# Retrospective Case-Control Studies of Rare Adverse Events Associated with Intranasal Steroids

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## I. Overall Research Design, Strategy and Rationale

**PURPOSE:** The purpose of this research is to explore putative associations between exposure to intranasal steroids and the subsequent development of glaucoma, cataract or adrenal insufficiency.

**GOALS OF STUDY IN RELATION TO OUTCOMES:** The goals of this study will be to determine the odds ratios for developing glaucoma or cataract in relation to recent and length of exposure to intranasal steroid or intranasal fluticasone, and to determine the odds ratio for developing adrenal Insufficiency after discontinuation of intranasal steroids or intranasal fluticasone.

**DESIGN:** Retrospective nested case-control studies

**RATIONALE:** The medical literature includes several studies on the putative association between intranasal steroids and the development of open-angle glaucoma and/or ocular hypertension, as well as studies on the relationship between cataract and prior exposure to intranasal steroids or fluticasone.

For example:

- Garbe et al. [1] undertook a case-control study to determine whether the use of inhaled and nasal glucocorticoids is associated with an increased risk of ocular hypertension or open-angle glaucoma. The OR was adjusted for age, sex, diabetes mellitus, systemic hypertension, use of ophthalmic and oral glucocorticoids, and characteristics of health care system use in the year before the index date. The data source was Quebec universal health insurance program for all elderly registered in the Regie de l'assurance maladie du Quebec (RAMQ) database.
  Garbe et al. identified all prescriptions for inhaled and nasal glucocorticoids that had been filled by cases and controls in the year before the index date and studied the risk

of current exposure for both routes of administration. We defined current exposure as a drug supply that continued into the 14-day period before the index date. To study the risk of prolonged exposure, Garbe et al. examined the risk in patients who had used inhaled or nasal steroids continuously for the last 3 or more months before the index date.
Overall, current use of inhaled and nasal glucocorticoids was not associated with an increased risk of ocular hypertension or open-angle glaucoma. Current users of high doses of inhaled steroids prescribed regularly for 3 or more months were at an increased risk with an OR of 1.44 (95% confidence interval, 1.01-2.06).
The adjusted odds ratios and 95% confidence intervals (CIs) for ocular hypertension or open-angle glaucoma according to continuous use or any other use of intranasal steroids were: 1.09 (0.87-1.37) for any use, and 1.02 (0.59-1.77) for continuous use.

- Ernst et al.[2] undertook a matched nested case–control analysis was performed in a population-based cohort of elderly people who had been dispensed medications for airway disease, as identified through a universal drug benefit plan.
  Inhaled corticosteroid use was associated with a dose-related increase in both the risk of all cataracts and severe cataracts requiring extraction, and the increase in risk of severe cataracts was apparent even at daily doses of 500 mg. An excess risk with nasal corticosteroids was not apparent for severe cataracts.
  Ernst et al. concluded that among the elderly, even low doses of inhaled corticosteroids are associated with a small but significant excess risk of cataracts requiring extraction. Such an excess risk was not observed with nasal corticosteroids. The adjusted relative risk (RR) of severe cataracts for the mean daily dose of inhaled (ICS) and nasal corticosteroid (NCS) in the 4-yr period prior to the index date were 1.24 (1.18-1.31) and 1.03 (0.99-1.07), respectively.

No other studies on intranasal steroid exposure and adrenal insufficiency were found in the literature at the time of writing the protocol.

- Mortimer et al.[3] evaluated oral and inhaled steroid exposure and adrenal insufficiency using a case-control study designed based on computerized general practice data from The Health Improvement Network, in which they
  From a cohort of 2.4 million people, 154 cases of adrenal insufficiency and 870 controls were identified. There was a dose related increased risk of adrenal insufficiency in people prescribed an oral corticosteroid with an odds ratio of 2.0 (95% CI 1.6 to 2.5) per course of treatment per year. Adrenal insufficiency was associated with a prescription for an inhaled corticosteroid during the 90 day period before the diagnosis with an odds ratio of 3.4 (95% CI 1.9 to 5.9) and this effect was dose related (p for trend 0.001). After adjusting for oral corticosteroid exposure, this odds ratio was reduced to 1.6 (95% CI 0.8 to 3.2) although the dose relation remained (p for trend 0.036).
  Mortimer et al. concluded that people prescribed an oral or inhaled corticosteroid are at a dose related increased risk of adrenal insufficiency although the absolute risk is small. This analysis suggests that the increased risk in people prescribed an inhaled corticosteroid is largely due to oral corticosteroid exposure, but inhaled corticosteroids may have an effect when they are taken at higher doses.

