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Registry study of immune-related adverse events using electronic patient-reported outcome in patients with cancer receiving immune checkpoint inhibitors: protocol for a multicenter cohort study

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ABSTRACT

Introduction: The use of immune checkpoint inhibitors (ICIs) is rapidly expanding in cancer treatment. ICI has a unique safety profile, known as immune-related adverse events (irAEs). The safety profile of ICIs lacks patient experience and perspectives. This study primarily aims to obtain a database for descriptive research on the status of irAEs using the Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) in patients with gastrointestinal cancer, lung cancer, and malignant pleural mesothelioma treated with regimens containing ICIs.

Methods and analysis: This is an ongoing, multicentre, observational study. Eligible patients must be aged at least 20 years and have been diagnosed with lung cancer, malignant pleural mesothelioma, or gastrointestinal cancer and plan to use ICIs. Participants will install the ePRO application and report adverse events via ePRO using PRO-CTCAE once weekly for up to 48 weeks. In addition, a registry will be established using background information obtained from medical records. The sample size is determined by one-year projection without using statistical methods. Statistical analyses will include point estimates and 95% confidence intervals for the incidence of each adverse event by cancer type and regimen at each time point.

Ethics and dissemination: This research will be conducted per the Declaration of Helsinki, the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, and the revised Personal Information Protection Law. The study protocol was approved by the Ethics Committee (approval ID T2021-0180) of Tokyo Medical University Hospital on October 15, 2021.

Registration details: The study began enrolling patients in December 2021. The target enrolment is 260; as of October 2022, 141 have been enrolled, and the enrolment is scheduled to end on June 30, 2023.

Trial registration number: UMIN000046418

STRENGTHS AND LIMITATIONS OF THE STUDY

- Insufficient information on symptom-related adverse events of regimens containing immune checkpoint inhibitors can be clarified.
- Multiple insights into adverse event monitoring using PRO-CTCAE via ePRO, which can collect adverse events in real-time without patient visits in Japanese clinical practice settings, can be provided.
- The selected items of PRO-CTCAE in this study were determined by reviewing previous literature and Japanese drug package inserts and discussed by the board-certified oncology pharmacy specialist and through patient public involvement.
- A limitation of this study is that patients cannot be evaluated for PRO-CTCAE items not selected by the investigator at the time of planning. Not all patient-reported safety profiles are available.

INTRODUCTION

In 2017, the number of malignant tumour (cancer) patients and deaths worldwide were 24.5 million and 9.6 million, respectively.[1] The number of cancer patients in Japan was 775,601 in 2009.[2] Cancer treatment centres on surgery, drug therapy, and radiation therapy. Recently, immunotherapy has attracted attention, and insurance coverage for immune checkpoint inhibitors (ICIs) is rapidly expanding. The following cancer types are currently covered by insurance in Japan: non-small cell lung cancer, small cell lung cancer, malignant pleural mesothelioma, oesophageal cancer, gastric cancer, colorectal cancer, hepatocellular cancer, head and neck cancer, breast cancer, cervical cancer, uterine cancer, urothelial cancer, renal cancer, melanoma, solid tumours with high microsatellite instability-high (MSI-H), tumour mutational burden-high (TMB-H), and Hodgkin's lymphoma. Among the cancers for which ICI is indicated, in which respiratory and gastrointestinal cancers are the most common, 103,715 cases were lung cancer, 122,632 gastric cancer, 116,342 colorectal cancer, 48,003 liver cancer, and 20,787 oesophagus cancer in 2009 in Japan.[2]

Adverse events in ICI treatment differ from those of conventional cytotoxic anticancer and molecular-targeted drugs in that they may present with specific autoimmune-like immune-related adverse events (irAEs).[3] Although irAEs are relatively common in the skin, gastrointestinal tract, liver, lung, and endocrine organs, they can theoretically occur anywhere in the body.[4] IrAEs can occur at any time after the start and even after the completion of ICI administration.[5] Ipilimumab is reported to cause more skin irAEs after 2–3 weeks, gastrointestinal and hepatic after 6–7 weeks, and endocrinal after 9 weeks.[6] In contrast, nivolumab is reported to cause more skin irAEs after 5 weeks; gastrointestinal, hepatic, and pulmonary after 7–8 weeks, endocrinal after 10 weeks, and renal after 15 weeks.[7] However, most irAEs were reported to occur within 6 months of prolonged treatment with nivolumab and were not cumulative.[8] Although careful monitoring is

recommended after ICI administration, there is no settled opinion on the monitoring period. IrAEs should be monitored by a physician or a physician's assistant. The response varies by organ, but as a general rule, the administration should be postponed or interrupted when ≥ Grade 2 is reached; systemic corticosteroids should be considered. After starting treatment with steroids, it is recommended that they be tapered off over several weeks while checking for irAE recurrence and subsequently discontinued or adjusted to a low-maintenance dose.[9, 10]

Patient-reported outcome (PRO) is defined as 'an evaluation method in which patients judge their symptoms and quality of life; the results are obtained without any intervention from doctors or other parties' by the Food and Drug Administration.[11] In recent years, adverse events assessment using PROs has gained prominence in oncology. Basch et al.[12] reported that adverse event assessments in providers and patients are inconsistent, with a tendency for providers to underestimate them. This problem led to the development of a PRO version of the Common Terminology Criteria for Adverse Events (CTCAE), PRO-CTCAE, in 2008. In a randomised controlled trial, a comparison of the pro-active approach with PRO-CTCAE using electronic PRO (ePRO) for adverse events with a conventional adverse event evaluation showed a significant difference in health-related quality of life and overall survival.[13] This study has attracted attention as a trial that will change clinical practice. The results have led to the use of PRO-CTCAE in many countries, including Japan.

Early detection and monitoring of irAEs are important, and PROs are useful.[14] However, Tolstrup et al.[15] noted that the procedure for selecting PRO-CTCAE items in patients receiving immunotherapy is not well established. They reported a method for selecting PRO-CTCAE questions for patients with malignant melanoma receiving immunotherapy. Studies of PRO-CTCAE in ICI-using patients have been reported in malignant melanoma and non-small cell lung cancer.[16, 17] Based on these studies, the

PRO-CTCAE is used as a questionnaire to evaluate irAE; however, few studies on irAE and PRO-CTCAE are available.

The present study, named RESPECT (REgistry Study of immune-related adverse events using electronic Patient-reported outcome in patiEnts with cancer receiving immune CheckpoinT inhibitors) study, aims to obtain a database for descriptive research on the status of irAEs, focusing on symptom-related adverse events in patients with cancer receiving regimens that include ICIs. In addition, it aims to determine the rate of symptom-related adverse events at each time point in the setting in which ePRO adverse event monitoring is performed.

METHODS AND ANALYSIS

Study design

This is an ongoing, multicentre, longitudinal, observational study. An observational study design is used to track the mode and course of irAEs, focusing on symptom-related adverse events. Participants will install the ePRO application and report adverse events weekly via ePRO using PRO-CTCAE. In addition, a registry will be established using background information obtained from medical records; ancillary studies will be conducted on the proportion of adverse event reporting by ePRO and those associated with ICIs.

