CNODES

Technical Analytical Protocol

The Effect of Proton-Pump Inhibitors on the Risk of Community-Acquired Pneumonia

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# DOCUMENT CONTROL

|  |  |  |
| --- | --- | --- |
| Version | Author(s) | Type of Change |
| 0.1 | KBF | Initial draft of detailed technical protocol |
| 0.2 | KBF | Incorporated comments from PE |
| 0.3 | KBF, DC | Major revisions based on PPI Ad-Hoc Committee Meeting, CNODES Meeting, and Scientific Protocol Version 0.4 |
| 1.0 | KBF | Modified exclusion criteria, addition of protocol amendments (#1-15) and clarifications (#2-14), revised outcome definition, minor changes for consistency and clarification following email feedback from PPI team, PPI Team Conference Call (November 25th, 2011), and beta-testing in Manitoba. |
| 2.0 | KBF, DC | Revised secondary objectives, addition of multiple observations per individual, revised analytical plan, removal of secondary (fatal) outcomes, revision of exclusion criteria, revision of covariates included in models, and revision of protocol clarifications. |
| 2.1 | KBF | Addition of protocol clarifications and amendments. |

Abbreviations: DC: Dan Chateau; KBF: Kristian Filion.

# BACKGROUND AND STUDY RATIONALE

The background and rationale for this study is described in the Scientific Protocol entitled, “The Effect of Proton-Pump Inhibitors on the Risk of Community-Acquired Pneumonia, Version 0.4”.

# STUDY OBJECTIVES AND HYPOTHESES

## Overall Study Objective

The overall aim of this study is to determine whether proton pump inhibitors (PPIs) increase the risk of incident hospitalization for community-acquired pneumonia (HCAP). This will be achieved by conducting a participant-level meta-analysis of retrospective cohort studies conducted in 8 databases (7 provincial databases and the General Practice Research Database [GPRD]) to investigate the effects of these agents in individuals with no history of hospitalization for pneumonia.

## Specific Study Objectives

* 1. The primary objective of this study is to determine whether the use of PPIs increases the risk of incident HCAP compared with non-use of PPIs among new-users of non-steroidal anti-inflammatory drugs (NSAIDS).
	2. The secondary objective is to examine the effect of gastric acid suppression agent potency on the risk of incident HCAP among new-users of NSAIDs.

## Study Hypotheses

1. Use of PPIs among new-users of NSAIDs with no history of HCAP will be associated with an increased risk of incident HCAP compared with non-use of PPIs.
2. PPIs will have greater effects on the risk of incident HCAP than histamine-2 receptor antagonists (H2RAs).

# STUDY DESIGN

To achieve the primary and secondary objectives, we will conduct a retrospective population-based cohort study within each of the 8 Canadian Network of Observational Drug Effect Studies (CNODES) databases. The results of these database-specific analyses will then be pooled via meta-analysis across databases to obtain summary treatment effects.

Although the study design described below is intended to be applied uniformly to all databases, there invariably will be some deviations from this protocol due to database-specific issues (e.g., dates of data availability, age of database participants, etc.). Please refer to Appendix I for a detailed description of database-specific protocol deviations.

**Note**: This study is using a new user design. Consequently, patients can enter the cohort multiple times provided that all inclusion criteria are met. Therefore, each included observation must have a unique identifier (e.g., record number) in addition to the patient-specific identifier (e.g., health plan number). It is possible that individuals may enter as exposed for one observation and unexposed for another observation. In a sensitivity analysis, we will restrict to a single (random) observation per patient.

**Note:** Please refer to the “Merging vs. Joining\_ Comparing the Data Step with SQL.pdf” guide in Dropbox.

## Study Population

* 1. **Source Population**

The source population for all analyses will consist of all individuals meeting the following criteria at cohort entry:

* Aged > 40 years;
* Prescribed an oral NSAID in either monotherapy or combination therapy (World Health Organization Anatomical Therapeutic Chemical [WHO ATC] Code M01A) for the first time between January 1, 1997 and March 31, 2011.
* NSAID prescription duration of > 28 days.
	1. **Cohort Entry Date**

Cohort entry will be defined by the date of a patient’s first prescription for an NSAID.

* 1. **Exclusion Criteria (at cohort entry)**

We will exclude all patients who meet any of the following criteria:

* Age < 40 years (or age < minimum age available, but including at least 1 full year of database history);
* Cohort entry date < January 1, 1997 (or cohort entry date < earliest date of available data + 365 days);
* Any prescription for a PPI (any route of administration), a H2RA (any route of administration, or an NSAID (oral, rectal, or parenteral) in the 183 days before cohort entry (eligible PPIs and H2RAs are defined in Section D.2.a; NSAIDS defined in Section D.1.a);
* A prescription for a drug used to treat tuberculosis (ATC Code J04A) in the 365 days before (and including the date of) cohort entry;
* A discharge abstract record of HCAP (ICD-9-CM code [in any field]: 480.x-487.x; ICD-10-CA code: J10.0 to J18.9) in the 365 days before (and including the date of) cohort entry;
* An extended emergency room visit for community-acquired pneumonia in the 365 days before (and including the day of) cohort entry. An extended emergency room visit will be defined as:
	+ One ICD billing code for pneumonia (ICD-9-CM code [in any field]: 480.x-487.x; ICD-10-CA code: J10.0-J18.9) received in an emergency room, without any code for pneumonia in the emergency room the day before; and
	+ A second code for pneumonia (same codes) either in the emergency room or in the hospital happening on the next calendar day.
	+ Codes can be claimed by either family physicians or specialists.
	+ **MB: did not apply this exclusion criteria**
* A discharge abstract record or physician billing code indicating a history of cancer (other than non-melanoma skin cancer) in the 365 days before (and including the date of) cohort entry (ICD-9 codes 140-172, 174-209; ICD-10 codes: C00-C96 other than C44);
* Less than 365 days of continuous observation time in the database prior to cohort entry to ensure complete assessment of relevant medical history and comorbidities;
* Hospitalized at the time of cohort entry (i.e., admission date < cohort entry date < discharge date);
* Any hospitalization with length of stay > 3 days (discharge date – admission date > 3 days) where the discharge date is < 30 days before the date of cohort entry.
	1. **Cohort Exit Definition**

Patients will be followed until the first of the following dates:

* The admission date for an incident HCAP (as defined in Section D.5);
* The admission date for any hospitalization with a length of stay greater than 3 days (i.e., discharge date – admission date > 3 days);
* The date of death from any cause;
* The date of departure from the database (either end of registration with the province’s drug prescription plan or registration at the GPRD Practice);
* End of follow-up (6 months);
* End of the study period (September 30, 2011).

## Exposure Definitions

For each objective, we will obtain all prescription information for all patients on the same day as cohort entry. Exposure will be defined at cohort entry using 3 mutually-exclusive categories, and analyses will follow an intention-to-treat approach.

Note: Patients exposed to both a PPI and H2RA on the day of cohort entry should be excluded from all analyses. Patients receiving two PPIs should be included in the PPI group.

* 1. **PPI Exposed**

Patients receiving a prescription or dispensation (depending on the database) for any oral PPI (either monotherapy or in combination therapy) on the same day as their first prescription for an NSAID will be considered exposed to PPIs. Included PPIs are defined in Table 1.

