WHISCON World Health Information Science Consultants, LLC

Protocol

The Risk of Esophageal Cancer in Relation to the Treatment and Prevention of Osteoporosis in Women

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Prepared for

Merck Research Laboratories

Merck contact:

PPD

Merck Research Laboratories
Mail stop UG1D-60
PO Box 1000
North Wales PA 19454-1099

PPD

PPD

WHISCON contacts:

PPD

PPD

World Health Information Science Consultants, LLC
70 Walnut Street
Wellesley, MA 02481

PPD

PPD

PPD

www.WHISCON.com

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1. Study Overview

The work will be undertaken in two phases.

The initial study will be a case-cohort study of cancer of the esophagus, nested in the General Practice Research Database (GPRD) population of women born in 1922 and later, for such time as they contributed information to the GPRD from 1996 through 2008. Women with active treatment for cancer will be censored as of their first treatment. This will involve all cases of cancer of the esophagus and 25,000 randomly sampled women from the GPRD. Lagged cumulative doses for high- and low-dose alendronate, etidronate, ibandronate, risedronate, raloxifene, calcitonin and Vitamin D plus calcium will be the primary exposures of interest, and information on possible confounding factors will be drawn from the GPRD records.

The second study will be an intention-to-treat cohort analysis. For each calendar quarter from 1996 through 2005, each woman born in 1922 and later who begins treatment for osteoporosis will be matched on year of birth to two women represented in the database at that time, drawn at random and with replacement from the full GPRD population, and followed through latest available data. Variance adjustments account for the possible membership in several cohorts by single individuals. This analysis draws on the "intention to treat" principal of clinical trial design in which patients are maintained in their initial treatment groups despite variations in adherence to the assigned regimen, and has been successfully applied in the past to GPRD data. [1, 2]

If the GPRD data support making the distinction, we will analyze adenocarcinoma of the esophagus (ACE) and squamous cell carcinoma of the esophagus (SCC) separately. Data manipulation and preparation for the two cell types will be done together, as simply esophageal cancer. Final analyses of the two cell types will parallel one another exactly.

2. Case-Cohort Data Preparation

Merck will provide to WHISCON the complete GPRD files of all women with any diagnosis of esophageal cancer from 1996 to 2008.[3] Merck will also provide the complete files for a simple random sample of 25,000 women with year of birth 1922 through 1953 (corresponding to birth cohorts that were, respectively, 74 years old in 1996

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[1] Hill AB. *Principles of Medical Statistics*. 9th Edition. Oxford University Press, New York, 1971, p. 260

[2] Hernán MA, Robins JM, García Rodríguez LA. In discussion of: Prentice RL, Pettinger M, Anderson GL. Statistical issues arising in the Women's Health Initiative. Biometrics. 2005;61:922–930.

[3] We anticipate about 2000 such cases.

through those that were 55 years old in 2008). Note that this data request will be made simultaneously with that described in Section 6, for the intent-to-treat analysis.

2.1. Check Data

In both esophageal cancer and random sample files, tabulate the following, with appropriate labels. Terms in bold are defined in the text when they first appear and again in Section 9.

1. Distribution of the number of records for each subject for each table in the data file
2. For each field in each table, the frequency of each code, with labels
3. Identification of service records for which there is no demographic file
4. Sex
5. Year of birth
6. Year of first date of appearance (**First Date**) in files by year of last date of appearance in files (**Last Date**)
7. Distribution in months (days / 30) of **Observation Time** = **Last Date - First Date**
   Mean, percentile distribution of **Observation Time**
8. Year, extracted from the date of first appearance of a diagnosis of esophageal cancer (**First Diagnosis Date**) by **Age First Diagnosis (= First Diagnosis Date – Birth Date)** in five-year increments

Criteria for acceptance for the above checks:

1. All tables that should be populated are, with plausible frequency
2. Valid codes with a plausible frequency distribution
3. Zero
4. All female
5. 1922 – 1953
6. Earliest of the year of **First Date** is 1996 or before
   Latest of the year of **Last Date** is 2008 or later
7. **Observation Time** is always greater than zero
8. All cases have a **First Diagnosis Date**
   Fewer than one percent of random sample have a **First Diagnosis Date**

2.2. Crosscheck Data Against Merck Feasibility Reviews

1. For the cases and the random sample controls, the distribution of year of **First StudyDrug Date** by year of **Last Date**, where **StudyDrug** is successively:
   a. High dose alendronate

b. Low dose alendronate
c. Etidronate
d. Risedronate
e. Ibandronate
f. Raloxifene
g. Calcitonin

2. For each user of a study drug, for each drug
    a. Calculate the length of the following windows, from the earlier date through one day before the later date:
        i. **Time Before StudyDrug. First Date** to **First StudyDrug Date**
        ii. **First Year StudyDrug. First StudyDrug Date** to minimum of (365, **Last Date**)
        iii. **Time After StudyDrug. First StudyDrug Date** to **Last Date**
    b. Calculate the number of endoscopies in each window
        i. **Endoscopies Before StudyDrug**
        ii. **Endoscopies First Year StudyDrug**
        iii. **Endoscopies After StudyDrug**
    c. Tabulate sums of window lengths and endoscopy counts in categories of window (before, first year, and after each of the study drugs)
    d. Calculate endoscopy rates per 100 person years in categories of window, as above

Evaluation criteria.

1. The distribution of alendronate initiation and time since initiation should resemble Figures 1a and 1b from the Merck feasibility assessment, reproduced in Section 8. The absolute numbers in the sample population need to be multiplied by the projection factor (Total population count/25,000).
2. The endoscopy rates for alendronate should be similar to those calculated by Merck, and should not be very different for other agents. The rates calculated by Merck were 1.68 per 100 woman years before alendronate, 0.67 in the first year of alendronate and 0.48 after alendronate.

3. Cases and Comparators

3.1. Identification from GPRD files

The study base, that is the person time from which cases appear, will consist of all women born between 1922 and 1953 represented in the GPRD for such time as they had had two years of experience recorded in the database, were aged 55 years and older

between 1996 and 2008, had not experienced any form of esophageal cancer or Paget's Disease and had not received oral or intravenous steroids or chemotherapy or radiotherapy, as indicated by GPRD codes.

The candidate cases that meet the study population criteria will be selected from the esophageal cancer data files. The codes that will be used to search for these women are:

GPRD Medical Code	Term Type	Read / OXMIS Code	Read / OXMIS Term
206100	READ	B105.00	Malignant neoplasm of lower third of oesophagus
215086	READ	B103.00	Malignant neoplasm of upper third of oesophagus
215087	READ	B10z.11	Oesophageal cancer
215262	READ	B801200	Carcinoma in situ of lower 1/3 oesophagus
233256	READ	B102.00	Malignant neoplasm of abdominal oesophagus
242287	READ	B101.00	Malignant neoplasm of thoracic oesophagus
242288	READ	B110111	Malignant neoplasm of gastro-oesophageal junction
255673	READ	ZV10016	[V]Personal history of malignant neoplasm of oesophagus
260668	READ	B10y.00	Malignant neoplasm of other specified part of oesophagus
260669	READ	B10z.00	Malignant neoplasm of oesophagus NOS
269913	READ	B106.00	Malignant neoplasm, overlapping lesion of oesophagus
270070	READ	B801.00	Carcinoma in situ of oesophagus
270071	READ	B801000	Carcinoma in situ of upper 1/3 oesophagus
274655	OXMIS	150 A	MALIGNANT NEOPLASM OESOPHAGUS
278979	READ	B10..00	Malignant neoplasm of oesophagus
278980	READ	B104.00	Malignant neoplasm of middle third of oesophagus
279147	READ	B801z00	Carcinoma in situ of oesophagus NOS
279162	READ	B905000	Neoplasm of uncertain behaviour of oesophagus
292873	OXMIS	150 B	SARCOMA OESOPHAGUS
297331	READ	B100.00	Malignant neoplasm of cervical oesophagus
297332	READ	B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
297506	READ	B801100	Carcinoma in situ of middle 1/3 oesophagus
303091	OXMIS	150 C	OESOPHAGUS CARCINOMA

The date of first appearance of any of these codes in a woman's GPRD record is the **Apparent Onset Date.**

We anticipate about 1000 candidate cases in 1996 through 2008 occurring after two years in the GPRD among women aged 55 years and older who had not experienced any form of esophageal cancer, breast cancer or Paget's Disease and had not received oral or intravenous steroids. If the number of candidate cases is fewer than 800, change the prior membership criterion to one year in the GPRD.