Patient and public involvement

The following two patient groups were asked to cooperate in participation: Non-Profit Organization Lung Cancer Patients Association One Step and General Incorporated Association Esophageal Cancer Survivor's Sharing. The research plan will include the advice given on PRO-CTCAE item selection, number of questions, and survey frequency. Advice will also be obtained at each stage of the process leading up to the publication of the results.

Study setting, participants, and recruitment

Recruitment is being performed at nine hospitals in Japan. The inclusion criterion is the diagnosis of lung cancer, malignant pleural mesothelioma, or gastrointestinal cancer in patients who plan to use an ICI and give their written consent to participate in the study, over 20 years old, and with Eastern Collaborative Oncology Group Performance Status (ECOG PS) of 0–3. Patients who do not have an ePRO-eligible device, have a severe psychiatric illness or cognitive dysfunction that affects filling out the survey form, or those with a native language that is not Japanese are excluded. The study pharmacist will invite eligible patients to participate in the study at each site. After starting treatment, participants will complete weekly ePROs, an adverse events monitoring questionnaires at week 12, and treatment satisfaction questionnaires at weeks 24 and 48. Observation shall be discontinued in the following cases: (1) if the participant requests to discontinue the adverse event evaluation using ePRO, (2) when follow-up is no longer possible due to hospital transfer, (3) death during follow-up, (4) if consent is withdrawn, and (5) loss to follow-up.

Outcome measures

Supplementary Table S1 shows the study schedule. We will use the PRO-CTCAE and the CTCAE v5.0 to assess adverse events. In addition, we will use Cancer Therapy Satisfaction Questionnaire (CTSQ) to assess treatment satisfaction.

Adverse events

Adverse events will be assessed using CTCAE v5.0, translated by the Japan Clinical Oncology Group as Clinician-Reported Outcome (ClinRO), and PRO-CTCAE as PRO. Since its development as a common toxicity criterion in 1984, the CTCAE has been the gold

standard as ClinRO for adverse event assessment and is widely used in clinical research, particularly in the field of oncology. The CTCAE v5.0 will be recorded from the medical record each time they are assessed; items corresponding to PRO-CTCAE will be mandatory. Meanwhile, the PRO-CTCAE, developed by the National Cancer Institute in 2008, consists of 80 items from the CTCAE version 4, extracting 78 symptoms that can be subjectively assessed by the patients and has been reworded to make them easier for patients to answer. Each item is assessed using one or more attributes, including presence/absence, frequency, severity, and/or interference with usual or daily activities. The original version has been evaluated for validity and reliability by Dueck et al.[18] The Japanese version of PRO-CTCAE has been validated for linguistic and psychometric validity by Miyaji et al.[19] and Kawaguchi et al.[20], respectively.

Treatment satisfaction

The CTSQ is a 16-item questionnaire developed by Pfizer to measure treatment satisfaction specifically with cancer treatment. It has three subscales, 'Expectations of Treatment', 'Feelings about Side Effects', and 'Satisfaction with Therapy', which are scored from 0 to 100. Higher scores indicate higher satisfaction. This questionnaire has been validated by Abetz et al.[21]

Sample size determination

The sample size was not calculated based on a statistical perspective. Considering the annual number of patients treated with ICIs at each site and the proportion of smartphone or tablet ownership for ePRO, and obtaining consent, a target enrolment number of at least 260 patients per year was set.

Data collection and timeline

The researcher will perform web registration for the participants' data using the electronic data capture (EDC) system, Viedoc 4 (Viedoc Technologies, Sweden). Participants will respond to the PROs using 3H P-Guardian (3H Clinical Trial Inc, Japan), an ePRO application, on their own device (smartphone or tablet) at 49 time points: at baseline and weeks 1–48 after initiating ICI therapy. The investigator will explain the details of this research to the patient. After obtaining patient consent, data on psychosocial background and PRO-CTCAE will be collected from the participant's electronic device. Data on demographics, medical history, and CTCAE v5.0- JCOG scores will be collected and entered into EDC and linked to baseline PRO data. An investigator will check ePRO data within the scope of daily practice and contact participants depending on the input status. They will also be asked to record treatment satisfaction at weeks 24 and 48. The investigator will then assess each participant's adverse events using CTCAE on the day of the presentation or during hospitalisation. Adverse event assessment using CTCAE and PRO-CTCAE will continue after treatment with ICI is discontinued. The study timeline is shown in Supplementary Table S1.

Data monitoring

The data centre is located at the Tohoku Graduate School of Medicine (Miyagi Prefecture, Japan). To protect participants' privacy, no personally identifiable information will be entered into the EDC. Data management and central data monitoring will be performed using the EDC. Establishment of a data monitoring committee and auditing is not planned for this study. Following the data entry of this study, the fixed data will be exported and deleted from the EDC and will be stored in the research office in electronic media for at least 10 years after the principal publication.

Harm

This is a non-interventional, non-invasive, observational study. Therefore, the burden on the participants is minimal. Participant contributions for time spent filling out questionnaires, installing applications, and communication costs for data transmission will be explained in writing and verbally in the consent explanation. Consent will be fully explained before enrolment, and participants can withdraw even while the questionnaire is being filled out.

Statistical analysis

The primary purpose is to obtain a database for descriptive research on the actual status of irAEs, focusing on symptom-related adverse events in patients with cancer receiving regimens that include ICIs. Furthermore, we aim to determine the incidence of symptom-related adverse events at each time point in an environment where ePRO-based adverse event monitoring is conducted in daily practice. Point estimates and 95% confidence intervals of the incidence of each adverse event at each time point by cancer type and regimen will be estimated. The treatment of missing values will not be specified in advance. In addition, we will examine the association between symptom-related adverse events and the extent of pharmacist actions and summarise the ePRO completion rate using descriptive statistics as the reality of pharmacist actions for PRO-CTCAEs.

ETHICS AND DISSEMINATION

Research ethical approval

This research will be conducted per the Declaration of Helsinki, the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and

Welfare, and the revised Personal Information Protection Law. The protocol was approved by the Ethics Committee of Tokyo Medical University Hospital (approval ID T2021-0180) on October 15, 2021. The version of the protocol became 1.1 in March 2022. The protocol has been reviewed by the Institutional Review Boards of the following research centres. Juntendo University Nerima Hospital, JR Tokyo General Hospital, Nippon Medical School Hospital, Kyorin University Hospital, Teine Keijinkai Hospital, Nihon University Itabashi Hospital, University of Miyazaki Hospital and Japanese Red Cross Tokushima Hospital.

Consent

The researchers will give the patients an informed consent form and explain the details of the study before enrolment. The participant's request to withdraw consent during or after the study will be accepted without any disadvantage.

Access to data

Investigators may use the EDC to review only case data collected at their site. In addition, only the data administrator at the data centre has access to the case data entered from each research site through the EDC.