Table 1. PPIs included as part of the PPI exposure definition.

|  |  |  |  |
| --- | --- | --- | --- |
| Name | ATC Code | WHO-DefinedDDD (mg) | Route of Administration |
| [Omeprazole](http://www.whocc.no/atc_ddd_index/?code=A02BC01&showdescription=yes) | A02BC01 | 20 | Oral |
| Omeprazole, Amoxicillin, and Metronidazole | A02BD01 | 20 | Oral |
| [Pantoprazole](http://www.whocc.no/atc_ddd_index/?code=A02BC02&showdescription=yes) | A02BC02 | 40 | Oral |
| Pantoprazole, Amoxicillin, and Clarithromycin | A02BD04 | 40 | Oral |
| [Lansoprazole](http://www.whocc.no/atc_ddd_index/?code=A02BC03&showdescription=yes) | A02BC03 | 30 | Oral |
| Lansoprazole, Amoxicillin, and Clarithromycin | A02BD07 | 30 | Oral |
| Lansoprazole, Amoxicillin, and Metronidazole | A02BD03 | 30 | Oral |
| Lansoprazole, Tetracycline, and Metronidazole | A02BD02 | 30 | Oral |
| [Rabeprazole](http://www.whocc.no/atc_ddd_index/?code=A02BC04&showdescription=yes) | A02BC04 | 20 | Oral |
| [Esomeprazole](http://www.whocc.no/atc_ddd_index/?code=A02BC05&showdescription=yes) | A02BC05 | 30 | Oral |
| Esomeprazole and Acetylsalicylic Acid | B01AC56 | 30 | Oral |
| Esomeprazole and Naproxen | M01AE52 | 30 | Oral |
| Esomeprazole, Amoxicillin, and Clarithromycin | A02BD06 | 30 | Oral |

Abbreviations: ATC = Anatomical Therapeutic Chemical; DDD = Defined Daily Dosage;

* 1. **H2RA Exposed**

Patients receiving a prescription or dispensation (depending on the database) for an H2RA on the same day as their first prescription for an NSAID will be considered exposed to H2RAs. Included H2RAs are defined in Table 2.

Table 2. H2RAs included as part of the H2RA exposure definition.

|  |  |  |  |
| --- | --- | --- | --- |
| Name | ATCCode | WHO-DefinedDDD (mg) | Route of Administration |
| [Cimetidine](http://www.whocc.no/atc_ddd_index/?code=A02BA01&showdescription=yes) | A02BA01 | 800 | Oral |
| [Ranitidine](http://www.whocc.no/atc_ddd_index/?code=A02BA02&showdescription=yes) | A02BA02 | 300 | Oral |
| [Famotidine](http://www.whocc.no/atc_ddd_index/?code=A02BA03&showdescription=yes) | A02BA03 | 40 | Oral |
| [Nizatidine](http://www.whocc.no/atc_ddd_index/?code=A02BA04&showdescription=yes) | A02BA04 | 300 | Oral |
| [Niperotidine](http://www.whocc.no/atc_ddd_index/?code=A02BA05&showdescription=yes) | A02BA05 | Not Available | Oral |
| [Roxatidine](http://www.whocc.no/atc_ddd_index/?code=A02BA06&showdescription=yes) | A02BA06 | 150 | Oral |
| [Ranitidine bismuth citrate](http://www.whocc.no/atc_ddd_index/?code=A02BA07&showdescription=yes) | A02BA07 | 800 | Oral |
| [Lafutidine](http://www.whocc.no/atc_ddd_index/?code=A02BA08&showdescription=yes) | A02BA08 | 20 | Oral |
| [Cimetidine, combinations](http://www.whocc.no/atc_ddd_index/?code=A02BA51&showdescription=yes) | A02BA51 | Not Available | Oral |
| [Famotidine, combinations](http://www.whocc.no/atc_ddd_index/?code=A02BA53&showdescription=yes) | A02BA53 | Not Available | Oral |

Abbreviations: ATC = Anatomical Therapeutic Chemical; DDD = Defined Daily Dosage;

* 1. **Unexposed**

The third category will be the reference category and will consist of patients not prescribed a PPI or H2RA on the same day as their first prescription for an NSAID.

## Accrual Start/End Dates

Please indicate in the Database-Specific Protocol Deviations the start and end dates used for your site.

# **Study Period**

* + - 1. Description of Events

Maximum follow-up of 180 days;

Maximum follow-up of 14 days;

Maximum follow-up of 30 days;

Maximum follow-up of 90 days.

* + - 1. Fixed Follow-up Regression Models

Maximum follow-up of 180 days.

## Outcomes: Incident HCAP

The primary outcome will be incident HCAP. HCAP will be defined using a validated algorithm based on ICD-10 discharge codes; the diagnostic algorithm and corresponding ICD-9 codes are found in Table 3.

Table 3. Codes included in validated diagnostic algorithm for pneumonia.

|  |  |
| --- | --- |
| Included ICD-10 Codes | Corresponding ICD-9 Codes |
| J10.0 | 487.0, 487.1 |
| J11.0 | 487.0 |
| J11.1 | 487.1 |
| J12.9 | 487.0, 480.9 |
| J13 | 481.x |
| J14 | 482.2 |
| J15.X | 482.0, 482.1, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.42, 482.49, 482.81, 482.82, 482.83, 482.89, 482.9, 483.0 |
| J16.8 | 483.8 |
| J17.0 | 484.7, 484.8\* |
| J17.2 |
| J17.3 |
| J17.8 |
| J18.0 | 485.X |
| J18.1 | 481.X |
| J18.8 | 486.X |
| J18.9 | 486.X |

\*ICD-9 codes 484.7 and 484.8 map to ICD-10 code J17.

To ensure that all HCAPs are truly community-acquired, please use the following algorithm:

* 1. A diagnosis of pneumonia with diagnosis type of most responsible (i.e., a type 1 diagnosis); AND
	2. The same diagnosis of pneumonia does not appear on the record under a different diagnosis code variable (diag02-diag16) with a diagnosis type of condition arising after the beginning of hospital observation or treatment (i.e., a type 2 diagnosis).

The date of HCAP should be defined by the date of hospital admission.