On this background, there is interest on the part of the sponsor to update the evidence base on the safety of intranasal steroids and the three main outcome groups of glaucoma/ocular hypertension, cataract and adrenal Insufficiency.

## II. Population Sample and Inclusion/Exclusion Criteria

**POPULATION SAMPLE:** The population sample will be drawn from the IMS Lifelink medical and pharmacy claims database for the time period, January 1, 2006 through December 31, 2011. The event time period (i.e., diagnosis of first allergic rhinitis and/or chronic rhinitis episode after a 12-month qualifying is January 1, 2007 through December 31, 2011. The qualifying period is a 12-month period prior to the first allergic rhinitis (AR) and/or chronic rhinitis (CR) diagnosis in which there are: no AR and/or CR diagnoses for cases; no sinusitis (acute or chronic) diagnoses for cases; no use of corticosteroids; and depending on the specific Diagnosis Group (i.e.: Glaucoma and/or Ocular Hypertension; Glaucoma; Cataract), no diagnoses for conditions comprising the specific Diagnosis Groups (e.g., no ICD-9 diagnosis codes that define cases in the Diagnosis Group of interest).

Using a random selection procedure for cases, IMS will pull three separate groups of cases and controls from the IMS Lifelink database – i.e., 50,000 glaucoma (GLAU)/ocular hypertension (OHTN) cases matched to up to 6 controls (or a total control subgroup up to 300,000); 50,000 cataract (CAT) cases matched to up to 6 controls (or a total control subgroup up to 300,000); and 10,000 adrenal insufficiency (ADINSUF) cases with up to 6 controls (or a total control subgroup up to 60,000).

**CASE and CONTROL DEFINITIONS:** Case and control definitions are shown in the following table.

| **Case and Control Definitions for the Three Diagnosis Groups of Interest** | |
|---|---|
| **Glaucoma/Ocular Hypertension Diagnosis Group** | |
| **Case Definition** | **Control Definition** |
| 1. Continuously enrolled in the IMS database with both medical and pharmacy claims for at least 1 year in the IMS database without having a diagnosis of glaucoma and/or ocular hypertension or having received treatment for these conditions, in order to quality as a new or incident case of Glaucoma and/or Ocular Hypertension Diagnosis Group.<br><br>Cases and controls may have an index date of the disease event in 2007, 2008, 2009, 2010, 2011, provided they are continuously enrolled for at least 12 months prior to the index data of the disease event. | 1. Controls will be selected from all non-cases in the database who visited an ophthalmologist or optometrist<br><br>2. Saw a relevant specialty of interest (ophthalmologist or optometrist) within +/- 1 year of case event date<br><br>3. Up to six controls will be matched by IMS to cases on: age (+/- 2years of case as of the case event date); and gender<br><br>4. A Control patient can only be assigned to one Case patient within Glaucoma and/or Ocular Hypertension Diagnosis Group. |