Confidentiality

Three types of personal information will be used in this study: medical record number, date of birth, and initials, which are the minimum required for identification and inquiry of the participant. In addition, the participant's medical history and social background, which fall under the category of personal information requiring special consideration, will be collected. The date of birth will be collected in EDC for age calculation. Participant IDs and initials will be used only in the correspondence table for each institution; this correspondence table will

not be provided to anyone other than the respective institutions. Sensitive personal information will be collected in the EDC for use as the study's participant background. The following measures will be taken to minimise the risk of information leakage when using personal information in this study. First, all data obtained will be used only for the stated purpose. EDC and ePRO systems that comply with the respective laws and regulations will be used. Second, each research institute will create its correspondence table, which will not be shared with other third-party institutions. Third, results will be analysed and reported in a non-personally identifiable format. Fourth, in other respects, the Declaration of Helsinki, the Act on the Protection of Personal Information, and the 'Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects' will be followed.

Dissemination policy

The results of this study will be presented at major domestic and international conferences and published in English.

DISCUSSION

This study aims to obtain a database for descriptive research on the status of irAEs, focusing on symptom-related adverse events. It is the first multicentre collaborative study in Japan. The profile of adverse events associated with ICIs differs from that of conventional cancer drugs. Their use has diversified from monotherapy to combination with cytotoxic regimens; management methods are not yet established. Furthermore, few studies presently use PRO-CTCAE to evaluate irAEs with ICIs. Therefore, this study will provide information on symptom-related adverse events for ICI-containing regimens in Japan, which is not fully available during the development phase of treatment.

This study's database will be used to estimate the cumulative incidence of symptom-related adverse events at 3, 6, 9, and 12 months, with 2 and 3 of the PRO-CTCAE response options (from none to 0, 1, 2, 3, and 4) as onset events by carcinoma and regimen, and the cumulative incidence of symptom-related. In addition, we are considering estimating the duration of each symptom-related adverse event by defining the worsening of an adverse event from baseline as an emergence event and the duration from the emergence of the adverse event to the return to baseline as the duration of a symptom-related adverse event. As mentioned earlier, there are still many unknowns regarding the occurrence of irAEs; this study's database may provide information on trends in the occurrence of irAEs by carcinoma and regimen. We are also considering summarising the records of ePRO confirmations with descriptive statistics and examining the association between symptom-related adverse events and the degree of pharmacist action (response options) as the reality of pharmacist action for PRO-CTCAEs. This item could be more clinically relevant, leading to early detection and treatment of irAEs through pharmacist action using the PRO-CTCAE. This could shorten the duration of treatment for irAEs, avoid serious events, and allow cancer treatment progression, demonstrating the pharmacist's professional ability and providing valuable feedback to patients and the medical community.

The study protocol has some limitations. First, the study is a hypothetical, unconventional, observational study. The number of patients was not determined by statistical methods but rather based on the number of patients at participating sites. Second, the items of symptom-related adverse events in this study were determined by reviewing previous literature and Japanese drug package inserts and discussed by the investigators (four oncology pharmacists). Therefore, it is impossible to collect information on the occurrence of other symptoms. Third, participants with cognitive impairments or psychiatric disorders and those unable to operate a smartphone or tablet are excluded from participation in this study.

Most of the excluded patients are likely to be older adults. Patients with cancer in real-world practice are often older adults; age differences may be a barrier between the study and real-world practice. Finally, the study did not employ an alarm function in the event of an urgent irAE. Therefore, the medical community should be contacted in the event of an urgent irAE.

The RESPECT trial may provide critical information for future treatment with ICIs in clinical practice by providing information on symptom-related adverse events that have not been adequately obtained during the therapeutic development phase. In addition, information about pharmacist actions after EDC confirmation could influence current outpatient follow-up.

Study status

The study began enrolling patients in December 2021. The target enrolment is 260; as of October 2022, 141 participants have been enrolled. Enrolment is scheduled to end on June 30, 2023. The research is conducted from October 15, 2021, to March 31, 2028.

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The authors thank, in advance, all the participants, investigators, and institutions that will be involved in this study.

Authors' contributions

AY contributed to the study conception and is the principal investigator. KA, TH, AT, DH, TF, TK, MS, and TY participated in the study's design. TF, TK, and TY played a primary role in designing the data management approach. TK and TY played a primary role in designing statistical analysis. TM, TM, TK, and TY will conduct data analysis and interpretation. KM, AT, TH, HA, YS, AK, MM, SO, CI, MF, NS, YT, MI, NM, TK, SH, AS,

YK, GA, YK, MO, TN, MO, TY, NM, AS, RI, KW, KI, ST, AU, TY, SW, and DT have carried out recruitment and collected the data. All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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Competing interests statement

None declared.

Patient and public involvement

PPI was conducted per the Patient and Public Involvement (PPI) Guidebook of the National Institute of Biomedical Research and Innovation (NIBIO)[22], Japan, at the research planning stage. The following two patient groups were asked to cooperate in participation: NPO Lung Cancer Patients Association One Step and General Incorporated Association Esophageal Cancer Survivor's Sharing.

Patient consent for publication

Consent was obtained directly from participants.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data Availability Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol 2019;5:1749–68.
2. Hori M, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 2015;45:884–91.
3. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33:1974–82.
4. Lemery S, Keegan P, Pazdur R. First FDA approval agnostic of cancer site - when a biomarker defines the indication. N Engl J Med 2017;377:1409–12.
5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68.
6. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691–7.
7. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017;35:785–92.
8. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015;27:450–61.
9. Japanese Society of Clinical Oncology. Guidelines for Cancer Immunotherapy, 2nd Edition. 2019
10. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy:

American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714–68.