## Potential Confounders

For all study objectives, a number of potential confounding factors will be considered and measured in the year prior to the cohort entry (i.e., cohort entry - date of confounder measurement < 365). These potential confounders are defined in the following table (Table 4).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Potential Confounder | Measurement | ICD-9-CM Code | ICD-10-CA Code | WHO ATC Code | VariableName | DatabaseCoding |
|  |  |  |  |  |  |  |
| Repeated Observation | - | - | - | - | R\_OBSERVATION | 0 = No1 = Yes |
| Total Number of Hospital Admissions | Discharge Abstract Record | - | - | - | ADMIT\_NUM | 0/1/2/3/4+ |
| Comorbidities: |
| Asthma | Discharge Abstract Record (Any Field); Physician Fee-for-Service Claims | 493.x | J45, J46 | - | P\_ASTHMA | 0 = No1 = Yes |
| Bronchiectasis | Discharge Abstract Record (Any Field); Physician Fee-for-Service Claims | 494.x | Q33.4, J47 | - | P\_BRONCHIECTASIS | 0 = No1 = Yes |
| Chronic Obstructive Pulmonary Diseases | Discharge Abstract Record (Any Field); Physician Fee-for-Service Claims | 490.x491.x492.x496.x | J40.x-J44.x | - | P\_COPD | 0 = No1 = Yes |
| Diabetes Mellitus | Discharge Abstract Record (Any Field), Physician Fee-for-Service Claims;  | - | - | A10 | P\_DIABETES | 0 = No1 = Yes |
| Non-Hospitalized Pneumonia | Physician Fee-for-Service Claims OR Emergency Room (provided it does not meet our definition of an extended pneumonia emergency room visit) | 480.x-487.x | J10.0-J18.9 | - | P\_CAP | 0 = No1 = Yes |
| Lifestyle Variables (Available in GPRD)\*: |
| Alcohol | Demographic Database | - | - | - | ETOH | 0 = Never1 = Ever |
| Body Mass Index | Demographic Database | - | - | - | BMI | 0 = < 20 kg/m21 = 20-24.9 kg/m22 = 25-29.9 kg/m23 = 30-34.9 kg/m24 = > 35 kg/m2 |
| Smoking | Demographic Database | - | - | - | SMOKING | 0 = Never1 = Ever |
| Residence: |
| Nursing Home | Demographic Database | - | - | - | NURSING\_HOME | 0 = No1 = Yes |
| Region | Demographic Database | - | - | - | URBAN | 0 = Rural1 = Urban |
| Prescriptions: |
| Total Number of Prescription Medications† | Prescription Claims | - | - | - | PRESCRIPT\_NUM | 0/1/2/3/4+ |
| PPI | Prescription Claims | - | - | See Section D.2 | P\_PPI\_6\_12 | 0 = No1 = Yes |
| H2RA | Prescription Claims | - | - | See Section D.2 | P\_H2RA\_6\_12 | 0 = No1 = Yes |
| NSAID | Prescription Claims | - | - | All M01A | P\_NSAID\_6\_12 | 0 = No1 = Yes |
| Immunosuppressive Medications | Prescription Claims | - | - | All L04 | IMMUNO | 0 = No1 = Yes |
| Influenza Vaccination Status | Prescription Claims | - | - | All J07BB  | FLU\_VAC | 0 = No1 = Yes |
| Inhaled Bronchodilators | Prescription Claims | - | - | All R03AAll R03BBAll R03D | INH\_BRONCHO | 0 = No1 = Yes |
| Inhaled Corticosteroids | Prescription Claims | - | - | All R03BA | INH\_CORTICO | 0 = No1 = Yes |
| Pneumococcal Vaccination Status | Prescription Claims | - | - | All J07AL | PNEU\_VAC | 0 = No1 = Yes |
| Systemic Antibiotics | Prescription Claims | - | - | All J01 | SYS\_ANTIBIOTICS | 0 = No1 = Yes |
| Systemic Corticosteroids | Prescription Claims | - | - | All H02 | SYS\_CORTICO | 0 = No1 = Yes |

\*In cases where lifestyle variables are recorded more than once in the year prior to cohort entry, use the data closest to the date of cohort entry.

†Not counting the PPI or H2RA used to define exposure status.

**MB: total number of prescriptions medications defined as number of different 4th level ATCs (1st 5 Characters of ATC) patient prescribed in year prior.**

# ANALYTICAL PLAN

1. Each site contributing data to this study should download the high-dimensional propensity score macro from Harvard University (http://www.drugepi.org/downloads/index.php) and adapt it to run on the site’s databases. There are two versions of the macro available – the use of either version is permitted. Version 2 has faster computation times.

**Note:** Analytical Plan steps 2-6 should be repeated as high-dimensional propensity scores should be created for:

* + 1. PPI users vs not exposed to PPI or H2RAs.
		2. H2RA users vs not exposed to PPI or H2RAs.
1. Assemble study populations as per Section D above:
2. According to Section D.2, define each patient observation as:
	* 1. Exposed to PPI (Exposure=1), or
		2. Not exposed to PPI or H2RA (Exposure=0)
3. Generate high dimensional propensity scores for each observation:
	* 1. 5 data dimensions: Hospital diagnoses, hospital procedures, ambulatory physician visit diagnoses, ambulatory physician visit fee items, prescription drug dispensation (NB: Provinces with lab values should not use these data as a 6th dimension as these data are not available for all provinces).
		2. Use 365 day period prior to and including the date of cohort entry to calculate prevalence of each code in each dimension. Prescriptions/dispensations for PPIs, H2RAs, and NSAIDs on the date of cohort entry should not be included.

**MB: PPIs, H2RAs, and NSAIDs not included at all in the drug data dimension dataset.**

* + 1. Identify empirical candidate covariates in each dimension

Number of covariates = 200

Granularity=3 digits for CCP procedure codes, 5 digits for CCI codes, 4 digit ICD-9 diagnoses and ICD-10 diagnoses, generic name for drugs (non-strength specific, example WHO ATC 5), 5 digit physician fee schedule code (in BC, may be different granularity in other provinces).

**Note:** For physician fee for service records, use the provincial standard (usually ICD-9). For hospitalization data, use CCI codes and ICD-10 diagnosis codes after conversion to ICD-10, and use CCP codes and ICD-9 codes before. Convert ICD-9 to ICD-10 using translation files (supplied by Manitoba) for diagnosis codes and procedure codes.

* + 1. Assess recurrence: Generate three covariates for each code:

Covariate\_once=1 if that code appeared at least once within the 365-day assessment period in the study population.

Covariate\_median=1 if that code appeared ≥ the median in the study population.

Covariate\_freq=1 if code appeared more than the 75th percentile in the study population.

* + 1. Calculate potential bias for each covariate:

If RRco >=1, then Bias =  [[Pc1(RRco - 1) + 1]/[ Pc0(RRco - 1) + 1]]

If RRco <1, then Bias =  [[Pc1((1/RRco) - 1) + 1]/[ Pc0((1/RRco) - 1) + 1]]

Where *Pc1* is the prevalence of the covariate in the exposed patients, *Pc0* is the prevalence of the covariate in the unexposed patients, and *RRco* is the RR between the covariate and the binary outcome variable.

* 1. Select the top 500 covariates across all dimensions according to highest multiplicative bias. Add demographic covariates, other predefined covariates (health care utilization and disease characteristics) and selected 2-way interaction terms [see Covariate Section F below for list of predefined covariates to always be included in the propensity score model].
	2. Use multivariate logistic regression to estimate propensity scores

PROC LOGISTIC DATA=<> DESCENDING;

MODEL EXPOSURE = [FORCE COVARIATES FROM SECTION F AND 500 COVARIATES SELECTED ABOVE];

 QUIT;

* 1. Plot distribution of PPI users and unexposed patients across levels of propensity score. Please provide the Methods Liaison and Project Lead with a histogram of your propensity score distribution.
1. Trim (i.e., exclude) observations if there are areas of non-overlap in the distribution of the propensity score between PPI users and unexposed patients (e.g., if the highest propensity score for PPI users is 0.90 but there are unexposed patients with propensity scores in the range of 0.90 to 0.99, then trim patients above 0.9. Similarly at the other tail of the distribution of the propensity score. Document your trimming procedure in Appendix IV.
2. Assign each patient observation to one of 10 categorical propensity score deciles (PSD1, PSD2, PSD3, … , PSD10), with a value of 1 for the decile to which they belong and 0 for the other deciles.
3. Assign each patient observation an ordinal propensity score decile value between 1 and 10 (PSDO).
4. Compute baseline characteristics for the complete set of observations included in the analysis (Table 5). Also compute baseline characteristics for the unique (random) observation sensitivity analysis (Table 5a).

