PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Hirata, Taiki; Kawaguchi, Takashi; Kanako, Azuma; Torii, Ayako; Usui, Hiroaki; Kim, Soan; Hayama, Tatsuya; Hirate, Daisuke; Kawahara, Yosuke; Kumihashi, Yuki; Chisaka, Tomomi; Wako, Tetsuya; Yoshimura, Akinobu; Miyaji, Tempei; Yamaguchi, Takuhiro

VERSION 1 – REVIEW

REVIEWER	Di Maio, Massimo Università degli Studi di Torino, Dipartimento di Oncologia, AO Ordine Mauriziano
REVIEW RETURNED	02-May-2023

GENERAL COMMENTS	The authors present a study conducted with the aim of collecting, by the collection of patient-reported outcomes using electronic devices, immune-related adverse events in patients receiving immunotherapy for the treatment of cancer. The topic is very modern, but I have some concerns. 1. It seems only pharmacists are involved in the study. Which is the role of the pharmacists and which the role, in this model, of nurses and oncologists? I have some concerns because pharmacists should not monitor adverse events without a strict cooperation and dialoghe with other healthcare operators. The model should be more precisely described about this. 2. Is the study only conducted with the aim of collecting and describing adverse events, or also to manage those adverse events in real time? In my opinion, the real advantage of the use of electronic devices is the proactive monitoring of symptoms and toxicities. This is not clear to me. 3. Why the study is limited to specific tumors? It should work for all patients with cancer receiving immunotherapy 4. Authors should better describe the association, if any, between the electronic platform used for the study and the patient health record. Electronic collection of symptoms and adverse events should be intrinsically connected with patients records, in order to allow improvement of their clinical management. Please explain better.

REVIEWER	Feng, Min

	Sun Yat-Sen University
REVIEW RETURNED	31-May-2023

GENERAL COMMENTS	There are some informations need to be issued: 1.The definition of the abbreviations in the abstract should be clearly clarified. 2.The adverse events mentioned in this submission are simply based on the questionnaires of the patients, but lacking of judgments from medical professionals, which may lead to misleading. It's better to state this limitation in the part of discussion.

REVIEWER	Davis Puente, Andrea Vanderbilt University Medical Center, Internal Medicine
REVIEW RETURNED	31-May-2023

GENERAL COMMENTS	Thank you for submitting this interesting manuscript. The paper describes a database to be used for research projects addressing ICIs and irAEs. This is an important area of research and one that can be difficult to systematically obtain data so I appreciate this project. See below for some comments and questions: 1. Page 4 Line 8 seems grammatically incorrect. Perhaps would read better as "ICIs have a unique safety profile." 2. Page 14 Line 54 - what is meant by the "development phase of treatment" and why is information on symptom related adverse events not available during that time? 3. More broadly, I would suggest commenting on the self reported nature of data collection in the limitations. What if patients mischaracterize their symptoms or are asymptomatic? 4. This work may be very helpful in describing the timelines for different irAEs. Can you elaborate on other potential projects or areas of study with this data? 5. Page 16 Line 12 - it may be helpful to elaborate on how this information can impact patient care. How would information on pharmacist actions after EDC confirmation influence outpatient follow up?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comment 1.
It seems only pharmacists are involved in the study. Which is the role of the pharmacists and which the role, in this model, of nurses and oncologists? I have some concerns because pharmacists should not monitor adverse events without a strict cooperation and dialoghe with other healthcare operators. The model should be more precisely described about this.
Response 1.
Thank you for your important point. In the “Data collection and timeline” section, the roles of physicians, pharmacists, and nurses were unclear due to the interchangeable use of the words “investigators” and “researchers”. We have revised this section to reflect this comment and clarified these roles. (Page 14, lines 17-54 Page 16, lines 43-44, limes 54-55)

Comment 2.
Is the study only conducted with the aim of collecting and describing adverse events, or also to manage those adverse events in real time? In my opinion, the real advantage of the use of electronic devices is the proactive monitoring of symptoms and toxicities. This is not clear to me.
Response 2.
Thank you for pointing this out. We agree that the advantage of adverse event monitoring with ePRO is the proactive approach. However, there is still insufficient evidence and environment to promote this proactive approach in Japan. Therefore, the primary objective of this study is to collect data on the actual implementation of ePRO to understand the patient-reported adverse events, and we also plan to analyze the actions of healthcare providers based on the data obtained by ePRO to examine the feasibility of using ePRO for adverse event monitoring.