3.2. Expert Review and Algorithm Development

For each candidate case, prepare a chronological listing of all services for a year before and after the **Apparent Onset Date**, but omitting drug prescription information. Using an abstraction and adjudication form, a physician epidemiologist familiar with the GPRD will review each for classification as adenocarcinoma of the esophagus (ACE), squamous cell cancer of the esophagus (SCC), cancer of the esophagus of other or unknown cell type, other cancer affecting the esophagus and not cancer of the esophagus. The reviewer will also specify the date of clinical onset.

For each adjudicated case, the reviewer will note on the abstraction and adjudication form the reasons for his or her decision, from which WHISCON will create an adjudication algorithm consisting of a series of exclusion and inclusion statements, based on combinations of items and their dates, as available in the GPRD record. The algorithm will be applied to the GPRD data to classify the potential cases and assign dates of clinical onset (**Adjudicated Onset Date)**. The reviewer will re-review cases in which the algorithmic allocation and the reviewer's adjudication differ. The re-review will result in either changing the adjudication of the case or modifying the algorithm. The new algorithm will be reapplied to the files of potential cases, again looking for discrepancies, which will be addressed as before. The process continues until the algorithm correctly represents the reviewer's judgment in these data.

3.3. Chart Validation

WHISCON will provide to Merck coded identification of 75 adjudicated cases and 25 adjudicated noncases.

Merck will seek documentation from the general practice charts through the GPRD team. Information to be collected on a standard form will include date of earliest symptoms, date of diagnosis, and histopathological findings. Merck will also request blinded records pertinent to the diagnosis.

Merck will transfer this information to WHISCON in a machine-readable form.

WHISCON will tabulate these findings against those of the case allocation resulting from the algorithm developed above. The interpretation of this table could be that the algorithmic adjudication is adequate for the study's purposes, or that it is adequate only if cell types are considered together, or that it is inadequate.[4] Adequacy will be taken as a predictive value positive of 90 percent or higher and a predictive value negative (among candidate cases adjudicated negative of 80 percent or higher. This correspondence will in any case be part of the final report and will prompt a sensitivity analysis of the results and consideration of chart validation for all potential cases.

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[4] Inadequacy of the adjudication would be entirely at odds with previous chart-validated examinations of esophageal cancer in the GPRD. See for example Lindblad M, Lagergren J, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 2005;14:444–50, also cited in Section 9.

3.4. Controls

For each case, identify all women from the comparison sample who have the same year of birth and are in the GPRD on the **Adjudicated Onset Date**. These, together with the case, form a matched set, with **Index Date** for all members of the set corresponding to the **Adjudicated Onset Date** of the case. Remove women who have an **Adjudicated Onset Date** before the **Index Date** (that is any prior cases), or any diagnostic code for breast cancer or Paget's disease, or who have received oral or intravenous steroids before the **Index Date**. A single woman may appear in the control group for more than one case.

4. Exposure

For each person in each matched set, the first step will be to extract the following data elements from the GPRD files, as available through the **Index Date**.

- GPRD identification number
- Body weight and BMI
- Tobacco and alcohol use. Treatment codes for smoking cessation advice and smoking cessation treatment.
- All dispensings of treatments for osteoporosis (see below)
- All dispensings of acid suppressant medications
- All mentions of GERD or esophagitis

From these elements, create the characteristics described below for each study subject.[5]

4.1. Treatment for Osteoporosis

For each case and control, identify all instances of exposure to the following treatment regimens.

[5] Note that time-varying characteristics that relate to medical treatment are accumulated up through 24 months before the **Index Date**, to allow for an induction period. Stable personal characteristics not likely to be affected by use of medications for osteoporosis (weight, smoking and drinking status, chronic acid suppressive therapy) are assessed at six months before **Index Date**. The interval is intended to provide assurance that these have not changed in response to early phases of an undiagnosed cancer. None of these characteristics is thought to be affected by treatments for osteoporosis. In the later, intention-to-treat phase of the study, they will be considered only as baseline factors before treatment.

1. Calcium and Vitamin D supplementation. Mention in the patient record of calcium and Vitamin D supplementation or prescriptions for ergocalciferol daily and calcium daily.
2. High dose alendronate. Alendronate 70 mg weekly or 10 mg daily
3. Low dose alendronate. Alendronate 35 mg weekly or 5 mg daily
4. Etidronate
5. Risedronate
6. Ibandronate
7. Raloxifene
8. Calcitonin

Exposure metrics**.** As of each subject's **Index Date, characte**rize for each treatment (1-7 above) exposure indices as follows:

StudyDrug Recent Initiator. First exposure to the treatment occurred in the 24 months preceding the **Index Date**. 1 – Yes; 0 – No.

StudyDrug Duration. Number of months of exposure up to 24 months before the **Index Date**.

StudyDrug Time Since First Exposure. Index Date minus **First StudyDrug Date** (days)**;** set to 1 if **First StudyDrug Date** is undefined.

StudyDrug Uncertain Initiation. 0 – **First StudyDrug Date** minus **First Date** is >182. 1 – otherwise.

StudyDrug Before Index. Collapse exposure measures for each drug into ever/never.

4.2. Covariates

For each subject, identify the following characteristics.

Reflux disease. At least 12 dispensings of proton pump inhibitors or H_2 receptor antagonists bracketing at least two diagnoses of reflux disease, at any time before **Index Date**.

Reflux Rx Days Dispensed. Number of dispensings of gastric acid suppressant medication at any time before **Index Date**.

Reflux Time Since. Time since qualification as reflux disease at any time before **Index Date**. **Endoscopy more than 24 months earlier.** Any endoscopy more than 730 days before the **Index Date**.

Endoscopy less than 24 months earlier. Any endoscopy in the 730 days preceding the **Index Date**.

BMI. Last body mass index, at least six months before **Index Date**.

Weight. Last weight, at least six months before **Index Date**.

Smoking. Last smoking status at least six months before **Index Date**.

Alcohol. Last alcohol consumption status, at least six months before **Index Date**.

4.3. Other Information

Identify or create, as appropriate, the following information.

Matched Set ID

Case/Control. "Case" if **Adjudicated Onset Date** is defined. Otherwise "Control".

Age at Index. Index Date minus **Birth Date**. Because of matching, control ages will be within a single year of the case age.

5. Case-Cohort Analysis

5.1. General Features of the Data

Describe the data.

- Tabulate all characteristics by **Case/Control**.
- Cross-tabulate for controls only, for each study drug
  StudyDrug Recent Initiator, StudyDrug Duration, StudyDrug Time Since First exposure
  by
  Age at Index, year of **Index Date**
- Cross tabulate the different **StudyDrug Before Index** (corresponding to each osteoporosis treatment) by one another, using a multiple-response table

5.2. Effect Estimates

Baseline factors. Perform a conditional logistic regression in the case-control matched sets, incorporating **Recent Initiator** for each of the drug classes, plus all the covariates listed in Sections 4.2 and 4.3 above (other than recent endoscopy), with suitable representation of the continuous measures, as dictated by the preliminary tabulations. To account for the repeated appearance of individuals in multiple matched sets, use robust variance estimates.[6] Perform a backwards selection by sequentially removing predictors with the smallest chi-square values until the least significant remaining predictor's chi-square corresponding to $p<0.2$.

Exposure. The first step is to identify the best available representation of each of the study drugs in the model, building on the variables calculated, starting from the baseline

[6] Barlow WE. Robust variance estimation for the case-cohort design. Biometrics 1994;50:1064-1072

model described above. Next, form a final model using the chosen exposure measure for each drug.

Exposure to each of the osteoporosis medications will be studied alternatively as a simple indicator and as a response surface for those with Uncertain Initiation Date = 0 on all drug classes.

Indicator variable (**StudyDrug >24 Months)**

- 1 – If **StudyDrug Time Since First exposure** > 730 days, 0 – Otherwise

Response surface

- Log (**StudyDrug Time Since First exposure**)
- Log (**StudyDrug Duration**)
- Log (**StudyDrug Time Since First exposure**) * Log (**StudyDrug Duration**)

If the Indicator and Response Surface representations do not differ at a p-value of 0.1 as measured by a likelihood ratio test on two degrees of freedom, retain only the Indicator in the final model, otherwise retain the better fitting exposure metric. Recalculate the final model, omitting only persons for whom **StudyDrug Uncertain Initiation** = 1 for study drugs requiring a Response Surface representation. If the Response Surface is retained for any variable, prepare a contour display of time since first exposure by duration of exposure, in which there are contour lines for RR=1, 1.5, 2, 3 and 5.

The coefficients corresponding to Indicator or the Response Surface variables as appropriate will be taken to represent effect of each of the osteoporosis medications on risk of esophageal cancer.