**MB: based on trimmed datasets.**

1. Characterize the event rates and follow-up time in the whole population (Table 6).

**MB: not whole population used, but the trimmed datasets used in modeling analysis.**

1. Create age- and sex-adjusted logistic regression models to estimate exposure-outcome associations for PPI users vs unexposed and H2RA users vs unexposed (Table 7):

PROC GENMOD DATA=<> **DESCENDING**;

 **CLASS <individual identifier>;**

MODEL OUTCOME = EXPOSURE FEMALE ~~AGE4054 AGE5564~~

~~AGE6574 AGE7584 AGE85PL~~ **AGE4049 AGE5059 AGE6069**

**AGE7079 AGE80PL** R\_OBSERVATION

/ DIST=BIN LINK=LOGIT;

REPEATED SUBJECT=<individual identifier>/TYPE=**EXCH**;

**ESTIMATE ‘Exposure OR’ EXPOSURE 1 / EXP;**

QUIT;

1. Outcome Model: Estimate exposure-outcome associations for PPI users vs unexposed and H2RA users vs unexposed (Table 7) adjusted for propensity score decile:
	* 1. Fixed (180-day) Follow-up Models, Logistic Regression with Generalized Estimating Equations (repeat for 2 exposure groups [PPI users, H2RA users]:

PROC GENMOD DATA=<> **DESCENDING**;

 **CLASS <individual identifier>;**

MODEL OUTCOME = EXPOSURE FEMALE ~~AGE4054 AGE5564~~

~~AGE6574 AGE7584 AGE85PL~~ **AGE4049 AGE5059 AGE6069**

**AGE7079 AGE80PL** P\_NSAID\_6\_12

P\_PPI\_6\_12 P\_H2RA\_6\_12 P\_CAP R\_OBSERVATION

PSD1 PSD2 PSD3 PSD4 PSD6 PSD7 PSD8 PSD9 PSD10

/ DIST=BIN LINK=LOGIT;

REPEATED SUBJECT=<individual identifier>/ TYPE=**EXCH**;

**ESTIMATE ‘Exposure OR’ EXPOSURE 1 / EXP;**

QUIT;

* + 1. Logistic regression models should only be run where there are at least 5 events per model parameter and a minimum of 30 events in total. Given the large number of unexposed individuals, this should not be an issue. However, should the number of events per parameter be insufficient, the following steps should be taken:
		2. Combine age groups (e.g., AGE4074, AGE75PL)
		3. Combine HDPS deciles (e.g., PSD12, PSD34, PSD56, etc.)

1. Sensitivity analysis excluding repeat observations. Repeat the logistic outcome models described in steps 9 and 10 but with only a single observation per individual. For each individual with multiple observations, select a random observation for the analysis.

OMIT the following statement from the SAS code:

 **CLASS <individual identifier>;**

REPEATED SUBJECT=<individual identifier>/TYPE=**EXCH**;

**Exclude R\_OBSERVATION variable from models**

1. Sensitivity analysis excluding observations with PPI, NSAID or H2RA prescriptions in the previous year. Repeat the logistic outcome models from steps 9 and 10 but excluding observations with a PPI, H2RA or NSAID in the 6 -12 months prior to the date of cohort entry.

Include the following statement in the SAS code **creating the** **dataset to be analyzed**:

WHERE P\_NSAID\_6\_12 NE 1 AND P\_PPI\_6\_12 NE 1 AND

P\_H2RA\_6\_12 NE 1;

**Create the R\_OBSERVATION variable new for this dataset.**

**Exclude P\_NSAID\_6\_12, P\_PPI\_6\_12, and P\_H2RA\_6\_12 from models.**

1. Repeat the logistic outcome models described in steps 9 and 10 but excluding crossovers (i.e., the unexposed patients who took a PPI or H2RA during follow-up, PPIs users also exposed to H2RAs during follow-up, and H2RA users also exposed to PPIs during follow-up).

 **Create the R\_OBSERVATION variable new for this dataset.**

1. Categorize exposure and events by propensity score decile, sex, and age group. This table will permit computation of network-wide summary statistics (Tables 8-11) and the calculation of summary Odds Ratios where regression models will not converge. Some sites may be unable to report this table due to small cell privacy restrictions. Summary Odds Ratios and CIs should be calculated on site and reported.

#

# COVARIATES

*Note on missing data: Do not impute missing values for demographic data. Exclude patients missing sex, For income and age, create another categorical variable (e.g., AGE\_UNK, INC\_UNK).*

*Include covariate data in the propensity score that occur on the date of cohort entry.*

Predefined covariates to ALWAYS be included in the propensity score model

1. Demographics and Lifestyle Variables:
	1. Index year
	2. Income category (use standard method in your province – please define as part of Appendix I)
	3. Alcohol
	4. Body Mass Index
	5. Smoking
2. Health care utilization:
	1. Hospitalized in previous year (yes=1 or no=0)
	2. > 4 distinct drugs (generic chemical name) in prior year (yes=1 or no=0)
	3. > 4 physician visits in prior year (yes=1 or no=0)
3. Disease Characteristics (See Section D.6 for Definitions)
	1. Asthma
	2. COPD
	3. Bronchiectasis
	4. Diabetes
4. Medications (see Section D.6 for WHO ATC codes):
	1. Immunosuppressive Agents
	2. Influenza Vaccine
	3. Inhaled Bronchodilators
	4. Inhaled Corticosteroids
	5. Pneumococcal Vaccine
	6. Systemic Antibiotics
	7. Systemic Corticosteroids

Predefined covariates to NOT be included in the propensity score model\*

1. Previous CAP (physician fee-for-service claims or ER visits [not meeting extended stay definition]: ICD-9 code [in any field]: 480.x-487.x; ICD-10 code: J10.0 to J18.9)

\*This variable may be included in the propensity score model if the number of events is too low. See explanation in Analytical Plan Section 10b.

# QUALITY ASSURANCE

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# DATA TABLES

Table 5. Demographic and clinical characteristics of all observations by exposure status at cohort entry\*.

|  |  |  |
| --- | --- | --- |
|  | PPI Analysis | H2RA Analysis |
|  | Exposed | Unexposed† | Exposed | Unexposed† |
| Number of Patients | N | % | N | % | N | % | N | % |
| Age (n, %) [Years] |  |  |  |  |  |  |  |  |
|  40-49 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  50-59 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  60-69 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  70-79 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  80+ | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Women (n, %) | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Year of Cohort Entry (n, %) |  |  |  |  |  |  |  |  |
|  1997 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  1998 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  1999 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2000 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2001 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2002 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2003 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2004 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2005 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2006 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2007 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2008 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2009 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2010 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2011 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| BMI (n, %) |  |  |  |  |  |  |  |  |
|  < 20 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  20-24.9 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  25-29.9 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  30-34.9 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  > 35 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Missing | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Smoking (n, %) |  |  |  |  |  |  |  |  |
|  Ever | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Never | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Missing | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Alcohol Use (n, %) |  |  |  |  |  |  |  |  |
|  Ever | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Never | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Missing | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Nursing Home (n, %) | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Urban (n, %) | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Comorbidities (n, %)\* |  |  |  |  |  |  |  |  |
|  Asthma | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Bronchiectasis | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  COPD | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Diabetes | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Non-hospitalized pneumonia | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Hospitalizations in the Year Preceding Cohort Entry (n, %) |  |  |  |  |  |  |  |  |
|  None | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  One | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Two | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Three | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Four or More | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Prescriptions in the Year Preceding Cohort Entry (n, %) |  |  |  |  |  |  |  |  |
|  None | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  One | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Two | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Three | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Four or More | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Medications (n, %)\* |  |  |  |  |  |  |  |  |
|  PPI | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  H2RA | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  NSAIDs | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Immunosuppressive Agents | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Influenza Vaccine | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Inhaled Bronchodilators | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Inhaled Corticosteroids | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Pneumococcal Vaccine  | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Systemic Antibiotics | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Systemic Corticosteroids | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |

Abbreviations: BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; H2RA = histamine-2 receptor antagonists; IQR = Inter-Quartile Range; NSAIDS = Non-Steroidal Anti-Inflammatory Drugs; PPI = Proton Pump Inhibitor.

\*Comorbidities and medication use are defined using data in the year prior to and including the date of cohort entry.† Because of trimming during the estimation of high dimensional propensity scores, small differences in the unexposed groups exist in the PPI and H2RA analyses.

Table 5a. Demographic and clinical characteristics of unique observations by exposure status at cohort entry\*.

|  |  |  |
| --- | --- | --- |
|  | PPI Analysis | H2RA Analysis |
|  | Exposed | Unexposed† | Exposed | Unexposed† |
| Number of Patients | N | % | N | % | N | % | N | % |
| Age (n, %) [Years] |  |  |  |  |  |  |  |  |
|  40-49 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  50-59 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  60-69 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  70-79 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  80+ | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Women (n, %) | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Year of Cohort Entry (n, %) |  |  |  |  |  |  |  |  |
|  1997 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  1998 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  1999 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2000 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2001 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2002 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2003 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2004 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2005 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2006 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2007 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2008 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2009 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2010 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  2011 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| BMI (n, %) |  |  |  |  |  |  |  |  |
|  < 20 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  20-24.9 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  25-29.9 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  30-34.9 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  > 35 kg/m2 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Missing | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Smoking (n, %) |  |  |  |  |  |  |  |  |
|  Ever | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Never | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Missing | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Alcohol Use (n, %) |  |  |  |  |  |  |  |  |
|  Ever | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Never | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Missing | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Nursing Home (n, %) | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Urban (n, %) | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Comorbidities (n, %)\* |  |  |  |  |  |  |  |  |
|  Asthma | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Bronchiectasis | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  COPD | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Diabetes | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Non-hospitalized pneumonia | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Hospitalizations in the Year Preceding Cohort Entry (n, %) |  |  |  |  |  |  |  |  |
|  None | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  One | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Two | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Three | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Four or More | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Prescriptions in the Year Preceding Cohort Entry (n, %) |  |  |  |  |  |  |  |  |
|  None | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  One | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Two | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Three | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Four or More | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
| Medications (n, %)\* |  |  |  |  |  |  |  |  |
|  PPI | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  H2RA | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  NSAIDs | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Immunosuppressive Agents | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Influenza Vaccine | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Inhaled Bronchodilators | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Inhaled Corticosteroids | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Pneumococcal Vaccine  | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Systemic Antibiotics | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |
|  Systemic Corticosteroids | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 | XX,XXX | 0.0 |

Abbreviations: BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; H2RA = histamine-2 receptor antagonists; IQR = Inter-Quartile Range; NSAIDS = Non-Steroidal Anti-Inflammatory Drugs; PPI = Proton Pump Inhibitor.

\*Comorbidities and medication use are defined using data in the year prior to and including the date of cohort entry.

† Because of trimming during the estimation of high dimensional propensity scores, small differences in the unexposed groups exist in the PPI and H2RA analyses.

Table 6. Patients, events, and follow-up time for HCAP.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  | HCAP Events (n) |
| Exposure | Number Exposed | Total Person-Years of Follow-up\* | 14 Days | 30 Days | 90 Days | 180 Days |
| Primary Analysis |  |  |  |  |  |  |
| PPI |  |  |  |  |  |  |
| H2RA |  |  |  |  |  |  |
| Unexposed |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| One Observation/Patient |  |  |  |  |  |  |
| PPI |  |  |  |  |  |  |
| H2RA |  |  |  |  |  |  |
| Unexposed |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Excluding PPI/H2RA/NSAID in the Previous Year: |  |  |  |  |  |  |
| PPI |  |  |  |  |  |  |
| H2RA |  |  |  |  |  |  |
| Unexposed |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Excluding Crossovers† |  |  |  |  |  |  |
| PPI |  |  |  |  |  |  |
| H2RA |  |  |  |  |  |  |
| Unexposed |  |  |  |  |  |  |

Abbreviations: H2RA = histamine-2 receptor antagonists; HCAP = Hospitalization for Community-acquired Pneumonia; PPI = Proton Pump Inhibitor.

\* Total number of person-years of follow-up based on the 180-day follow-up period.

† Excluding crossovers and allowing for multiple observations per patient.

Table 7. Effect of PPI or H2RA use on the odds of HCAP among users of NSAIDS.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Exposed | Unexposed | Age- and Sex-Adjusted | Fully Adjusted |
| Outcome | Event | No Event | Event | No Event | Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval |
| PPI Analysis |  |  |  |  |  |  |  |  |
| Primary Analysis |  |  |  |  |  |  |  |  |
| 1 Observation/Patient |  |  |  |  |  |  |  |  |
| Excluding PPI/H2RA/NSAID in the Previous Year |  |  |  |  |  |  |  |  |
| Excluding Crossovers |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| H2RA Analysis |  |  |  |  |  |  |  |  |
| Primary Analysis |  |  |  |  |  |  |  |  |
| 1 Observation/Patient |  |  |  |  |  |  |  |  |
| Excluding PPI/H2RA/NSAID in the Previous Year |  |  |  |  |  |  |  |  |
| Excluding Crossovers |  |  |  |  |  |  |  |  |

Abbreviations: H2RA = histamine-2 receptor antagonists; HCAP = Hospitalization for Community-acquired Pneumonia; NSAIDS = Non-Steroidal Anti-Inflammatory Drugs; PPI = Proton-Pump Inhibitor.

