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Experiencing the risk of overutilising opioids among patients with chronic non-cancer pain in ambulatory care (ERONA): the protocol of an exploratory, randomised controlled trial

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ABSTRACT

Introduction The US opioid crisis and increasing prescription rates in Europe suggest inappropriate risk perceptions and behaviours of people who prescribe, take or advise on opioids: physicians, patients and pharmacists. Findings from cognitive and decision science in areas other than drug safety suggest that people's risk perception and behaviour can differ depending on whether they learnt about a risk through personal experience or description. Experiencing the risk of overutilising opioids among patients with chronic non-cancer pain in ambulatory care (ERONA) is the first-ever conducted trial that aims at investigating the effects of these two modes of learning on individuals' risk perception and behaviour in the long-term administration of WHO-III opioids in chronic non-cancer pain.

Methods and analysis ERONA—an exploratory, randomised controlled online survey intervention trial with two parallel arms—will examine the opioid-associated risk perception and behaviour of four groups involved in the long-term administration of WHO-III opioids: (1) family physicians, (2) physicians specialised in pain therapy, (3) patients with chronic (≥3 months) non-cancer pain and (4) pharmacists who regularly dispense narcotic substances. Participants will be randomly assigned to one of two online risk education interventions, description based or experiencebased. Both interventions will present the best medical evidence available. Participants will be queried at baseline and after intervention on their risk perception of opioids' benefit–harm ratio, their medical risk literacy and their current/intended risk behaviour (in terms of prescribing, taking or counselling, depending on study group). A follow-up will occur after 9 months, when participants will be queried on their actual risk behaviour. The study was developed by the authors and will be conducted by the market research institution IPSOS Health.

Ethics and dissemination The study was approved by the Institutional Review Board of the Max Planck Institute for Human Development. Results will be disseminated through peer-reviewed journals, conference presentations and social media.

Trial registration number DRKS00020358.

Strengths and limitations of this study

- Experiencing the risk of overutilising opioids among patients with chronic non-cancer pain in ambulatory care is the first-ever investigation of the role of description versus experience-based learning of risks and their effects on individuals' risk perception and risk behaviour in the area of drug safety.
- The evidence generated by the project will most likely influence not only future communication of risks for WHO-III opioid administration but also risk communication for other potent drugs with risks that are difficult to observe due to latency and/or rarity.
- The effectiveness of the risk information interventions partly depends on the validity, completeness and quality of existing medical evidence for WHO-III opioid administration.
- The use of non-probability sampling, while economically and logistically advantageous, may elevate the risk of self-selection bias.
- Multiple strategies will be put in place to minimise the risk of sampling, recruitment and participation bias (eg, non-respondent analysis).

INTRODUCTION

Prescribing opioids can make sense. For instance, most patients do experience adequate pain reduction when strong opioids are used to treat acute or cancer pain.[1] There is little evidence, however, for the effectiveness of strong opioids or their superiority over other analgesics in patients with chronic non-cancer pain.[2] Despite this lack of sufficient evidence,[3 4] the idea began to flourish in the US medical community in the early 1990s that opioids were effective and safe for patients with chronic non-cancer pain as well. Due to the confluence of aggressive and fraudulent marketing by the pharmaceutical industry and a healthcare system that incentivises

doctors per unit of prescription, the USA soon faced one of its worst public health crises in decades: the opioid epidemic. Each day, about 130 US citizens die of an opioid overdose;[5] in 2017 more US citizens died from an opioid overdose than from HIV-related or AIDS-related illnesses at the peak of the AIDS epidemic.[6] Although European healthcare systems appear to have been insulated from an opioid epidemic, prevalence data on prescription trend in Europe (eg, in the Netherlands[7] and Germany[8]) document considerable increases in prescriptions of strong opioids over the last decades as well. In Germany alone about 80% of all patients receiving WHO-III opioids have chronic non-cancer pain, even though national evidence and consensus-based guidelines (S3)[9] recommend against this treatment, and these patients are often opioid naive when they are directly prescribed a strong opioid.[8]