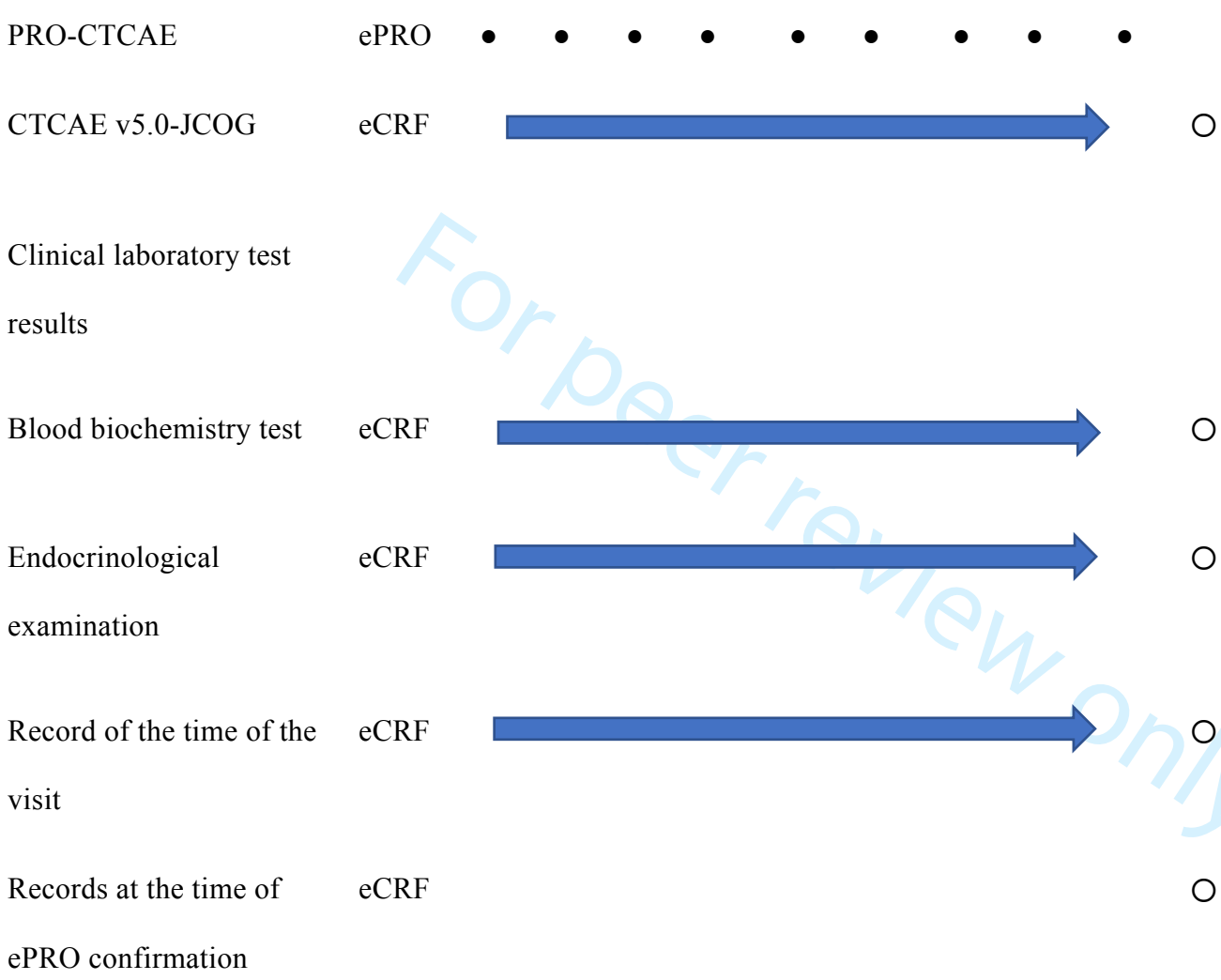
11. Food and Drug Administration, Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Health Qual Life Outcomes 2006;4:79.
12. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 2009;101:1624–32.
13. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318:197–8.
14. Tolstrup LK, Bastholt L, Dieperink KB, et al. The use of patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: a randomized controlled pilot trial. J Patient Rep Outcomes 2020;4:88.
15. Tolstrup LK, Bastholt L, Zwisler AD, et al. Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. J Patient Rep Outcomes 2019;3:19.
16. Mamoor M, Postow MA, Lavery JA, et al. Quality of life in long-term survivors of advanced melanoma treated with checkpoint inhibitors. J Immunother Cancer 2020;8:e000260.
17. Steffen McLouth LE, Lycan TW, Levine BJ, et al. Patient-reported outcomes from patients receiving immunotherapy or chemoimmunotherapy for metastatic non-small-cell lung cancer in clinical practice. Clin Lung Cancer 2020;21:255–263.e4.
18. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common

Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 2015;1:1051–9.

19. Miyaji T, Iioka Y, Kuroda Y, et al. Japanese translation and linguistic validation of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). J Patient Rep Outcomes 2017;1:8.
20. Kawaguchi T, Azuma K, Sano M, et al. The Japanese version of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE): psychometric validation and discordance between clinician and patient assessments of adverse events. J Patient Rep Outcomes 2017;2:2.
21. Abetz L, Coombs JH, Keininger DL, et al. Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. Value Health 2005;8 Suppl 1:S41–53.
22. Japan Agency for Medical Research and Development [online]. https://www.amed.go.jp/ppi/guidebook.html. (accessed 15 Jan 2023)

Supplementary Table S1. Study timeline

Week		0	1–11	12	13–23	24	25–35	36	37–47	48	Periodic report form	At any time	When terminated or cancelled
Eligibility verification	eCRF	○											
Background													
Participant Background	eCRF	○											
Psychosocial background	ePRO	●											
ECOG PS	eCRF	○											
Adverse events													



Satisfaction	CTSQ	ePRO		●	●
A questionnaire on ePRO use		ePRO	●		
irAE (Suspected/confirmed)					○
Change of outcome/treatment					○

(e)PRO, (electronic) Patient-Reported Outcome; JCOG, Japan Clinical Oncology Group; CTSQ, Cancer Therapy Satisfaction Questionnaire; irAE, Immune-related adverse events; eCRF, Electronic case report form.

○, Medical Professionals Valuation; ●, Participant assessment.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7

	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11-12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13-14

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Registry study of immune-related adverse events using electronic patient-reported outcome in patients with cancer receiving immune checkpoint inhibitors: protocol for a multicenter cohort study

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Registry study of immune-related adverse events using electronic patient-reported outcome in patients with cancer receiving immune checkpoint inhibitors: protocol for a multicenter cohort study

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ABSTRACT

Introduction: The use of immune checkpoint inhibitors (ICIs) is rapidly expanding in cancer treatment. ICIs have a unique safety profile, characterised by immune-related adverse events (irAEs). The safety profile of ICIs lacks patient experience and perspectives. This study primarily aims to obtain a database for descriptive research on the status of irAEs using the Patient-Reported Outcomes version of the Common Terminology Criteria (PRO-CTCAE) in patients with gastrointestinal cancer, lung cancer, and malignant pleural mesothelioma treated with regimens containing ICIs.

Methods and analysis: This is an ongoing, multicentre, observational study in Japan. Eligible patients must be at least 20 years and have been diagnosed with lung cancer, malignant pleural mesothelioma, or gastrointestinal cancer and plan to use ICIs. Participants will install the electronic PRO (ePRO) application and report adverse events via ePRO using PRO-CTCAE once weekly for up to 48 weeks.A registry will be established using

background information obtained from medical records. The sample size is determined by one-year projection without using statistical methods. Statistical analyses will include point estimates and 95% confidence intervals for the incidence of each adverse event by cancer type and regimen at each time point.

Ethics and dissemination: This research will be conducted per the Declaration of Helsinki, the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, and the revised Personal Information Protection Law. The study protocol was approved by the Ethics Committee (approval ID T2021-0180) of Tokyo Medical University Hospital on October 15, 2021.

Registration details: The study began enrolling patients in December 2021. The target enrolment is 260; as of October 2022, 141 have been enrolled, and the enrolment is scheduled to end on June 30, 2023.