Table 8. Stratum-specific results for PPIs and H2RAs and the risk of HCAP with multiple observations per patient.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   |   | PPI Analysis | H2RA Analysis |
|   |   |   | Exposed | Unexposed | Exposed | Unexposed |
| PS Decile | Female | AGE<65 | Event+ | Event- | Event+ | Event- | Event+ | Event- | Event+ | Event- |
| 1 | 1 | 1 |   |   |   |   |   |   |   |   |
| 1 | 0 | 1 |   |   |   |   |   |   |   |   |
| 1 | 1 | 0 |   |   |   |   |   |   |   |   |
| 1 | 0 | 0 |   |   |   |   |   |   |   |   |
| 2 | 1 | 1 |   |   |   |   |   |   |   |   |
| 2 | 0 | 1 |   |   |   |   |   |   |   |   |
| 2 | 1 | 0 |   |   |   |   |   |   |   |   |
| 2 | 0 | 0 |   |   |   |   |   |   |   |   |
| 3 | 1 | 1 |   |   |   |   |   |   |   |   |
| 3 | 0 | 1 |   |   |   |   |   |   |   |   |
| 3 | 1 | 0 |   |   |   |   |   |   |   |   |
| 3 | 0 | 0 |   |   |   |   |   |   |   |   |
| 4 | 1 | 1 |   |   |   |   |   |   |   |   |
| 4 | 0 | 1 |   |   |   |   |   |   |   |   |
| 4 | 1 | 0 |   |   |   |   |   |   |   |   |
| 4 | 0 | 0 |   |   |   |   |   |   |   |   |
| 5 | 1 | 1 |   |   |   |   |   |   |   |   |
| 5 | 0 | 1 |   |   |   |   |   |   |   |   |
| 5 | 1 | 0 |   |   |   |   |   |   |   |   |
| 5 | 0 | 0 |   |   |   |   |   |   |   |   |
| 6 | 1 | 1 |   |   |   |   |   |   |   |   |
| 6 | 0 | 1 |   |   |   |   |   |   |   |   |
| 6 | 1 | 0 |   |   |   |   |   |   |   |   |
| 6 | 0 | 0 |   |   |   |   |   |   |   |   |
| 7 | 1 | 1 |   |   |   |   |   |   |   |   |
| 7 | 0 | 1 |   |   |   |   |   |   |   |   |
| 7 | 1 | 0 |   |   |   |   |   |   |   |   |
| 7 | 0 | 0 |   |   |   |   |   |   |   |   |
| 8 | 1 | 1 |   |   |   |   |   |   |   |   |
| 8 | 0 | 1 |   |   |   |   |   |   |   |   |
| 8 | 1 | 0 |   |   |   |   |   |   |   |   |
| 8 | 0 | 0 |   |   |   |   |   |   |   |   |
| 9 | 1 | 1 |   |   |   |   |   |   |   |   |
| 9 | 0 | 1 |   |   |   |   |   |   |   |   |
| 9 | 1 | 0 |   |   |   |   |   |   |   |   |
| 9 | 0 | 0 |   |   |   |   |   |   |   |   |
| 10 | 1 | 1 |   |   |   |   |   |   |   |   |
| 10 | 0 | 1 |   |   |   |   |   |   |   |   |
| 10 | 1 | 0 |   |   |   |   |   |   |   |   |
| 10 | 0 | 0 |   |   |   |   |   |   |   |   |

Abbreviations: H2RA = histamine-2 receptor antagonists; HCAP = Hospitalization for Community-acquired Pneumonia; PPI = Proton-Pump Inhibitor.

Table 9. Stratum-specific results for PPIs and H2RAs and the risk of HCAP with one observation per patient.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   |   | PPI Analysis | H2RA Analysis |
|   |   |   | Exposed | Unexposed | Exposed | Unexposed |
| PS Decile | Female | AGE<65 | Event+ | Event- | Event+ | Event- | Event+ | Event- | Event+ | Event- |
| 1 | 1 | 1 |   |   |   |   |   |   |   |   |
| 1 | 0 | 1 |   |   |   |   |   |   |   |   |
| 1 | 1 | 0 |   |   |   |   |   |   |   |   |
| 1 | 0 | 0 |   |   |   |   |   |   |   |   |
| 2 | 1 | 1 |   |   |   |   |   |   |   |   |
| 2 | 0 | 1 |   |   |   |   |   |   |   |   |
| 2 | 1 | 0 |   |   |   |   |   |   |   |   |
| 2 | 0 | 0 |   |   |   |   |   |   |   |   |
| 3 | 1 | 1 |   |   |   |   |   |   |   |   |
| 3 | 0 | 1 |   |   |   |   |   |   |   |   |
| 3 | 1 | 0 |   |   |   |   |   |   |   |   |
| 3 | 0 | 0 |   |   |   |   |   |   |   |   |
| 4 | 1 | 1 |   |   |   |   |   |   |   |   |
| 4 | 0 | 1 |   |   |   |   |   |   |   |   |
| 4 | 1 | 0 |   |   |   |   |   |   |   |   |
| 4 | 0 | 0 |   |   |   |   |   |   |   |   |
| 5 | 1 | 1 |   |   |   |   |   |   |   |   |
| 5 | 0 | 1 |   |   |   |   |   |   |   |   |
| 5 | 1 | 0 |   |   |   |   |   |   |   |   |
| 5 | 0 | 0 |   |   |   |   |   |   |   |   |
| 6 | 1 | 1 |   |   |   |   |   |   |   |   |
| 6 | 0 | 1 |   |   |   |   |   |   |   |   |
| 6 | 1 | 0 |   |   |   |   |   |   |   |   |
| 6 | 0 | 0 |   |   |   |   |   |   |   |   |
| 7 | 1 | 1 |   |   |   |   |   |   |   |   |
| 7 | 0 | 1 |   |   |   |   |   |   |   |   |
| 7 | 1 | 0 |   |   |   |   |   |   |   |   |
| 7 | 0 | 0 |   |   |   |   |   |   |   |   |
| 8 | 1 | 1 |   |   |   |   |   |   |   |   |
| 8 | 0 | 1 |   |   |   |   |   |   |   |   |
| 8 | 1 | 0 |   |   |   |   |   |   |   |   |
| 8 | 0 | 0 |   |   |   |   |   |   |   |   |
| 9 | 1 | 1 |   |   |   |   |   |   |   |   |
| 9 | 0 | 1 |   |   |   |   |   |   |   |   |
| 9 | 1 | 0 |   |   |   |   |   |   |   |   |
| 9 | 0 | 0 |   |   |   |   |   |   |   |   |
| 10 | 1 | 1 |   |   |   |   |   |   |   |   |
| 10 | 0 | 1 |   |   |   |   |   |   |   |   |
| 10 | 1 | 0 |   |   |   |   |   |   |   |   |
| 10 | 0 | 0 |   |   |   |   |   |   |   |   |

Abbreviations: H2RA = histamine-2 receptor antagonists; HCAP = Hospitalization for Community-acquired Pneumonia; PPI = Proton-Pump Inhibitor.