Unwarranted opioid prescriptions are part of a systemic pattern found in western healthcare systems: Despite scientific evidence suggesting otherwise, a considerable number of medical interventions continue to be endorsed in the medical literature[10] and to persist in daily clinical routine.[11] One reason for this persistence is that many physicians do not possess the knowledge required to correctly interpret medical statistics. Instead, they are misled by framing effects that arise from the use of relative—as opposed to absolute—risk formats for describing treatment effects,[12–16] have difficulty calculating the positive predictive value of tests[17–20] and are confused by other statistics.[21 22] This lack of medical risk literacy results in unrealistic views of the benefit–harm ratio of screening tests[23 24] and treatments,[25] which in turn result in undesirable variations in care[26] and avoidable adverse events in patients. Transparent statistical formats (eg, absolute instead of relative risks)[27] and visualisations (eg, fact boxes)[28 29] remedy some of the observed risk illiteracy[22 30] but do not completely eliminate it.[23 30] An explanation for this puzzling finding may come from cognitive and decision sciences, where research has shown that risk perception and behaviour can rest on whether individuals learn about a risk through personal experience or via descriptive information (eg, printed medical evidence, guidelines, patient information). Depending on whether an individual has experienced a certain risk and/or received descriptive information on the risk, they can overestimate, underestimate or correctly estimate and weigh the risk. For instance, an individual who personally experiences a rare but health-threatening risk may, for some time afterward, attribute a significantly higher probability to that risk than is objectively warranted (*recency effect*).[31 32] Conversely, if an individual experiences many episodes without a particular risk—'experience samples' are often too small to allow for observing a rare risk (eg, drug dependence)—they may behave as though they are underestimating or underweighing the risk.[33–35] In the absence of personal experience, descriptive risk information (on benefit or harm) may have an excessive psychological influence on risk perception and the corresponding health-related action (eg, lack of adherence or overenthusiasm for a drug). If an individual has both personal experience and descriptive information, personal experience—which usually feels more concrete, transparent and trustworthy (regardless of whether it actually is or not)[36]—is likely to prevail over description.[37] Simulating experience can help combat the undesired behavioural consequences of different states of knowledge about a risk. For instance, in financial decision making, investors' risk perception and behaviour improved when they learnt about the volatility and risk of a stock market investment by randomly experiencing a relevant past return distribution via an interactive simulation (simulated experience) than when they were presented with descriptive graphs depicting the investment's past returns.[38] Similarly, laypeople were better at estimating the positive predictive value of a diagnostic test when they received risk information in an experienced-based format as compared with a descriptive format.[39] To date, however, nothing is known about whether these different modes of learning about risks—also known as the *description-experience gap*[34]—would have an impact on the risk perception and behaviour of people—namely, physicians, patients and pharmacists—involved in medical settings of drug safety concerns such as long-term administration of WHO-III opioids.

In this article, we thus report the protocol of the exploratory, randomised controlled trial experiencing the risk of overutilising opioids among patients with chronic non-cancer pain in ambulatory care (ERONA), which aims to systematically investigate for the very first time in the setting of long-term administration (≥3 months) of WHO-III opioids for chronic non-cancer pain (1) whether physicians', patients' and pharmacists' current risk perception and behaviour (in terms of prescription, medication intake and counselling) depend on whether they have learnt of drug-associated risks from description and/or experience (epistemic state of knowledge); (2) whether intervening with an experience-based risk intervention (interactive simulation) or a descriptive risk intervention (fact box)—both of which provide evidence-based information on the effectiveness of long-term administration of WHO-III opioids in chronic non-cancer pain—would have different effects on these individuals' risk perception and drug-related behaviour and (3) whether individuals' risk perception and behaviour—in its initial state and in its propensity to change—is moderated by medical risk literacy. The evidence generated by our study will be relevant for risk communication not only with respect to opioid administration but also to administration of potent drugs in general, which all have associated risks that are difficult to observe and experience due to latency and/or rarity.

The project ERONA is funded by a grant from the German Federal Ministry of Health (BMG) under the guideline 'Risk perception and risk behaviour among stakeholders involved in settings of drug safety concern.'

METHODS AND ANALYSIS

Study oversight

ERONA is an exploratory, randomised controlled online survey intervention trial with two parallel groups and three primary endpoints: objective risk perception, subjective risk perception and risk behaviour. It examines the long-term administration of WHO-III opioids in chronic non-cancer pain. Randomisation will be performed as block randomisation with a 1:1 allocation. Endpoints will be measured at baseline, immediately after either intervention, and in a follow-up 9 months later. The authors of this paper developed the content and design of the study. IPSOS Health (Nuremberg, Germany) will programme the online version of this intervention trial and conduct it using national samples of family physicians, physicians specialised in pain therapy, pharmacists and patients with chronic non-cancer pain. Participant recruitment and data collection are planned to begin in April 2020 and to be completed—including the follow-up 9 months later—at the end of April 2021.

