SAP for EHDEN HMB

Martin Lavallee

Asieh Golozar

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# 1. Background

This study is a continuation of a Bayer heavy-menstrual bleed (HMB) study that described first, the incidence rate of HMB; two, describe clinical characteristics of women diagnosed with HMB; and third describe the treatment pathways in five healthcare databases covering the UK, Germany, France and the US from the time period of 2000 to 2022. The first part of this study was exclusively an internal study within Bayer. The second part of the HMB study has similar objectives to part 1 with the key difference being a focus on European databases (UK CPRD) and public expansion of the analysis to data providers involved in the European databases in the European Health Data and Evidence Network (EHDEN). The purpose of this document is elaborate on the study design constructed by Odysseus Data Services. A separate protocol has been written by Bayer for HMB part 2.

# 2. Research Questions

* What are the characteristics of women diagnosed with HMB in terms of demographics, comorbidities, procedures, and comedication?
* What are the treatment patterns for HMB?
* What is the incidence of HMB across different countries and data sources?

# 3. Objectives

## 3.1 Primary Objectives

The primary objectives of this study are to:

* Describe demographics and baseline clinical characteristics of women of reproductive age diagnosed with HMB between 2000 and 2022 across a network of European healthcare databases.
* Describe treatment utilization and longitudinal treatment pathways of women of reproductive age diagnosed with HMB across different countries and data sources between the years 2000 and 2022 across a network of European healthcare databases.
* Estimate incidence of HMB among women between the ages of 11 to 55 between the years 2000 and 2022 across a network of European healthcare databases.

# 4. Study Design

This large-scale retrospective cohort study will be conducted across a network of European healthcare databases standardized to the OMOP CDM. Databases assessed in this study are either: a) Bayer data assets (CPRD GOLD and AURUM) or b) participating EHDEN data-partners. The final list of EHDEN data partners will be provided in the Data Sources section.

The study period begins on January 1, 1999 (or earliest date of data availability following this date) and ends at the latest date of data availability in each database. Persons involved in this study must have a minimum of one-year prior observation in the database, therefore the indexing period begins on January 1, 2000.

The study population for this study are women between the ages of 11 and 55 who have a first-time diagnosis of HMB, given that they have at least 365 days of continuous observation prior to the index date. More details of the study population are found in the study population section.

## 4.1 Study Population

The study population are women between the ages of 11 to 55 who with a diagnosis of heavy-menstrual bleeding (index event) between the years 2000 and 2022. Women entering the HMB cohort must have a minimum of 365 days of prior observation. Female patients are excluded from the cohort if they have one of the following criteria:

1. Observation of a hysterectomy or bilateral ovariectomy
2. Observation of a menopause diagnosis
3. Observation of other gynecological bleeding (vaginal bleeding outside the menstrual cycle)

Female patients are followed up until end of continuous observation or observation of one for the follow, whichever occurs first:

1. Death
2. Turning age 55 (indicating transition into natural menopause)
3. Observation of a hysterectomy or bilateral ovariectomy
4. Observation of a menopause diagnosis

### 4.1.1 Incidence Denominator Cohort

For the incidence calculation, the denominator is women with any kind of healthcare (index event) observed between the years of 2000 and 2022. Women in the denominator cohort must have a minimum of 365 days of prior observation.

Female patients are followed up until end of continuous observation or observation of one for the follow, whichever occurs first:

1. Death
2. Turning age 55 (indicating transition into natural menopause)
3. Observation of a hysterectomy or bilateral ovariectomy
4. Observation of a menopause diagnosis

Concepts and logic for the cohort definitions of the study population and incidence denominator will be supplied in the *CohortDetails* supplementary file.

## 4.2 Exposure Definition

There is no exposure definition in this study.

## 4.3 Outcome Definition

There is no outcome definition in this study.

# 5. Data Sources

The data sources for this study include a) Bayer OMOP assets of UK CPRD and Optum Claims and b) European databases that are part of EHDEN. All databases used in this study have been standardized to the OMOP CDM.