Trial registration number: UMIN000046418

STRENGTHS AND LIMITATIONS OF THE STUDY

- Insufficient information on symptom-related adverse events of regimens containing immune checkpoint inhibitors can be clarified.
- Multiple insights into adverse event monitoring using PRO-CTCAE via ePRO, which can collect adverse events in real-time without patient visits in Japanese clinical practice settings, can be provided.
- The selected items of PRO-CTCAE in this study were determined by reviewing previous literature and Japanese drug package inserts and discussed by a board-certified oncology pharmacy specialists and through patient public involvement.

- A limitation of this study is that patients cannot be evaluated for PRO-CTCAE items not selected by the investigator at the time of planning. Not all patient-reported safety profiles are available.

INTRODUCTION

In 2017, the number of malignant tumour (cancer) patients and deaths worldwide were 24.5 million and 9.6 million, respectively.[1] The number of cancer patients in Japan was 775,601 in 2009.[2] Cancer treatment centres on surgery, drug therapy, and radiation therapy. Recently, immunotherapy has attracted attention, and insurance coverage for immune checkpoint inhibitors (ICIs) is rapidly expanding. The following cancer types are currently covered by insurance in Japan: non-small cell lung cancer, small cell lung cancer, malignant pleural mesothelioma, oesophageal cancer, gastric cancer, colorectal cancer, hepatocellular cancer, head and neck cancer, breast cancer, cervical cancer, uterine cancer, urothelial cancer, renal cancer, melanoma, solid tumours with high microsatellite instability-high (MSI-H), tumour mutational burden-high (TMB-H), and Hodgkin's lymphoma. Among the cancers for which ICIs are indicated, in which respiratory and gastrointestinal cancers are the most common, 103,715 cases were lung cancer, 122,632 gastric cancer, 116,342 colorectal cancer, 48,003 liver cancer, and 20,787 oesophageal cancer in 2009 in Japan.[2]

Adverse events in ICI treatment differ from those of conventional cytotoxic anticancer and molecular-targeted drugs in that they may present with specific autoimmune-like immune-related adverse events (irAEs).[3] Although irAEs are relatively common in the skin, gastrointestinal tract, liver, lung, and endocrine organs, they can theoretically occur anywhere in the body.[4] IrAEs can occur at any time after the start and even after the completion of ICI administration.[5] Ipilimumab is reported to cause more skin irAEs after 2–3 weeks, gastrointestinal and hepatic after 6–7 weeks, and endocrinal after 9 weeks.[6] In

contrast, nivolumab is reported to cause more skin irAEs after 5 weeks; gastrointestinal, hepatic, and pulmonary after 7–8 weeks, endocrinal after 10 weeks, and renal after 15 weeks.[7] However, most irAEs were reported to occur within 6 months of prolonged treatment with nivolumab and were not cumulative.[8] Although careful monitoring is recommended after ICI administration, there is no settled opinion on the monitoring period. IrAEs should be monitored by a physician or a physician's assistant. The response varies by organ, but as a general rule, the administration should be postponed or interrupted when ≥ Grade 2 is reached; systemic corticosteroids should be considered. After starting treatment with steroids, it is recommended that they be tapered off over several weeks while checking for irAE recurrence and subsequently discontinued or adjusted to a low-maintenance dose.[9, 10]

Patient-reported outcome (PRO) is defined as ‘an evaluation method in which patients judge their symptoms and quality of life; the results are obtained without any intervention from doctors or other parties’ by the Food and Drug Administration.[11] In recent years, adverse event assessment using PROs has gained prominence in oncology. Basch et al.[12] reported that adverse event assessments in providers and patients are inconsistent, with a tendency for providers to underestimate them. This problem led to the development of a PRO version of the Common Terminology Criteria for Adverse Events (CTCAE), PRO-CTCAE, in 2008. In a randomised controlled trial, a comparison of the pro-active approach with PRO-CTCAE using electronic PRO (ePRO) for adverse events with a conventional adverse event evaluation showed a significant difference in health-related quality of life and overall survival.[13] This study has attracted attention as a trial that will change clinical practice. The results have led to the use of PRO-CTCAE in many countries, including Japan.

Early detection and monitoring of irAEs are important, and PROs are useful.[14] However, Tolstrup et al.[15] noted that the procedure for selecting PRO-CTCAE items in

patients receiving immunotherapy is not well established. They reported a method for selecting PRO-CTCAE questions for patients with malignant melanoma receiving immunotherapy. Studies of PRO-CTCAE in ICI-using patients have been reported in malignant melanoma and non-small cell lung cancer.[16, 17] Based on these studies, the PRO-CTCAE is used as a questionnaire to evaluate irAE; however, few studies on irAE and PRO-CTCAE are available.

In Japan, pharmacists play an important role in the rapidly advancing field of cancer pharmacotherapy. Particularly, with the increase in outpatient cancer treatment, there have been many reports on the importance and usefulness of outpatient consultations conducted by pharmacists. This report suggests that in addition to routine tasks such as checking lab values and providing medication guidance, working with physicians and nurses to conduct pre- and post-consultation interviews not only benefits patients but also helps to reduce the burden on medical staff and improve the quality of care.[18, 19]

The present study, named RESPECT (REgistry Study of immune-related adverse events using electronic Patient-reported outcome in patiEnts with cancer receiving immune CheckpoinT inhibitors) study, aims to obtain a database for descriptive research on the status of irAEs, focusing on symptom-related adverse events in patients with cancer receiving regimens that include ICIs. In addition, it aims to determine the rate of symptom-related adverse events at each time point in the setting in which ePRO adverse event monitoring is performed.

METHODS AND ANALYSIS

Study design

This is an ongoing, multicentre, longitudinal, observational study. An observational study design is used to track the mode and course of irAEs, focusing on symptom-related adverse

events. Participants will install the ePRO application and report adverse events weekly via ePRO using PRO-CTCAE. In addition, a registry will be established using background information obtained from medical records; ancillary studies will be conducted on the proportion of adverse event reporting by ePRO and those associated with ICIs.

Patient and public involvement

The following two patient groups were asked to cooperate in participation: Non-Profit Organization Lung Cancer Patients Association One Step and General Incorporated Association Esophageal Cancer Survivor's Sharing. The research plan will include the advice given on PRO-CTCAE item selection, number of questions, and survey frequency. Advice will also be obtained at each stage of the process leading up to the publication of the results.

Study setting, participants, and recruitment

Recruitment is being performed at nine hospitals in Japan. The inclusion criterion is the diagnosis of lung cancer, malignant pleural mesothelioma, or gastrointestinal cancer in patients who plan to use an ICI and give their written consent to participate in the study, over 20 years old, and with Eastern Collaborative Oncology Group Performance Status (ECOG PS) of 0–3. Patients who do not have an ePRO-eligible device, have a severe psychiatric illness or cognitive dysfunction that affects filling out the survey form, or those with a native language that is not Japanese are excluded. The study pharmacist will invite eligible patients to participate in the study at each site. After starting treatment, participants will complete weekly ePROs, an adverse events monitoring questionnaires at week 12, and treatment satisfaction questionnaires at weeks 24 and 48. Observation shall be discontinued in the following cases: (1) if the participant requests to discontinue the adverse event evaluation

using ePRO, (2) when follow-up is no longer possible due to hospital transfer, (3) death during follow-up, (4) if consent is withdrawn, and (5) loss to follow-up.

