fact that this action is only taken when an update of the SmPC is considered insufficient to minimise the risk and urgent communication to healthcare professionals is warranted [36]. What is considered insufficient or urgent, however, might be more ambiguous to define; in our study, this decision seemed to vary among the participants.

With regard to the attributes of the safety issue, the source of information, the level of causality, and the increased frequency of the ADR were all significant and of comparable importance, showing that regulators considered the three attributes similarly when evaluating a safety issue. Regulators were most concerned about the amputation ADR, followed by DKA and bone fractures. Although all the ADRs in the study are considered serious according to regulatory guidelines [37], there might be various reasons for the higher concern for amputations, such as permanent consequences and negative effects on patients' physical and psychological wellbeing, and the high mortality rates [38–40]. Interestingly, a qualitative study conducted among physicians in the USA and Australia found that physicians did not question the increased risk of DKA with the use of the SGLT2 inhibitors, but were more uncertain about the increased risk of amputations. Some of the reasons for the uncertainty were the low frequency of the risk and not being able to establish a physiological mechanism. Future studies are needed to assess potential differences in perspectives between physicians and regulators [41].

Regarding the demographic characteristics, our study showed that women were more concerned than men. This is in line with previous studies showing that women are generally more concerned and worried than men regarding various risks (e.g., exposure to chemicals or cancer) [42–45]. Our study has expanded this previous knowledge to the field of risk communication for medicines. Regarding age, our results showed that younger participants were more concerned than older participants. Previous studies have shown that worry regarding personal matters decreases with age [46, 47]; while we evaluated other people's risk and not personal risk, the same direction was maintained. There were also differences by region, the largest being between