The study was approved by the Institutional Ethics Board of the Max Planck Institute for Human Development (Ethic Approval ID for pilot tests: A 2019-32; for RCT: A 2020-05) and registered at the German Register for Clinical Studies—a primary register of the International Clinical Trial Registry Platform of the WHO (http://apps.who.int/trialsearch/). The registered protocol will be constantly updated and its current state is permanently accessible without restrictions via the online platforms of the German Register for Clinical Studies and the Clinical Trial Registry Platform of the WHO. Table 1 describes ERONA on the basis of all items required by the WHO Trial Registration Data Set.

Sample frame

The sample frame will comprise accredited offline and online panels of IPSOS Health consisting of general populations of family physicians, physicians specialised in pain therapy, pharmacists and patients with chronic non-cancer pain. Using a multilayered strategy, IPSOS will recruit potentially eligible physicians and pharmacists via its panels and business directories (eg, directory of the National Association of Statutory Health Insurance Physicians) and will recruit patients by direct contact through their treating physicians, chronic pain support groups and pain prevention programmes. All participants will be reimbursed for participation by IPSOS Health.

Sample selection

The goal of ERONA is to learn about the risk perception and risk behaviour of the individuals who are directly involved in the chain of long-term administration of WHO-III opioids in chronic non-cancer pain. The following groups were identified as part of the medication process in clinical routine: (1) family physicians licensed to prescribe narcotic substances (BtM), (2) physicians specialised in pain therapy, (3) patients (≥18 years) with chronic (≥3 months) non-cancer pain and (4) pharmacists who regularly dispense narcotic substances such as strong opioids. Family physicians who are not licensed to prescribe narcotics, patients suffering from other types of pain (eg, cancer-associated or acute) and pharmacists who do not regularly dispense narcotic substances will be excluded from participation. To identify eligible participants, IPSOS Health will first screen its panels and the general population for potential candidates per group, then verify eligibility using screener questions asked by trained interviewers during an initial telephone contact. If an eligible candidate expresses interest in participating, they will be sent an email with a link to the actual online study. After clicking on the link, participants will first receive sufficient information on the study ahead. They will then be asked to provide informed consent. If informed consent is provided, they will move on to the actual online survey.

Interventions

ERONA consists of two waves (see figure 1). In the initial study phase (T1), participants will be randomly assigned to one of two interventions—a description-based or an experience-based risk information format (see figure 2)—and queried on the primary and secondary endpoints (see *Outcomes*) at baseline and immediately after the interventions via a group-specific online-based questionnaire (see *Questionnaire*). After 9 months (T2), participants will again be queried on the endpoint risk behaviour.

ERONA implements two types of intervention formats in order to test whether different modes of learning about the medical risk of WHO-III opioids differently affect participants' risk perception and risk behaviour: (a) a fact box[40] to represent a description-based risk information format (intervention 1) and (b) an interactive simulation to represent an experience-based risk information format (intervention 2; see figure 2). Both interventions (fact box, interactive simulation) present information on the benefits and harms of the WHO-III opioids in absolute risks, adjusted to the same denominator (here: per 100 people) and compared with a control group (here: non-opioids or placebo). The difference between fact boxes (intervention 1, figure 2A) and the interactive simulation (intervention 2, figure 2B) is that the first is a visual, tabular format that typically presents all information on the benefits and harms at once and in a static form for a given point in time (eg, after 6 months of therapy), whereas the latter presents information actively and sequentially over time within an 'experimental' population. For instance, the interactive simulation enables participants to directly observe how the effectiveness of opioids changes over time by moving a horizontal slider; they can also explore specific risks of interest by activating and deactivating respective buttons (see lower part of figure 2B). These differences in interactivity between the two risk information formats may—beyond potentially triggering different cognitive mechanisms—also affect how much attention participants are willing to pay to each format.