5.3. Unmeasured Confounders

The **StudyDrug Recent Initiator** variables will be measures of residual confounding. If these are elevated for any agent, the treatment effects above will be interpreted in light of this confounding, and the adjusted estimate on the log scale will be the contrast "**StudyDrug >24 Months**" minus "**StudyDrug Recent Initiator**".[7]

5.4. Risk-Dependent Exit from Treatment

In any response surface model, will consider an inverse association between treatment duration and risk to be evidence of risk-dependent exit from the treatments and will drop treatment duration from the model.[8]

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[7] This interpretation is based on the assumption that treatments for osteoporosis cannot have a substantial impact on cancer incidence in the first two years since initiation of therapy. Therefore, any apparent risk must be based on a higher prevalence of long-standing risk factors in persons receiving treatment.

[8] Users of bisphosphonates with reflux esophagitis may be more likely to discontinue treatment, either because the symptoms of reflux are misinterpreted as side effects of

6. Intention-to-Treat Analysis Overview

As noted in Section 5.4, there will be a way of identifying possible effects of risk-dependent exit from treatment groups, but the demonstration does not offer an adjustment for the effects of this phenomenon. Moreover, an inverse association between treatment duration and risk addresses only the most severe issue raised by the possible time-varying interrelations between treatment continuation and treatment effects. We have assumed in the case-cohort analysis that treatment does not affect the status of other covariates. The next analytic step will be an intention-to-treat analysis to address the problem of selective exit from the treatment groups and of covariates that may be intermediate variables between exposure and outcome.[9]

Consider the cohort of women who initiate treatment with study drugs in a single quarter. Take the first quarter of 2000 for concreteness. Most of these women will have not prior treatment with any of the study drugs. A few will have had prior treatment. Imagine that each initiator is matched to a woman of the same birth year and treatment history and initiators and comparators are followed to the end of observation time for an event. This is an intention-to-treat analysis. Each cohort so formed offers an unbiased estimate of the effect of treatment initiation, and is unaffected by subsequent changes in dosing. The overall intention-to-treat analysis forms all such cohorts, all of which are unbiased, and analyzes them in a single stratified analysis. Since a single woman may participate in several of these cohorts, the correlation of her outcomes in the different cohorts needs to be accounted for in the variance estimate, but does not affect the point estimate of effect.

Robust variance estimates permit the calculation of effects when the individual contributes to multiple comparison groups.

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treatment, or because treatment exacerbates symptomatology that had previously been tolerable or ignored. In either case, the effect would be to remove these women at substantially elevated risk for esophageal cancer from the treatment. This would not affect the analyses of those "ever exposed" to each agent or the Time since First Exposure, but would distort apparent duration-response effects, with the users of shortest users appearing to be at the highest risk, after adjustment for time since first exposure. If this pattern arises, focus causal interpretation on the "ever-exposed" exposure metrics.

[9] Since precursors of esophageal cancer may give rise to esophageal symptoms like those that result from drug use, women with precursor conditions may have shorter average duration of treatment, and without precursors may predominate among those with longer treatment. This is a "healthy user" effect. The dose response function would range from elevated risk at short durations of treatment to an apparent protective effect with longer duration, both by comparison to nonusers.

6.1. Data Preparation

6.1.1. Exposed cohorts

Merck will provide the full records of all women born 1922 and later who have any prescription for osteoporosis therapy with any of the osteoporosis treatments described above, except for Vitamin D and calcium, between 1996 and 2008. These are:

1. High dose alendronate. Alendronate 70 mg weekly or 10 mg daily
2. Low dose alendronate. Alendronate 35 mg weekly or 5 mg daily
3. Etidronate
4. Risedronate
5. Ibandronate
6. Raloxifene
7. Calcitonin

For non-empty values of **First StudyDrug Date,** assign each woman a value for

Osteoporosis Regimen (the Study Drug)

Cohort Entry Date (=**First Study Drug Date**)

Baseline Prior StudyDrug. For each Study Drug, whether or not there was any exposure before the **Cohort Entry Date.** 0 – No. 1 – Yes.

Note that a woman who uses more than one of the treatments above will have several **Osteoporosis Regimen** variables and a corresponding number of **Cohort Entry Date** variables.

Women with chemotherapy or radiotherapy as indicated by GPRD codes prior to **First Study Drug Date** will be not be included in the cohorts. Women with chemotherapy or radiotherapy after **First Study Drug Date** will be censored from the cohort as of date of first treatment.

6.1.2. Comparison cohorts

Link all **Cohort Entry Dates** for exposed women to the women's **Birth Dates**, and **GPRD ID**s. For each **Cohort Entry Date** and year of **Birth Date**, draw from the GPRD database who have the same year of birth, are represented in the GPRD on the **Cohort Entry Date** and have exactly the same values for the **Baseline Prior StudyDrug** variables as of the **Cohort Entry Date**. If this number exceeds two, draw two at random. Each triplet of an osteoporosis initiator and her two matched comparators should be assigned a **Cohort Match Set ID.** Members of each match set are assigned the initiator's **Cohort Entry Date.** Note that this data request will be made simultaneously with the case-cohort data request described in Section 2.2.

Women can appear multiply as initiators of different osteoporosis regimens can be sampled repeatedly as a non-initiators in many cohorts. In practice, because there are 40 cohorts and the sampling fractions will be about one in 1000 for comparators for each

cohort, each woman in a cohort has approximately a four percent chance of being selected into another. For this reason it will be necessary to carry each subject's **GPRD ID** number into the analyses.

For all subjects, assign a **Cohort Entry Date** as the **First StudyDrug Date** for the women chosen because of use of a study drug and as the same date for their matched random sample women.

The data checks below are very similar those in Section 2.1. Some of variables are variations on the corresponding case-cohort study variables, with the **Cohort Entry Date** substituted here for the **Index Date**. The acceptance criteria are modified accordingly.

6.1.3. Check Data

Separately for the random sample and the treatment files, tabulate, with appropriate labels:

1. Distribution of the number of records for each subject for each table in the data file
2. For each field in each table, the frequency of each code
3. Identification of service records for which there is no demographic file
4. Sex
5. Year of birth
6. Year of **Cohort Entry Date** by year of **Last Date**
7. Mean, percentile distribution of **Cohort Observation Time** (**Last Date** minus **Cohort Entry Date**); frequency distribution of **Cohort Observation Time** in months (days / 30)
8. Year of **Adjudicated Onset** by **Age**

Criteria for acceptance for the above checks. For each, distributions are similar in users of study drugs (collectively) and comparators. In addition,

1. All tables that should be populated are
2. Valid codes with distributions similar to those seen in tasks under Section 2.1.
3. Zero
4. All female
5. 1922 or later
6. Earliest **Cohort Entry Date** is in 1996
   Latest **Last Date** is in 2008 or 2009
7. **Cohort Observation Time** is always greater than zero
8. Fewer than one percent have an **Adjudicated Onset Date.**

6.1.4. Crosscheck Against Early Merck Feasibility Reviews.

1. The distribution of year of **Cohort Entry Date** by year of **Last Date**
2. For each user of a study drug, for each drug
    a. Calculate the length of the following windows, from the earlier date through one day before the later date:
        i. **Time Before StudyDrug. First Date** to **First StudyDrug Date**
        ii. **First Year StudyDrug. First StudyDrug Date** to minimum of (365, **Last Date**)
        iii. **Time After StudyDrug. First StudyDrug Date** to **Last Date**
    b. Calculate the number of endoscopies in each window
        i. **Endoscopies Before StudyDrug**
        ii. **Endoscopies First Year StudyDrug**
        iii. **Endoscopies After StudyDrug**
    c. Tabulate sums of window lengths and endoscopy counts in categories of window (before, first year, and after each of the study drugs)
    d. Calculate endoscopy rates per 100 person years in categories of window, as above

Evaluation criteria.

1. The distribution of alendronate initiation and time since initiation should resemble Figures 1a and 1b from the Merck feasibility assessment, reproduced in the Appendix.
2. The endoscopy rates for alendronate should be similar to those calculated by Merck, and should not be very different for other agents. The rates calculated by Merck were 1.68 per 100 woman years before alendronate, 0.67 in the first year of alendronate and 0.48 after alendronate.

6.2. Cohort Formation

For every three-month period, beginning in the first quarter of 1996 assign all initiators and their comparators (women sharing **Cohort Match Set ID** with the initiator) into an initiation cohort. Do this by assigning to each individual a year-quarter cohort ID (**Y-Q Cohort ID)**: 1996-1, 1996-2, …, 2005-3, 2005-4.

