Chronic Obstructive Pulmonary Disease Outcomes Among Individuals in Japan Who Switched to Heated Tobacco Products Compared to Those Who Continued Smoking or Formerly Smoked Combustible Cigarettes: Protocol for a Real-World Retrospective Study

Helene Karcher, Makoto Hibino, Shinichi Higashiue, Daniel Boakye, Badrul Chowdhury, Patrick Picavet, Mohamad Haidar, Adam Lenart

Submitted to: JMIR Research Protocols
on: March 04, 2025

Table of Contents

Chronic Obstructive Pulmonary Disease Outcomes Among Individuals in Japan Who Switched to Heated Tobacco Products Compared to Those Who Continued Smoking or Formerly Smoked Combustible Cigarettes: Protocol for a Real-World Retrospective Study

Helene Karcher[1] PhD; Makoto Hibino[2] MD; Shinichi Higashiue[3] MD, PhD; Daniel Boakye[1] PhD; Badrul Chowdhury[1] MD, PhD; Patrick Picavet[1] MD; Mohamad Haidar[1] PhD; Adam Lenart[1] PhD

[1] PMI R&D, Philip Morris Products S.A., Neucha?tel, Switzerland Neuchatel CH
[2] Department of Respiratory Medicine, Shonan Fujisawa Tokushukai Hospital, Kanagawa, Japan Kanagawa JP
[3] Tokushukai Medical Corporation, Tokyo, Japan Tokyo JP

Corresponding Author:
Helene Karcher PhD

PMI R&D, Philip Morris Products S.A., Neucha?tel, Switzerland
Quai Jeanrenaud 5 - 2000 Neuchâtel, Switzerland
Neuchatel
CH

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory disease that is highly associated with smoking. Despite widespread knowledge of the health risks of smoking, many patients with COPD continue to smoke. Growing evidence suggests that alternatives to combustible cigarettes (CIG), such as heated tobacco products (HTP), may be less harmful.

Objective: To evaluate the impact of switching from CIG to HTP on the time to subsequent COPD exacerbations in patients who have had a COPD-related hospitalization.

Methods: This retrospective cohort study will be conducted in Japan using electronic health data and tobacco exposure data from questionnaires and consumer databases. The study will invite approximately 30,000 patients who had a COPD-related hospitalization between May 2016 and December 2022. The first of these hospitalizations will be considered a patient's study Index Event. The primary outcome is the time from Index Event to subsequent COPD exacerbation (a composite outcome of subsequent COPD-related hospitalization and all-cause mortality); patients will be observed until March 2025. The primary exposure groups are HTP use and CIG use, respectively, pre- and post-index. We will use weighted Cox proportional hazard models, with propensity score weighting to balance potential confounders, to compare the primary outcome between the primary exposure groups. We will also compare the primary outcome between exclusive HTP users and ancillary exposure groups of dual users of CIG and HTP and former CIG smokers. Secondary outcomes include all-cause mortality, pneumonia-related hospitalization, COPD-related hospitalizations, and all-cause hospitalizations and will be assessed in primary and ancillary exposure groups.

Results: The study described in this protocol intends to assess whether there is a longer time to subsequent COPD hospitalizations and all-cause mortality for HTP users compared to CIG smokers

Conclusions: This protocol describes the first large-scale study that will identify patients with COPD from a nationally representative healthcare database and evaluate the history of tobacco product usage from multiple sources. Additionally, this study protocol is the first in the tobacco medical literature that embraces real-world data providing information on HTP use from various tobacco product exposure sources. This will also be the first study to assess the relationship between HTP use and mortality in this patient population. Given the limited evidence on the health effects of HTP in COPD, the results of this study will provide real-world insights into the effects of switching to HTP use compared to continued CIG smoking in patients with COPD. Clinical Trial: Not applicable

(JMIR Preprints 04/03/2025:73436)

DOI: https://doi.org/10.2196/preprints.73436

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http
No. Please do not make my accepted manuscript PDF available to anyone.

Original Manuscript

Original Paper

Helene Karcher*[1], PhD; Makoto Hibino[2], MD; Shinichi Higashiue[3], MD, PhD; Daniel Boakye[1], PhD; Badrul Chowdhury[1], MD, PhD; Patrick Picavet[1], MD; Mohamad Haidar[1], PhD; Adam Lenart[1], PhD;

[1]PMI R&D, Philip Morris Products S.A., Neuchâtel, Switzerland
[2]Department of Respiratory Medicine, Shonan Fujisawa Tokushukai Hospital, Kanagawa, Japan
[3]Tokushukai Medical Corporation, Tokyo, Japan
*Corresponding Author:
Helene Karcher, PhD
Philip Morris Products S.A.,
Quai Jeanrenaud 5,
CH-2000 Neuchâtel,
Switzerland
helene.karcher@pmi.com
Tel: +41 (76) 405 5690

Chronic Obstructive Pulmonary Disease Outcomes Among Individuals in Japan Who Switched to Heated Tobacco Products Compared to Those Who Continued Smoking or Formerly Smoked Combustible Cigarettes: Protocol for a Real-World Retrospective Study

Short title: Protocol for a retrospective study of subsequent COPD exacerbations among heated tobacco product users and cigarette smokers

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory disease that is highly associated with smoking. Despite widespread knowledge of the health risks of smoking, many patients with COPD continue to smoke. Growing evidence suggests that alternatives to combustible cigarettes (CIG), such as heated tobacco products (HTP), may be less harmful.
Objective: To evaluate the impact of switching from CIG to HTP on the time to subsequent COPD exacerbations in patients who have had a COPD-related hospitalization.
Methods: This retrospective cohort study will be conducted in Japan using electronic health data and tobacco exposure data from questionnaires and consumer databases. The study will invite approximately 30,000 patients who had a COPD-related hospitalization between May 2016 and December 2022. The first of these hospitalizations will be considered a patient's study Index Event. The primary outcome is the time from Index Event to subsequent COPD exacerbation (a composite outcome of subsequent COPD-related hospitalization and all-cause mortality); patients will be observed until March 2025. The primary exposure groups are HTP use and CIG use, respectively, pre- and post-index. We will use weighted Cox proportional hazard models, with propensity score weighting to balance potential confounders, to compare the primary outcome between the primary exposure groups. We will also compare the primary outcome between exclusive HTP users and ancillary exposure groups of dual users of CIG and HTP and former CIG smokers. Secondary outcomes include all-cause mortality, pneumonia-related hospitalization, COPD-related hospitalizations, and all-cause hospitalizations and will be assessed in primary and ancillary exposure groups.
Results: The study described in this protocol intends to assess whether there is a longer time to subsequent COPD hospitalizations and all-cause mortality for HTP users compared to CIG smokers
Conclusions: This protocol describes the first large-scale study that will identify patients with COPD from a nationally representative healthcare database and evaluate the history of tobacco product usage from multiple sources. Additionally, this study protocol is the first in the tobacco medical literature that embraces real-world data providing information on HTP use from various tobacco product exposure sources. This will also be the first study to assess the relationship between HTP use and mortality in this patient population. Given the limited evidence on the health effects of HTP in COPD, the results of this study will provide real-world insights into the effects of switching to HTP use compared to continued CIG smoking in patients with COPD.

Keywords: Smokers; Japan; Electronic Health Records; Propensity Score; Retrospective Studies; Tobacco Products; Pulmonary Disease, Chronic Obstructive; Surveys and Questionnaires

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating respiratory disease and a major cause of non-cancer mortality globally [1]. In 2022, the overall COPD death rate in Japan was 13.7 per 100,000 people (23.6 per 100,000 males and 4.2 per 100,000 females), which accounted for 1.1% of deaths in that year [2]. The risk of morbidity, and possibly mortality, is even higher in those with (vs. without) a history of exacerbations or respiratory events; analysis of administrative claims data of 20,212 patients with COPD in Japan showed a significantly higher rate of severe acute exacerbations in patients with prior respiratory events (0.199 per patient-year) compared to those without (0.022 per patient-year) [3]. It is well known that smoking cessation is associated with reduced risk of smoking-attributable diseases [4, 5]. Even though the world-wide prevalence of smoking has substantially decreased over the past two decades (from ~33% in 2000 to ~20% in 2022), the World Health Organization (WHO) reported that there were approximately 1.245 billion current tobacco users world-wide in 2022 [6]. The WHO has projected this number to decrease only slightly to about 1.197 billion by 2030. In some countries, adults who still smoke now have access to non-combustible tobacco/nicotine-containing products that are considered less harmful than combustible cigarettes (CIG) [7, 8].

Heated tobacco products (HTP) are an example of smoke-free alternatives that are considered less harmful. Rather than burning tobacco as in CIG smoking, HTP function by heating the tobacco at significantly lower temperatures to produce aerosols for inhalation [9]. Aerosol chemistry analyses showed an average reduction of 90–95% in the levels of harmful and potentially harmful constituents in the aerosol compared to those produced in CIG smoke [10-12]. Biomarker studies also showed favorable changes in biomarkers of potential harm upon switching from CIG to HTP use compared to continued CIG smoking [13-17]. Moreover, results from human studies have suggested a trend of improved pulmonary function with switching from CIG to HTP in terms of increased forced expiratory volume in 1 second measured by spirometry [16, 18]. A longitudinal study found, on average, a decreased frequency of exacerbations in 19 patients switching to HTP compared to a matched group of 19 other patients who continued CIG smoking, suggesting an effect of HTP in clinically important measures of COPD outcomes [19]. However, all these findings need to be interpreted with caution due to their limited sample sizes. Not all studies have reported appreciable improvements in pulmonary function following a switch to HTP [20]. These studies hint at initial promises for patients with COPD who switch from smoking to HTP but also highlight the need for more conclusive evidence.