*Table 1: Data Sources used in study*

| Name | Country | Type | Size | Availability | Description |
| --- | --- | --- | --- | --- | --- |
| CPRD  AURUM | UK | EHR |  |  | Primary care data from a participating electronic system in England |
| CPRD  GOLD | UK | EHR |  |  | Primary care data from across the UK |
| Optum Claims | US | Claims |  |  | US commercial claims covering all 50 states |
| Hospital del Mar | Spain | EHR |  |  | Hospital data from Barcelona Spain |
| Ministry of Health | Israel | EHR |  |  |  |

The above table will be expanded upon receiving information of the EHDEN participants.

# 6. Analysis Plan

## 6.1 Cohort Diagnostics

Prior to running any specific analysis, we will evaluate the HMB cohort using the OHDSI R package CohortDiagnostics(1). This package produces metrics such as cohort counts in the database, incidence rates (by calendar year, age and gender), time distributions, cohort attrition and breakdown of index events. Evaluation of these metrics helps ensure that the clinical cohort is indeed reliable in capturing HMB in the OMOP database.

## 6.2 Baseline Characteristics

We assess baseline characteristics based on an observation window of 365 to 1 days prior to the index date. Categorical covariates are reported as counts and frequencies. Continuous covariates are reported as median, 25th and 75th percentile.

**Demographics**

* Age at HMB diagnosis as 5-year categories
* Age at HMB diagnosis as continuous
* Race (if available)
* Ethnicity (if available)
* Year of HMB Diagnosis (per calendar year)

**BMI (if available) continuous and in following categories**

* Underweight (< 18.5 kg/m^2)
* Normal Weight (18.5 - 24.9 kg/m^2)
* Overweight (25.0 - 29.9 kg/m^2)
* Obese (30.0 - 39.9 kg/m^2)
* Morbidly obese (> 40.0 kg/m^2)

**Comorbidity Scores**

* Charlston Comorbidity Score (as a continuous score)
* CHADs2Vasc (as a continuous score)

**Concept-based**

* Drug Era individual and rolled up to ATC2 Categories
* Condition Era individual and rolled up to ICD10 Chapters

**Note**: Concept-based covariates are based on prevalence concepts accumulated via FeatureExtraction (2).

**Cohort-based**

* Conditions
  + Diabetes Mellitus
  + Polycystic Ovary Syndrome (PCOS)
  + Dysmenorrhea
  + Pain
  + Anemia
  + Iron deficiency anemia
* Drugs
  + Antithrombotic Agents
  + Antidepressants
  + Tamoxifen
  + Antipsychotics
  + Gonadal Steroids
* Procedures
  + Endometrial ablation
  + Uterine artery embolization (UAE)
  + Myomectomy
  + Blood transfusion

Concepts and logic for these cohort definitions will be supplied in the *CohortDetails* supplementary file.

**Underlying Causes of HMB**

In addition to assessing characteristics at baseline we also calculate the prevalence of underlying causes of HMB. We observe the prevalence of underlying causes of HMB within the interval of 183 days before and after index HMB. We limit the observation to the first occurrence of the underlying cause. The underlying causes of HMB are:

* Uterine endometrial polyps
* Adenomyosis
* Uterine leiomyoma (fibroids) (subserous or intramural)
* Uterine malignancy and endometrial hyperplasia
* Coagulopathy / coagulation disorders
* Ovulatory dysfunction (including hypothyroidism, polycystic ovary syndrome, adrenal disorders, hyperprolactinemia, hypothalamic disorders)
* Endometrial dysfunction
* Iatrogenic HMB
* Endometriosis
* Idiopathic menorrhagia

The logic and concept set for the cohort definitions for these underlying causes of HMB will be supplied in the *CohortDetails* supplementary document.

## 6.3 Treatment Patterns

In this study we assess the treatment patterns for female patients with HMB which encompasses three metrics:: first, the prevalence of drug use at certain time windows post-index; second, the patterns of treatments (called treatment pathways) including single drugs and combinations of treatment; and third, the length of time spent taking the drug exposures of interest, both as single exposures or in combination. The drug exposures of interest are:

* Tranexamic acid (B02AA02)
* Progestin only regimens:
  + Medroxyprogesterone acetate (MPA) (G03AC06)
  + Oral norethindrone acetate (NETA) (G03DC02)
  + Desogestrel (G03AC09)
  + Etonogestrel implant (G03AC08)
* Non-steroidal anti-inflammatory drugs (NSAIDs) (M01A)
* Combined oral hormonal contraceptives
  + Dienogest and estradiol (G03AB08; sequential combinations)
  + Nomegestrol and estradiol (G03AA14; fixed combinations)
* Selective progesteron receptor modulators (G03AD02, G03XB02)
* Danazol (G03XA01)
* Gonadotropin releasing hormone analogues (L02AE)
* Intrauterine devices (G02BA)
* Iron preparations (B03A)