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| 2. Any diagnoses, procedures, or medications for open-angle Glaucoma or unspecified glaucoma or ocular hypertension (as defined with ICD-9 code list) or Ocular Hypertension by an Ophthalmologist or Optometrist.<br>a. 365.0: borderline glaucoma (including the diagnosis of ocular hypertension),<br>b. 365.1: open-angle glaucoma<br>c. 365.3 glucocorticoid-induced glaucoma, and<br>d. 365.9 unspecified glaucoma<br>e. NOTE: ICD9 365.7 is used to code glaucoma stage, and will be used in a subset analysis.<br>f. 365.04, ocular hypertension<br>3. A patient cannot be a Case and a Control for the same diagnosis group (i.e. Glaucoma/Ocular HTN)<br>4. >39 years of age<br>5. Enrollment for at least 1 year without having a diagnosis of OHT or OAG or having received treatment for these conditions, in order to quality as a new or incident case of glaucoma | 5. A patient cannot be a Case and a Control within Glaucoma and/or Ocular Hypertension Diagnosis Group. |
| **Cataract Diagnosis Group** | |
| **Case Definition** | **Control Definition** |
| 1. Continuously enrolled in the IMS database with both medical and pharmacy claims for at least 1 year in the IMS database without having a diagnosis of cataract or having received treatment for this conditions, in order to quality as a new or incident case of Cataract Diagnosis Group.<br>Cases and controls may have an index date of the disease event in 2007, 2008, 2009, 2010, 2011, provided they are continuously enrolled for at least 12 months prior to the index data of the disease event.<br>2. Any diagnoses, procedures, or medications for Cataract by an Ophthalmologist or Optometrist.<br>a. 366.45: drug-induced cataract | 1. Controls will be selected from all non-cases in the database who visited an ophthalmologist or optometrist<br>2. Saw a relevant specialty of interest (ophthalmologist or optometrist) within +/- 1 year of case event date<br>3. Up to six controls will be matched by IMS to cases on: age (+/- 2years of case as of the case event date); and gender<br>4. A Control patient can only be assigned to one Case patient within the Cataract Diagnosis Group.<br>5. A patient cannot be a Case and a Control within the Cataract Diagnosis Group. |

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|---|---|
| b. 336.9: unspecified cataract<br>c. 13: surgery of the lens for lens extraction or insertion of prosthetic lens<br>3. A patient cannot be a Case and a Control for the same diagnosis group (i.e. Cataract)<br>4. >39 years of age | |
| **Adrenal Insufficiency Diagnosis Group** | |
| **Case Definition** | **Control Definition** |
| 1. Continuously enrolled in the IMS database with both medical and pharmacy claims for at least 1 year in the IMS database without having a diagnosis of adrenal insufficiency or having received treatment for these conditions, in order to quality as a new or incident case of Adrenal Insufficiency Diagnosis Group.<br>Cases and controls may have an index date of the disease event in 2007, 2008, 2009, 2010, 2011, provided they are continuously enrolled for at least 12 months prior to the index data of the disease event.<br>2. Consulted a physician and either: i.e., had a diagnosis of adrenal insufficiency (i.e., adrenal suppression, insufficiency or crisis including Addison's disease) or ii. received medical treatment for these conditions.<br>3. Any diagnosis with the following ICD-9 codes:<br>a. 255.41: adrenal insufficiency/glucocorticoids deficiency (includes adrenal crisis, adrenal insufficiency NOS, corticoadrenal insufficiency NOS, combined glucocorticoids and mineralcorticoid deficiency, Addison's crisis, Addison's disease NOS)<br>b. 255.9: unspecified disorder of adrenal glands<br>4. A patient cannot be a Case and a Control for the same diagnosis group (i.e. Glaucoma/Ocular HTN)<br>5. >12 years of age | 1. Controls will be selected from all non-cases in the database who visited a physician<br>2. Saw any physician within +/- 1 year of case event date<br>3. Up to six controls will be matched by IMS to cases on: age (+/- 2years of case as of the case event date); and gender<br>4. A Control patient can only be assigned to one Case patient within the Adrenal Insufficiency Diagnosis Group.<br>5. A patient cannot be a Case and a Control within the Adrenal Insufficiency Diagnosis Group. |

**INCLUSION AND EXCLUSION CRTIERIA:** The inclusion and exclusion criteria for the three outcome populations are shown in the table, below.