Table 10. Stratum-specific results for PPIs and H2RAs and the risk of HCAP, excluding those with a PPI, H2RA, or NSAID in the previous year, and allowing multiple observations per patient.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   |   | PPI Analysis | H2RA Analysis |
|   |   |   | Exposed | Unexposed | Exposed | Unexposed |
| PS Decile | Female | AGE<65 | Event+ | Event- | Event+ | Event- | Event+ | Event- | Event+ | Event- |
| 1 | 1 | 1 |   |   |   |   |   |   |   |   |
| 1 | 0 | 1 |   |   |   |   |   |   |   |   |
| 1 | 1 | 0 |   |   |   |   |   |   |   |   |
| 1 | 0 | 0 |   |   |   |   |   |   |   |   |
| 2 | 1 | 1 |   |   |   |   |   |   |   |   |
| 2 | 0 | 1 |   |   |   |   |   |   |   |   |
| 2 | 1 | 0 |   |   |   |   |   |   |   |   |
| 2 | 0 | 0 |   |   |   |   |   |   |   |   |
| 3 | 1 | 1 |   |   |   |   |   |   |   |   |
| 3 | 0 | 1 |   |   |   |   |   |   |   |   |
| 3 | 1 | 0 |   |   |   |   |   |   |   |   |
| 3 | 0 | 0 |   |   |   |   |   |   |   |   |
| 4 | 1 | 1 |   |   |   |   |   |   |   |   |
| 4 | 0 | 1 |   |   |   |   |   |   |   |   |
| 4 | 1 | 0 |   |   |   |   |   |   |   |   |
| 4 | 0 | 0 |   |   |   |   |   |   |   |   |
| 5 | 1 | 1 |   |   |   |   |   |   |   |   |
| 5 | 0 | 1 |   |   |   |   |   |   |   |   |
| 5 | 1 | 0 |   |   |   |   |   |   |   |   |
| 5 | 0 | 0 |   |   |   |   |   |   |   |   |
| 6 | 1 | 1 |   |   |   |   |   |   |   |   |
| 6 | 0 | 1 |   |   |   |   |   |   |   |   |
| 6 | 1 | 0 |   |   |   |   |   |   |   |   |
| 6 | 0 | 0 |   |   |   |   |   |   |   |   |
| 7 | 1 | 1 |   |   |   |   |   |   |   |   |
| 7 | 0 | 1 |   |   |   |   |   |   |   |   |
| 7 | 1 | 0 |   |   |   |   |   |   |   |   |
| 7 | 0 | 0 |   |   |   |   |   |   |   |   |
| 8 | 1 | 1 |   |   |   |   |   |   |   |   |
| 8 | 0 | 1 |   |   |   |   |   |   |   |   |
| 8 | 1 | 0 |   |   |   |   |   |   |   |   |
| 8 | 0 | 0 |   |   |   |   |   |   |   |   |
| 9 | 1 | 1 |   |   |   |   |   |   |   |   |
| 9 | 0 | 1 |   |   |   |   |   |   |   |   |
| 9 | 1 | 0 |   |   |   |   |   |   |   |   |
| 9 | 0 | 0 |   |   |   |   |   |   |   |   |
| 10 | 1 | 1 |   |   |   |   |   |   |   |   |
| 10 | 0 | 1 |   |   |   |   |   |   |   |   |
| 10 | 1 | 0 |   |   |   |   |   |   |   |   |
| 10 | 0 | 0 |   |   |   |   |   |   |   |   |

Abbreviations: HCAP = Hospitalization for Community-acquired Pneumonia; PPI = Proton-Pump Inhibitor.

Table 11. Stratum-specific results for PPIs and H2RAs and the risk of HCAP, excluding crossovers, and allowing multiple observations per patient.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   |   | PPI Analysis | H2RA Analysis |
|   |   |   | Exposed | Unexposed | Exposed | Unexposed |
| PS Decile | Female | AGE<65 | Event+ | Event- | Event+ | Event- | Event+ | Event- | Event+ | Event- |
| 1 | 1 | 1 |   |   |   |   |   |   |   |   |
| 1 | 0 | 1 |   |   |   |   |   |   |   |   |
| 1 | 1 | 0 |   |   |   |   |   |   |   |   |
| 1 | 0 | 0 |   |   |   |   |   |   |   |   |
| 2 | 1 | 1 |   |   |   |   |   |   |   |   |
| 2 | 0 | 1 |   |   |   |   |   |   |   |   |
| 2 | 1 | 0 |   |   |   |   |   |   |   |   |
| 2 | 0 | 0 |   |   |   |   |   |   |   |   |
| 3 | 1 | 1 |   |   |   |   |   |   |   |   |
| 3 | 0 | 1 |   |   |   |   |   |   |   |   |
| 3 | 1 | 0 |   |   |   |   |   |   |   |   |
| 3 | 0 | 0 |   |   |   |   |   |   |   |   |
| 4 | 1 | 1 |   |   |   |   |   |   |   |   |
| 4 | 0 | 1 |   |   |   |   |   |   |   |   |
| 4 | 1 | 0 |   |   |   |   |   |   |   |   |
| 4 | 0 | 0 |   |   |   |   |   |   |   |   |
| 5 | 1 | 1 |   |   |   |   |   |   |   |   |
| 5 | 0 | 1 |   |   |   |   |   |   |   |   |
| 5 | 1 | 0 |   |   |   |   |   |   |   |   |
| 5 | 0 | 0 |   |   |   |   |   |   |   |   |
| 6 | 1 | 1 |   |   |   |   |   |   |   |   |
| 6 | 0 | 1 |   |   |   |   |   |   |   |   |
| 6 | 1 | 0 |   |   |   |   |   |   |   |   |
| 6 | 0 | 0 |   |   |   |   |   |   |   |   |
| 7 | 1 | 1 |   |   |   |   |   |   |   |   |
| 7 | 0 | 1 |   |   |   |   |   |   |   |   |
| 7 | 1 | 0 |   |   |   |   |   |   |   |   |
| 7 | 0 | 0 |   |   |   |   |   |   |   |   |
| 8 | 1 | 1 |   |   |   |   |   |   |   |   |
| 8 | 0 | 1 |   |   |   |   |   |   |   |   |
| 8 | 1 | 0 |   |   |   |   |   |   |   |   |
| 8 | 0 | 0 |   |   |   |   |   |   |   |   |
| 9 | 1 | 1 |   |   |   |   |   |   |   |   |
| 9 | 0 | 1 |   |   |   |   |   |   |   |   |
| 9 | 1 | 0 |   |   |   |   |   |   |   |   |
| 9 | 0 | 0 |   |   |   |   |   |   |   |   |
| 10 | 1 | 1 |   |   |   |   |   |   |   |   |
| 10 | 0 | 1 |   |   |   |   |   |   |   |   |
| 10 | 1 | 0 |   |   |   |   |   |   |   |   |
| 10 | 0 | 0 |   |   |   |   |   |   |   |   |

Abbreviations: HCAP = Hospitalization for Community-acquired Pneumonia; PPI = Proton-Pump Inhibitor.

# APPENDIX I – DATABASE-SPECIFIC PROTOCOL DEVIATIONS

To be drafted after consultation with ad-hoc project team.

# APPENDIX II – PROTOCOL AMENDMENTS

Note: All subsequent changes to the protocol will be made as amendments listed here.

1. Table 4 should state that diabetes is defined by prescription claims data rather than discharge abstract record or physician fee-for-service claims.

# APPENDIX III – PROTOCOL CLARIFICATIONS

1. Since the completion of the scientific protocol, the minimum duration of database time, and duration of assessment of previous PPI, NSAID, and HCAP was reduced from 730 days to 365 days. Consequently, duration of covariate assessment was also reduced to 365 days prior to cohort entry. There have also been changes made to the secondary objectives and the analytical plan.
2. Question: Why is an intention-to-treat approach being used rather than a time-dependent analysis?

Answer: The NSAID cohort approach is being used to avoid confounding by indication with GERD. Modeling exposure using a time-dependent approach would re-introduce this confounding by indication. Rather than modeling exposure as a time-dependent variable, crossovers are excluded in sensitivity analyses to examine the impact of exposure misclassification on treatment effects.

1. Question: If a patient receives two dispensations of 15 days each, are they eligible for cohort entry?

Answer: No, they are not eligible for cohort entry. Patients need to receive the full 28 day prescription/dispensation at once to be eligible for cohort entry. No future prescriptions can be used to create a 28-day prescription.