There remains a dearth of large, high-quality, long-term studies assessing the impact of HTP use by patients with COPD [21] and no real-world study to date. The study protocol presented in this paper is designed to bridge this gap. Study enrollment will reach out to approximately 30,000 patients with COPD, with a long follow-up period of up to 9 years for some eligible patients. This will help overcome the small sample size and short study duration that limited data interpretability in prior studies. Another strength is the use of a Japanese database that captures the healthcare experience of patients receiving medical care from a nationally representative hospital network. Also, multiple data sources will be used to assess tobacco exposure history, including questionnaires and consumer databases.

The study intends to address existing gaps in knowledge regarding HTP use in patients with COPD. For instance, no published studies examine the impact of switching from CIG to HTP on mortality in patients with COPD. As this is one of the study objectives, the results will likely provide early clues for this outcome in answering an important and highly relevant public health question. Overall, this study intends to provide real-world evidence in the rapidly growing area of research on long-term health effects of HTP use.

Study Objectives

Primary Objective

The primary objective is to compare the time from a patient's first COPD-related hospitalization, which occurred between May 1, 2016 and December 31, 2022 (ie, Index Event), to the composite outcome of a subsequent COPD-related hospitalization or all-cause mortality between comparable groups of HTP users and CIG smokers.

Secondary Objectives

The secondary objectives are to assess additional outcomes (mortality and respiratory outcomes) in patients with different tobacco product use patterns:

- To compare the time from the Index Event to all-cause mortality between comparable groups of:

  i) HTP users versus CIG smokers,

  ii) HTP users versus former smokers, and

  iii) HTP users versus dual users of CIG and HTP (hereafter, dual users; see **Table 1** for definition)

- To compare the time from the Index Event to a first pneumonia-related hospitalization between comparable groups of:

  i) HTP users versus CIG smokers,

  ii) HTP users versus former smokers, and

  iii) HTP users versus dual users

- To compare the number and rate of recurrent COPD-related hospitalizations and all-cause hospitalizations per year after the Index Event by comparable tobacco groups (CIG smokers, HTP users, dual users, and former smokers)

- To compare the time from the Index Event to the composite outcome of subsequent COPD-related hospitalization or all-cause mortality between comparable groups of:

  i) HTP users versus former smokers, and

  ii) HTP users versus dual users

- To evaluate whether the time from the Index Event to the composite outcome of a subsequent COPD-related hospitalization or all-cause mortality varies for HTP users by their total number of years since switching (ie, regardless of Index Date)

Table 1. Tobacco exposure groups and definitions

CIG smokers	HTP users	Dual users of CIG and HTP	Former smokers
• Smoked ≥ 1 CIG daily *AND* • Did not use HTP or used HTP	• Used ≥ 1 HTP consumable daily *AND* • Did not smoke CIG or smoked	• Smoked ≥ 1 CIG daily *AND* • Used ≥ 1 HTP consumable daily	• Did not use any tobacco product *AND* • Smoked ≥ 100 CIG in the lifetime or

consumables less than daily	less than daily		smoked ≥ 1 CIG daily for at least 1 year prior to the Index Event

CIG, combustible cigarette; HTP, heated tobacco product.

Methods

Study Design

This is a protocol for a retrospective cohort study assessing the risk of subsequent COPD exacerbations in association with tobacco use habits in Japanese COPD patients. The conduct of the study will leverage the Tokushukai Medical Group Database (TMG), an electronic healthcare database that includes real-world patients who sought medical care at a hospital that is part of the Tokushukai Medical Corporation, a healthcare network of about 75 hospitals in Japan. Information on tobacco exposure history will be collected using questionnaires completed by patients or their relatives. Additionally, consumer data on the purchase history of tobacco products will be obtained and linked to questionnaire responses to enable validation of patterns of tobacco product use, where applicable. The study protocol, informed consent form (ICF), enrollment outreach materials, and questionnaires were reviewed and approved by the Tokushukai Group's Ethics Committee (approval number: TGE02548-008).

Patients who have experienced at least one COPD-related hospitalization between May 1, 2016 and December 31, 2022 (ie, Index Event), as identified in the TMG, will be pre-screened for study eligibility (**Figure 1**). Those who are considered potentially eligible will be sent a study invitation package via postal mail using their personally identifiable information recorded in the TMG (PII; eg, name, address, etc.). If there is no reply to the initial outreach, another attempt will be made within 3 weeks of initial contact. In the study invitation package, there will be an ICF, a data request form (DRF; for querying and linking across data sources), a Tobacco Exposure Questionnaire (TEQ) for patients to complete, and a Relatives' Questionnaire (RQ) for relatives to complete. In case patients are deceased or are unable to provide consent on their own, any of their relatives or legal guardian, as the case may be, can participate in the study on behalf of the patient by returning the signed ICF and DRF. Relatives do not need to return the TEQ but will complete the RQ that is designed for proxy assessment of the patient's tobacco exposure history and provision of mortality information in case of the patient's death. **Figure 1** presents an overview of the design and data flow for this study.

Following data collection and prior to merging the tobacco exposure and healthcare data for the analysis of the study objectives, two separate raw datasets will be created to conduct a data check on exposure history and events. The results of the data checks will inform the patterns of tobacco product use and time to events in the overall study cohort to orient the main study analysis [22].

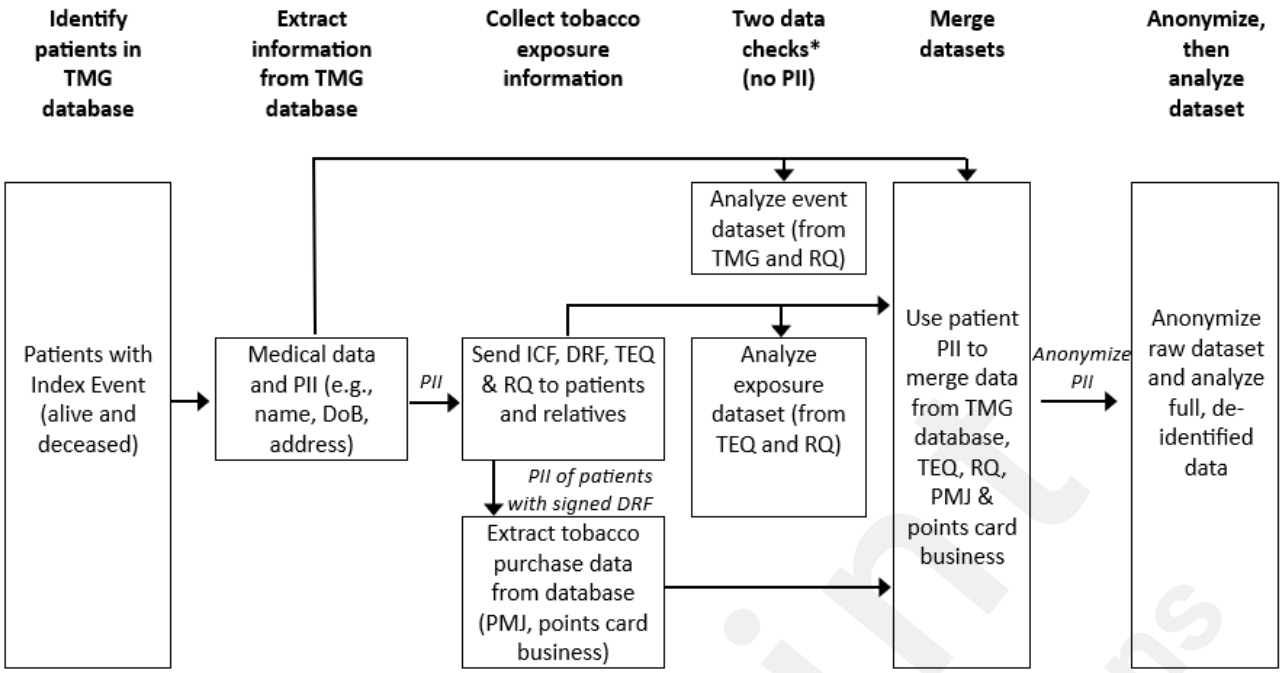


Figure 1. Overview of study design and data flow.

DoB, date of birth; DRF, data request form for permission to access consumption data; ICF, informed consent form; PMJ, Philip Morris Japan; PII, personally identifiable information (eg, combination of full name, date of birth, and address); RQ, Relatives' Questionnaire (to be completed by relatives of deceased and alive patients [those unable to complete the questionnaire themselves] to collect tobacco exposure and mortality data); TEQ, Tobacco Exposure Questionnaire; TMG, Tokushukai Medical Group.

*Data checks will be performed using data of patients whose ICF has been signed.

Figure 2 summarizes the time frames regarding eligibility assessment, cohort entry period, and exposure and outcome assessment windows. The discharge date of the first COPD-related hospitalization between May 1, 2016 and December 31, 2022 is the patient's cohort entry date. Study inclusion eligibility for each patient will be assessed based on medical data available prior to the respective cohort entry date. Outcomes will be assessed during the study follow-up period, which starts from the cohort entry date (ie, Index Date). Exposure status will be assessed pre- and post-index date until the end of the study follow-up period (March 31, 2025).