| **Exclusion Criteria for the Outcome Populations of Interest** | |
|---|---|
| **Case and Control Exclusion Criteria** | |
| **Glaucoma and Ocular Hypertension Diagnosis Group** | |
| 1. Patients on oral steroid replacement therapy in the year prior to the index date | |
| 2. Cushing's Disease, at any time over the study period | |
| 3. Age unavailable | |
| 4. GLAUCOMA ICD9 DIAGNOSTIC EXCLUSIONS | |
| 365.02 | BORDERLINE GLAUC W/ANAT NARROW ANG |
| 365.06 | PRIMARY ANG CLOS W/O GLAUCOMA DAMGE |
| 365.13 | PIGMENTARY OPEN-ANGLE GLAUCOMA |
| 365.14 | OPEN-ANGLE GLAUCOMA OF CHILDHOOD |
| 365.20 | UNSPEC PRIMARY ANG-CLOSURE GLAUCOMA |
| 365.21 | INTERMITTENT ANGLE-CLOSURE GLAUCOMA |
| 365.22 | ACUTE ANGLE-CLOSURE GLAUCOMA |
| 365.23 | CHRONIC ANGLE-CLOSURE GLAUCOMA |
| 365.24 | RESIDUAL STAGE ANG-CLOSURE GLAUCOMA |
| 365.41 | GLAUC ASSOC W/CHAMB ANG ANOMALIES |
| 365.42 | GLAUCOMA ASSOC W/ANOMALIES IRIS |
| 365.43 | GLAUC ASSOC W/OTH ANT SEG ANOMALIES |
| 365.44 | GLAUCOMA ASSOC W/SYSTEMIC SYNDROMES |
| 365.51 | PHACOLYTIC GLAUCOMA |
| 365.52 | PSEUDOEXFOLIATION GLAUCOMA |
| 365.59 | GLAUCOMA ASSOC W/OTH LENS DISORDERS |
| 365.60 | GLAUC ASSOC W/UNSPEC OCULR DISORDER |
| 365.61 | GLAUCOMA ASSOC W/PUPILLARY BLOCK |
| 365.62 | GLAUC ASSOC W/OCULAR INFLAMMATIONS |
| 365.63 | GLAUCOMA ASSOC W/VASCULAR D/O EYE |
| 365.64 | GLAUCOMA ASSOCIATED W/TUMORS/CYSTS |
| 365.65 | GLAUCOMA ASSOCIATED W/OCULAR TRAUMA |
| 365.81 | HYPERSECRETION GLAUCOMA |
| 365.82 | GLAUC W/INCR EPISCLERAL VENUS PRESS |
| 365.83 | AQUEOUS MISDIRECTION |
| 365.89 | OTHER SPECIFIED GLAUCOMA |
| 92020 | SPECIAL EYE EVALUATION |
| 92081 | VISUAL FIELD EXAMINATION(S) |
| 92082 | VISUAL FIELD EXAMINATION(S) |
| 92083 | VISUAL FIELD EXAMINATION(S) |
| 92100 | SERIAL TONOMETRY EXAM(S) |
| 92120 | TONOGRAPHY & EYE EVALUATION |
| 92130 | WATER PROVOCATION TONOGRAPHY |
| 92132 | CMPTR OPHTH DX IMG ANT SEGMT |

| | |
|---|---|
| 92133 | CMPTR OPHTH IMG OPTIC NERVE |
| 92135 | OPHTH DX IMAGING POST SEG |
| 92140 | GLAUCOMA PROVOCATIVE TESTS |
| 66500 | INCISION OF IRIS |
| 66625 | REMOVAL OF IRIS |
| 66761 | REVISION OF IRIS |
| 66762 | REVISION OF IRIS |

**Cataract Diagnosis Group**

1. Patients on oral steroid replacement therapy in the year prior to the index date
2. Cushing's Disease, at any time over the study period
3. Age unavailable
4. CATARACT ICD9 DIAGNOSTIC EXCLUSIONS