6.3. Covariates

Identify baseline covariates, similar to those in Section 4.2, but tied to the date of initiation of osteoporosis treatment in the treated and the same calendar day in the untreated comparator women.

Baseline Alcohol. Last description of alcohol consumption before **Cohort Entry Date**.

Baseline BMI. Last body mass index before **Cohort Entry Date**.

Baseline Endoscopy >24 Months. Any endoscopy more than 730 days before the **Cohort Entry Date**.

Baseline Endoscopy ≤ 24 Months. Any endoscopy in the 730 days preceding the **Cohort Entry Date**.

Baseline Reflux disease. At least 12 dispensings of proton pump inhibitors or H_2 receptor antagonists bracketing at least two diagnoses of reflux disease, at any time before **Cohort Entry Date**. Reflux disease will be classed by the number of dispensings of gastric acid suppressant medication and time since first dispensing, in the same manner as osteoporosis treatments.

Baseline Smoking. Last smoking status before **Cohort Entry Date**.

Baseline Weight. Last weight before **Cohort Entry Date**.

Baseline Prior StudyDrug. For each Study Drug, whether or not there was any exposure before the **Cohort Entry Date.**

6.4. Outcome

Link the previously identified cases of adenocarcinoma of the esophagus to these files to obtain **Adjudicated Onset Date**.

6.5. Analysis

1. Characterize the cohorts at baseline
    a. Cohort accrual for each **Osteoporosis Regimen** by calendar quarter
    b. Tabulate each covariate's distribution by **Osteoporosis Regimen**
    c. Tabulate current drug exposure class by initial drug exposure class as of annual increments of time since **Cohort Entry Date**
2. Perform a stratified proportional hazards analysis by pooled logistic regression,
    a. Time metric: time since **Cohort Entry Date**
    b. Stratification: **Y-Q Cohort ID**
    c. Predictors
        i. Osteoporosis Regimen
        ii. Baseline covariates
    d. Failure: carcinoma of the esophagus
        i. Adenocarcinoma
        ii. Squamous cell carcinoma
    e. Censoring: end of follow-up or occurrence of other cancer
    f. Robust variance estimates to account for the appearance of subjects in multiple initiation cohorts[10]

[10] See ROBUST SAS software system macro to obtain robust, or empirical, variance estimates. Allison PD. Logistic regression using the SAS system. Cary, NC: SAS Institute, Inc, 1999

7. Other Considerations

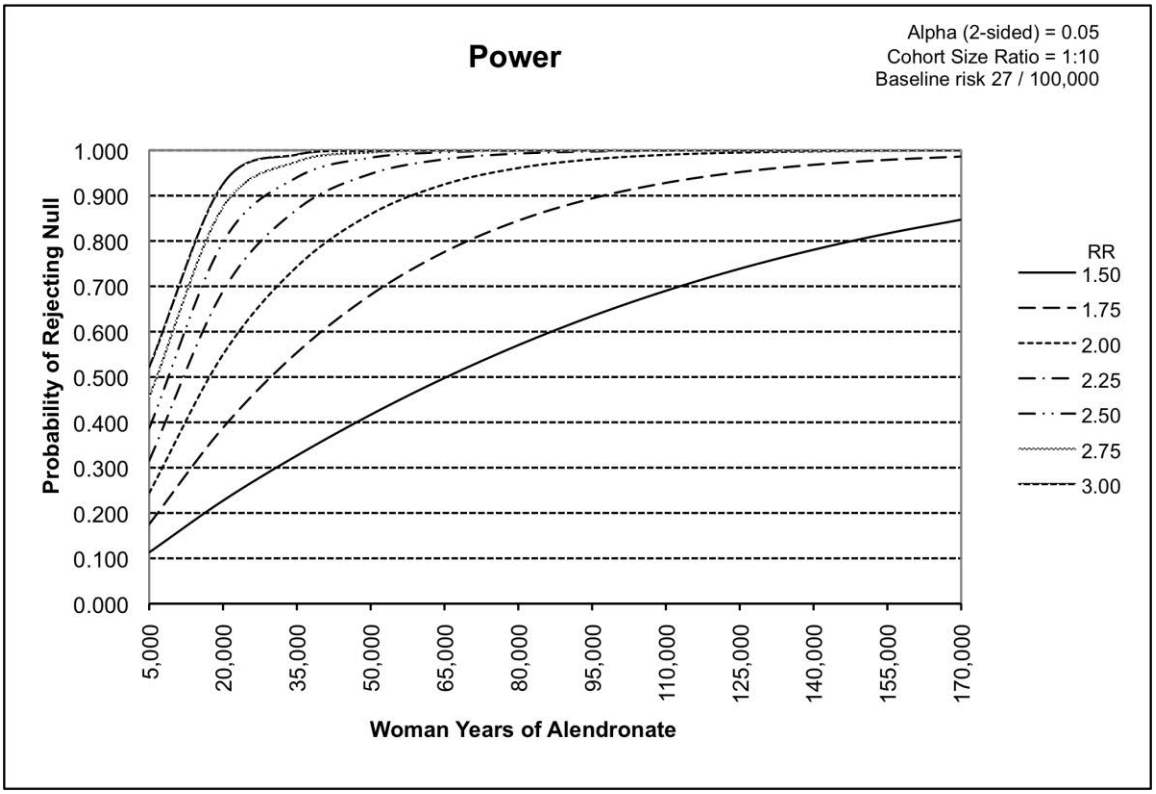
7.1. Study Size and Power

According to the Merck staff review of the GPRD, there were approximately 253,000 person years of follow-up for some 82,000 alendronate users through 2008. Uptake grew rapidly only beginning in 2001, so that the amount of long-term follow-up is limited. Among subjects with at least six months of alendronate use, there are 200,000 person years of experience, of which about 33,000 (16.4%) is beyond five years since first use, 48,000 (24.0%) fall between three and five years following first use.

While these follow-up periods are relatively short for studies of carcinogenesis, it is important to bear in mind that the observations giving rise to this research include cancers arising on the average within 3.0 years of first treatment, the shortest period being only six months.[11] The observation period corresponding best to the hypothesis implied by Wysowski's observation begins at six months. Taking a somewhat more conservative period of 24 months as the lag time before we would expect to see a carcinogenic effect, as proposed in the analysis, we can estimate approximately 90,000 (253,000 total less 82,000 first-year follow-up and some what fewer second-year follow-up) person years of alendronate exposure. The earlier-estimated esophageal cancer incidence of 27 per 100,000 per year in women age 60 and above in the GPRD yields an expected count of 46 exposed cases. This count corresponds to the null hypothesis of no carcinogenic effect.

Since this is a nested case-control study with complete case ascertainment and a very high control to case ratio, the power considerations are identical those of a study in the underlying cohort.

If the reference category of nonusers (Vitamin D + calcium only) is tenfold larger than the cohort of alendronate users, we can derive the power of this analysis to detect various relative risks. The graph that follows gives the power to detect relative rates of esophageal cancer from 1.5 to 3.0 in person-year pools ranging from 5,000 to 160,000, assuming a baseline rate of 27 per 100,000 per person-year.



The proposed study will have 85 percent power to detect a rate ratio of 1.75 in the full follow-up time of 90,000 woman years with at least 24 months elapsed since exposure, and a 90 percent power to detect a rate ratio of 2.25 in the 33,000 woman years at least five years from alendronate initiation.

7.2. Human Subjects

Merck will seek approval for this research from the GPRD's Ethical Review Board.

7.3. Dissemination

The purpose of this work is to provide a timely evaluation of some key safety and efficacy aspects of the use of treatments for osteoporosis. WHISCON will assist Merck Research Laboratories in the preparation of presentation slide deck based on the findings of the study.

WHISCON will prepare and submit for publication a manuscript based on this work. This publication will acknowledge Merck Research Laboratories support. Authorship will follow the usual rules for scientific publication.

8. Background

8.1. Reports of Esophageal Cancer Following Alendronate

At the beginning of 2009, Dianne Wysowski of the US Food and Drug Administration published an account of 23 case reports submitted to the FDA concerning esophageal cancer diagnosed following initiation of alendronate treatment.[11] The average interval from onset of treatment to diagnosis was three years. Dr. Wysowski also noted that there had been 31 cases following alendronate in Europe and Japan, with a split between daily and weekly use of eight cases to nine. Six of seven cases with histological information had adenocarcinoma and one had a squamous cell carcinoma.