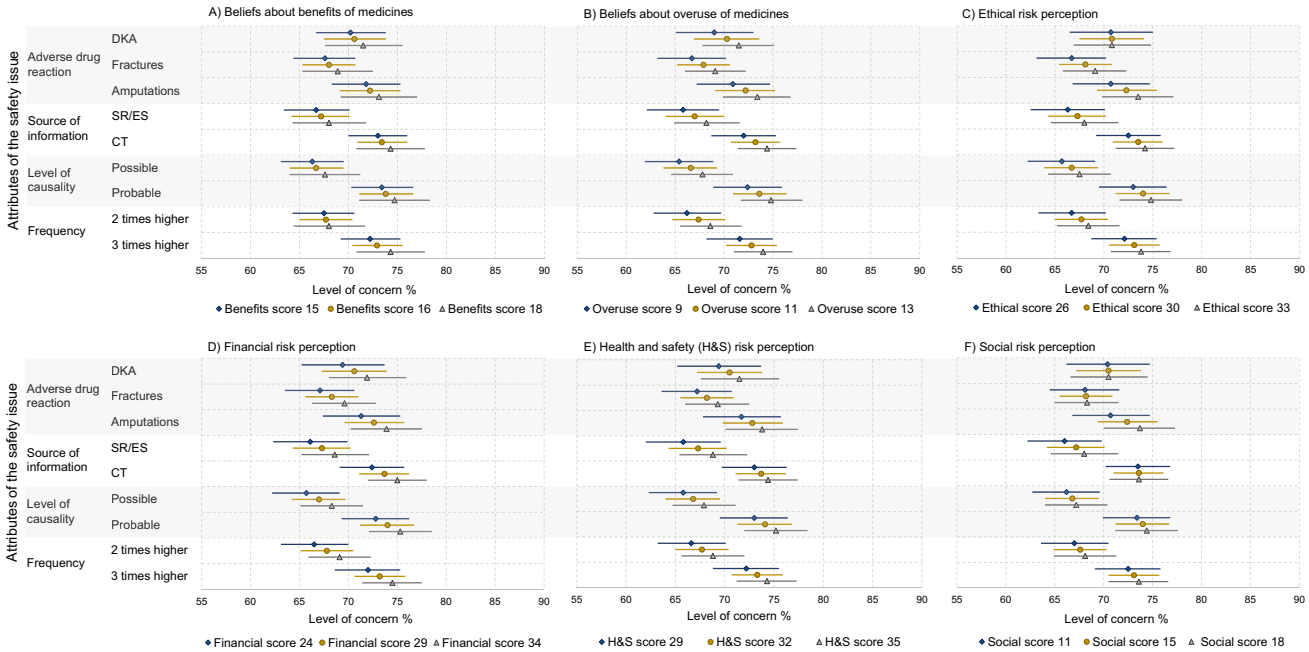

Fig. 5 Estimated marginal means of regulators' concern with 95% CI for each attribute level stratified by **A** beliefs about the benefits of medicines, **B** beliefs about the overuse of medicines, **C** ethical risk perception, **D** financial risk perception, **E** health and safety risk perception, and **f** social risk perception. The estimated marginal means reflect the predicted outcome for each level of a factor averaged over all possible combinations of the levels of the other factors in the model. *DKA* diabetic ketoacidosis, *SR* spontaneous reports, *ES* epidemiological studies, *CT* clinical trials, *CI* confidence interval. To represent continuous variables various groups were created using the value of the variable at the 25th, 50th and 75th percentiles. The complete *x*-axes ranged from 0 to 100%

Northern and Eastern Europe. This difference has been seen in previous studies in which safety communications issued by regulatory agencies around the world and in various European countries were assessed [5, 10, 48]. In these previous studies, reasons such as regional differences in the number of patients prescribed the medicines or differences in national policies were mentioned to explain the outcomes [6, 49]. While region was not the main determinant of variation in our study, it showed an effect on regulators' concern. Further research is needed to assess the causes and implications of these differences.

For the demographic characteristics of gender, age and region, there was an interaction with the source of information. Differences in concern between genders, age and regions were smaller if the information had been derived from clinical trials. Despite causality having been established independently for each scenario, clinical trials seemed to be considered a more reliable source of information. This effect might be explained by the fact that the included ADRs are natural complications of T2DM and that clinical trials include a control population, which allows better discrimination of ADRs occuring from the natural course of disease. Therefore, we cannot discard that the importance of the source of information may be different for ADRs that are not natural complications of the disease. The trend shown in this study supports historical views; clinical trials are traditionally considered a more reliable source of information than real-world evidence, obtained for example from spontaneous reports or epidemiological studies [50, 51]. As highlighted in regulatory reports, it is necessary to provide clear guidance and education regarding how real-world data can provide robust and well-trusted evidence, which will be crucial for the success of ongoing initiatives encouraging its use in regulatory decisions [52, 53].

Our study did not detect differences between regulators with and without experience in post-marketing assessments, nor between those with and without experience in endocrinology. This finding differs from those of previous studies that found experience to be relevant in medicine regulatory decisions [15, 16, 54]. A possible reason for the discrepancy might be methodological differences, as our study assessed experience as a binary variable while other studies assessed years of experience.

With regard to the regulators' attitudes, both regulators' beliefs about medicines and general risk perception were associated with their concern or interacted with the attributes of the safety issues. To our knowledge, the relationship between medicine regulatory decisions and beliefs about medicines has not been assessed previously. However, attitudes have seemed to shape individuals' actions and perceptions of benefits and risks in various areas [55–58]. In our study, beliefs about benefits and overuse of medicines had

an effect on regulators' concern, but beliefs about harm of medicines did not. Regulators' harm beliefs seemed to be lower than those observed in the general population [59, 60]. A previous study also showed that patients had more negative beliefs about medicines than medical specialists [61]. The limited variation among the regulators' scores of harm beliefs might explain the lack of effect on the level of concern for the safety issues. Higher risk perception towards most of the domains was associated with higher concern. Similar relationships have previously been found in other fields and populations [62–64]. Moreover, a study that assessed risk perception and seriousness of harm during the benefit-risk assessment of various medicines among European regulators obtained a similar outcome [16]. Our study has extended previous knowledge by showing that risk perception also can have an effect on regulators' concern for post-marketing safety issues and their opinions on the need to communicate. Nevertheless, current evidence is limited and further research regarding the extent of these effects and on explanations of the observed differences is needed.