| | |
|---|---|
| 366.11 | PSEUDOEXFOLIATION OF LENS CAPSULE |
| 366.20 | UNSPECIFIED TRAUMATIC CATARACT |
| 366.21 | LOC TRAUMATIC OPACITIES CATARACT |
| 366.22 | TOTAL TRAUMATIC CATARACT |
| 366.23 | PARTLY RESOLVED TRAUMATIC CATARACT |
| 366.32 | CATARACT INFLAMMATORY OCULAR D/O |
| 366.33 | CATARACT W/OCULR NEOVASCULARIZATION |
| 366.34 | CATARACT DEGENERATIVE OCULAR D/O |
| 366.41 | DIABETIC CATARACT |
| 366.42 | TETANIC CATARACT |
| 366.43 | MYOTONIC CATARACT |
| 366.46 | CATARACTW/RAD&OTH PHYS INFLUENCES |
| 366.50 | UNSPECIFIED AFTER-CATARACT |
| 366.51 | SOEMMERINGS RING |
| 366.52 | OTH AFTER-CATARACT NO OBSCUR VISION |
| 366.53 | AFTER-CATARACT, OBSCURING VISION |
| 366.8 | OTHER CATARACT |

**Adrenal Insufficiency Diagnosis Group**

1. Patients on oral steroid replacement therapy (hydrocortisone)
2. Cushing's Disease
3. Age unavailable

## III. Strategies, Definitions and Data Sources for Determining Exposure

**STRATEGIES FOR DETERMINING EXPOSURES AND HEALTH OUTCOMES:**

GLAU/OHTN Diagnosis Group and Cataract Diagnosis Group:

One strategy will be to define Intranasal steroid in relation to one or more prescriptions for an intranasal steroid within 5 days of the first diagnosis of allergic rhinitis (AR) and/or chronic rhinitis (CR) with or without a concurrent acute or chronic sinusitis (ASIN, CSIN) diagnosis in patients with no history in the 12 months prior to the AR or CR diagnosis of: AR, CR, ASIN, or CSIN; or exposure to corticosteroids. The case will be followed forward to a diagnosis of GLAU

and/or OHTN, or a diagnosis of CAT (depending on the Diagnosis Group being assessed). Current and continuous use of intranasal steroids (INS) and of intranasal fluticasone (INS-FLUT) will be assessed as a drug supply for INS or INS-FLUT that continued into the 14-day period before the disease index date, and use of INS or INS-FLUT at least 3 months before the index date. The regression analysis will include various co-variates (see below in this section).

A second strategy will also be considered in which subjects will be required to have been enrolled in the database for at least 1 year without having had a diagnosis of a condition in the Diagnosis Group of interest (i.e., either GLAU/OHTN, or CAT) or having received treatment for these conditions, who consulted an ophthalmologist and who either had a diagnosis of ocular hypertension or open-angle glaucoma or received medical or surgical treatment for these conditions. The index date for the case will be the first of these new or incident case-defining events. INS or INS-FLUT exposure will be assessed by looking back for 12 months prior to the index date, using the same definitions for current and continuous use as noted above. Similar co-variates will be used in the regression analysis.

**DEFINITIONS:**

- Intranasal Steroids: Beclomethasone, Budesonoide, Flunisolide, Fluticasone, Mometasone Triamcinolone
- Exposure to Intranasal Steroids: Prescriptions for intranasal steroids that had been filled in the year before the index date
- Continuous Use of Intranasal Steroids: Use of intranasal steroids at least 3 months before the index date
- Current Exposure: A drug supply for intranasal steroids that continued into the 14-day period before the index date.
- Covariates include age, sex, systemic hypertension, diabetes mellitus, current exposure to ophthalmic, oral and inhaled glucocorticoids, characteristics of health care system use in the year before the index date, exposure to CYP-inhibitors, and exposure to certain HIV medications. These covariates are known from the literature to be related to increased risk of GLAU/OHTN and/or CAT.
    - Definition of systemic hypertension: filling a prescription for the following antihypertensive medications before the index date: thiazide diuretics, centrally acting antiadrenergic agents, peripherally acting antiadrenergic agents, ßadrenergic blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and vasodilators.
    - Definition of diabetes mellitus: any use of oral hypoglycemic therapy or insulin before the index date.
    - Definition of health care system use characteristics in the year before the index date (as markers for general ill health): number of prescriptions filled for all drugs, number of patient-specific physician claims for services, and number of days hospitalized.
    - A list of CYP-inhibitors and HIV medications will be identified from the pharmacy claims data in the IMS LifeLink database.