Three months after Dr. Wysowski's report, a number of letters appeared in *The New England Journal of Medicine* in response. Skeptical correspondents noted the very short time interval between treatment and cancer occurrence, the very large number of bisphosphonate users worldwide, the lack of an expected count of esophageal cases, and the voluntary nature of the FDA reporting system.[12]

Two correspondents found lower rates of esophageal cancer in bisphosphonate users that in a comparator group. Using data from Danish national registers, Abrahamsen and colleagues compared 13,678 people who had a fracture and filled a prescription for a bisphosphonate to fracture patients who did not fill such a prescription, matched for age, sex and fracture type.[13] Only a third as many alendronate users as nonusers developed esophageal cancer over a mean follow-up time of 2.8 years that produced 37 cases in all (RR=0.35; 95% CI 0.14 – 0.85). Gastric cancers (48 cases) showed no such deficit in the alendronate users, suggesting that there was not a general "healthy user effect" with respect to upper GI cancers. Daniel Solomon and colleagues at the Brigham and Women's Hospital in Boston compared Medicaid records of women receiving bisphosphonates with those of women using raloxifene or calcitonin.[14] The rates were lower in bisphosphonate users than comparators, though the very small number of cases left wide confidence intervals for the rate ratio (0.06 – 4.72).

The scant quantitative data thus do not support an elevated risk of esophageal cancer in users of bisphosphonates, and if anything point to a reduction.

---

[11] Wysowski DK. Reports of esophageal cancer with oral bisphosphonate use (letter). N Engl J Med 2009;360(1):89-90.

[12] Hofbauer LC, Miehlke S; Robins HI, Holen KD; Shaheen NJ; Siris EJ, Oster MW; Bilezkian JP. More on reports of esophageal cancer with oral bisphosphonate use (letters). N Engl J Med 2009;360(17):1790-1791

[13] Abrahamsen B, Eiken P, Eastell R. More on reports of esophageal cancer with oral bisphosphonate use (letter). N Engl J Med 2009;360(17):1789

[14] Solomon DH, Patrick A, Brookhart MS. . More on reports of esophageal cancer with oral bisphosphonate use (letter). N Engl J Med 2009;360(17):1789-1790

8.2. Esophageal Cancer

Holmes and Vaughan have recently presented a very complete review of the known epidemiology and risk factors for esophageal cancer, which we summarize here.[15] The risk factors differ for squamous cell cancer and adenocarcinoma of the esophagus (SCC and ACE, respectively). Both smoking and alcohol consumption raise the risk of SCC by as much as 10-fold, whereas the elevations in ACE seen with smoking are much more modest, about 1.5-fold. Obesity by contrast predisposes substantially to ACE, but not SCC. Holmes and Vaughn find "a strong and consistent association between GERD symptoms and ACE …; estimated ORs range from 2.5 to greater than 40, with higher risk associated with severe or long- standing disease." Although higher socioeconomic status and a higher intake of fruits and vegetables appear to protect against both type of cancer, the effects are modest.

Lindblad and colleagues examined the incidence of esophageal cancer in the General Practice Research Database (GPRD) from 1994 through 2001.[16] They present the following table of incidence rates:

Variable	Person-years	Esophageal cancer		
		n	Incidence rate (per 100,000 person-years)	Incidence rate ratio (95 % CI)
Total	4,340,207	909	20.9	
Sex				
Female	2,300,962	305	13.3	1.00 (reference)
Male	2,039,245	604	29.6	2.51 (2.18-2.88)
Age groups (y)				
40-49	1,315,159	35	2.7	1.00 (reference)
50-59	1,163,475	118	10.1	3.73 (2.56-5.45)
60-69	924,320	248	26.8	9.98 (7.00-14.22)
70-79	725,970	360	49.6	19.23 (13.58-27.21)
>80	211,283	148	70.0	28.23 (19.49-40.88)

Taking the incidence in females as approximately two-thirds of the population incidence, and calculating the crude incidence age 60 and over at 40.6 per 100,000 yields an estimate of 27 cases per 100,000 years in women over the age of 60.

Luis García Rodríguez and colleagues used the GPRD to examine the elevated risk of esophageal adenocarcinoma in chronic users of acid-suppressant medications. The cohort was limited to persons with "esophageal" indications, consisting of reflux

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[15] Holmes RS, Vaughan TL. Epidemiology and Pathogenesis of Esophageal Cancer. Semin Rad Oncol 2007;17(1):2-9

[16] Lindblad M, Lagergren J, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 2005;14:444–50

symptoms, esophagitis, Barrett's esophagus or hiatal hernia.[17] They found no elevated risk for long-term acid suppression therapy in persons with gastroduodenal indications, consisting of gastritis, dyspepsia, indigestion, and epigastric pain.

García Rodríguez and colleagues demonstrated several relevant features of the GPRD in their study esophageal cancer.[17]

- There was essentially perfect correspondence between the electronic record and the general practitioners' paper records for the ascertainment and histological classification of cancers of the stomach and esophagus.
- Expert review of the electronic record in users of acid suppressant therapy permitted a separation of gastroduodenal and esophageal indications.
- Among 10,000 randomly selected controls, data on smoking was available in 77%, alcohol consumption in 65% and body mass index in 64%

For the present study, it will be important to distinguish between SCC and ACE, focusing on the latter. GERD and obesity will be key risk factors.

8.3. Management of Osteoporosis

The following is excerpted with minor edits from the 2006 position statement of The North American Menopause Society.[18]

> All postmenopausal women should be encouraged to employ lifestyle practices that reduce the risk of bone loss and osteoporotic fractures: maintaining a healthy weight, eating a balanced diet, obtaining adequate calcium and vitamin D, participating in appropriate exercise, avoiding excessive alcohol consumption, not smoking, and using measures to prevent falls. Periodic reviews of calcium and vitamin D intake and lifestyle behaviors are useful. After menopause, a woman's risk of falls should be assessed at least annually.
>
> Bone mineral density (BMD) testing is indicated for:
>
> - All postmenopausal women with medical causes of bone loss
> - All postmenopausal women aged 65 and older
>
> BMD testing should be considered for healthy postmenopausal women younger than age 65 who have one or more of the following risk factors:

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[17] García Rodríguez LA, Lagergren J, Linblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case-control study in the UK. Gut 2006;55:1538–1544

[18] Excerpted from: North American Menopause Society (NAMS). Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause 2006 May-Jun;13(3):340-67.

- Previous fracture (other than skull, facial bone, ankle, finger, and toe) after menopause
- Thinness (body weight <127 lb [57.7 kg] or BMI <21 kg/m2)
- History of hip fracture in a parent
- Current smoking

When BMD testing is indicated, dual energy x-ray absorptiometry (DXA) is the preferred technique. The total hip, femoral neck, and posterior-anterior lumbar spine should be measured, using the lowest of the three BMD scores.

In postmenopausal women, the need for prescription osteoporosis therapy is based on a combination of BMD and risk factors. Osteoporosis drug therapy is recommended in the following populations:

- All postmenopausal women who have had an osteoporotic vertebral fracture
- All postmenopausal women who have BMD values consistent with osteoporosis (i.e., T-score worse than or equal to −2.5)
- All postmenopausal women who have a T-score from −2.0 to −2.5 plus at least one of the following risk factors for fracture: thinness, history of fragility fracture (other than skull, facial bone, ankle, finger, and toe) since menopause, and history of hip fracture in a parent

Bisphosphonates are the first-line drugs for treating postmenopausal women with osteoporosis. Alendronate and risedronate reduce the risk of both vertebral and nonvertebral fractures. Whether there are differences in fracture protection among the bisphosphonates is uncertain. It is likely that all produce greater relative and absolute fracture risk reductions in women with more severe osteoporosis.

The selective estrogen-receptor modulator (SERM) raloxifene is most often considered in postmenopausal women with low bone mass or younger postmenopausal women with osteoporosis who are at greater risk of spine fracture than hip fracture. It prevents bone loss and reduces the risk of vertebral fractures, but its effectiveness in reducing other fractures is uncertain. Extraskeletal risks and benefits are important when considering raloxifene therapy.

Calcitonin is not a first-line drug for postmenopausal osteoporosis treatment, as its fracture efficacy is not strong and its BMD effects are less than those of other agents. However, it is an option for women with osteoporosis who are more than 5 years beyond menopause. Calcitonin therapy may reduce vertebral fracture risk in women with osteoporosis, although the evidence documenting fracture protection is not strong. It is not recommended for treating bone pain, except bone pain from acute vertebral compression fractures.

During therapy, it is appropriate to reevaluate the treatment goals and the choice of medication on an ongoing basis through periodic medical examination and follow-up BMD testing. Measurement of BMD has limited use in predicting the effectiveness of antiresorptive therapies for reducing fracture risk. In addition, fracture risk reductions from therapy occur much more rapidly than bone density changes. An appropriate interval for repeat BMD testing is 2 years.