1. Question: If a patient has an NSAID in 2003 without 1 year of prior data, the patient is excluded based on exclusion criteria. If that same patient has another NSAIDs in 2007 without any NSAIDs, PPI, or H2RA in the prior year, does he enter the cohort?

Answer: Yes, this patient meets our definition of a new user and should enter the cohort. Patients may enter the cohort multiple times and should be included for all NSAID prescription that meets all inclusion criteria.

1. Question: If a patient receives a short-term NSAID (e.g., 10 days) in 2003 and a 30 days prescription in 2007, are they eligible for cohort entry?

Answer: Since this patient does not have an oral, rectal, or parenteral prescription for an NSAID in the 6 months prior to their 2007 prescription, they should enter the cohort based on their 2007 prescription.

1. Question: Should analyses be adjusted for multiple comparisons?

Answer: No, we will not be adjusting for multiple comparisons.

1. Question: For previous HCAP exclusions, is it 1 year from admission or discharge?

Answer: Patients with less than one year between the discharge date for a previous HCAP and cohort entry should be excluded.

1. Question: The HCAP codes used for exclusion differ from those used to define the outcome. Please confirm that this is correct.

Answer: The outcome is defined using a validated algorithm. The exclusion codes are broader to ensure that we are truly capturing incident HCAP.

1. Question: Should cardio-protective ASA be included as an NSAID?

Answer: No acetylsalicylic acid prescriptions/dispensations (regardless of dosage) should be included in the NSAID cohort. It is not found in the WHO ATC M01A category and thus does not meet our inclusion criteria.

1. Throughout the protocol, the term “prescriptions” is used. This term has been used interchangeably with dispensations as some sites record prescriptions issued whereas most sites capture prescriptions filled or dispensations. Please specify in the database-specific protocol deviations whether prescription data represent prescriptions issued or prescriptions filled.
2. Question: In tables where number of HCAP are categorized according to duration of follow-up, please specify if categories are mutually exclusive (e.g., HCAP within 14, 30, 90 and 180 days: does this mean 1-14, 15-30, 31-90, and 91-180 or do you want 0-14, 0-30, 0-90, and 0-180).

Answer: These categories are not mutually exclusive. They are examining cumulative events (i.e., 0-14, 0-30, 0-90, and 0-180).

1. Question: For the variable total number of prescription medication (in Table 4), what counts as a prescription medication? We assume each individual generic drug should be counted as a different drug, irrespective of dosage. So we would count the different common denomination codes received. Please confirm this is correct (as opposed to number of drug classes received, or even number of different drugs with different dosages counting as different drugs).

Answer: Please count the number of individual generic drugs, regardless of dosage. This should not include the PPI or H2RA from the day of cohort entry.

1. For sites that do not have influenza and pneumococcal vaccination, these variables will need to be omitted from the high dimensional propensity score. Please specify this omission in the database-specific protocol deviations.
2. Question: Given the hospital bed shortage in some provinces, should extended emergency room visits for community-acquired pneumonia be included as events?

Answer: Before deciding on the inclusion of these extended emergency room visits as events at all sites (versus database-specific protocol deviations), all sites should determine how many additional events would be identified by the following criteria:

* One ICD billing code for pneumonia (ICD-9-CM code [in any field]: 480.x-487.x; ICD-10 code: J10.0-J18.9) received in an emergency room, without any code for pneumonia in the emergency room the day before; and
* A second code for pneumonia (same codes) either in the emergency room or in the hospital happening on the next calendar day.
* Codes can be claimed by either family physicians or specialists

Sites unable to examine this issue due to lack of emergency room data should specify so in the database-specific protocol deviations (both for this analysis as well as the exclusion of previous HCAPs and the definition of the covariate “non-hospitalized, community-acquired pneumonia”).

Post-Script: This is only an issue in Quebec, who will include these events in their primary analysis. They will also conduct sensitivity analyses excluding ER visits as outcomes.

1. Question: If a patient receives both a PPI and H2RA, should they be excluded?

Answer: If a patient receives both a PPI and H2RA, they should be excluded.

1. Question: If a patient receives multiple PPIs on the day of cohort entry, should they be excluded?

Answer: They should be included in the PPI group.

1. Question: What should I do if I am missing prescription duration?

Answer: If you have the number of pills dispensed and the dosage, duration of NSAID prescription should be estimated using:

 Estimated Duration = dosage x quantity / defined daily dosage

1. Question: If patients receive two dispensations for NSAIDs of 15 days each for the same DIN, should they be included?

Answer: No, they should be excluded. Multiple dispensations or prescriptions should not be used to piece together a 28-day duration.

1. Question: How should we handle consecutive hospitalizations?

Answer: If the date of discharge is either the same day or the day before the date of next admission, the discharge should be considered an administrative one, and the two hospitalizations should be combined as one.

1. To avoid hospital-acquired pneumonia, patients hospitalized with a length of stay > 3 days will now be censored on the date of admission.
2. Question: If a patient is discharged from hospital on the day of cohort entry, are they eligible?

Answer: Yes, provided that the length of stay (discharge date – admission date) is < 3 days.

1. Covariate assessment includes diagnoses and prescriptions on the day of cohort entry. Covariates should include those where cohort entry - date of confounder measurement < 365 days.
2. Question: When I count number of hospital admissions, should I count only hospitalizations with at least one night spent in hospital (i.e., minimum length of stay = 1)?
3. Answer: Yes, there is a minimum length of stay of 1 day to count as a hospitalization.
4. Question: If there are two consecutive hospitalizations with lengths of stay of 0, should these be added to produce a hospitalization of 1 day?
5. Answer: While we are adding lengths of stay for consecutive hospitalizations, since neither of these stays meet our criteria for a hospitalization, they should not be combined to create a hospitalization.
6. Question: Total number of prescription medications: it is specified not to count PPI or H2RA on cohort entry but should we count the cohort entry NSAIDs?
7. Answer: No, please do not count the NSAID, PPI, or H2RA from the date of cohort entry.
8. Question: The definition of repeated observation is unclear. Is it:
	1. 0 for first t0 of a patient and 1 for all subsequent t0; or
	2. 1 for all patients having more than one t0?
9. Answer: It is 0 for first t0 of a patient and 1 for all the following t0.
10. Question: Is there a minimum length of stay for a HCAP? For example, if the admission date = discharge date, does this count as a hospitalization?
11. Answer: Events should have a minimum length of stay of one day (discharge date - admission date > 1). Observations admitted and discharged on the same day should not be included as events unless they die in-hospital.
12. Question: Should I exclude anyone with a hospitalization before cohort where the discharge date is missing?
13. Answer: Please exclude observations with a missing discharge date if the patient was admitted within the 6 months prior to cohort entry.
14. Question: What about censoring those with a missing discharge date for hospitalizations occurring after cohort entry?
15. Answer: Yes, please censor observations on the date of admission if there is a missing discharge date.

# APPENDIX IV – DATABASE-SPECIFIC DETAILS OF TRIMMING OF PROPENSITY SCORE DISTRIBUTION

|  |  |
| --- | --- |
| Database | Details of Trimming |
| GPRD |  |
| Maritimes |  |
| Quebec |  |
| Ontario |  |
| Manitoba |  |
| Saskatchewan |  |
| Alberta |  |
| British Columbia |  |