Table 1 ERONA described by items from the WHO Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	Deutsches Register Klinischer Studien DRKS00020358
Date of registration in primary registry	07 January 2020
Secondary identifying numbers	
Source(s) of monetary or material support	German Federal Ministry of Health (BMG), Max Planck Institute for Human Development (Berlin, Germany)
Primary sponsor	German Federal Ministry of Health (BMG)
Secondary sponsor(s)	Max Planck Institute for Human Development (Berlin, Germany)
Contact for public queries	OW (wegwarth@mpib-berlin.mpg.de)
Contact for scientific queries	OW (wegwarth@mpib-berlin.mpg.de) Max Planck Institute for Human Development (Berlin, Germany)
Public title	Experiencing the Risks of Overutilising Opioids Among Patients with Chronic Non-cancer Pain in Ambulatory Care
Scientific title	Experiencing the Risks of Overutilising Opioids Among Patients with Chronic Non-cancer Pain in Ambulatory Care (ERONA): an exploratory, randomised controlled trial
Countries of recruitment	Germany
Health condition(s) or problem(s) studied	Long-term administration of WHO-III opioids in chronic non-cancer pain
Intervention(s)	Educational interventions: experience-based (interactive simulation) versus description-based (fact box) risk intervention presenting medical evidence on the benefit–harm ratio of WHO-III opioids Comparator: Baseline for within-group comparisons, description-based risk intervention for between-group comparisons
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion criteria: (1) family physicians licensed to prescribe narcotic substances (BtM), (2) physicians specialised in pain therapy, (3) patients (≥18 years) with chronic (≥3 months) non-cancer pain and (4) pharmacists regularly dispensing narcotic substances such as strong opioids Exclusion criteria: family physicians not licensed to prescribe narcotic substances, patients suffering from cancer-associated or acute pain and pharmacists not regularly dispensing narcotic substances
Study type	Interventional Allocation: block randomisation. Parallel assignment masking: blind to subject Primary purpose: increase of risk literacy in the context of drug safety concerns
Anticipated date of first enrolment	April 2020
Anticipated date of completion of data collection (including follow-up)	April 2021
Target sample size	4×300 = 1200
Recruitment status	Recruiting
Primary outcome(s)	(a) Objective risk perception; (b) subjective risk perception; (c) risk behaviour (physicians=prescription behaviour, patients=intake behaviour, pharmacists=counselling behaviour)
Key secondary outcomes	(a) Differences in risk perception and behaviour as a function of how a person learnt about the risks; (b) differences in risk perception and behaviour as a function of an individual's medical risk literacy; (c) concordance between actual risk behaviour reported at 9-month follow-up and intended change in risk behaviour reported immediately after the intervention

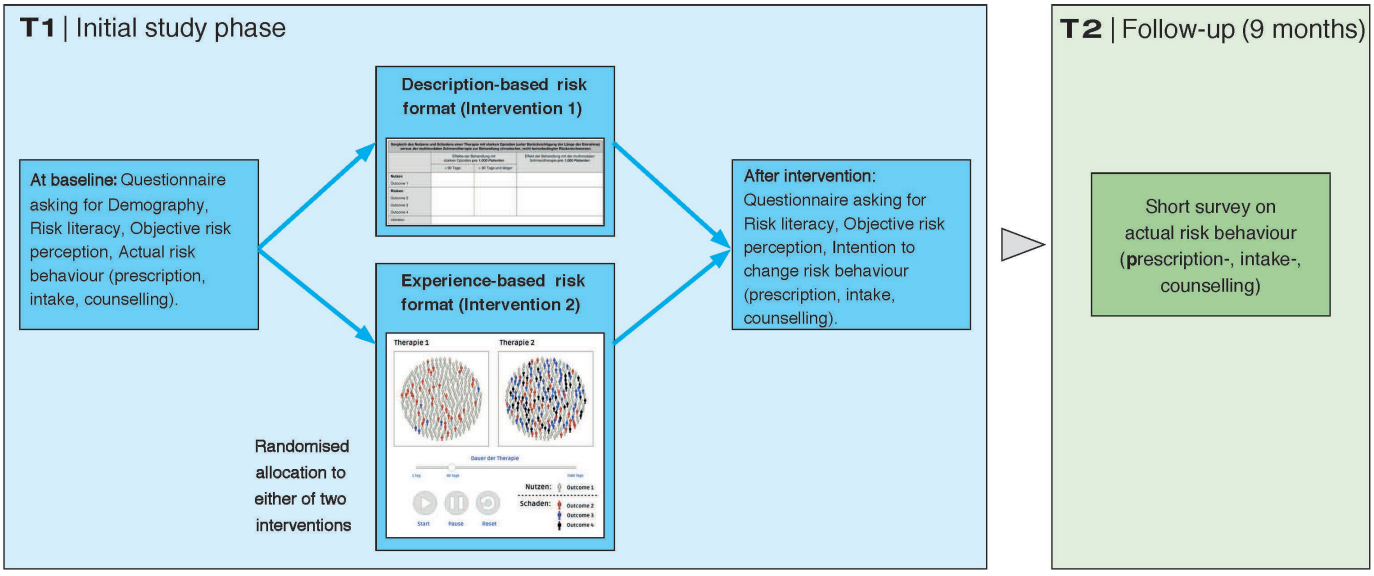


Figure 1 Study design of the exploratory, randomised controlled trial experiencing the risk of overutilising opioids among patients with chronic non-cancer pain in ambulatory care.