ADRENAL INSUFFICIENTY DIAGNOSIS GROUP

For assessing the possible relationship between adrenal insufficiency and INS or INS-FLUT exposure, cessation of INS or INS-FLUT will be a key event marker in relation to the time period prior to a diagnostic event of adrenal insufficiency. As noted above, cases by definition have a 12-month qualifying lead-in period with no diagnosis of adrenal Insufficiency. A 28-day cut-off period for exposure to INS or INS-FLUT will be used, in terms of a comparison of continuous INS use over the period of adrenal insufficiency diagnosis, $\leq$ 28 days pre-adrenal insufficiency diagnosis, and > 28 days pre-adrenal insufficiency diagnosis. The main group of interest will be the group that uses INS for $\geq$ 90 days and discontinues INS 1-28 days prior to a diagnosis of adrenal insufficiency.

**DATA SOURCES:**

**IMS LifeLink Health Plan Claims Database:** The IMS LifeLink Health Plan Claims Database has more than 100 data contributors, 88 million enrollees and 72 million patients. The data set provides a complete picture of patient interactions within the healthcare system. The data is representative of the national, commercially insured population on a variety of demographic measures, including age and gender. Enrollees represented within the data set include employer sponsored plans, and individuals purchasing coverage in the marketplace and government sponsored but commercially administered Medicaid and Medicare plans.

**IMS LifeLink Pharmacy Claims Database:** The IMS LifeLink Pharmacy claims database (NCPDP) contains history back to 2001. It represents patients receiving prescriptions via retail pharmacy. The NCPDP prescription claims represent dispensed prescriptions for approximately 55% of all pharmacies making up more than 2 billion prescriptions per year. The prescription data samples nearly 59,000 pharmacies in the US and includes cash, Medicaid and third party transactions. The data is nationally representative and is available in near real-time.

The IMS pharmacy claims also provide standard fields for patient demographics for age and gender, zip codes, GP_2, GP_3 and label name, NDC number, generic code, data filled, new refill, Dec quantity (declared quantity), days supply, daily average consumption (DACON, calculated by dividing the total days supply of a product by the total units – i.e., tablets, capsules, milliliters, etc.) dispensed, provider. Length of exposure will be estimated based on days supply of any intranasal steroids or intranasal fluticasone.

IMS will provide UCSF will a list of medications in the IMS Lifelink pharmacy claims database by NDC number. From this list, UCSF will define NDC number groupings for intranasal corticosteroids, ophthalmic corticosteroids, inhaled corticosteroids, oral corticosteroids, dermal corticosteroids, drug exclusions relating to treatments for glaucoma and cataract in the 12 month period prior to first AR or CR.

**HIPAA Compliance:** All IMS Lifelink claims data are certified HIPAA-compliant with all de-identified patients being assigned a longitudinally stable identifier.

**DATA DICTIONARY:**

The IMS Lifelink dictionary is appended.

## IV. Study Size

Based on the size of the dataset, and the work on power tables for nested case control studies by Pang (i.e., Occup Environ Med 1999;56:67–69), 500 matched case-control sets using four controls per case would give a power of .81 for a relative risk of 1.5, and a power of .91 using eight controls per case. It is anticipated that the total number of cases derived from 50,000 cases will be in well in excess of 1%.

## V. Methods for Assembling Study Data

IMS will provide to UCSF matched cases and controls: 50,000 cases and 300,000 controls for the GLAU/OHTN Diagnosis Group; 50,000 cases and 300,000 controls for the CAT Diagnosis Group; and 10,000 patients with adrenal insufficiency and 60,000 controls.

Linkage of Medical and Pharmacy Claims from IMS Databases: IMS will generate unique patient identification codes for the extracted databases containing medical and pharmacy claims for the specified years. The unique patient number will be derived from the patient ID numbers found in the medical and pharmacy claims. IMS will document this procedure as well its related quality control process and provide this information to UCSF for review and for the data archive.

The data from IMS will comprise the above stated datasets, the IMS documentation of the datasets and the data dictionary for reference.