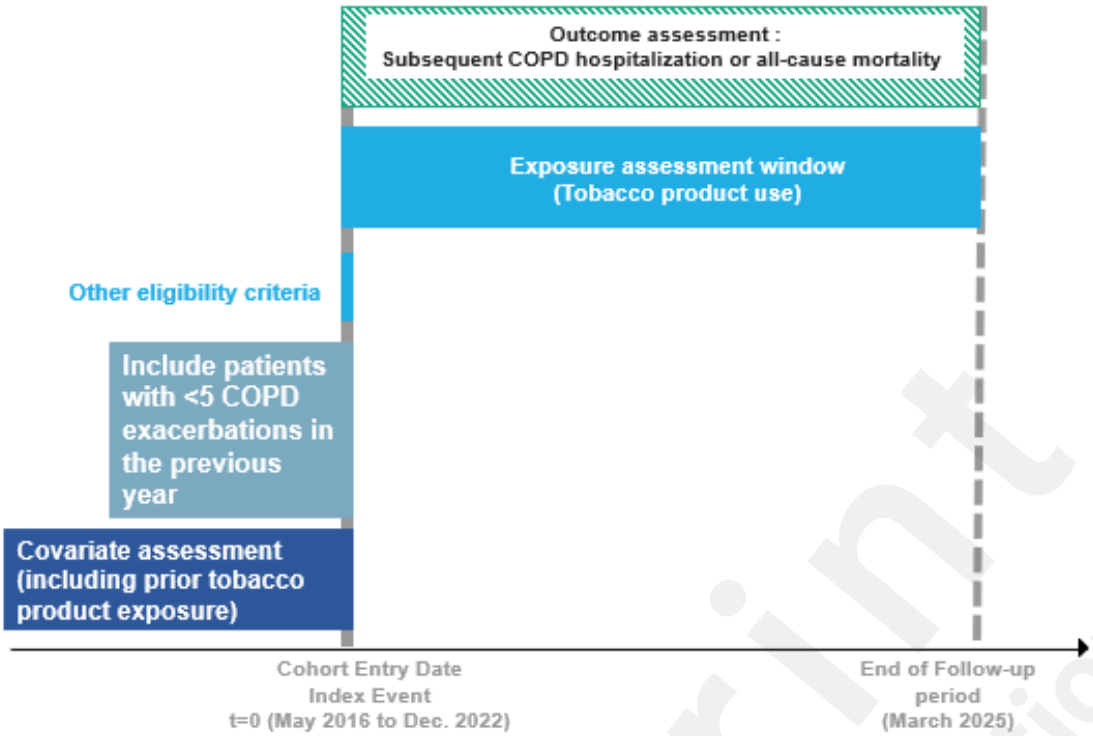


Figure 2. Study period overview. Note: The start of the exposure assessment window (here at Index event) is illustrative and will be determined after data checks on exposure and events.

COPD, chronic obstructive pulmonary disease.

Participants and Setting

The observational period for this study will be from May 1, 2016 (corresponding to the national availability of HTP in Japan) to March 31, 2025. Based on feasibility counts within the TMG, it is anticipated that approximately 30,000 patients could be eligible. The study invitation will be sent to all potentially eligible patients to maximize the final number of enrollments. The final study cohort will consist of patients who meet the study inclusion criteria and none of the exclusion criteria (**Table 2**).

Table 2. Study eligibility criteria

Inclusion criteria	• Patients with any healthcare encounter records in the TMG • Patients with record of the Index Event between May 1, 2016 and December 31, 2022 • Age 40 years or older at the time of the Index Event • Patients of any sex • Patients or relatives who can understand the information provided in the ICF and have signed it
Exclusion criteria	• Patients who have had 5 or more COPD-related hospitalizations in the 12 months prior to the Index Event • Never smokers: a patient who had either never smoked or had smoked < 100 CIG in their lifetime up until the questionnaire completion data (to be excluded because the prevalence of never smoking among patients with COPD is extremely low) • Patients having the following disease/s prior to the Index Event: bronchiectasis, active tuberculosis (defined as a tuberculosis diagnosis in the 12 months prior to the Index Event), cystic fibrosis, pulmonary fibrosis, pulmonary embolism, and lung cancer (Appendix I). • Tobacco industry employees or their first-degree relatives • Employees of the study sponsor and its affiliates or other organizations involved in the study

CIG, combustible cigarette; COPD, chronic obstructive pulmonary disease; ICF, informed consent form; TMG, Tokushukai Medical Group Database.

Data Sources and Collection

There are several data sources for the conduct of this study:

1. TMG: Health and related data from electronic medical records in the database will be used for patient identification, assessment of cohort entry eligibility, and assessment of study outcomes and covariates.

2. Questionnaires: Patients will answer a modified version of the About TEQ (which is part of the ABOUT-Toolbox™) designed specifically for this study for the retrospective assessment of tobacco exposure [23]. Relatives responding to the invitation on behalf of patients (alive or deceased) will complete the RQ for the assessment of tobacco exposure and information on mortality that occurred outside of the Tokushukai hospital network (if applicable).

3. Consumer databases (**Appendix II**): Classification of tobacco exposure group (**Table 1**) will be based on patient-/relative-reported information on consumption (questionnaires above). Additionally, data will be obtained from the Philip Morris Japan *IQOS*® Database and other Japanese consumer points card business databases. The DRF completed by patients/relatives will provide consent to access patients' purchase history of tobacco products. This data, whenever available, will be reviewed together with the individual's self-reported exposure to tobacco products (information in the TEQ will take priority). The proportion of the study population with information in these databases and the level of concordance between the questionnaires and databases will be presented as study results.

Variables

Tobacco Exposure Definition

Patients will be divided into four mutually exclusive groups based on their reported tobacco use pattern (daily average) between the pre-index date period and the end of follow-up (**Table 1**).

Assignment of patients into the exposure groups will be based on their product usage pattern during the exposure assessment window. Specifically, as aforementioned, a data check will be performed using an exposure dataset that consists of data on tobacco exposure history from the TEQ or RQ and the index date for each patient. The aim of the exposure data check is to assess the persistence on (ie, duration of use of) each type of product use (CIG, HTP, dual use, and no use) will be assessed [22]. The exposure dataset will not contain any information on health outcomes.

A patient will be censored at the (i) time of a change in tobacco usage pattern during the follow-up period (ie, changing from one exposure group to another according to the study definition, **Table 1**), (ii) occurrence of an outcome, (iii) exit from the TMG, or (iv) end of the follow-up period. **Figures 3 and 4** provide an illustration of tobacco exposure for eight hypothetical patients during their follow-up period: **Figure 3** presents how exposure data will be captured, and **Figure 4** presents how an exposure group will be assigned for data analysis.