To counteract this potential problem, the fact box format will be set up as a Mouselab (E J Johnson, Monitoring information processing and decisions: The mouselab system, 1991), in which all information continues to be presented in a static form for a given point in time but, instead of presenting all information at once, requires participants to access the numerical information on the benefits and harms by moving the mouse pointer over the respective boxes on the screen. To prevent participants from abandoning risk information interventions prematurely, the move-on button will be deactivated for 3 min.

Both formats provide the best available medical evidence—retrieved through a systematic rapid review[41] by the Institute for Evidence in Medicine (for the Cochrane Germany Foundation)—on the effectiveness of long-term administration of WHO-III opioids in chronic non-cancer pain compared with either non-opioids or a placebo, depending on the availability of valid data. The rapid review approach implements the established methods of a systematic review—including assessing the risk of performance or selection bias, data synthesis/meta-analysis and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence (eg, publication and indirectness bias)—while delivering a final product in a timely manner using evidence summaries. As the project was funded under a guideline concerning risk perception and risk behaviour in settings of drug safety concern, one of the main objectives of the evidence synthesis for the long-term use of WHO-III opioids was to identify and evaluate studies that provide numerical information not only on benefits but also on harms and that also report endpoints for 3 months and longer. The reason for selecting this time frame is that currently no sufficient evidence supports a use of (strong) WHO-III opioids in patients with chronic non-cancer pain in terms of meaningful benefits over the point of 3 months but evidence that indicates considerable harms (eg, drug dependence). For this reason, German medical guidelines generally recommend against administration of (strong) WHO-III opioids for longer than 3 months. Exceptions are made for clearly defined, substantiated indications (eg, lower back pain, when other analgesics have proved to be ineffective), but caution is advised and these exceptions are associated with a number of requirements (eg, regular psychological assessment, continuous offering of alternatives) as the fact remains that WHO-III opioids are associated with considerable harms. So even for the few substantiated indications the goal is to move away from the administration of strong opioids as soon as possible and to find an alternative therapy.

Based on a systematic evidence synthesis that included a screening of more than 10 000 studies, a team of experts from anaesthesiology, biostatistics, cognitive science and drug safety agreed on the presentation of the following six endpoints: (1) reduction in pain (30% or more), (2) improvement of physical function (30% or more), (3) risk of falls including fractures, (4) risk of drug abuse including addiction, (5) risk of dizziness and (6) side effects such as obstipation, nausea and vomiting.

To ensure a reasonable operationalisation of endpoints (eg, when asking for objective risk estimations) and valid intervention formats that present precise numerical risk information on benefits and harms, the focus of ERONA was narrowed to long-term administration of WHO-III opioids in the context of chronic non-cancer pain (ICD-10: R52.1, R52.2, 52.9, M 54.9), particularly in light of this being a major drug safety concern.

Survey questionnaire

Characteristics of participants (eg, age, gender, education (patients)), years of profession (physicians/pharmacists))