## VI. Procedures for Data Management

Documentation of Data Management: A full log of decisions used in the cleaning and programming of the dataset provided by IMS Health to UCSF will be kept by the study team. This is the responsibility of the PI and the main programmer.

Key datasets pertaining to the filtering of cases to the final sets of included and excluded cases of each group per the study protocol will be maintained and as needed described in separate documentation. Key analyses that are the basis for the final report will be maintained with the main data base and filtered subsets. Documentation of how missing and uninterpretable data has been interpreted and handled will be done.

Statistical Software and Hardware: **STATA and** SAS 9.3 will be the main statistical software used for analysis of data. The data will be stored in the UCSF secure mainframe used for investigator databases and accessible to selected study personnel only, as well as desk top computers (Dell XPS) which are password protected and reside in locked offices.

Archiving: Data will be archived and stored in a way that protects PHI, through pass-code protected files on a password protected computer with a separate password protected back-up hard drive which are located in a locked room in a suite with access by permission through a centrally controlled punch key coding system linked to UCSF Security. These procedures will be consistent with University policy as implemented by the UCSF Committee on Human Research and defined in the approved IRB application for this study.

The study archive will include:

- Study protocol and copies of all approved modifications.
- A final report of the study.
- All source data. A printed sample of the master computer data file(s).
- Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see section V-C: Study Conduct).
- The log of decisions used in the cleaning and programming of the dataset provided by IMS Health to UCSF will be kept by the study team.
- Copies of computer printouts, including relevant execution code that form the basis of any tables, graphs, discussions, or interpretations in the final report. Any manually developed calculations shall be documented on a work sheet and similarly retained.

- Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits.
- Original documents for the following research materials shall be included in the archives: research notebooks/file; coder modification file. signed and dated copies of the research protocol and final report.
- IRB application and approval letter.

## VII. Statistical Analysis

pre-adrenal insufficiency diagnosis The main analysis will estimate the odds ratio of the dependent variable of an observation being a case (disease outcome present, event = 1) versus control (disease outcome absent, event = 0) using conditional (fixed effects) logistic regression. The analysis will use the 'clogit' procedure in STATA, which uses fixed effects to model the data conditional on the matches between cases and controls. The clogit procedure uses a maximum likelihood method for estimation, specifically, the exact conditional likelihood.

Both univariate and multivariate regressions will be run; the multivariate analysis will likely be used for the final results. The univariate analysis will model the dependent variable as a function of the exposure variable only. The multivariate regression analysis will model the dependent variable as a function of the exposure variable(s), and explanatory variables to account for effect modifiers and confounders.

There are four groups of explanatory variables. The first group of explanatory variables consist of demographic information (age and sex) and calendar time period of the index date. The cases and controls will be matched on these variables with a ratio of an average of six controls to one case. The match on gender will be exact. The match on age will be approximate (i.e., each control will be at most to two years older or younger than the corresponding case at the time of the index date). The match on calendar time will be approximate with the index date of control within one year before or after that of the matched case. These variables will define the basic risk set for the nested case-control study design, and the final analysis will

match on these three variables. The second group of variables will consist of indicator variables for exposure to other forms of steroid drugs (e.g., exposure to oral or dermal steroids in the same timeframe as the exposure, such as current use into the 14-day period prior to the index date). The third group of variables will consist of indicator variables for exposure to conditions and treatments (i.e., 12 months prior to the index date in general unless otherwise noted) that might alter susceptibility to the outcome as a function of exposure to intranasal steroids (e.g., use of anti-diabetics, anti-hypertensives, CYP inhibitors, anti-retrovirals (HIV medications) 90-days prior to the index date, and pituitary disease/surgery (for adrenal insufficiency). The fourth group of variables will consist of descriptors of prior utilization of healthcare services 12 months prior to the index date in order to control of detection bias due to differential exposure to diagnostic opportunities. Three categories of utilization will be assessed: physician visits, hospitalizations, and prescription drug use.