If drug-related adverse effects occur, appropriate management strategies should be instituted. If adverse effects persist, switching to another agent may be required.

The treatment of osteoporosis needs to be long term in most women.

8.4. Expected Sources of Confounding and Other forms of Bias

Six of seven cases with histology reported by Wysowski had adenocarcinoma of the esophagus, and the prior hypothesis to be addressed most specifically addresses ACE. However, as most of the reported cases did not mention histology, we need to carry cancers with both cell types as separate outcomes, recalling that their risk factors differ.

The prior evidence sufficiently strong that smoking and alcohol are risk factors essentially only for SCC. Finding this distinction in the data will strongly support the belief that we have been successful in separating cell types, and by contrast that a finding that smoking and alcohol consumption appear to predict ACE should be taking as *prima facie* evidence of misclassification between the cell types.

Failure to control adequately for smoking could introduce an apparent association between smoking and ACE. Smoking affects bone mineral density and the recommendations noted earlier carry smoking as an indication for studies of bone mineral density in women under age 65. Selective screening in younger smokers could produce a detection bias that would to an apparent association.

The most important risk factors for adenocarcinoma of the esophagus gastro-esophageal reflux disease (and Barrett's esophagus) and obesity.

The disease complex consisting of gastroesophageal reflux disease and Barrett esophagus is strongly predictive of adenocarcinoma.[19] To the extent that the precedent conditions are symptomatic, they mirror upper gastrointestinal side effects associated with alendronate use.[20,21] (Whether those effects are caused by alendronate, or merely the result of confounding, as argued by Donahue *et al*. is not relevant.) Although none of

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[19] Shaheen NJ, Richter JE. Barrett's esophagus. Lancet 2009; 373:850–61

[20] Donahue JG, Chan KA, Andrade SE, Beck A, Boles M, et al. (2002) Gastric and duodenal safety of daily alendronate. Arch Intern Med Apr 22; 162(8): 936–42

[21] Grosso A, Douglas I, Hingorani A, MacAllister R, Smeeth L (2009) Oral bisphosphonates and risk of atrial fibrillation and flutter in women: a self- controlled case-series safety analysis. PLoS ONE 4(3): e4720. doi:10.1371/journal.pone.0004720

these symptoms is a contraindication to the initiation of alendronate therapy, they may nonetheless dissuade physicians from prescribing alendronate, and it seems highly likely that their appearance after alendronate initiation would be interpreted as a drug side effect and would lead to discontinuation.

Confounding by obesity is possible, but is less clearly a risk than is confounding by GERD and Barrett's esophagus. Obesity predisposes to Barrett's esophagus.[19] High glycemic load has been associated with esophageal cancer in heavier (BMI≥25) but not in thinner Italians.[22] Heavy women are less likely to have osteoporosis than are thin women, so that thin (possibly lower risk) women are the patients more likely to be treated with bisphosphonates.

The chronic nature of alendronate treatment raises the possibility that the esophageal symptoms that could lead to alendronate discontinuation might be the result of (1) GERD or Barrett's esophagus (and thus prognostic of esophageal cancer) or (2) alendronate itself or (3) alendronate-induced irritation making an independently occurring esophagitis more evident.[23] Recently developed techniques for the analysis of observational studies essentially reformulate the problem of risk-dependent exit from therapy as a series of reinitiated trials analyzed using an intent-to-treat paradigm. A single subject may exist in different treatment groups in successive "trials," and the correlation between responses is handled using robust variance estimates.[24, 25]

8.5. The General Practice Research Database[26]

8.5.1. Exposure to alendronate and length of follow-up

The GPRD from 1995 through 2007 has approximately 82,000 patients who were prescribed alendronate at least once. About 70% of those initial prescriptions were written between 2002-2007, suggesting a large shift in prescribing practice for

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[22] Augustin, LS, Gallus, S, Franceschi, S, et al.. Glycemic index and load and risk of upper aero-digestive tract neoplasms (Italy). Cancer Causes Control 2003;14:657–62

[23] These complex relations between ongoing treatment and risk add to the baseline confounding that might arise if pre-existing symptoms of reflux form a practical impediment to alendronate therapy.

[24] Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008 Nov;19(6):766-79.

[25] Hernán MA, Robins JM. Authors' Response, Part I: Observational studies analyzed like randomized experiments best of both worlds. Epidemiology 2008:19(6):789-792

[26] This information is taken from a review performed by Merck staff. Figures can be found in Miteva Y, Santora A, Chandler J, Adams J, Lubwama R, Kou D, Bortnichak E. Feasibility Assessment of a Retropsective Database Study in Esophageal Cancer. Memorandum. April 1, 2009

osteoporosis following publication of the WHI trial in 2002. Thus, the long-term follow-up for those prescribed alendronate before 2002 is based on relatively few patients. Total amount of follow–up for all alendronate users in the GPRD database is 253,129 person-years, but there are relatively few patients who contribute 5 or more years of follow up. Total amount of follow-up for patients who have used alendronate for 6 months or more is 200,277 person-years. Figure 1 depicts the prescribing pattern over time and the relationship to years of follow-up.

Figure 1a: GPRD: Recent increase in patients with index alendronate prescription since 2001 but with limited long term follow-up

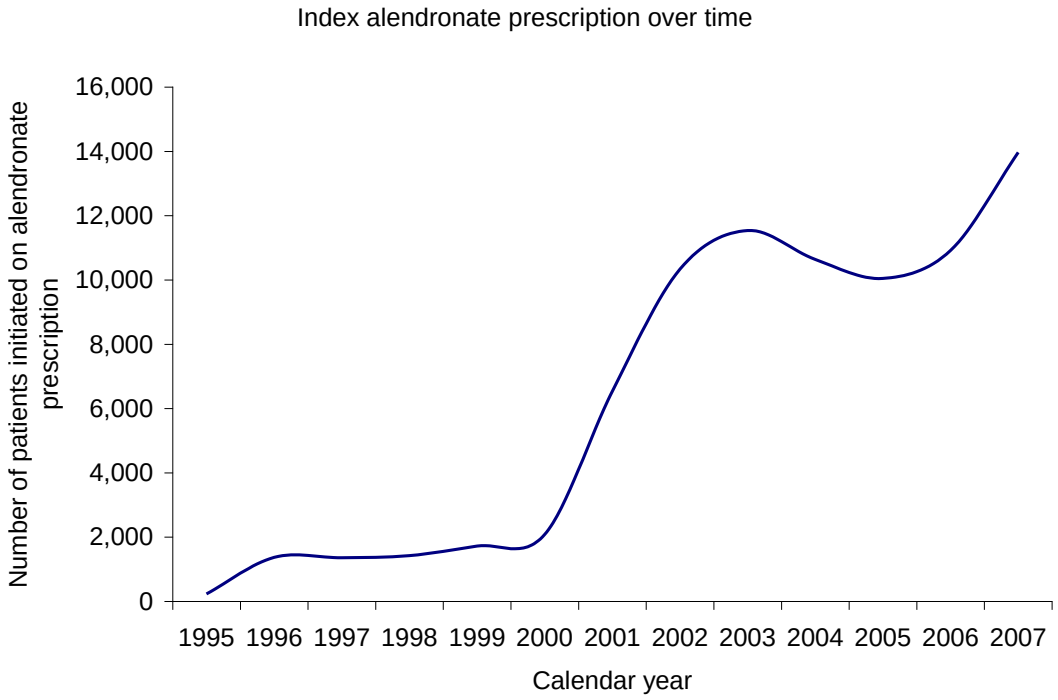
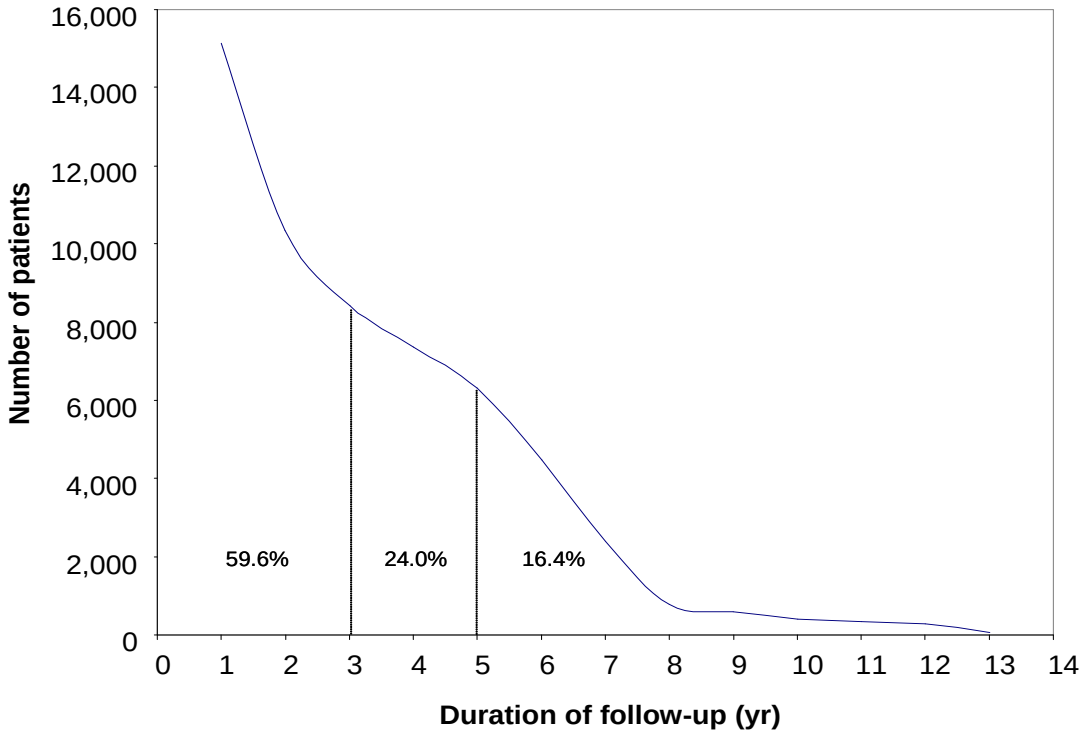