Although there are many detailed guidelines and recommendations in place to support the European regulatory decision-making process, our study suggests that several demographic characteristics and regulators' attitudes also affect the perceived need to communicate about post-marketing safety issues. This knowledge is useful to better understand what, in addition to the use of guidelines and recommendations, can influence the regulatory decision-making process.

4.1 Strengths and Limitations

A strength of this study is the high completion rate (68%) and large sample size, including participants covering most European countries. However, while all participants in the study were involved in the assessment of human medicinal products in Europe, only a part of them were members of European committees and working parties, and thus regularly involved in actual regulatory decision-making. The main limitation of this study is that the presented cases were a simplification of the actual information assessed at the time of evaluating safety issues. As a result, participants' choices might have been different from those made in real situations. Nevertheless, the study has provided a common background and achieved its aim of assessing the heterogeneity of regulators' opinions regarding risk communication when given identical information. In addition, the study only contained three ADRs related to SGLT2 inhibitors; therefore, the results may not be generalisable to other ADRs, classes of medicines or diseases. As a general limitation of this type of studies, the results could vary depending on the levels of the attributes. To reduce such effects, we used levels that were as close as possible to those in reality. We also attempted to minimise intrinsic limitations from survey studies, such as anchoring or fatigue bias, by randomising the order in which the ADRs were presented. Finally, we explored the effect of only a limited number of characteristics and attitudes in this study. Future studies are needed to confirm our findings, evaluate the influence of possible confounding factors on the observed differences (e.g., differences in answering tendencies of the VAS), assess other potentially influencing factors (e.g., inclination for transparency, personal experience with a disease or ADR, or personality traits), and evaluate the practical relevance of the results.

5 Conclusion

Our study shows that regulators' levels of concern are associated with their opinions regarding the need to communicate about safety issues. The level of concern can be influenced by the attributes of the safety issue as well as the regulators' demographic characteristics and attitudes. These findings support current regulatory procedures that are based on guidelines for the decision-making process and involve decisions that are made by a group of experts rather than by individuals. In addition, our findings imply that a group of experts that is diverse in demographic characteristics and attitudes can ensure that various views are incorporated in deciding whether to communicate or not regarding safety issues.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-022-01270-4.

Acknowledgements The authors would like to thank the people who piloted the survey and the regulators who responded to it.

Authors' Contributions SRM, DP, STdV, HH and PM contributed to the formulation of the research question of this study and collected the data. SRM and DP analysed the data. All authors contributed to the interpretation of the data. SRM and SdV drafted the manuscript. All authors reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

Data availability The datasets generated or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Funding The study was conducted in the context of the PROMINENT project. This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement number 754425.

Conflicts of interest Sonia Roldan Munoz, Douwe Postmus, Sieta T de Vries, Liana Gross-Martirosyan, Priya Bahri, Hans Hillege, and Peter

G M Mol have no conflicts of interest relevant to the contents of this study.

Ethics approval The Medical Ethics Review Board of the University Medical Center Groningen (METc UMCG) concluded that an ethical approval was not needed for this study (reference number M21.271770).

Consent to participate The participants provided informed consent to participate in this survey study.

Data availability The datasets generated or analysed during the current study are available from the corresponding author on reasonable request.

Code availability The R scripts used for this study are available from the corresponding author on reasonable request.

Consent to publish Participants were informed that the study results would be published in a scientific journal.

Disclaimer The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the Dutch Medicines Evaluation Board, the European Medicines Agency, or any of their committees.

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