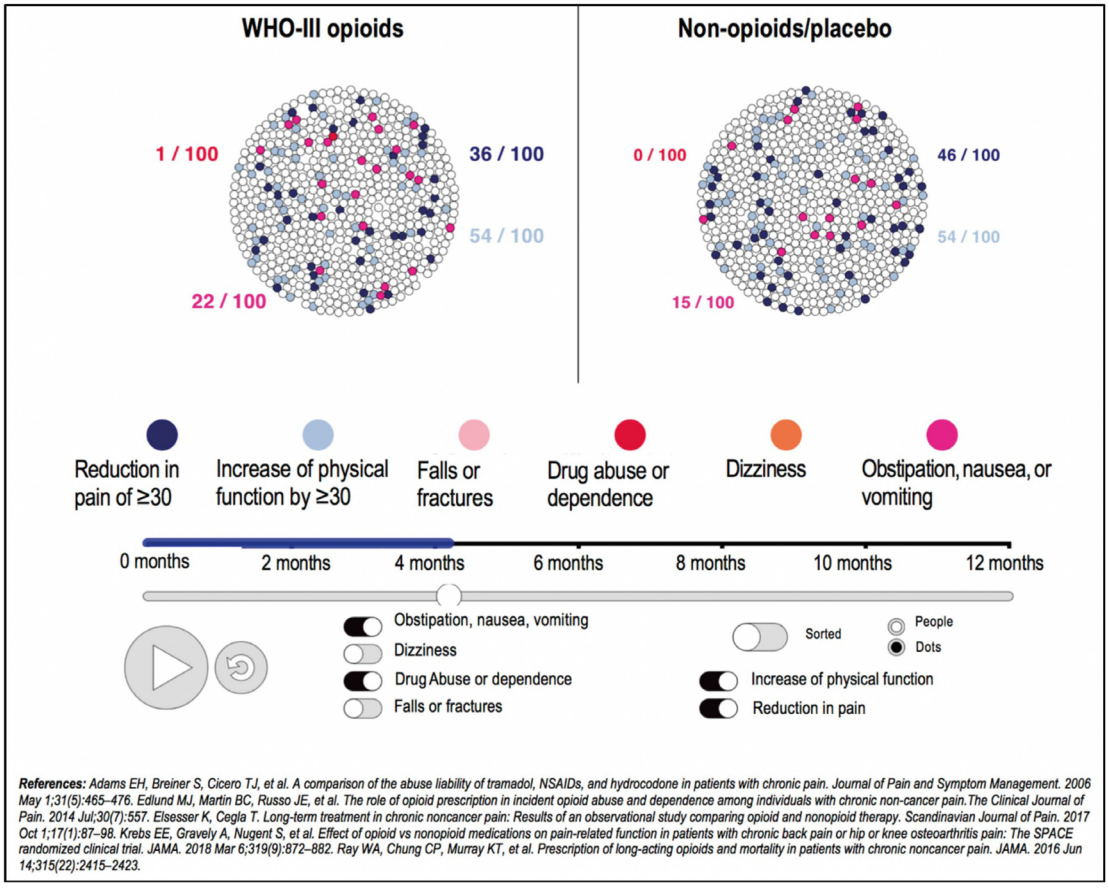
Figure 2A.

Benefits and harms of a therapy with WHO-III opioids or non-opioids/placebo for treating chronic noncancer pain. *All numbers refer to patients who took either therapy for 6 months or longer.*

	100 with WHO-III opioiden	*100 Non-opioids or placebo*
Benefits		
How many patients report a reduction in pain of 30% or more?	41	54
How many patients report an increase in physical function of 30% or more?	60	60
Harms		
How many patients experience falls and, as a consequence, fractures?	8	8
How many patients misuse the drug and potentially become addicted?	6	1
How many patients suffer from dizziness?	27	6
How many report side effects such as obstipation, nausea, or vomiting?	65	45

References: *Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. Journal of Pain and Symptom Management. 2006 May 1;31(5):465–476. Edlund MJ, Martin BC, Russo JE, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic non-cancer pain.The Clinical Journal of Pain. 2014 Jul;30(7):557. Elsesser K, Cegla T. Long-term treatment in chronic noncancer pain: Results of an observational study comparing opioid and nonopioid therapy. Scandinavian Journal of Pain. 2017 Oct 1;17(1):87–98. Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. JAMA. 2018 Mar 6;319(9):872–882. Ray WA, Chung CP, Murray KT, et al. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA. 2016 Jun 14;315(22):2415–2423.*

Figure 2B.



References: *Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. Journal of Pain and Symptom Management. 2006 May 1;31(5):465–476. Edlund MJ, Martin BC, Russo JE, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic non-cancer pain.The Clinical Journal of Pain. 2014 Jul;30(7):557. Elsesser K, Cegla T. Long-term treatment in chronic noncancer pain: Results of an observational study comparing opioid and nonopioid therapy. Scandinavian Journal of Pain. 2017 Oct 1;17(1):87–98. Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. JAMA. 2018 Mar 6;319(9):872–882. Ray WA, Chung CP, Murray KT, et al. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA. 2016 Jun 14;315(22):2415–2423.*

Figure 2 Examples of the two risk information formats: (A) description-based format (fact box) and (B) experience-based format (interactive simulation).