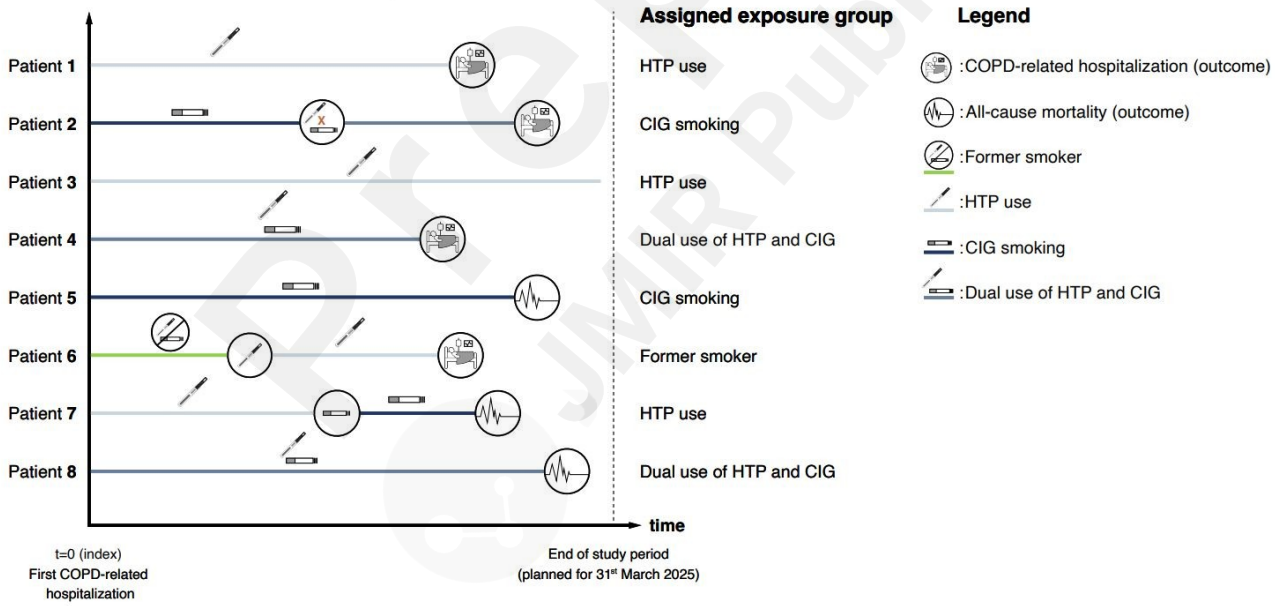


Figure 3

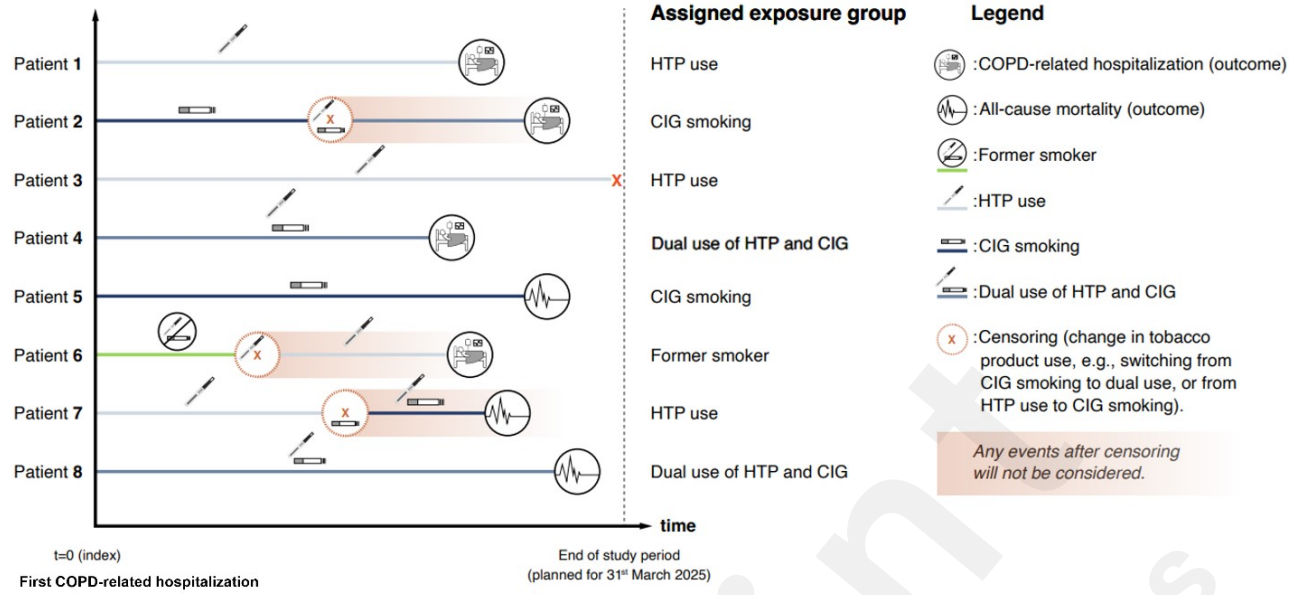


Figure 4

Figure 3 and 4. Classification of patients into exposure groups before exploring their association with outcomes: (**Figure 3**) Exposure data expected to be collected, (**Figure 4**) Exposure data used to classify patients into exposure groups. The symbol 'X' in the figure represents patient censoring at the end of study period, and a circle with a product inside signifies a switch to use of that product. Note: The start of the exposure assessment window (here at index) is illustrative and will be determined after data checks on exposure and on events.

CIG, combustible cigarette; COPD, chronic obstructive pulmonary disease; HTP, heated tobacco product.

Outcome Definition

Primary Outcome

The primary outcome is a composite outcome of subsequent COPD-related hospitalization and all-cause mortality following the Index Event. Subsequent COPD-related hospitalizations will be identified from the International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes recorded in the TMG at patient discharge (see ICD-10 codes listed in **Appendix III**) [24]. All-cause mortality will be identified in the TMG based on information (listed in **Appendix III**) from the discharge summary (inpatient deaths), while the questionnaires completed by relatives will be used to ascertain mortality occurring outside the Tokushukai hospital network.

COPD-related hospitalizations with an admission date occurring within 2 weeks of the Index Event will be considered the same event [25]. In such a scenario, the first hospitalization within the study period will be considered the Index Event. Similarly, when assessing the number of recurrent COPD-related hospitalizations during the study period to address the secondary objectives, only hospital admissions separated by at least 2 weeks will be considered as distinct events.

A data check will be performed using an event dataset that consists of health outcomes data obtained from the TMG and RQ (for mortality information). The aim of the event data check is to assess the number of outcome events, the drivers of the composite outcome, and the time between index date and outcome event [22]. The event dataset will not contain any information on tobacco exposure.

Secondary Outcomes

To address the secondary objectives, subsequent COPD-related hospitalization and all-cause mortality will be assessed in patients who are dual users and former CIG smokers who have quit smoking. Additionally, pneumonia-related hospitalization will be assessed as a secondary outcome and will be identified in a similar manner to COPD-related hospitalization (see **Appendix III**).

Covariates

Patients' medical records will be accessed from the TMG. The extracted information will include demographics and medical and vaccine information. A list of some of the relevant covariates and comorbidities can be found in **Appendices IV** and **V**.

Sample Size

The minimum sample size required for the analysis of the primary objective is 9,683 participants (6,457 CIG smokers and 3,181 HTP users) and 851 events. Calculation of this size estimate has accounted for 10% of missing data (on exposure, covariates, and outcomes) and propensity score weighting of data (inflation by 30%). The study will be statistically powered if the number of events is met, irrespective of the minimum size required. However, if the number of events identified is insufficient, the study will be reconsidered as exploratory.

This sample size estimation was calculated based on estimates from the literature. Based on a 2020 study conducted in Japan, the ratio of current CIG smokers to current HTP users is assumed to be around 2:1 (prevalence of 25.9% vs 10.9%) [26]. For COPD-related hospitalizations following smoking cessation, an article summarizing three prospective studies reported a hazard ratio (HR) of 0.58 for former smokers compared to continued smokers [27]. As there is no data comparing subsequent COPD events with HTP use and CIG smoking, we assume the risk for HTP users to be between that of CIG smokers and former smokers. We therefore assumed an HR of 0.79 for HTP users (vs. CIG smokers) for the primary outcome, which is the midpoint between the expected impact of smoking cessation (HR: 0.58) and a null effect (HR: 1.00). Finally, regarding exacerbation rates, an article reported a 1-year event rate of 9% for COPD inpatient or outpatient exacerbations among current smokers with a COPD diagnosis [28]. As our study does not consider outpatient COPD-related visits, we assume that the event rate might be lower. For this reason and over a period of up to 5 years of follow-up, we estimate a conservative event rate of 15%. The assumptions used for the sample size calculation are summarized in **Appendix VI.**

Data protection and privacy

Throughout the conduct of the study, only Tokushukai Information System, the data management department for the TMG, will have access to patients' PII. After data collection and the exposure and event data checks, a contract research organization (CRO) managing the study will use patient' identification number (a pseudonymized patients' number created by the Tokushukai Information System) to merge the tobacco exposure data (from TEQ, RQ, and consumer databases) and healthcare data (from TMG). The CRO will anonymize the merged dataset following local data protection regulations and the General Data Protection Regulation and will only use the anonymized data for analysis. The study sponsor will not have access to patients' PII and will receive anonymized data only.

Statistical Analysis

Descriptive statistics will be performed to summarize the distribution of sociodemographic characteristics (eg, age), lifestyle factors, and clinical characteristics for the four exposure groups. Categorical variables will be summarized using frequency and percentages, while continuous variables will be summarized using mean and standard deviation.

Methods of Analysis

Kaplan-Meier survival curves will be used to report on the time from the Index Event to subsequent COPD-related hospitalization or all-cause mortality for the four exposure subgroups. The study hypothesis under the primary objective (that HTP users will have a longer time to a subsequent

COPD hospitalization or all-cause mortality than CIG smokers) will be based on one-sided statistical testing at a significance level of 2.5%. All other statistical tests will be two-sided with a significance level of 5%, unless otherwise specified.

For the analysis of the primary outcome, a weighted Cox proportional hazard model will be used to compare time from Index Event to subsequent COPD-related hospitalization or all-cause mortality between comparable exposure groups of HTP users and CIG smokers (reference group). The secondary objectives related to the analysis of time from Index Event to the secondary outcomes will be performed using the same analysis strategy as for the primary outcome. For all the analyses using Cox proportional hazards model, the proportional hazard assumption will be tested.

It is important to note that the statistical approach will not be restricted to censoring of patients at the time of a change in tobacco product usage pattern during the follow-up period. Other approaches will be explored, e.g., different exposure assessment windows, marginal structural models using time-varying exposure after Index Event.

Plans for Addressing Confounding

For the primary outcome, a propensity score weighting method will be applied to balance potential confounding factors between both exposure groups, using CIG smokers as the reference. The following variables will be considered as confounders and included in the propensity score weighting: age, sex, income, year of Index Event, body mass index, pack-year of CIG smoking, number of COPD-related hospitalizations in the 12 months prior to the Index Event, length of hospital stay during the Index Event, history of asthma, source of tobacco exposure data (patient or relative), and history of major cardiovascular disease (myocardial infarction, heart failure, and stroke), diabetes, pneumonia-related hospitalization in the 12 months prior to the Index Event, and COPD medications at Index Event (if the information is available in the TMG). Propensity score weighting will also be used for the analysis of the other study outcomes. For the outcome accounting for death as a competing risk, a frailty model will be used.

Missing Data

The pattern of missingness will be analyzed, and the characteristics of participants with and without missing data will be compared. For variables with a large proportion of missing data (ie, ≥ 30% of the study sample defined *a priori*), imputations for missing data will be considered. However, variables with more than 50% missing data (defined *a priori*) will be removed entirely from the statistical model.

Results

Data collection is anticipated to be completed in the second quarter of 2025. Data quality review and statistical analyses should commence in the third quarter of 2025 and results are expected to be published in 2026.

Discussion

This protocol describes a large-scale, long-term, retrospective cohort study that aims to evaluate the impact of switching from CIG smoking to HTP use compared to continued CIG smoking, dual use, and quitting CIG on the time to developing subsequent COPD exacerbations in a cohort of patients who have had a COPD-related hospitalization. The study intends to leverage the use of an existing database from an established hospital network in Japan, which is the country with the longest history of HTP use. The results from this study might help adult CIG smokers who do not quit to make more informed decisions regarding tobacco product use. In addition, this study may provide valuable insights into the impact that switching to HTP has on outcomes of long-term conditions, which is an expanding area of research with comparatively few real-world studies.

Strengths of the Study

A major strength of this proposed study is its use of an existing large healthcare database to identify eligible patients. The TMG compiles medical information from approximately 75 hospitals and over 13 million patients [29] and is therefore a rich source of real-world data. Using this database will likely also improve the generalizability of the study results, as it is representative of the general Japanese COPD population.

Another strength of this proposed study is its large sample size, with almost 10,000 patients expected to be included in the analysis of the primary objective. Previous studies have been hampered by their limited sample size, which may explain the mixed results reported so far [16, 18-20, 30].

In addition, the study cohort could potentially have a total follow-up period of 8 years and 11 months for patients identified early in the Index Period. This distinguishes the study from several prior studies, which were limited by their duration, with follow-up ranging between 90 days and 5 years [16, 18, 19]. The longer duration of this study's follow-up and the large sample size should enable the assessment of both short-term and long-term effects of HTP use.

