Appendix 5
Methodology for UHC Pregnancy Study

Retrospective Study of Pregnancy Incidence in Accutane-Treated Females and **Matched Controls in the UnitedHealthcare Database**

Study Methodology

Selection of Accutane User and Accutane Non-User Groups

The Accutane user population was selected as follows:

- Patients who had pharmacy dispensing claims between October 1, 1994 and September 30, 1999 with any Accutane drug codes (see Appendix A) from the three UnitedHealthcare plans were identified.
- Patients whose first Accutane dispensing date was on or after April 1, 1995 were selected. The date of the first Accutane dispensing was recorded as the index date. Patients with the first dispensing date prior to April 1, 1995 were excluded from this study because they lacked the six months of data prior to the first Accutane dispensing needed for the screening period.
- The Accutane user population was further restricted to patients who had non-Medicare and non-Medicaid plans. This ensures that the study patients would not receive additional coverage outside of UnitedHealthcare plans.
- Patients who had enrollment gaps of over 32 days during the six-month screening period were excluded to ensure the completeness of the claims.

- Only Accutane patients between 12 and 49 years of age at the index date were selected.

The selection algorithm for the Accutane non-user population identified a group of substantially similar patients:

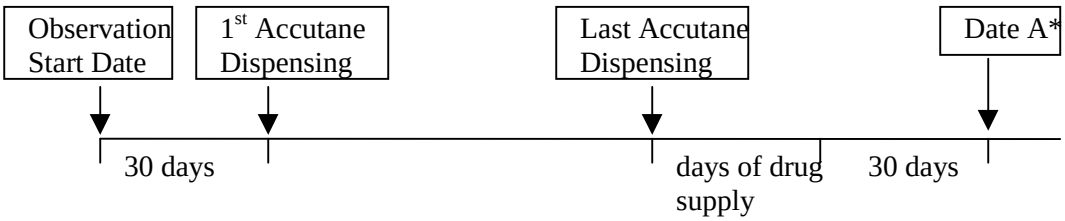
- For each Accutane user, we initially identified 45 randomly chosen non-users of Accutane matched on health plan, gender, and birth year. Non-users who had Medicare or Medicaid plans were excluded.
- Dates of enrollment of the non-users were reviewed, and non-users were retained for analysis if their membership dates included the entire six-month screening period for the corresponding Accutane user.

An Accutane user was required to have at least four matched non-users. If there were more than five eligible matched non-users, we randomly selected five for each user. Seventy Accutane users were excluded from this study because there were fewer than four matched non-users available. The failure to identify matched non-users was related to the small base population size in 1995-1996 in Florida. We can see no real chance of bias by excluding them from the study.

The female subsets from the Accutane user and non-user populations were selected as the study populations, including 2,532 female Accutane users and 12,636 female Accutane non-users.

Observation Period

The person-days of observation for each Accutane user were calculated beginning on the 30th day prior to the date of the first Accutane dispensing. Follow-up continued until the earliest of the following dates: 30 days after the last day of Accutane supply, UnitedHealthcare disenrollment date, or study end date (September 30, 1999). The line chart below describes the ascertainment of observation start and end dates.



*Min (Date A, patient disenrollment date in UnitedHealthcare, 9/30/1999)= Observation End Date

An Accutane dispensing occurring any time during observation period and more than 86 days (i.e., 30 days plus eight weeks of recommended off-drug period before starting a new therapy) after the previous dispensing was considered re-treatment. For a patient experiencing multiple episodes of Accutane treatment, the first episode was included in this study, and the episodes of re-treatment were excluded. There were a total of 424,889 person-days of observation for the 2,532 female Accutane users.

The observation period for the matched non-users started from the calendar date of the 30th day before the first Accutane dispensing in the corresponding Accutane user and continued to the observation end date in the corresponding Accutane user, or until the date of the non-user disenrollment from the UnitedHealthcare plan, whichever occurred first. Each Accutane non-user had a maximum duration of observation equal to the observation period of the corresponding Accutane user. There were a total of 1,995,034 person-days of observation for the 12,636 female Accutane non-users.