will be obtained prior to administering the survey questionnaires. Participants will be queried by a group-specific questionnaire at three points in time (figure 1): at baseline, immediately after intervention, and in a follow-up 9 months later. At baseline the following aspects will be covered: (a) origin (experience/description) of participants' current state of knowledge of specified outcomes of benefits and harms of long-term WHO-III opioid administration in the setting of chronic non-cancer pain; (b) participants' objective risk perception, operationalised by questions such as 'How many people out of 100 taking WHO-III opioids for 3 months or longer, do you think, will experience a reduction in pain of at least 30% or more?'; (c) participants' subjective risk perception, measured using a 5-point Likert Scale ranging from 'the benefits of WHO-III opioids clearly outweigh the harms' to 'the harms of WHO-III opioids clearly outweigh the benefits'; (d) participants' medical risk literacy, investigated via an adapted version of the validated Critical Risk Interpretation Test[42] and (e) participants' risk behaviour (physicians: prescription behaviour, patients: intake behaviour, pharmacists: counselling behaviour). Patients and physicians will also be asked about some group-specific aspects. In the case of patients, we additionally aim to learn about the medical discipline of the practitioner who first prescribed the WHO-III opioid, what condition the patients are being treated for with the opioids, whether they had tried therapies other than opioids first (and if so, which), and to what extent patients' current level of pain impairs their quality of life (validated Korff Scale).[43] For physicians, we intend to learn which WHO-III substances they prescribe and how often, and what emotional factors (eg, feeling helpless in the presence of a patient suffering from chronic pain) may influence their choice to prescribe strong opioids in spite of medical evidence indicating that they should not. After the intervention, all participants will be queried again on their objective risk perception and asked whether they intend to change their current prescription behaviour, intake behaviour or counselling behaviour. In a follow-up 9 months later participants will once again be asked for their actual prescription behaviour, intake behaviour or counselling behaviour in order to ascertain the longevity of effects of each of the risk information interventions. Each outcome—except medical risk literacy—will be measured by a series of questions developed by the authors for the purpose of the study. To ensure comprehensiveness, the content of the study was piloted with members of each target population and, if necessary, be revised on the basis of feedback from these participants.

Outcomes measures

Primary endpoints for analysis between the two arms of interventions and within each group of intervention are the differences in (a) objective risk perception (categorical), (b) subjective risk perception (continuous) and (c) risk behaviour (categorical). Objective risk perception will be measured—at baseline and directly after intervention—through a series of questions on the benefits and harms of long-term administration of WHO-III opioids in chronic non-cancer pain. The proportion of correct responses will be dichotomised into ≤/>50% of questions correct for analysis. Actual risk behaviour—measured at baseline and 9 months later—will be operationalised through a series of questions investigating the current prescription behaviour of physicians, opioid intake behaviour of patients and counselling on opioids in pharmacists. The endpoint is dichotomised by the proportion of people reporting a behaviour favouring/not favouring opioids.

Secondary outcomes for analysis between the two arms of interventions are (a) the differences in risk perception and behaviour as a function of how a person learnt about the risks (categorical) and (b) differences in risk perception and behaviour as a function of an individual's medical risk literacy (continuous). Secondary outcomes for analysis within each intervention arm are the concordance (categorical) between actual risk behaviour reported after 9 months and the intended change in risk behaviour reported immediately after the intervention. We will also report descriptive information—measured at baseline—on potential emotional aspects affecting physicians' long-term administration of opioids (categorical) and on patients' levels of impaired quality of life due to pain (continuous) and explore whether and how these aspects influence the prescription habits of physicians and the intake behaviour of patients and their responses to the intervention, respectively.

Sample size

We aim to survey national samples that are roughly representative of each of the target groups in the general population. Because ERONA is the first-ever comparative investigation of the role of description versus experience-based learning of risks and their effects on individuals' risk perception and risk behaviour in the setting of drug safety concerns, no evidence from other studies currently exists to inform effect size estimates, meaning that all basic effect sizes had to be estimated. In other settings, where either fact boxes were compared with interventions other than an interactive simulation or an interactive simulation with an intervention other than a fact box, differences between formats ranging from 12.0% to 43.5% were observed.[28 44 45] To be on the conservative side, our sample size calculation uses the lower bound of the effect sizes found in other settings. For between-intervention group comparisons, to detect a 15% difference between the two intervention groups in their final risk behaviour (eg, reduction in patients taking WHO-III opioids)—currently assumed to be 50% in the description-based intervention group and 35% in the experience-based intervention group—and tested at a two-sided 5% level with a power of 80% at a 1:1 division (experience vs description), 150 participants are needed per arm. For the within-intervention group comparisons, to detect a minimum 15% absolute increase