Outcome measures

Table 1 shows the study schedule. We will use the PRO-CTCAE and the CTCAE v5.0 to assess adverse events. In addition, we will use Cancer Therapy Satisfaction Questionnaire (CTSQ) to assess treatment satisfaction.

Table 1. Study timeline (summary)

Week		0	12	24	36	48
Eligibility verification	eCRF	○				
Background						
Participant Background	eCRF	○				
Psychosocial background	ePRO	●				
ECOG PS	eCRF	○				
Adverse events						
PRO-CTCAE	ePRO	●	●	●	●	●
CTCAE v5.0-JCOG	eCRF	→	→	→	→	→
Laboratory data	eCRF	→	→	→	→	→
Record of the time of the visit	eCRF	→	→	→	→	→
Records at the time of ePRO confirmation	eCRF	→	→	→	→	→
Satisfaction (CTSQ)	ePRO			●		●
A questionnaire on ePRO use	ePRO		●			
irAE (Suspected/confirmed)		→	→	→	→	→

(e)PRO, (electronic) Patient-Reported Outcome; JCOG, Japan Clinical Oncology Group; CTSQ, Cancer Therapy Satisfaction Questionnaire; irAE, Immune-related adverse events; eCRF, Electronic case report form.

○, Medical Professionals Valuation; ●, Participant assessment

Adverse events

Adverse events will be assessed using CTCAE v5.0, translated by the Japan Clinical Oncology Group as Clinician-Reported Outcome (ClinRO), and PRO-CTCAE as PRO. Since its development as a common toxicity criterion in 1984, the CTCAE has been the gold standard as ClinRO for adverse event assessment and is widely used in clinical research, particularly in the field of oncology. The CTCAE v5.0 will be recorded from the medical record each time they are assessed; items corresponding to PRO-CTCAE will be mandatory. Meanwhile, the PRO-CTCAE, developed by the National Cancer Institute in 2008, consists of 80 items from the CTCAE version 4, extracting 78 symptoms that can be subjectively assessed by the patients and has been reworded to make them easier for patients to answer. Each item is assessed using one or more attributes, including presence/absence, frequency, severity, and/or interference with usual or daily activities. The original version has been evaluated for validity and reliability by Dueck et al.[20] The Japanese version of PRO-CTCAE has been validated for linguistic and psychometric validity by Miyaji et al.[21] and Kawaguchi et al.[22], respectively.

Treatment satisfaction

The CTSQ is a 16-item questionnaire developed by Pfizer to measure treatment satisfaction specifically with cancer treatment. It has three subscales, ‘Expectations of Treatment’, ‘Feelings about Side Effects’, and ‘Satisfaction with Therapy’, which are scored from 0 to 100. Higher scores indicate higher satisfaction. This questionnaire has been validated by Abetz et al.[23]

Sample size determination

The sample size was not calculated based on a statistical perspective. Considering the annual number of patients treated with ICIs at each site and the proportion of smartphone or tablet ownership for ePRO, and obtaining consent, a target enrolment number of at least 260 patients per year was set.

Data collection and timeline

The study pharmacist will perform web registration for the participants' data using the electronic data capture (EDC) system, Viedoc 4 (Viedoc Technologies, Sweden). Participants will respond to the PROs using 3H P-Guardian (3H Clinical Trial Inc, Japan), an ePRO application, on their own device (smartphone or tablet) at 49 time points: at baseline and weeks 1–48 after initiating ICI therapy. The oncologist and/or study pharmacist will explain the details of this research to the patient. After obtaining patient consent, data on psychosocial background and PRO-CTCAE will be collected from the participant's electronic device. Data on demographics, medical history, and CTCAE v5.0- JCOG scores will be collected and entered into EDC and linked to baseline PRO data. The study pharmacist will review ePRO data within the scope of their routine daily practice and, based on this information, share information with physicians and nurses, and contact and respond to participants, but there are no restrictions or interventions since this is for research study purposes.After the study pharmacist has reviewed the ePRO data, they will record in the EDC whether they have contacted the physician, nurse, or patient, and if so, the details of that action. They will also be asked to record treatment satisfaction at weeks 24 and 48. Adverse event assessment using CTCAE and PRO-CTCAE will continue after treatment with ICIs is discontinued. The study timeline is shown in Table 1.

Data monitoring

The data centre is located at the Tohoku Graduate School of Medicine (Miyagi Prefecture, Japan). To protect participants' privacy, no personally identifiable information will be entered into the EDC. Data management and central data monitoring will be performed using the EDC. Establishment of a data monitoring committee and auditing are not planned for this study. Following the data entry of this study, the fixed data will be exported and deleted from the EDC and will be stored in the research office in electronic media for at least 10 years after the principal publication.

Harm

This is a non-interventional, non-invasive, observational study. Therefore, the burden on the participants is minimal. Participant contributions for time spent filling out questionnaires, installing applications, and communication costs for data transmission will be explained in writing and verbally in the consent explanation. Consent will be fully explained before enrolment, and participants can withdraw even while the questionnaire is being filled out.

Statistical analysis

The primary purpose is to obtain a database for descriptive research on the actual status of irAEs, focusing on symptom-related adverse events in patients with cancer receiving regimens that include ICIs. Furthermore, we aim to determine the incidence of symptom-related adverse events at each time point in an environment where ePRO-based adverse event monitoring is conducted in daily practice. Point estimates and 95% confidence intervals of the incidence of each adverse event at each time point by cancer type and regimen will be estimated. The treatment of missing values will not be specified in advance. In addition, we will examine the association between symptom-related adverse events and the extent of

pharmacist actions and summarise the ePRO completion rate using descriptive statistics as the reality of pharmacist actions for PRO-CTCAEs.

ETHICS AND DISSEMINATION

Research ethical approval

This research will be conducted per the Declaration of Helsinki, the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, and the revised Personal Information Protection Law. The protocol was approved by the Ethics Committee of Tokyo Medical University Hospital (approval ID T2021-0180) on October 15, 2021. The version of the protocol became 1.1 in March 2022. The protocol has been reviewed by the Institutional Review Boards of the following research centres. Juntendo University Nerima Hospital, JR Tokyo General Hospital, Nippon Medical School Hospital, Kyorin University Hospital, Teine Keijinkai Hospital, Nihon University Itabashi Hospital, University of Miyazaki Hospital and Japanese Red Cross Tokushima Hospital.

Consent

The study pharmacist and/or the oncologist will give the patients an informed consent form and explain the details of the study before enrolment. The participant's request to withdraw consent during or after the study will be accepted without any disadvantage.