Ascertainment of Pregnancy Occurring in Accutane Users in the Observation Period

A four-stage process was used to ascertain pregnancies occurring in the observation period for Accutane users. This process is described below and outlined schematically in Figure 1.

Stage I: Initial Ascertainment of All Possible Pregnancy Services Occurring Within a Time Interval Compatible with the Period of Accutane Use

Study subjects were identified who had at least two codes on different dates for pregnancy-related services, or at least one delivery (live or still birth), induced or spontaneous abortion code, or one prenatal vitamin dispensing between 280 days prior to the first Accutane dispensing and 365 days after the end of observation period. This time interval was used to include any pregnancy that could be logically compatible with the period of Accutane therapy. One hundred and eleven females met these criteria.

Stage II: Generating Initial Algorithms for Estimating Dates of Conception

Estimated dates of conception (provided as a range of dates) were calculated on the basis of the following algorithms:

- If there was a delivery code, the estimated date of conception was assigned to be in the range of 36 to 41 weeks prior to the date of the first delivery code.
- If there was an induced abortion code, the estimated date of conception was assigned to be in the range of 8 to 24 weeks prior to the date of the first induced abortion code.
- If there was a spontaneous abortion code, the estimated date of conception was assigned to be in the range of 6 to 24 weeks prior to the date of the first spontaneous abortion code
- If the diagnosis, procedure, or drug codes that were related to pregnancy were not in the categories of delivery or abortion, the estimated date of conception was assigned to be in the range of 1 to 6 months prior to the date of the first occurrence of such a pregnancy-related code.

Using the method described above, 38 of the 111 female Accutane users identified in Stage I had their estimated dates of conception (reported as a range of dates) overlap with at least one day in the observation period.

Stage III: Cross-Validation of the Initial Algorithms for Estimating Dates of Conception with Claims Profiles, and the Refinement of the Initial Algorithms

All of the claims from the 38 female Accutane users identified from Stage II were manually reviewed to determine evidence of pregnancy state occurring during the observation period. From this claims data review, it was determined that ten female Accutane users were likely to have been pregnant during the observation period.

Based on the experience gained from reviewing the claims profiles of these 38 Accutane users, we refined our computerized algorithms for estimating the range of conception dates to apply to all of the 111 possible pregnancies identified from Stage I:

- If there was a delivery code, the estimated date of conception was assigned to be in the range of 36 to 41 weeks prior to the date of the first delivery code.
- If there was an induced abortion code, the estimated date of conception was assigned to be in the range of 8 to 24 weeks prior to the date of the first induced abortion code.
- If there was a spontaneous abortion code, the estimated date of conception was assigned to be in the range of 6 to 24 weeks prior to the date of the first spontaneous abortion code.
- If there were no delivery or abortion codes and there was a procedure code for an alpha fetoprotein test (CPT 82105), the estimated date of conception was assigned to be in the range of 12 to 20 weeks prior to the date of the first alpha fetoprotein test code.
- If there were no delivery, abortion, or alpha fetoprotein test codes, then we looked for the first pregnancy examination code (V72.4), pregnancy test code (CPT 84702, 84703, 81025), or obstetric panel test code (CPT 80055). The estimated date of conception was assigned to be in the range of 30 to 90 days prior to the first date when any of these codes occurred.

For a small proportion of patients with inconsistent results indicating delivery, spontaneous abortion, or induced abortion codes within 7 days of each other, the event occurring on the latest date was chosen to calculate dates of conception.

Stage IV: Testing of the Refined Algorithms

The refined algorithms from Stage III were applied to all of the 111 possible pregnancies identified from Stage I. Twelve pregnancies were identified through the use of the refined algorithms, and all of the ten pregnancies validated through review of their claims profiles were captured. Note that for two of the 12 patients (having manual review of claims), incorrect designations of pregnancy in the claims database were identified by the algorithms because of presumed miscodings for pregnancy-related services.

Figure 1 **Four Stage-Process of Ascertaining Pregnancies Occurring in the Observation for Accutane Users**