Two measures of utilization will be used: (a) utilization as measured by claims for each unit of service; and (b) utilization measured by unique physician visits, hospital admissions and number of prescription drugs used. The utilization variables will be classified using several approaches – i.e., (a) as indicator variables for any versus no utilization; (b) as indicator variables for tertiles of the common distribution of utilization across cases and controls; (c) as indicator variables for no utilization, and tertiles of the common distribution of utilization across cases and controls for subjects that had any history of utilization; (d) as count variables (i.e., the count of the utilization measure: claims for the claim measure of utilization; physician visit, hospital admissions, and number of prescription drugs used, as appropriate for the each approach to the measurement of utilization), with the count measure being treated as a continuous variable. The rank transformation will be used to create a robust measure of the utilization count. The main analysis will determine which approach is most robust in terms of stability.

The cases and controls will be matched on the first group of variables constituting the risk set (sex, age, and index date). The main analysis will use parametric statistical adjustment for the second through fourth group of variables, which were entered as explanatory variables in the logistic regression.

Several diagnostics, sensitivity and robustness analyses will be used to evaluate the performance of the regression specification and estimates, including: influence statistics delta-Beta (for sensitivity of the regression coefficients to groups of observations) and delta-Chi-square (for sensitivity of fit to groups of observations) for the logistic regression predictions; predictive performance of logistic regression; sensitivity to matching scheme estimating the main regression with different approaches to matching; analysis of effect of different treatment of utilization variables; assessment of alternative methods of analyzing utilization and exposure to examine the homogeneity of effect.

For glaucoma and cataract, the main regression will be stratified by one or more levels of utilization. Additional exploratory analysis may be done using different types of utilization (physician visits, hospital admissions, and number of prescription drugs used) to determine the effect on the coefficients and fit.

Both STATA and SAS statistical software will be used in the analyses.

## VIII. Quality Assurance Procedures

Source data verification will be done by IMS, consistent with procedures that IMS in providing LifeLink medical and pharmacy claims data researchers. The analytical modeling will be based to the extent possible by information in the medial literature. Documentation of all programming will be undertaken, including definitions and strategies of data extractions and analyses. Reference documents of such documentation will be created and retained as part of the final report. As needed, redundant analysis may be done to verify results.

## IX. Limitations: Study Design, Data Sources, and Analytic Methods

Documentation of diagnoses and pharmaceutical use is dependent on the prescriber and dispenser, as well as the administrators of the health plan and pharmacy databases. In general, the IMS database is considered robust, and there is no reason to believe that cases would be uniquely subject to documentation errors and omissions than controls.

It is possible that there are unknown/unidentified factors that create confounding and cannot be resolved. If family and history and race are an important risk factors for certain Diagnostic Groups (e.g., glaucoma and cataract), then an imbalance in the case and control selection could affect the magnitude of the odds ratios. Family history of GLAU or CAT and race are not captured in the health and pharmacy claims databases used in this study. In addition, OTC medicines, such as antihistamines which have been associated with glaucoma, are not captured in the IMS LifeLink database. Antihistamines may be used for allergies, just as INS medications are.

We cannot confirm that date of disease onset, if the conditions are subclinical in nature. However, if the emergence of glaucoma or cataract is associated with the initiation of INS therapy with or without the presence of underlying risk factors for the condition, then the study will be able to address this potential concern. If the relationships between INS exposure and GLAU and CAT are long term in nature, then this will be a limitation of the study. For our diagnostic groups of interest, we will define the date of disease diagnosis based on the date the ICD-9 code first appeared on insurance claims.

Prescription drug claims are included in the IMS data set only if they were submitted and paid. Hence, we may underestimate INS use if patients did not submit claims for their antimicrobial prescriptions. This would likely not have significant impact given size of the study.

## X. Institutional Review Board

The IRB approval will be obtained from the UCSF Committee on Human Research.

[1] Garbe E et al., Inhaled and Nasal Glucocorticoids and the Risks of Ocular Hypertension or Open-angle Glaucoma. JAMA. 1997;277:722-727

[2] Ernst P. et al. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. Eur Respir J 2006; 27: 1168–1174.

[3] Mortimer KJ et al. Oral and inhaled corticosteroids and adrenal insufficiency: a case-control study Thorax 2006;61:405–408.