Furthermore, the ability to objectively ascertain study outcomes from electronic medical records will help reduce full dependence on patient self-reports, which might be inaccurate and subject to bias. Comparing data from the consumer databases with patient/relative-reported consumption data may also assist in assessing the degree of recall bias, as this can provide an alternative method of assessing exposure and prevent reliance on patient self-reports alone, although their usefulness is likely limited by linkage challenges and/or incomplete information. Merging the anticipated self-report tobacco exposure data and consumer data on purchases of tobacco products, if feasible, can create a unique dataset to assess the concordance between the different data sources. The opportunity to compare data on purchases versus consumptions of tobacco products can inform the design of future studies on the utilities of these real-world data sources.

Finally, unlike several other studies that assessed various biomarkers of exposure and of potential harm, this study intends to assess clinically measurable outcomes (ie, severe COPD exacerbations and mortality), which are more easily interpretable and applicable to the general public's understanding of the effects of switching from CIG to HTP. In addition, no prior study has assessed the potential for subsequent COPD events with HTP use, and the findings from this study will be beneficial for this patient subgroup.

Limitations of the Study

Several limitations of this study are inherent to its observational design. First, the study is designed to estimate the time to having a subsequent event in a population that already had at least one. It is possible that any benefit of switching to HTP instead of continuing CIG smoking is less marked at this stage of COPD. Nevertheless, frequent and severe exacerbations have been observed among patients with prior respiratory events [3], and the findings from this study will still be relevant to individuals who fall within this category. Next, recall bias for the assessment of type and level of tobacco product exposure is a concern for this study due to its reliance on patients' and relatives' recollection to complete the questionnaires, with some patients having to remember their patterns of tobacco use as far back as 8 years. Relatives' recollection of a deceased person's past behavior would likely be biased towards unhealthy habits, which may lead to an overestimation of the duration and type of tobacco exposure. Using consumer databases to obtain data on the purchase of tobacco products as a proxy for consumption might help estimate the degree of this bias and further facilitate the interpretation of the study findings. However, even this might not be an accurate representation as people can purchase tobacco products for others or use the points cards inconsistently.

Furthermore, data completeness is a potential concern, as data on tobacco use, covariates, and/or the study outcomes may be missing. This will be mitigated by using imputations for covariates with limited missing values. However, variables that have a significant proportion of missing values (eg,

> 50%) may be removed entirely from the statistical model. Deaths occurring outside the Tokushukai hospital network may be missed, as the TMG mainly captures in-patient mortality within its healthcare network, and this may lead to an underestimation of mortality and misclassification of the study outcome. We will mitigate this by ascertaining information on the patient's survival status from their relatives, but this only works for relatives who share the same mailing address with the patient and for those whose address did not change, as the TMG does not have contact details for relatives. Also, in cases where a patient visits a hospital outside the Tokushukai network, subsequent COPD-related hospitalizations may be missed.

Finally, the study results may be affected by confounding due to the observational nature of the study. Our use of propensity score weighting to balance potential confounders may minimize some confounding, but residual confounding due to unmeasured (eg, level of physical exercise) or misclassified confounders (eg, concomitant medications) remains a concern. Additionally, reverse causality is a possible bias, with CIG smokers who are known to have a higher risk of adverse health outcomes being more likely to switch to HTP. To address this concern, the total years of HTP use and the total duration of CIG smoking will also be analyzed.

Conclusion

This proposed study aims to significantly contribute to the limited existing evidence regarding the effects of switching from CIG to HTP in comparison to continued CIG smoking, dual use, and quitting CIG on COPD outcomes and mortality by generating long-term evidence based on real-world data. It will focus on patients who have experienced severe exacerbations of COPD that required hospitalization, using a retrospective cohort design with follow-up data spanning approximately 9 years. We expect the enrollment for this study to be 3 orders of magnitude greater than that of previous studies assessing the risk of COPD-related outcomes in smokers of CIG compared to users of alternative products. This larger sample size will likely enhance the precision of our findings. Additionally, this study protocol is the first in the tobacco medical literature to embrace real-world data involving HTP use from various sources in a multimodal approach. In particular, it considers multiple data sources related to tobacco exposure, including tobacco purchase information from consumer databases. The results, if informative, will be important in guiding recommendations for patients with COPD while providing evidence to support public health policies. Additionally, these results will contribute to our understanding of the effects of HTP use and can serve as a foundation for future research exploring various health outcomes related to this alternative tobacco product.

Acknowledgments

Medical writing support (including preparation of the draft manuscript under the direction and guidance of the authors, incorporating authors' comments for each draft, assembling tables and figures, grammatical editing, and referencing) was provided by UBC S.A. and was funded by Philip Morris Products S.A.

Declarations of Interest

Ethics approval and consent to participate

The study was approved by the Tokushukai Group's Ethics Committee, Japan, under the tracking number (TGE02548-008).

Consent for publication

Not applicable

Availability of data and materials

Not applicable for study protocols.

Competing interests

HK, AL, DB, PP, BC, and MHaidar are employees of Philip Morris Products S.A. BC, PP, and Mhaidar hold stock in Philip Morris International. HK previously worked for Novartis Pharma A.G. and receives fees for her duties as the Editor-in-Chief of Epidemiologic Methods, a De Gruyter journal. MHaidar previously worked for Kantar Health. BC and MHibino are clinical trial investigators. MHibino is employed by Shonan Fujisawa Tokushukai Hospital and has received speaker fees from Chugai Pharmaceutical Co. Ltd, Ono Pharmaceutical, AstraZeneca, MSD-Merck, and Eli Lilly. SH is employed by Tokushukai Medical Corporation. PP previously worked for Vectura Fertin Pharma. DB was previously employed by the University of the West of Scotland.

Funding

Philip Morris Products S.A. is the sole source of funding and sponsor of the research proposed in the protocol.

Authors' contributions

All authors equally contributed to the manuscript draft, review, and final approval.

Abbreviations

CIG: combustible cigarettes
COPD: chronic obstructive pulmonary disease
CRO: contract research organization
DoB: date of birth
DRF: data request form
HR: hazard ratio
HTP: heated tobacco products
ICD-10: International Classification of Diseases, Tenth Revision
ICF: informed consent form
MI: myocardial infarction
PII: personally identifiable information
PMJ: Philip Morris Japan
RQ: Relatives' Questionnaire
TEQ: Tobacco Exposure Questionnaire
TMG: Tokushukai Medical Group Database

References

1. World Health Organization. Chronic obstructive pulmonary disease (COPD). 2024; URL: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-%28copd%29 [accessed 2024-10-04]
2. Ministry of Health:Labour and Welfare. Cause of death. 2022; URL: https://www.mhlw.go.jp/english/database/db-hw/lifetb22/dl/lifetb22-04.pdf [accessed 2024-10-04]
3. Ding B, Zaha R, Makita N, Graham S, Lambrelli D, Huse S, et al. History of respiratory events prior to a first COPD diagnosis and future exacerbations: A longitudinal observational cohort database study in Japan. Int J Chron Obstruct Pulmon Dis. 2023;18:247-258 [doi: 10.2147/copd.S389297].
4. World Health Organization. Tobacco and coronary heart disease. 2020; URL: https://www.who.int/publications/i/item/9789240010628 [accessed 2024-10-04]
5. Sheikh M, Mukeriya A, Shangina O, Brennan P, Zaridze D. Postdiagnosis smoking cessation and reduced risk for lung cancer progression and mortality: A prospective cohort study. Ann Intern Med. 2021;174(9):1232-1239 [doi: 10.7326/m21-0252].
6. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000–2030. 2024; URL: https://www.who.int/publications/i/item/9789240088283 [accessed 2024-10-04]
7. Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: a compelling harm reduction alternative to cigarettes. Harm Reduct J. 2019;16(1):62 [doi: 10.1186/s12954-019-0335-1].
8. McNeill A, Simonavicius E, Brose L, Taylor E, East K, Zuikova E, et al. Nicotine vaping in England: An evidence update including health risks and perceptions. In: Disparities OoHIa, editor. London: King's College London; 2022.
9. Cozzani V, Barontini F, McGrath T, Mahler B, Nordlund M, Smith M, et al. An experimental investigation into the operation of an electrically heated tobacco system. Thermochimica Acta. 2020;684:178475.
10. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K, Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 2018;113(11):2099-2106 [doi: 10.1111/add.14365].
11. Li X, Luo Y, Jiang X, Zhang H, Zhu F, Hu S, et al. Chemical analysis and simulated pyrolysis of Tobacco Heating System 2.2 compared to conventional cigarettes. Nicotine Tob Res. 2019;21(1):111-118 [doi: 10.1093/ntr/nty005].
12. Yuki D, Kikuchi A, Suzuki T, Sakaguchi C, Huangfu D, Nagata Y, et al. Assessment of the exposure to selected smoke constituents in adult smokers using in-market heated tobacco products: a randomized, controlled study. Sci Rep. 2022;12(1):18167 [doi: 10.1038/s41598-022-22997-1].
13. Gale N, McEwan M, Camacho OM, Hardie G, Proctor CJ, Murphy J. Changes in biomarkers after 180 days of tobacco heating product use: a randomised trial. Intern Emerg Med. 2021;16(8):2201-2212 [doi: 10.1007/s11739-021-02798-6].
14. Gale N, McEwan M, Hardie G, Proctor CJ, Murphy J. Changes in biomarkers of exposure and biomarkers of potential harm after 360 days in smokers who either continue to smoke, switch to a tobacco heating product or quit smoking. Intern Emerg Med. 2022;17(7):2017-2030 [doi: 10.1007/s11739-022-03062-1].
15. Haziza C, de La Bourdonnaye G, Donelli A, Skiada D, Poux V, Weitkunat R, et al. Favorable changes in biomarkers of potential harm to reduce the adverse health effects of smoking in smokers switching to the Menthol Tobacco Heating System 2.2 for 3 months (part 2). Nicotine Tob Res. 2020;22(4):549-559 [doi: 10.1093/ntr/ntz084].

16. Lüdicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, et al. Effects of switching to a Heat-Not-Burn tobacco product on biologically relevant biomarkers to assess a candidate modified risk tobacco product: A randomized trial. Cancer Epidemiol Biomarkers Prev. 2019;28(11):1934-1943 [doi: 10.1158/1055-9965.Epi-18-0915].
17. Martin F, Talikka M, Ivanov NV, Haziza C, Hoeng J, Peitsch MC. A meta-analysis of the performance of a blood-based exposure response gene signature across clinical studies on the Tobacco Heating System 2.2 (THS 2.2). Front Pharmacol. 2019;10:198 [doi: 10.3389/fphar.2019.00198].
18. Lüdicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N, et al. Effects of switching to the Menthol Tobacco Heating System 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: A randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (part 2). Nicotine Tob Res. 2018;20(2):173-182 [doi: 10.1093/ntr/ntx028].
19. Polosa R, Morjaria JB, Prosperini U, Busà B, Pennisi A, Gussoni G, et al. Health outcomes in COPD smokers using heated tobacco products: a 3-year follow-up. Intern Emerg Med. 2021;16(3):687-696 [doi: 10.1007/s11739-021-02674-3].
20. Harada S, Sata M, Matsumoto M, Iida M, Takeuchi A, Kato S, et al. Changes in smoking habits and behaviors following the introduction and spread of Heated Tobacco Products in Japan and its effect on FEV(1) decline: A longitudinal cohort study. J Epidemiol. 2022;32(4):180-187 [doi: 10.2188/jea.JE20210075].
21. Morjaria JB, Campagna D, Caci G, O'Leary R, Polosa R. Health impact of e-cigarettes and heated tobacco products in chronic obstructive pulmonary disease: current and emerging evidence. Expert Rev Respir Med. 2022;16(11-12):1213-1226 [doi: 10.1080/17476348.2023.2167716].
22. Wang SV, Schneeweiss S. Data checks before registering study protocols for health care database analyses. JAMA. 2024;331(17):1445-1446 [doi: 10.1001/jama.2024.2988].
23. Chrea C, Acquadro C, Afolalu EF, Spies E, Salzberger T, Abetz-Webb L, et al. Developing fit-for-purpose self-report instruments for assessing consumer responses to tobacco and nicotine products: the ABOUT™ Toolbox initiative. F1000Res. 2018;7:1878 [doi: 10.12688/f1000research.16810.1].
24. International Statistical Classification of Diseases and Related Health Problems 10th Revision. 2019; URL: https://icd.who.int/browse10/2019/en [accessed 2024-10-04]
25. Jones TPW, Brown J, Hurst JR, Vancheeswaran R, Brill S. COPD exacerbation phenotypes in a real-world five year hospitalisation cohort. Respir Med. 2020;167:105979 [doi: 10.1016/j.rmed.2020.105979].
26. Odani S, Tabuchi T. Prevalence of heated tobacco product use in Japan: the 2020 JASTIS study. Tob Control. 2022;31(e1):e64-e65 [doi: 10.1136/tobaccocontrol-2020-056257].
27. Godtfredsen NS, Vestbo J, Osler M, Prescott E. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. Thorax. 2002;57(11):967-972 [doi: 10.1136/thorax.57.11.967].
28. Au DH, Bryson CL, Chien JW, Sun H, Udris EM, Evans LE, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. J Gen Intern Med. 2009;24(4):457-463 [doi: 10.1007/s11606-009-0907-y].
29. Kinugasa Y, Llamas-Covarrubias MA, Ozaki K, Fujimura Y, Ohashi T, Fukuda K, et al. Post-Coronavirus disease 2019 syndrome in Japan: An observational study using a medical database. JMA j. 2023;6(4):416-425 [doi: 10.31662/jmaj.2023-0048].
30. Hirai K, Tanaka A, Homma T, Kawahara T, Oda N, Mikuni H, et al. Characteristics of and reasons for patients with chronic obstructive pulmonary disease to continue smoking, quit smoking, and switch to heated tobacco products. Tob Induc Dis. 2021;19:85 [doi: 10.18332/tid/142848].

Appendices

Appendix I. ICD-10 codes for the diseases in the exclusion criteria.

Disease	ICD-10 codes
Tuberculosis	*A15 Respiratory tuberculosis, bacteriologically and histologically confirmed* *A16 Respiratory tuberculosis, not confirmed bacteriologically or histologically* *A17 Tuberculosis of nervous system* *A18 Tuberculosis of other organs* *A19 Miliary tuberculosis*
Bronchiectasis	*J47 Bronchiectasis*
Cystic fibrosis	*E84 Cystic fibrosis* ▪ E84.0 Cystic fibrosis with pulmonary manifestations ▪ E84.1 Cystic fibrosis with intestinal manifestations ▪ E48.8 Cystic fibrosis with other manifestations ▪ E84.9 Cystic fibrosis, unspecified
Pulmonary fibrosis	*J84 Other interstitial pulmonary diseases* ▪ J84.1 Other interstitial pulmonary diseases with fibrosis
Pulmonary embolism	*I26 Pulmonary embolism* ▪ I26.0 Pulmonary embolism with mention of acute cor pulmonale ▪ I26.9 Pulmonary embolism without mention of acute cor pulmonale
Lung cancer	*C34 Malignant neoplasm of bronchus and lung*
Source of ICD-10 code definitions: https://icd.who.int/browse10/2019/en	

Appendix II. Additional data source descriptions.

Philip Morris Japan *IQOS* database	The Philip Morris Japan (PMJ) *IQOS* database includes information on purchases of *IQOS* devices (a type of heated tobacco product [HTP]). The data request form (DRF) completed by patients or their relatives will provide consent to access patients' HTP purchase history from the PMJ database, by searching the database with a combination of personally identifiable information (PII) such as sex, email address, and phone number.
Points card business databases	Some points card businesses in Japan have fidelity programs that track purchases of tobacco products (eg, combustible cigarette [CIG] or HTP sticks). The DRF completed by patients or their relatives will provide consent to access patients' tobacco product purchase history from the points card business databases in Japan, by searching the database with a combination of PII.

Appendix III. ICD-10 codes for identification of Index Event and study outcomes.

Index Event/Outcome	ICD-10 codes
COPD-related hospitalization	*J41 Simple and mucopurulent chronic bronchitis* ▪ J41.0 Simple chronic bronchitis ▪ J41.1 Mucopurulent chronic bronchitis ▪ J41.8 Mixed simple and mucopurulent chronic bronchitis *J42 Unspecified chronic bronchitis* *J43 Emphysema* ▪ J43.1 Panlobular emphysema ▪ J43.2 Centrilobular emphysema ▪ J43.8 Other emphysema ▪ J43.9 Emphysema, unspecified *J44 Other chronic obstructive pulmonary disease* ▪ J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection ▪ J44.1 Chronic obstructive pulmonary disease with acute exacerbation, unspecified ▪ J44.8 Other specified chronic obstructive pulmonary disease ▪ J44.9 Chronic obstructive pulmonary disease, unspecified
COPD-related mortality	Any death recorded with COPD ICD-10 codes defined above
All-cause mortality	Death due to any ICD-10 code
Pneumonia-related hospitalization (only for outcome identification)	▪ J12 Viral pneumonia, not elsewhere classified ▪ J13 Pneumonia due to *Streptococcus pneumoniae* ▪ J14 Pneumonia due to *Haemophilus influenzae* ▪ J15 Bacterial pneumonia, not elsewhere classified ▪ J16 Pneumonia due to other infection organisms, not elsewhere classified ▪ J17 Pneumonia in diseases classified elsewhere ▪ J18 Pneumonia, organism unspecified
All-cause hospitalization	Hospitalization due to any cause
Source of ICD-10 code definitions: https://icd.who.int/browse10/2019/en	

Appendix IV. Covariates to be extracted from the Tokushukai Medical Database.

- Date of birth
- Sex
- Income information
- Smoking status (smoking index (number of cigarettes per day and by years of smoking))
- Height and weight
- Clinical laboratory information (eg, glycated hemoglobin)
- Comorbidities prior to the Index Event (ICD-10 codes attached) with their date of diagnosis (Appendix V):
    - Cardiovascular diseases: myocardial infarction, stroke, heart failure
    - Asthma
    - Cancer (any malignant type other than lung cancer)
    - Diabetes
    - Pneumonia-related hospitalization 12 months prior to the Index Event
- COPD medications/respiratory maintenance treatment (procedures)
- Respiratory function-related test data, where possible
- Respiratory rehabilitation treatment
- Flu, pneumococcal, and COVID-19 vaccination history, where possible

Appendix V. ICD-10 codes for comorbidities.