Comment 3.
Why the study is limited to specific tumors? It should work for all patients with cancer receiving immunotherapy
Response 3.
Thank you for pointing this out. As mentioned above, the current status of ePRO dissemination and its implementation system in daily practice in Japan is not sufficient, and we could not cover all cancer types. This is an important point that affects generalizability, so we have added it to the Limitations section. (Page 19, lines 3-8)

Comment 4.
Authors should better describe the association, if any, between the electronic platform used for the study and the patient health record. Electronic collection of symptoms and adverse events should be intrinsically connected with patients records, in order to allow improvement of their clinical management. Please explain better.
Response 4.
As stated by the reviewers, we agree that it is important to explain how the patient-entered ePRO data was handled from the patient's perspective. In clinical trials for drug development, patients may not be able to review their own adverse event data confidently, but in this study, which was conducted in a manner similar to routine daily practice, patients, as well as the study pharmacist and/or the oncologist, were able to view ePRO adverse event reports. This description has been added to the Data collection and timeline. (Page 14, lines 36-49)

Reviewer: 2
Comment 1.
The definition of the abbreviations in the abstract should be clearly clarified.
Response 1.
Thank you for pointing this out. We have made the appropriate corrections to the ePRO abbreviations. (Page 3, line 56)

Comment 2.
The adverse events mentioned in this submission are simply based on the questionnaires of the patients, but lacking of judgments from medical professionals, which may lead to misleading. It's better to state this limitation in the part of discussion.
Response 2.
Thank you for your suggestion. The assessment by a clinician, ClinRO, which the reviewer states is important, is definitely important and is described in the “Adverse events” section (P13) as being assessed using the CTCAE, a gold standard tool, in this study. The background section also discusses the problem that this ClinRO assessment of adverse events may underestimate symptoms. The draft guidance indicates that the FDA recommends that both CTCAE and PRO-CTCAE be used as the standard, or core set, for adverse event assessment. (No references are cited because it is a

draft guidance.) The PRO-CTCAE is not just a questionnaire, but a well-defined and reliable tool, and adverse event assessment using both PRO and ClinRO is desirable. We recognise that adverse event assessment by ClinRO alone is more misleading, especially with regard to symptoms.

Reviewer: 3
Comment 1.
Page 4 Line 8 seems grammatically incorrect. Perhaps would read better as "ICIs have a unique safety profile."
Response 1.
Thank you for pointing this out. We have corrected it (Line 2 of the abstract and Page 3, line 36).
Comment 2.
Page 14 Line 54 - what is meant by the "development phase of treatment" and why is information on symptom related adverse events not available during that time?
Response 2.
Thank you for pointing this out. This wording was misleading. We have revised the manuscript so that it is understood that this is a clinical trial for approval that uses only ClinRO for adverse event assessment. (Page 18, line 19 and Page 19, line 15)

Comment 3.
More broadly, I would suggest commenting on the self reported nature of data collection in the limitations. What if patients mischaracterize their symptoms or are asymptomatic?
Response 3.
Thank you for your suggestion about PRO in general. The PRO scale used in clinical studies such as PRO-CTCAE is a well-defined and reliable tool and has been shown to have psychometric properties. These psychometric properties are the data that provide interpretation to the reviewer's questions. The “Adverse events” section also references the literature on the psychometric properties of the PRO scale to help readers interpret it.

Comment 4.
This work may be very helpful in describing the timelines for different irAEs. Can you elaborate on other potential projects or areas of study with this data?
Response 4.
Thank you for your kind comments. As the reviewer commented, we agree with the reviewer that the strength of the adverse event assessment obtained from this registry is its ability to provide a time-considering adverse event assessment. We have added this to the manuscript. (Page 19, lines 36-45)

Comment 5.
Page 16 Line 12 - it may be helpful to elaborate on how this information can impact patient care. How would information on pharmacist actions after EDC confirmation influence outpatient follow up?
Response 5.
As the reviewer pointed out, it is important to know what pharmacists did with the information obtained by the ePRO, and we are tracking this as a study. In the "Data collection and timeline" section, we clarified that we are collecting dat on the pharmacists’ actions. (Page 14, lines 36-49)

Again, thank you for your valuable feedback on this issue. We believe that the paper will be better as a result of the revisions made based on your feedback.

We sincerely hope that it will also be accepted.

Sincerely,

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VERSION 2 – REVIEW

REVIEWER	Di Maio, Massimo Università degli Studi di Torino, Dipartimento di Oncologia, AO Ordine Mauriziano
REVIEW RETURNED	24-Oct-2023

GENERAL COMMENTS	I have no further comments