in 'objective risk perception' (measured by a set of questions on participants' estimates of benefits and harm outcomes and dichotomised by a cut-off of ≤/>50% of questions correct) from a currently assumed proportion of 20% of participants per group answering more than 50% of risk perception questions correctly at baseline to 35% after either intervention, tested at a two-sided 5% level with a power of 80%, 122 study participants in each arm are needed. Furthermore, to detect a 15% difference (from an assumed proportion of 65% of participants favouring WHO-III opioids at baseline to 50% after intervention) between the initially reported risk behaviour at baseline and the intended risk behaviour right after the intervention (measured by a series of questions on intended behaviour and dichotomised by an intended/not intended change), tested at a two-sided 5% level with a power of 80%, 150 study participants in each arm are needed. If both endpoints are tested simultaneously (in a hierarchical test procedure), a total of 300 participants per study group are required for answering both questions. To allow for non-response and ineligibility on invitation, IPSOS Health will factor this number by 6 and draw four random samples of about 1800 participants per group from their panels.

Data analysis plan

To ensure completeness of data, the online questionnaire will not allow for item non-response. Multiple responses from single participants will be managed using a deduplication procedure for online surveys.[46] Categorical data will be descriptively analysed by frequency distributions and percentages. For continuous data, measures of central tendency and variability will be used where values are normally distributed, whereas medians and the IQR will be used to describe data that are not normally distributed. Differences between groups (eg, between the two intervention groups per study population) will be assessed using independent sample t-tests or Mann-Whitney U tests (for continuous variables), χ^2 tests (for categorical variables) and analysis of variance or Kruskal-Wallis tests (where more than two groups are being compared). Independent predictors (eg, risk literacy) of risk perception and risk behaviour (eg, long-term opioid administration) will be identified by using regression analysis. Data will be stored and analysed with IBM SPSS Statistics V.26.

To control for non-response bias,[47] we will collect information about sex, age and education/professional experience of participants who do not complete the survey or do not respond to the survey invitation and compare their characteristics with the characteristics of those who responded to the survey.

Patient involvement

Patients (n=18) with chronic non-cancer pain and long-term WHO-III opioid intake (>3 months)—recruited from the outpatient pain clinic of the Charité—Universitätsmedizin Berlin (n=13) and practices of family medicine physicians (n=5), respectively—participated in assessing the phrasing of the questionnaire (n=13) and the comprehensibility of the educational interventions (n=5). There is no plan to involve patients in the recruitment process and in conducting the study. It is planned to disseminate results of the trial to patients via social and print media and via direct contacts to patient groups consisting of patient with chronic non-cancer pain.

ETHICS AND DISSEMINATION

The exploratory, randomised controlled trial ERONA has been approved by the independent Institutional Ethics Board of the Max Planck Institute for Human Development, Berlin (Germany) (Ethic Approval ID for pilot tests: A 2019-32; for RCT: A 2020-05) and will be conducted in accordance with the international standards of the Declaration of Helsinki, the Ethical Principals of Psychologists and the Code of Conduct of the American Psychological Association. An information sheet explaining the purpose and procedure in detail will preface each survey; informed consent will be obtained online from each participant immediately thereafter and before the participant enters the actual online survey. The content of the trial was developed by authors of this paper. Data will be analysed by the authors. Data will be collected by the independent market research institution IPSOS Health (Nuremberg, Germany). IPSOS Health will assign codes to each participant during data collection to ensure that no personally identifiable information of participants will become available to the authors of this trial when receiving the final data sheets after study completion. The separation of data collection (IPSOS Health) from data analysis/data dissemination (authors of the paper) thereby ensures high-stake data security and anonymity for each individual participating in our study.

The findings of our trial will be disseminated using a multilayered strategy for addressing both the academic community and the general public. For the academic community, we will publish all relevant data in an open-access repository (Open Science Framework, https://osf.io) and in peer-reviewed journals and present our findings at national and international conferences. To reach out to the general public, we will use social media (eg, Facebook, Twitter), print media (eg, newspapers), broadcast media (eg, radio, television) and patient/stakeholder engagement activities (eg, patient forums, stakeholder meetings).

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