For the treatment patterns analysis, we must define a set of drug exposure cohorts where the index event of each cohort is prescription of one of the drugs of interest between the years of 2000 and 2022. People remain in the cohort if they are females between the ages of 11 to 55 and have at least 365 days of prior observation. A person's time in the cohort prior to exit is determined by a drug era. The drug era is the span of time a person is considered continuously exposed to the same treatment. Eras are built by binding successive drug exposure events into a single duration where the person is inferred to be continuing use of that same treatment. We allow for a maximum of 30 days between drug exposure records to consider them part of the same era. Thus, if a person has two of the same drug exposures within 30 days of each other, they are bundled into one era where the time elapsed is marked by the date of the successive exposure. This also means that if there is a gap greater than 30 days between the same treatment, this would indicate two separate eras in the treatment history for the individual person. A person is observed in the drug exposure cohort until either the end of a continuous era or one of the following censoring events, whichever occurs first:

1. Death
2. Turning age 55 (indicating transition into natural menopause)
3. Observation of a procedure of one of the following procedures: hysterectomy, oophorectomy, UAE, ablation, myomectomy
4. Observation of a menopause diagnosis

### 6.3.1 Prevalence of Drug Exposures

The first metric in our treatment landscape analysis is the prevalence of drug exposure over a set of defined time intervals. Prevalence is defined as the proportion of the at-risk population who used the medications of interest during the interval. The time windows for prevalence of drug exposures for women in the HMB cohort are: at index, 1 to 183 days, 184 to 365 days, 366 to 730 days, and 731 to 1825 days post index. We report the count and percentage for each drug exposure cohort (from the listed above) at each time window.

### 6.3.2 Constructing the treatment history

Treatment discontinuation is defined when there is a gap of at least 30 days between successive exposures of the same treatment. A treatment combination is defined as an overlap in two different exposures of at least 30 days. This means if two drugs are being taken by the same patient for at least 30 days it is considered a treatment combination. If the overlap of two drugs is less than 30 days, it is considered a switch to the drug whose era persists. For example, if drug A starts first and then overlaps with drug B for 15 days, with drug B continuing onward, the treatment history would consider this a switch from drug A to drug B and no combination.

### 6.3.3 Treatment Pathways

For each female with HMB, we determine the sequence of treatments taken throughout the patient history. Treatment pathways are reported if there are at least 100 patients accounted in the sequence. The treatment sequence results will be displayed using a Sankey diagram, complemented by a summary table that shows the enumeration of each specific sequence.

### 6.3.4 Time to Discontinuation

Using the treatment history, we calculate the median (and 95% confidence interval) time spent on a specific drug using the Kaplan-Meier (KM) methodology. Events are censored if the persons had an observation of death, menopause, turns 65 or has had a procedure (hysterectomy, myomectomy, UAE or ablation). Combinations of treatments will be handled as its own era in the calculation of time to discontinuation.

## 6.4 Procedure use post-index

In this analysis we are also interested in procedures used after the HMB diagnosis between the years of 2000 and 2022. The procedures of interest are:

* Hysterectomy
* Endometrial ablation
* Uterine artery embolization (UAE)
* Myomectomy
* IUD

For the procedure analysis we define cohorts where the index event for the procedure cohort is a first time occurrence of one of the procedures of interest in the patient history. Women in the procedure cohort must have at least 365 days of prior observation.

We report the prevalence of each procedure during the following time intervals: 1 to 183 days, 184 to 365 days, 366 to 730 days, and 731 to 1825 days post index. We report the count and percentage for each procedure of interest (from the listed above) at each time interval. In addition we report the median, 25th and 75th percentile of the duration of time to intervention.

## 6.5 Incidence Analysis

The overall and yearly incidence rate of HMB is calculated in each participating database. The numerator in the incidence calculation is the HMB target cohort defined in Section 4.1 and the denominator is the cohort of women with a healthcare visit as defined in Section 4.1.1. Incidence rate is defined based on the following formula:

The incidence will be calculated using the IncidencePrevalence package from DARWIN (3).

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