Access to data

The study pharmacist and/or the oncologist may use the EDC to review only case data collected at their site. In addition, only the data manager at the data centre has access to the case data entered from each research site through the EDC.

Confidentiality

Three types of personal information will be used in this study: medical record number, date of birth, and initials, which are the minimum required for identification and inquiry of the participant. In addition, the participant's medical history and social background, which fall under the category of personal information requiring special consideration, will be collected. The date of birth will be collected in EDC for age calculation. Participant IDs and initials will be used only in the correspondence table for each institution; this correspondence table will not be provided to anyone other than the respective institutions. Sensitive personal information will be collected in the EDC for use as the study's participant background.

The following measures will be taken to minimise the risk of information leakage when using personal information in this study. First, all data obtained will be used only for the stated purpose. EDC and ePRO systems that comply with the respective laws and regulations will be used. Second, each research institute will create its correspondence table, which will not be shared with other third-party institutions. Third, results will be analysed and reported in a non-personally identifiable format. Fourth, in other respects, the Declaration of Helsinki, the Act on the Protection of Personal Information, and the 'Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects' will be followed.

Dissemination policy

The results of this study will be presented at major domestic and international conferences and published in English.

DISCUSSION

This study aims to obtain a database for descriptive research on the status of irAEs, focusing on symptom-related adverse events. It is the first multicentre collaborative study in Japan. The profile of adverse events associated with ICIs differs from that of conventional cancer drugs. Their use has diversified from monotherapy to combination with cytotoxic regimens; management methods are not yet established. Furthermore, few studies presently use PRO-CTCAE to evaluate irAEs with ICIs. Therefore, this study will provide information on symptom-related adverse events for ICI-containing regimens in Japan, which is not fully available during the clinical trials in which adverse events were assessed only by ClinRO.

This study's database will be used to estimate the cumulative incidence of symptom-related adverse events at 3, 6, 9, and 12 months, with 2 and 3 of the PRO-CTCAE response options (from none to 0, 1, 2, 3, and 4) as onset events by carcinoma and regimen. In addition, we are considering estimating the duration of each symptom-related adverse event by defining the worsening of an adverse event from baseline as an emergence event and the duration from the emergence of the adverse event to the return to baseline as the duration of a symptom-related adverse event. As mentioned earlier, there are still many unknowns regarding the occurrence of irAEs; this study's database may provide information on trends in the occurrence of irAEs by carcinoma and regimen. We are also considering summarising the records of ePRO confirmations with descriptive statistics and examining the association between symptom-related adverse events and the degree of pharmacist action (response options) as the reality of pharmacist action for PRO-CTCAEs. This item could be more clinically relevant, leading to early detection and treatment of irAEs through pharmacist action using the PRO-CTCAE. This could shorten the duration of treatment for irAEs, avoid serious events, and allow cancer treatment progression, demonstrating the pharmacist's professional ability and providing valuable feedback to patients and the medical community.

The study protocol has some limitations. First, the study is a hypothetical, unconventional, observational study, and it does not include patients with all cancer types for which ICIs can be administered. Additionally, the number of patients was not determined by statistical methods but rather based on the number of patients at participating sites. Therefore, there are limitations with respect to generalizability. Second, the items of symptom-related adverse events in this study were determined by reviewing previous literature and Japanese drug package inserts and discussed by four oncology pharmacists. Therefore, it is impossible to collect information on the occurrence of other symptoms. Third, participants with cognitive impairments or psychiatric disorders and those unable to operate a smartphone or tablet are excluded from participation in this study. Most of the excluded patients are likely to be older adults. Patients with cancer in real-world practice are often older adults; age differences may be a barrier between the study and real-world practice.

The RESPECT trial may provide critical information for future treatment with ICIs in clinical practice by providing information on symptom-related adverse events that have not been adequately obtained during the clinical trials conducted before approval. In fact, the adverse event assessments from our registry will not only provide the "worst grade during time period" used in general cancer clinical trials, but also provide cumulative incidence rates and changes over time by ICIs, their regimens, or by cancer type, based on temporal changes such as onset and resolution of adverse event ratings.

Study status

The study began enrolling patients in December 2021. The target enrolment is 260; as of October 2022, 141 participants have been enrolled. Enrollment is scheduled to end on June 30, 2023. The research is to be conducted from October 15, 2021, to March 31, 2028.

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Authors' contributions

AY contributed to the study conception and is the principal investigator. KA, TH, AT, DH, TF, TK, MS, and TY participated in the study's design. TF, TK, and TY played a primary role in designing the data management approach. TK and TY played a primary role in designing statistical analysis. TM, TM, TK, and TY will conduct data analysis and interpretation. KM, AT, TH, HA, YS, AK, MM, SO, CI, MF, NS, YT, MI, NM, TK, SH, AS, YK, GA, YK, MO, TN, MO, TY, NM, AS, RI, KW, KI, ST, AU, TY, SW, and DT have carried out recruitment and collected the data. All authors have read and approved the final manuscript and meet the criteria for authorship as established by the International Committee of Medical Journals Editors.

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Competing interests statement

None declared.

Patient and public involvement

PPI was conducted per the Patient and Public Involvement (PPI) Guidebook of the National Institute of Biomedical Research and Innovation (NIBIO)[24], Japan, at the research planning stage. The following two patient groups were asked to cooperate in participation: NPO Lung Cancer Patients Association One Step and General Incorporated Association Esophageal Cancer Survivor's Sharing.

Patient consent for publication

Consent was obtained directly from participants.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Open access

Data Availability Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol 2019;5:1749–68.
2. Hori M, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol 2015;45:884–91.
3. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33:1974–82.
4. Lemery S, Keegan P, Pazdur R. First FDA approval agnostic of cancer site - when a biomarker defines the indication. N Engl J Med 2017;377:1409–12.
5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68.
6. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691–7.
7. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017;35:785–92.
8. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015;27:450–61.
9. Japanese Society of Clinical Oncology. Guidelines for Cancer Immunotherapy, 2nd Edition. 2019
10. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy:

American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714–68.

