Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP)

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Design and implementation of a collaborative research program between the FDA, HMO Research Network, Vanderbilt University, and Kaiser Permanente Northern and Southern California

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ABSTRACT

Knowledge about safe medication use during pregnancy is limited, yet about two of every three women take at least one prescription medication during pregnancy, furthermore, there is a lack of rigorous studies evaluating birth outcomes associated with *in utero* exposure to medications. The Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) is intended to provide a mechanism for collaborative pharmacoepidemiological research to address the safety of pharmaceutical product exposure during pregnancy, through the development of standardized data requirements and of the necessary data linkages of mother-infant pairs to conduct multi-site investigations. This presentation will describe the program, the types of data collected, and progress to date. The current MEPREP population includes female health plan members of 11 distinct health management entities within three research centres who have delivered an infant between January 1, 2001 and December 31, 2007, along with the administrative and birth certificate data on over one million children linked to mothers. There is information on all the medications those mothers took, as well as most of the outcomes of the babies. One of the benefits of this dataset is the information that could be investigated, such as birth weight, fetal growth, congenital anomalies, perinatal conditions, etc., against various demographics of the women in the dataset. The population size within the dataset suggests that various parameters could be studied with at least a modest degree of power.

Introduction

After original exchanges with the U.S. Food and Drug Administration (FDA) to seek their help in assisting with efforts to validate findings in various studies (e.g., SSRIs and tricyclics during pregnancy, calcium channel blockers and beta-blockers during pregnancy), the FDA indicated their preference to fund a large network to perform such reviews systematically and to develop an ongoing relationship for conducting studies. Working with the FDA over two years to develop this collaborative program, the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP), sponsored by the FDA, was launched over a year ago. The aim of MEPREP is to provide a mechanism for collaborative pharmacoepidemiological research to address the safety of pharmaceutical product exposure during pregnancy, through the development of standardized data requirements and of the necessary data linkages of mother-infant pairs to conduct multi-site investigations. At the present, there is every indication that this will be an ongoing project. Three research centres comprise MEPREP: Kaiser Permanente Northern and Southern California (two plans with a total amount of about 8 million people), Tennessee Medicaid Population (through Vanderbilt University), and HMORN CERT (eight health plans in the HMO Research Network Center on Education and Research on Therapeutics). There are 11 distinct health management entities within these three research centres.

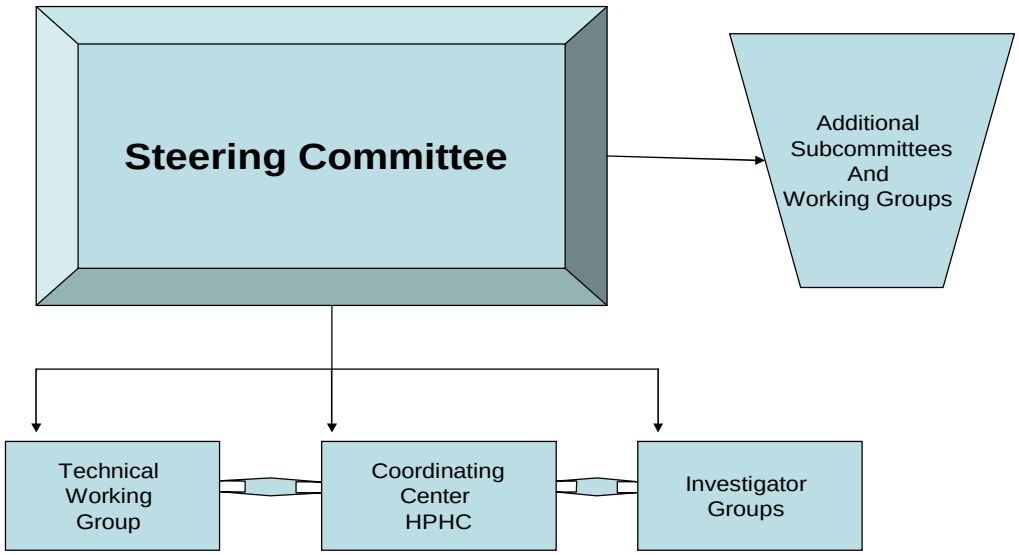
The current study population includes female health plan enrollees who have delivered an infant between January 1, 2001 and December 31, 2007, along with the children born to these women. This is not always a simple process, given that the father but not the mother may be registered with the health plan, or surnames given to infants may not be consistent with the plan subscriber, and so on. The infants have been linked to the mothers and typically, on both, the longitudinal administrative data that is available within these large health care systems can be collected. Such data includes enrolment dates, demographic information, data on diagnoses and procedures, prescription medications, vaccinations, and the like. Linking to birth certificates is also in place - these contain a large amount of useful data often collected by a nurse in each hospital who interviews the mother about smoking and drinking habits and asks some questions about family history. There is usually also a careful, although not always correct, elucidation of the race of the mother and father. All these data are entered onto the birth certificate, which is linked whenever possible. The data elements within the datasets are validated through medical record review when feasible.

At this time 2008 data are being added, as part of the annual update of standardized datasets.

Program Governance

MEPREP has a steering committee with primary responsibility for leadership (Figure 1). It is made up of representatives from each of the research centres and from the FDA. The Committee oversees program activities, determining priority areas for research; approving study protocols; reviewing abstracts, presentations and manuscripts; and advising on matters of publicity and public relations. Within the Steering Committee, there are the Technical Working Group, The Coordinating Center, and the Investigator Groups.

FIG. 1 MEPREP Governance



The Technical Working Group works to maintain consistency and integrity among the sites, developing data file specifications and ensuring that the variables are in order and identical; we are currently validating data elements across sites.