Figure 1b: GPRD: Limited long term follow up in the majority of patients prescribed alendronate.,



9. Terms Used in this Document

9.1. All Study Subjects

Adjudicated Onset. Day-Month-Year of onset of esophageal cancer, as determined by the final case-defining algorithm. Undefined for non-cases.

Age First Diagnosis. First Diagnosis Date minus **First Date**

Endoscopies After StudyDrug

Endoscopies Before StudyDrug

Endoscopies First Year StudyDrug

Endoscopies. Counts of endoscopic procedures during different time windows in relation to each of the study drugs

First Date. Day-Month-Year of earliest appearance in files

First Diagnosis Date. Day-Month-Year of earliest appearance of an esophageal cancer code in files. Undefined if no such code.

First StudyDrug Date. Day-Month-Year of first recorded prescription. Undefined if no recorded prescription

First LowDoseAlendronate Date

First HighDoseAlendronate Date

First Calcitonin Date

First Ibandronate Date

First Raloxifene Date

First Risedronate Date

GPRD ID

Last Date. Day-Month-Year of latest appearance in files

Observation Time. **Last Date** – **First Date**

Time windows. Pairs of Day-Month-Year values, for each study drug

First Year StudyDrug. First StudyDrug Date, Minimum of (**First StudyDrug Date** + 365, **Last Date**)

Time After StudyDrug. First StudyDrug Date, **Last Date**

Time Before StudyDrug. First Date, **First StudyDrug Date**

9.2. Cases and Controls

Age at Index. Index Date minus Birth Date, categorized into 5-year groups

Alcohol. Last alcohol consumption, at least six months before **Index Date**.

Apparent Onset Date. The date of first appearance of any of the esophageal cancer codes in a woman's GPRD record is the

BMI. Last body mass index, at least six months before **Index Date**.

Case/Control status

Endoscopy less than 24 months earlier. Any endoscopy in 730 days at any time before **Index Date**.

Endoscopy more than 24 months earlier. Any endoscopy more than 730 days before the **Index Date**.

*Exposure metrics***.** As of each subject's **Index Date**, characterize for each treatment (1-7 above) exposure indices as follows:

StudyDrug Recent Initiator. Index Date minus **StudyDrug First Date** is <730. 1 – Yes; 0 – No.

StudyDrug Duration. Number of days of therapy prescribed up to 24 months before **Index Date**; set to 1 if **First StudyDrug Date** is undefined

StudyDrug Time Since First Exposure. Index Date minus **First StudyDrug Date** (days)**;** set to 1 if **First StudyDrug Date** is undefined.

StudyDrug Uncertain Initiation. 0 – **First StudyDrug Date** minus **First Date** >182. 1 – otherwise.

StudyDrug Before Index. 1 – **First StudyDrug Date** less than **Index Date** 0 – otherwise

StudyDrug >24 Months.1 – If **StudyDrug Time Since First exposure** > 730 days, 0 – Otherwise

Index Date. For each case, the **Adjudicated Onset Date**. For each control, the **Adjudicated Onset Date** of her matched case.

Matched Set ID

Reflux disease. At least 12 dispensings of proton pump inhibitors or H_2 receptor antagonists bracketing at least two diagnoses of reflux disease, at any time before **Index Date**.

Reflux Rx Days Dispensed. Number of dispensings of gastric acid suppressant medication at any time before **Index Date**.

Reflux Time Since. Time since qualification as reflux disease at any time before **Index Date**.

Smoking. Last smoking status at least six months before **Index Date**.

Weight. Last weight, at least six months before **Index Date**.

9.3. Intention-to-Treat Cohort

Cohort Entry Date. StudyDrug First Date for persons who enter because of use of a study drug. The corresponding date for randomly sampled women matched to study drug initiators.

Cohort Match Set ID. A unique match set identifier assigned to all members of a triplet (study drug initiator and two random comparison women).

Cohort Observation Time (**Last Date** minus **Cohort Entry Date**)

1. **Osteoporosis Regimen.** This is the treatment pattern in the first month following **Cohort Entry Date** of the study drug. Possible values are.
    a. High dose alendronate. Alendronate 70 mg weekly or 10 mg daily
    b. Low dose alendronate. Alendronate 35 mg weekly or 5 mg daily
    c. Etidronate
    d. Risedronate
    e. Ibandronate
    f. Raloxifene
    g. None

Y-Q Cohort ID. Year and quarter of **Cohort Entry Date**. 1996-1, 1996-2, …, 2005-3, 2005-4.

Baseline Alcohol. Last description of alcohol consumption before **Cohort Entry Date**.

Baseline BMI. Last body mass index before **Cohort Entry Date**.

Baseline Endoscopy >24 Months. Any endoscopy more than 730 days before the **Cohort Entry Date**.

Baseline Endoscopy ≤ 24 Months. Any endoscopy in the 730 days preceding the **Cohort Entry Date**.

Baseline Prior StudyDrug. For each Study Drug, whether or not there was any exposure before the **Cohort Entry Date.** 0 – No. 1 – Yes.

Baseline Reflux Disease. At least 12 dispensings of proton pump inhibitors or H_2 receptor antagonists bracketing at least two diagnoses of reflux disease, at any time before **Cohort Entry Date**.

Baseline Reflux Rx Days Dispensed. Number of dispensings of gastric acid suppressant medication**.**

Baseline Reflux Time Since. Time since qualification as reflux disease.

Baseline Smoking. Last smoking status before Cohort Entry Date.

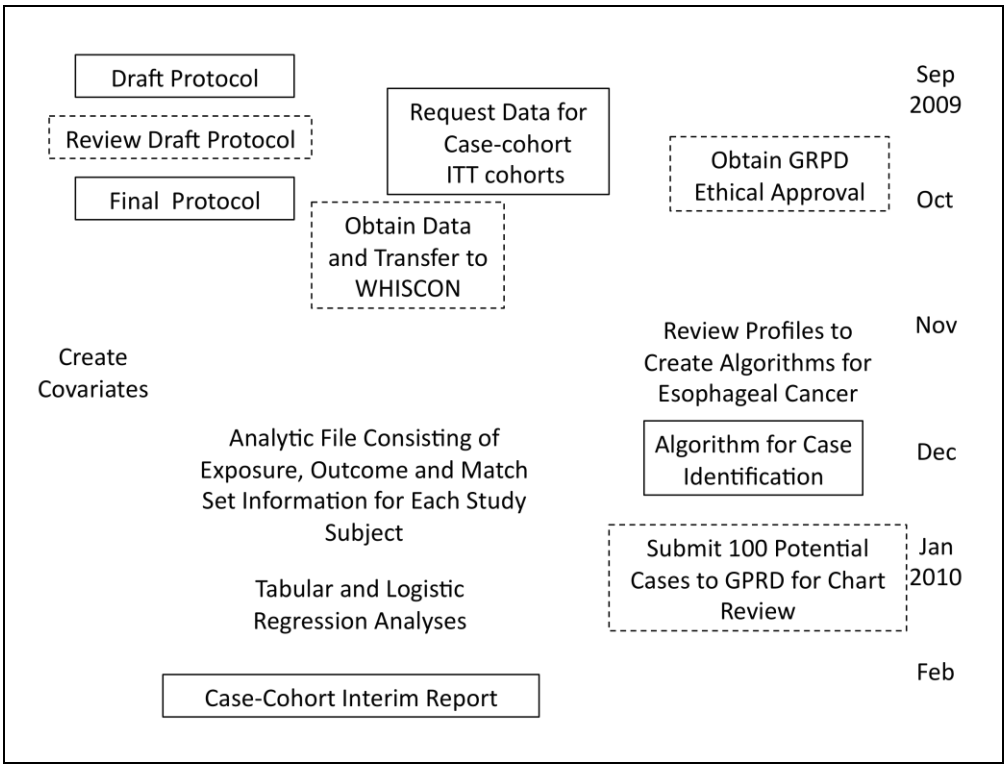
Baseline Weight. Last weight before Cohort Entry Date.