Comorbidities	ICD-10 codes
Myocardial Infarction (MI)	*I21 Acute MI* ▪ I21.0 Acute transmural MI of anterior wall ▪ I21.1 Acute transmural MI of inferior wall ▪ I21.2 Acute transmural MI of other sites ▪ I21.3 Acute transmural MI of unspecified site ▪ I21.4 Acute subendocardial MI ▪ I21.9 Acute MI, unspecified *I22 Subsequent MI* ▪ I22.0 Subsequent MI of anterior wall ▪ I22.1 Subsequent MI of inferior wall ▪ I22.8 Subsequent MI of other sites ▪ I22.9 Subsequent MI of unspecified site *I25.8 Other forms of chronic ischemic heart disease (Any condition in I21-I22 and I24 specified as chronic or with a stated duration of more than 4 weeks [more than 28 days] from onset)*
Stroke	*I60 Subarachnoid hemorrhage* ▪ I60.0 Subarachnoid hemorrhage from carotid siphon and bifurcation ▪ I60.1 Subarachnoid hemorrhage from middle cerebral artery ▪ I60.2 Subarachnoid hemorrhage from anterior communicating artery ▪ I60.3 Subarachnoid hemorrhage from posterior communicating artery ▪ I60.4 Subarachnoid hemorrhage from basilar artery ▪ I60.5 Subarachnoid hemorrhage from vertebral artery ▪ I60.6 Subarachnoid hemorrhage from other intracranial arteries *I61 Intracerebral hemorrhage* ▪ I61.0 Intracerebral hemorrhage in hemisphere, subcortical ▪ I61.1 Intracerebral hemorrhage in hemisphere, cortical ▪ I61.2 Intracerebral hemorrhage in hemisphere, unspecified ▪ I61.3 Intracerebral hemorrhage in brain stem ▪ I61.4 Intracerebral hemorrhage in cerebellum ▪ I61.5 Intracerebral hemorrhage, intraventricular ▪ I61.6 Intracerebral hemorrhage, multiple localized ▪ I61.8 Other intracerebral hemorrhage ▪ I61.9 Intracerebral hemorrhage, unspecified *I62 Other nontraumatic intracranial hemorrhage* ▪ I62.0 Nontraumatic subdural hemorrhage ▪ I62.1 Nontraumatic extradural hemorrhage ▪ I62.9 Intracranial hemorrhage (nontraumatic), unspecified *I63 Cerebral infarction* ▪ I63.0 Cerebral infarction due to thrombosis of precerebral arteries ▪ I63.1 Cerebral infarction due to embolism of precerebral arteries ▪ I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

	▪ I63.3 Cerebral infarction due to thrombosis of cerebral arteries ▪ I63.4 Cerebral infarction due to embolism of cerebral arteries ▪ I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries ▪ I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic ▪ I63.8 Other cerebral infarction ▪ I63.9 Cerebral infarction, unspecified *I64 Stroke, not specified as hemorrhage or infarction* *I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction* ▪ I65.0 Occlusion and stenosis of vertebral artery ▪ I65.1 Occlusion and stenosis of basilar artery ▪ I65.2 Occlusion and stenosis of carotid artery ▪ I65.3 Occlusion and stenosis of multiple and bilateral precerebral arteries ▪ I65.8 Occlusion and stenosis of other precerebral artery ▪ I65.9 Occlusion and stenosis of unspecified precerebral artery *I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction* ▪ I66.0 Occlusion and stenosis of middle cerebral artery ▪ I66.1 Occlusion and stenosis of anterior cerebral artery ▪ I66.2 Occlusion and stenosis of posterior cerebral artery ▪ I66.3 Occlusion and stenosis of cerebellar arteries ▪ I66.4 Occlusion/ stenosis of multiple and bilateral cerebral arteries ▪ I66.8 Occlusion and stenosis of other cerebral artery ▪ I66.9 Occlusion and stenosis of unspecified cerebral artery *I67 Other cerebrovascular diseases* ▪ I67.0 Dissection of cerebral arteries, nonruptured ▪ I67.1 Cerebral aneurysm, nonruptured ▪ I67.2 Cerebral atherosclerosis ▪ I67.3 Progressive vascular leukoencephalopathy ▪ I67.4 Hypertensive encephalopathy ▪ I67.6 Nonpyogenic thrombosis of intracranial venous system ▪ I67.7 Cerebral arteritis, not elsewhere classified ▪ I67.8 Other specified cerebrovascular diseases ▪ I67.9 Cerebrovascular disease, unspecified *G46 Vascular syndromes of brain in cerebrovascular diseases* ▪ G46.0 Middle cerebral artery syndrome ▪ G46.1 Anterior cerebral artery syndrome ▪ G46.2 Posterior cerebral artery syndrome ▪ G46.3 Brain stem stroke syndrome ▪ G46.4 Cerebellar stroke syndrome ▪ G46.5 Pure motor lacunar syndrome ▪ G46.6 Pure sensory lacunar syndrome ▪ G46.7 Other lacunar syndromes ▪ G46.8 Other vascular syndromes of brain in cerebrovascular diseases
Heart failure	*I50 heart failure* ▪ I50.0 Congestive heart failure

	▪ I50.1 Left ventricular failure ▪ I50.9 Heart failure, unspecified
Asthma	*J45 Asthma* ▪ J45.0 Predominantly allergic asthma ▪ J45.1 Nonallergic asthma ▪ J45.8 Mixed asthma ▪ J45.9 Asthma, unspecified
Diabetes	*E11 Type 2 diabetes mellitus* ▪ E11.0 Type 2 diabetes mellitus with coma ▪ E11.1 Type 2 diabetes mellitus with ketoacidosis ▪ E11.2 Type 2 diabetes mellitus with renal complications ▪ E11.3 Type 2 diabetes mellitus with ophthalmic complications ▪ E11.4 Type 2 diabetes mellitus with neurological complications ▪ E11.5 Type 2 diabetes mellitus with peripheral circulatory complications ▪ E11.6 Type 2 diabetes mellitus with other specified complications ▪ E11.7 Type 2 diabetes mellitus with multiple complications ▪ E11.8 Type 2 diabetes mellitus with unspecified complications ▪ E11.9 Type 2 diabetes mellitus without complications *E14 Unspecified diabetes mellitus* ▪ E14.0 Unspecified diabetes mellitus with coma ▪ E14.1 Unspecified diabetes mellitus with ketoacidosis ▪ E14.2 Unspecified diabetes mellitus with renal complications ▪ E14.3 Unspecified diabetes mellitus with ophthalmic complications ▪ E14.4 Unspecified diabetes mellitus with neurological complications ▪ E14.5 Unspecified diabetes mellitus with peripheral circulatory complications ▪ E14.6 Unspecified diabetes mellitus with other specified complications ▪ E14.7 Unspecified diabetes mellitus with multiple complications ▪ E14.8 Unspecified diabetes mellitus with unspecified complications ▪ E14.9 Unspecified diabetes mellitus without complications
Pneumonia-related hospitalization	As defined above in Appendix I
Cancer	*C00-C97 Malignant neoplasms except for C34 (malignant neoplasm of bronchus and lung) as it is part of the exclusion criteria*
Source of ICD-10 code definitions: https://icd.who.int/browse10/2019/en	

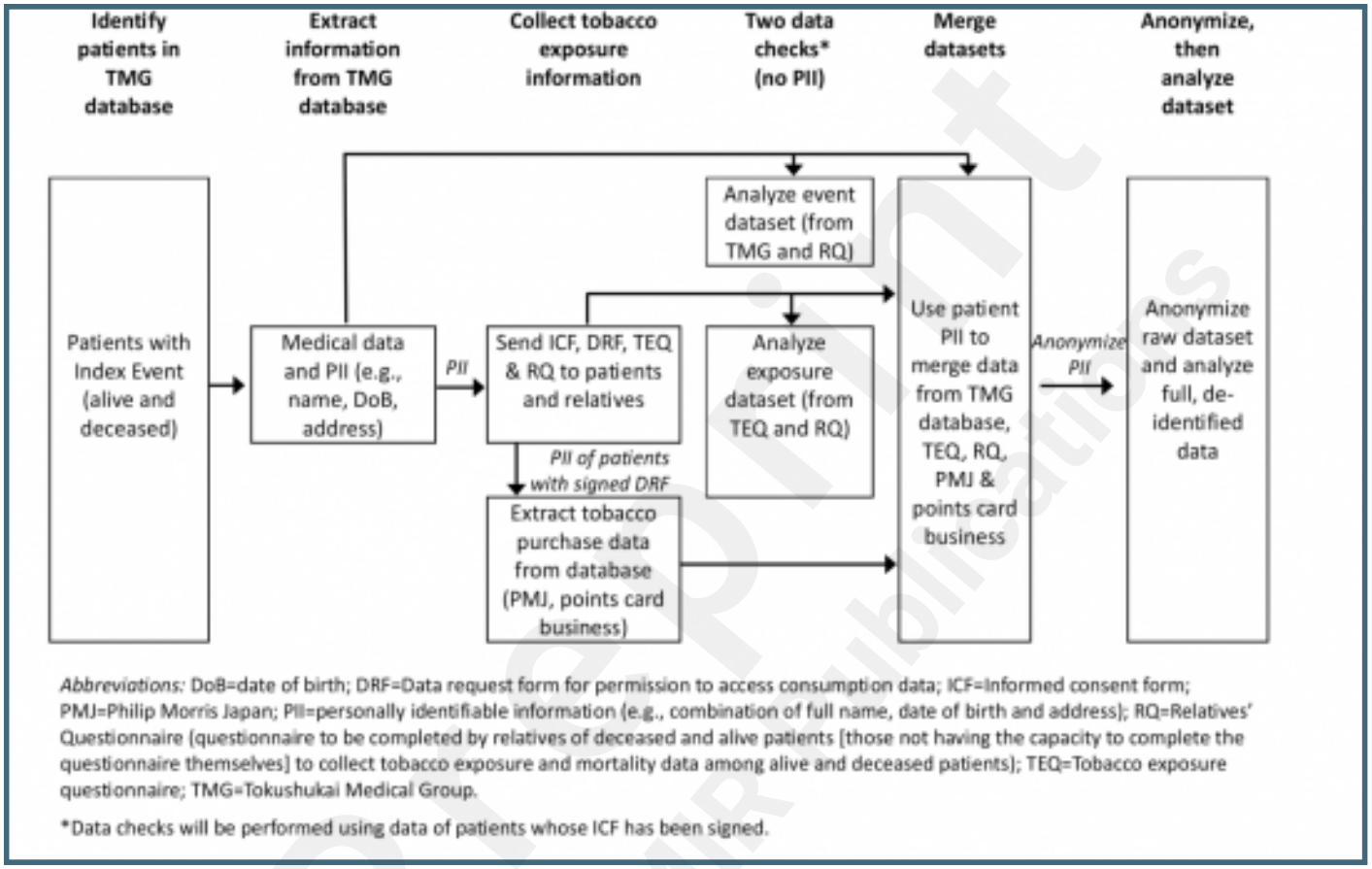
Appendix VI. Assumptions used for the sample size calculation.