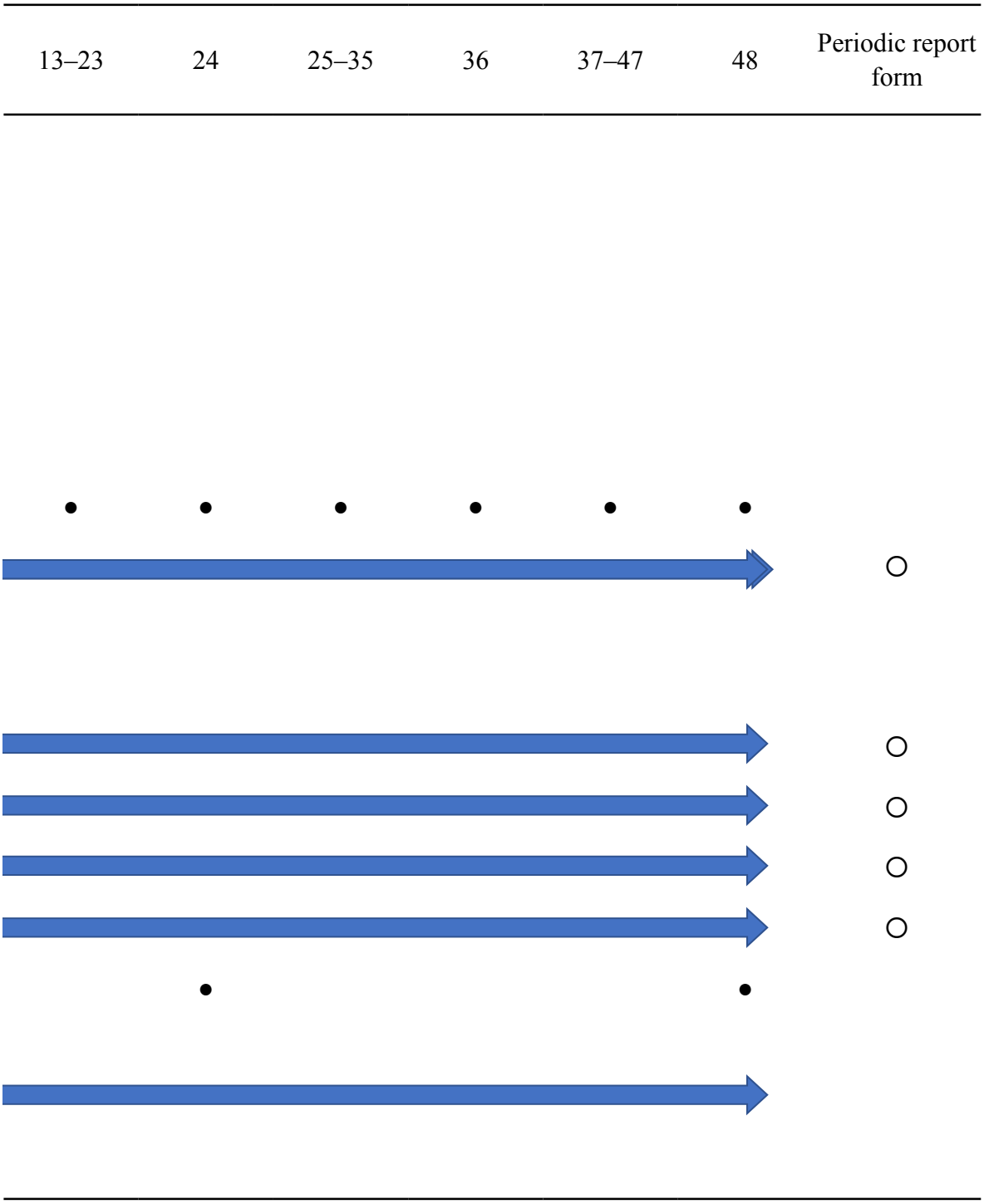
11. Food and Drug Administration, Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Health Qual Life Outcomes 2006;4:79.
12. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 2009;101:1624–32.
13. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318:197–8.
14. Tolstrup LK, Bastholt L, Dieperink KB, et al. The use of patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: a randomized controlled pilot trial. J Patient Rep Outcomes 2020;4:88.
15. Tolstrup LK, Bastholt L, Zwisler AD, et al. Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. J Patient Rep Outcomes 2019;3:19.
16. Mamoor M, Postow MA, Lavery JA, et al. Quality of life in long-term survivors of advanced melanoma treated with checkpoint inhibitors. J Immunother Cancer 2020;8:e000260.
17. Steffen McLouth LE, Lycan TW, Levine BJ, et al. Patient-reported outcomes from patients receiving immunotherapy or chemoimmunotherapy for metastatic non-small-cell lung cancer in clinical practice. Clin Lung Cancer 2020;21:255–263.e4.
18. Makio I, Yusuke M et al. Function of and need for a pharmaceutical outpatient clinic run by oncology pharmacy specialists. Japanese Journal of Pharmaceutical Health Care and Sciences. 2015;41;254–65.

19. Yoshitaka S, Sachiko H et al. Survey of the efficacy of long-term and successive pharmaceutical care in outpatient chemotherapy by oncology pharmacy specialists. Journal of the Pharmaceutical Society of Japan, 2018;138;1409–16.
20. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 2015;1:1051–9.
21. Miyaji T, Iioka Y, Kuroda Y, et al. Japanese translation and linguistic validation of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). J Patient Rep Outcomes 2017;1:8.
22. Kawaguchi T, Azuma K, Sano M, et al. The Japanese version of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE): psychometric validation and discordance between clinician and patient assessments of adverse events. J Patient Rep Outcomes 2017;2:2.
23. Abetz L, Coombs JH, Keininger DL, et al. Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. Value Health 2005;8 Suppl 1:S41–53.
24. Japan Agency for Medical Research and Development [online]. https://www.amed.go.jp/ppi/guidebook.html. (accessed 15 Jan 2023)

Table 1. Study timeline

Week		0	1–11	12
Eligibility verification	eCRF	○		
Background				
Participant Background	eCRF	○		
Psychosocial background	ePRO	●		
ECOG PS	eCRF	○		
Adverse events				
PRO-CTCAE	ePRO	●	●	●
CTCAE v5.0-JCOG	eCRF	▬	▬	▬
Laboratory data				
Clinical laboratory test results				
Blood biochemistry test	eCRF	▬	▬	▬
Endocrinological examination	eCRF	▬	▬	▬
Record of the time of the visit	eCRF	▬	▬	▬
Records at the time of ePRO confirmation	eCRF	▬	▬	▬
Satisfaction (CTSQ)	ePRO			
A questionnaire on ePRO use	ePRO			●
irAE (Suspected/confirmed)		▬	▬	▬
Change of outcome/treatment				

(e)PRO, (electronic) Patient-Reported Outcome; JCOG, Japan Clinical Oncology Group; CTSQ, C
○, Medical Professionals Valuation; ●, Participant assessment.



Cancer Therapy Satisfaction Questionnaire; irAE, Immune-related adverse events; eCRF, Ele

At any time	When terminated or cancelled
○	
	○

ectronic case report form.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported (page numbers)	RECORD items	Location in manuscript where items are reported (page numbers)
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	(1)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	(6-8)		
Objectives	3	State specific objectives, including any prespecified hypotheses	(9)		
Methods					
Study Design	4	Present key elements of study design early in the paper	(9)		

Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	(10-11)		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	(10-11)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	(17-18)

Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	(18)		

Bias	9	Describe any efforts to address potential sources of bias	(18-19)		
Study size	10	Explain how the study size was arrived at	(17)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	(17-18)		

Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(19)		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	N/A
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	N/A

Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	(15)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for nonparticipation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	N/A		

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	N/A		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounderadjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
Discussion					
Key results	18	Summarise key results with reference to study objectives	(22-24)		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	(23-24)		
		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	(24)		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	(26)		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	(16)

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.