Initial Osteoporosis Regimen. Study Drug prescribed at **First StudyDrug Date** taking on the following values.

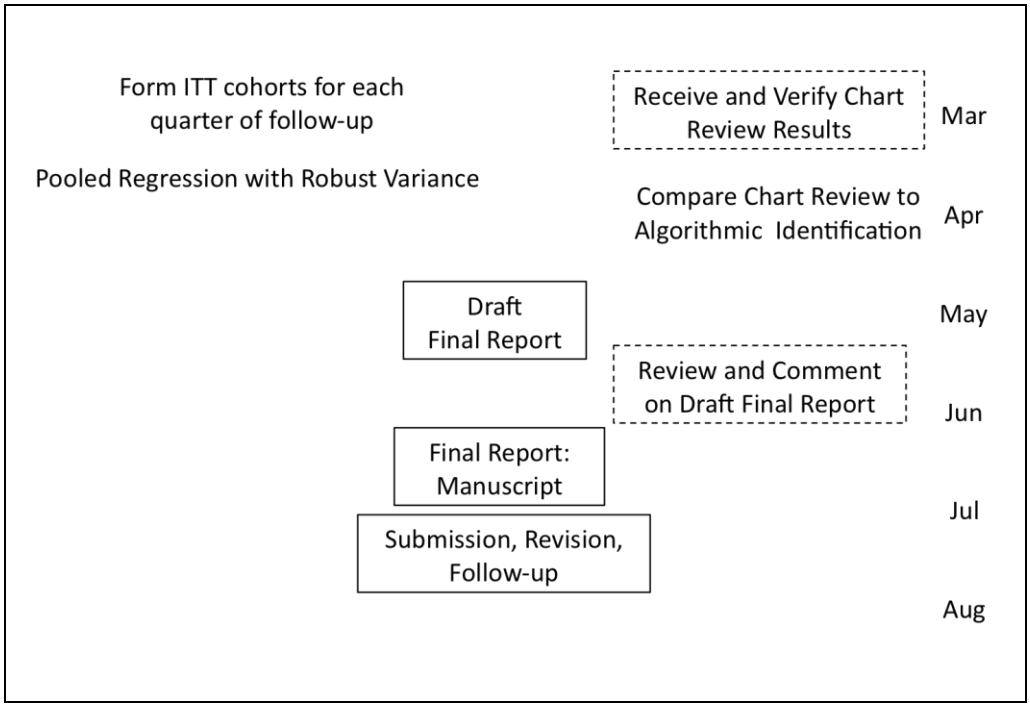
8. High dose alendronate. Alendronate 70 mg weekly or 10 mg daily
9. Low dose alendronate. Alendronate 35 mg weekly or 5 mg daily
10. Risedronate
11. Ibandronate
12. Raloxifene
13. Calcitonin

10. Timing

The following chart lays out the sequence of events for the first phase of the study, culminating in the report of the case-cohort analysis. WHISCON deliverables appear in boxes. Merck activities appear in boxes with dashed lines. Unboxed activities will be performed by WHISCON and its subcontractor IMS.



The second phase supports the intention-to-treat analysis and final report of the project, as outlined below.



11. Protocol Amendments, January 15, 2010

Section and line numbers refer to the Protocol of December 17, 2009.

11.1. Removing upper limit to age at follow-up

11.1.1. The change and its implications

Women will be followed throughout such person time as meets the criteria that the year of observation is 1996 through 2008 and that the woman is 55 years of age or older.

This change will be implemented in the existing study files provided by Merck to WHISCON, which provide data on women born in the years 1922 through 1953. The purpose of the change is to extend follow-up beyond 75 years of age, and to permit the entry of into the study of initiators who begin therapy at 75 years of age and older, along with comparator women.

The change will have the effect of increasing the average length of follow-up of study subjects, since women will not age out of the cohort on their 75th birthdays. As in the original protocol, women who begin treatment before age 55 are eligible for analysis and age into the cohort on their 55th birthday (their exposure status being taken from their earlier treatments). Women who initiate therapy at age 75 years or above and who were born in 1922 and later will be added to the exposed cohorts. Women born before 1922 (who were at least 75 years old at the beginning of 1996) will continue to be omitted from the study. As a result of the limitation to women born 1922 and later, among those older than 75 years at initiation during the study period of 1996 through 2008, there will be a positive correlation between year of birth and age at initiation.

11.1.2. Detailed implementation

Section /paragraph/line

1/2/2	Change "aged 55 to 74 years" to "born in 1922 and later, for such time as they contributed information to the GPRD from 1996 through 2008."
1/3/2	Change "aged 50-69" to "born in 1992 and later".
3.1/1/2	After "women", insert "born between 1922 and 1952".
3.1/1/3	Change "through 74 years" to "years and older".
3.1/3/3	Change "55-74 years old" to "aged 55 years and older".
6.1.1/1/1	Change "aged 50-69" to "born 1922 and later".
6.1.1/1/3	Change "2005" to "2008".
6.1.3/2/List item 5	Change "1926-1955" to "1922 or later".

11.2. Treatments

11.2.1. The change and its implications

Etidronate is mentioned as one of the treatments for osteoporosis to be examined, in some parts of the protocol, but not throughout. The changes involve insertion of etidronate in all places where treatments are mentioned. An initial mention of treatments for osteoporosis specifies dosing data, which are not used elsewhere in the protocol, except for alendronate. The unnecessary dose mentions will be deleted.

The changes do not affect the plan of the study or analysis.

11.2.2. Detailed implementation

Section /paragraph/line

1/3/7 Insert "etidronate, " before "ibandronate".

2.2/1 Insert "c. Etidronate" as the item following "Low dose alendronate." Renumber subsequent items accordingly.

4.1/1 Delete dosing data from all items.

4.1/1/After item 3 Insert "4. Etidronate". Renumber subsequent items accordingly.

9.3/**Initial Osteoporosis Regimen** Insert "Eitronate" as the item following "Low dose alendronate." Renumber all items, starting with "High dose alendronate" as item 1.

11.3. Omission of Study Subjects with Prior Chemotherapy or Radiotherapy

11.3.1. The change and its implications

Women with any code for chemotherapy or radiotherapy prior to disease onset or corresponding matched time will be removed from the case-cohort study. In the intent to treat analysis, women with chemotherapy or radiotherapy before treatment onset will be removed from the cohort, and women with chemotherapy or radiotherapy after treatment onset will be censored as of the time of first chemotherapy or radiotherapy.

The change will have the effect of removing women with active treatment for cancer, which may affect both the likelihood of receiving treatments for osteoporosis and of developing esophageal caner.

11.3.2. Detailed implementation

Section /paragraph/line

1./2/3 Insert "Women with active treatment for cancer will be censored as of their first treatment."

3.1/1/4 Delete ", breast cancer".

3.1/1/4 Insert at the end of the sentence “or chemotherapy or radiotherapy as indicated by GPRD codes”.

3.4/1/5 Delete “breast cancer”. Insert after “steroids”: “or chemotherapy or radiotherapy as indicated by GPRD codes”

6.1.1/end Insert a new paragraph “Women with chemotherapy or radiotherapy as indicated by GPRD codes prior to **First Study Drug Date** will be not be included in the cohorts. Women with chemotherapy or radiotherapy after **First Study Drug Date** will be censored from the cohort as of date of first treatment.”

11.4. Definition of "months"

11.4.1. The change and its implications

Months have been defined throughout as equal to 30 days. This removes ambiguity in which months might be confused with calendar months, and very slightly shorten intervals defined in months by any other convention.

11.4.2. Detailed implementation

2.1/Item 7 and 6.1.3/Item 8 Change "30.4375" to "30".