Parameter	Assumed Value	Rationale
Significance level, alpha	2.5%, one-sided	Based on the primary objective of the study
Power	90%	To reduce the risk of type II error
Index period	From May 1, 2016 to December 31, 2022	To allow enough time for a follow-up period
Average estimated follow-up period	5 years	The minimum follow-up period will be less than 2 years, and the maximum follow-up period will be 8 years, so an average of 5 years was chosen for the calculation
Ratio of CIG smokers to HTP users	2:1	Based on the number of current CIG smokers and HTP users in Japan in 2020 (prevalence of 25.9% vs 10.9% respectively) [26]
Proportion of CIG smokers having first subsequent COPD hospitalization over 5 years	15%	From a literature report of first outpatient and inpatient COPD events
HR	0.79	The HR was assumed based on a literature reported COPD-related hospitalizations for quitters compared to those who continued CIG smoking [27]
Missing data after enrollment	10%	Assumption
Propensity score weighting inflation	30%	Assumption
Abbreviations: CIG, combustible cigarettes; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; HTP, heated tobacco product		

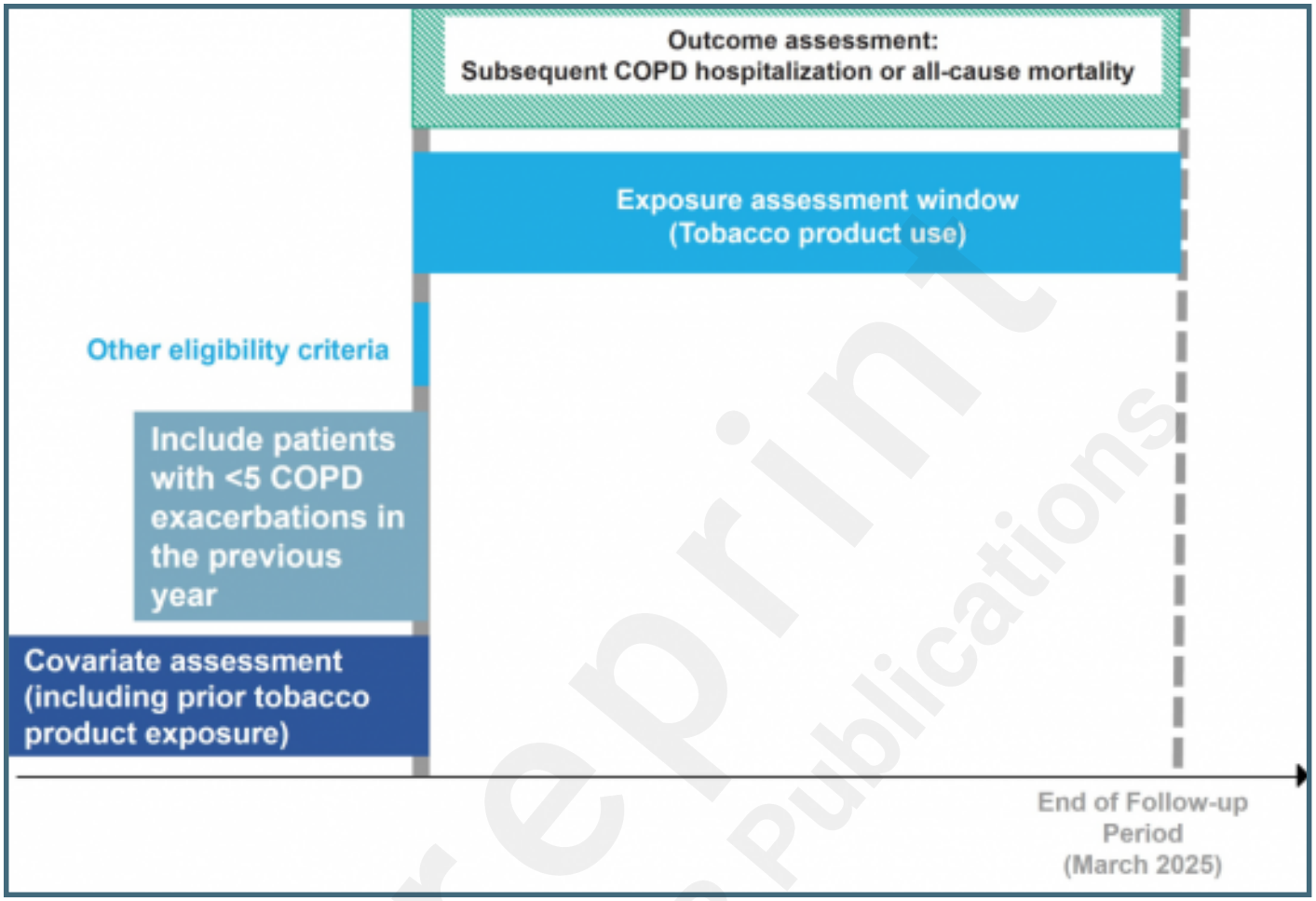
Supplementary Files

Figures

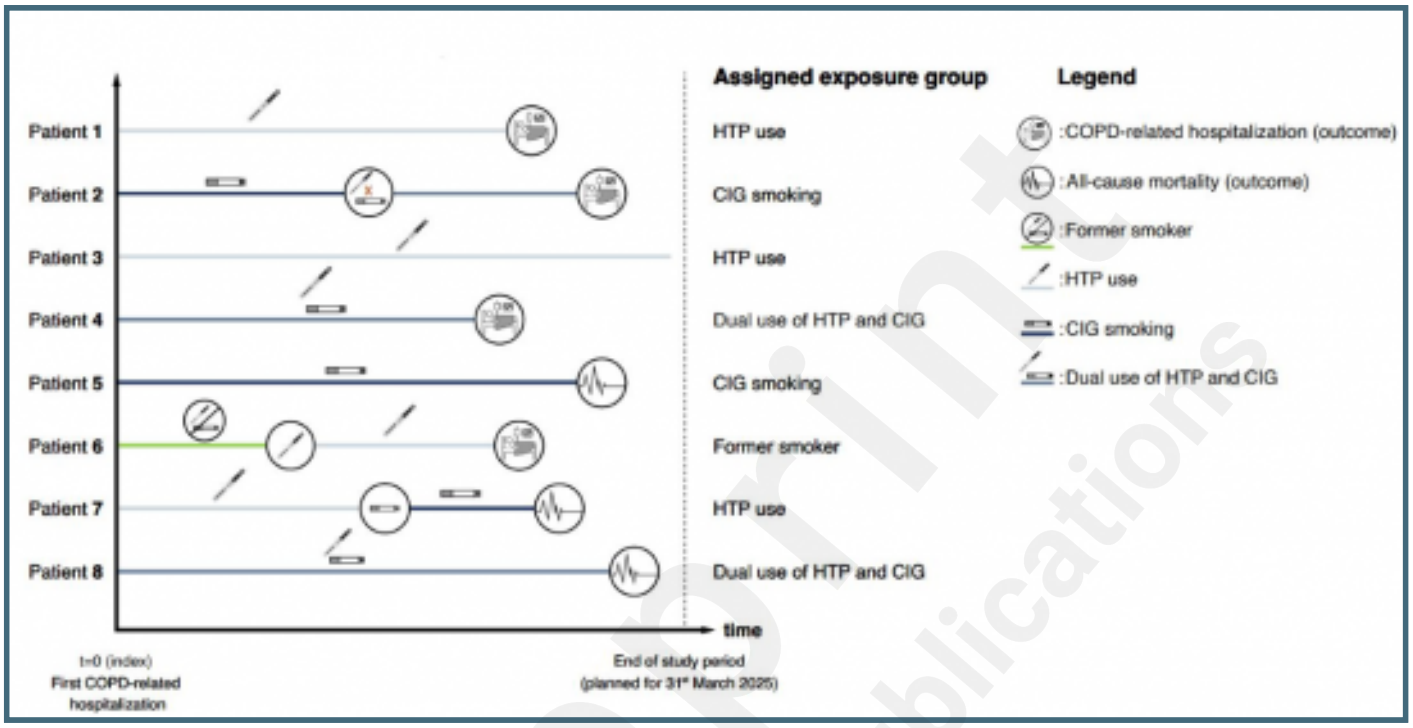
Overview of study design and data flow. DoB, date of birth; DRF, data request form for permission to access consumption data; ICF, informed consent form; PMJ, Philip Morris Japan; PII, personally identifiable information (eg, combination of full name, date of birth, and address); RQ, Relatives' Questionnaire (to be completed by relatives of deceased and alive patients [those unable to complete the questionnaire themselves] to collect tobacco exposure and mortality data); TEQ, Tobacco Exposure Questionnaire; TMG, Tokushukai Medical Group. *Data checks will be performed using data of patients whose ICF has been signed.



Study period overview. Note: The start of the exposure assessment window (here at Index event) is illustrative and will be determined after data checks on exposure and events. COPD, chronic obstructive pulmonary disease.



Classification of patients into exposure groups before exploring their association with outcomes: (Figure 3) Exposure data expected to be collected, (Figure 4) Exposure data used to classify patients into exposure groups. The symbol ‘X’ in the figure represents patient censoring at the end of study period, and a circle with a product inside signifies a switch to use of that product. Note: The start of the exposure assessment window (here at index) is illustrative and will be determined after data checks on exposure and on events.



Classification of patients into exposure groups before exploring their association with outcomes: (Figure 3) Exposure data expected to be collected, (Figure 4) Exposure data used to classify patients into exposure groups. The symbol ‘X’ in the figure represents patient censoring at the end of study period, and a circle with a product inside signifies a switch to use of that product. Note: The start of the exposure assessment window (here at index) is illustrative and will be determined after data checks on exposure and on events. CIG, combustible cigarette; COPD, chronic obstructive pulmonary disease; HTP, heated tobacco product.