The Coordinating Center holds is responsible for facilitating and organizing all program activities, such as:

- Directing the development and maintenance of program datasets,
- Leading validation activities, and
- Providing expertise on study design, statistical analysis, and data processing and management.

The Investigator Groups comprise the investigators from each of the 11 HMOs and are responsible for identifying who will lead a particular study and which investigators will be involved. They are primarily responsible for maintaining and following the study protocols.

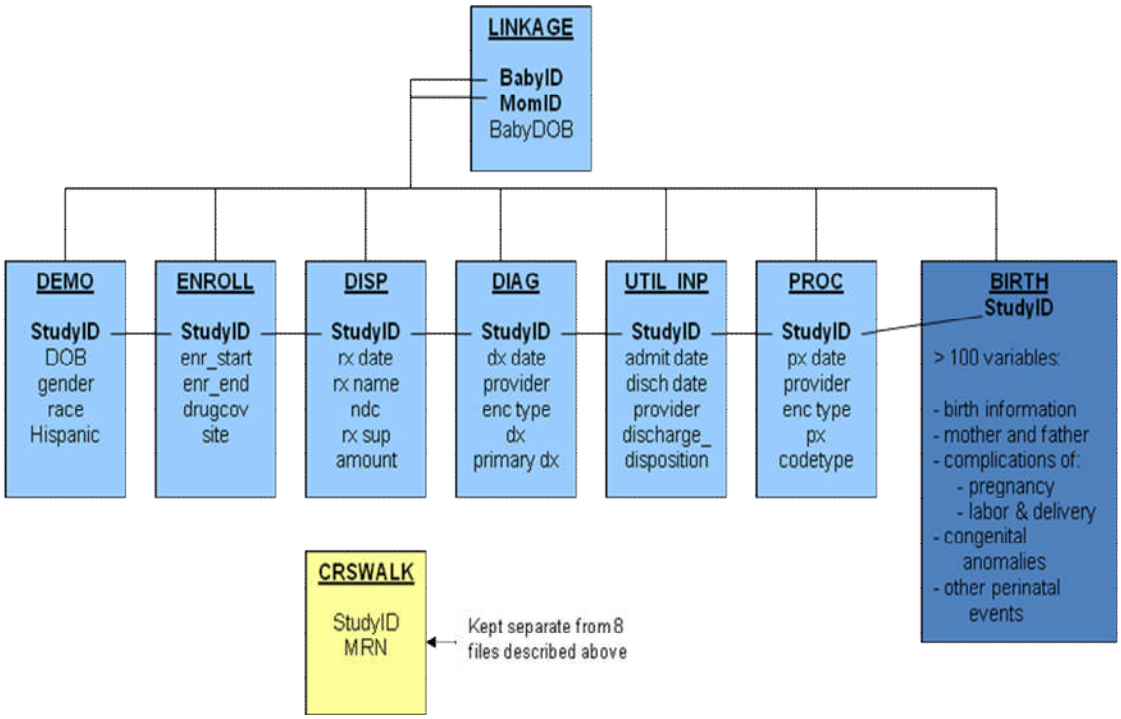
There are written policies on publication, data sharing, how to collaborate with outside investigators, and how to deal with conflicts of interest, trying to be as transparent as possible. Patient confidentiality is guarded assiduously.

Creation and Maintenance of Standardized Datasets

The mothers and infants are linked by various methods which have different degrees of certainty. A StudyID is created for each specific linkage between a mother and a baby. Site specific data issues are incorporated into the dataset and data file specifications.

At each of the HMOs, the files are maintained behind a firewall using Virtual Data Warehouse (VDW) as the model—the data are not accessible from outside. These files contain information for linked mothers and infants, 2000-2007, i.e., one year prior to the first possible delivery.

FIG. 2 Data File Specifications



The linked data files for mothers and children are (Figure 2):

- **LINKAGE** mother and infant linkage file
- **DEMO** demographic information
- **ENROLL** health plan membership information
- **DISP** pharmacy dispensing data
- **DIAG** diagnosis information
- **UTIL_INP** inpatient stay dates and facility information
- **PROC** procedure information
- **BIRTH** birth certificate data, containing over 100 variables
- **CRSWALK** file linking patient medical record number or health plan identification number to StudyID

The StudyID is linked to all the data elements. There is also a link to the medical record number in the CRSWALK file, which is kept separate from the dataset so that the information is de-identified but can be re-identified if needed. In addition, diagnoses made in the outpatient setting and in the emergency department are linked to these data.

Program Progress

The first year of the project is just ending. A manuscript is being drafted to describe MEPREP to the general medical community. Validation through chart reviews and of select elements of the datasets is underway at each of the HMOs; and work plans have been developed to identify deliveries at HMORN sites and to perform quality checks (e.g., to ensure that mothers are not under 9 years old or over 99 years old) on administrative and birth certificate data for all FDA contract sites. The Coordinating Center is addressing any potential issues with the sites and there is ongoing documentation of all the data quality steps being taken.

The mother/infant linkage process has been completed at all the sites; administrative files have been created; applications for birth certificate data have been completed—hopefully to the end of 2008 by end of Summer 2010; and documentation is underway. In addition, a number of feasibility studies are being conducted to address capabilities for studying certain topics (for example, to look at the feasibility of studying infants born to women with diabetes).

Population Encompassed by MEPREP

There are administrative and birth certificate data on over one million children linked to mothers in MEPREP. There is information on all the medications those mothers took, as well as, by and large, the outcomes of the babies. Table 1 shows the population breakdown by maternal age at delivery.

TABLE 1 MEPREP Population to Date

Maternal Age	Count	%
<20	**106,636**	**10**
20-24	**247,495**	**24**
25-29	**272,341**	**27**
30-34	**241,996**	**24**
35-39	**125,283**	**12**
40+	**29,146**	**3**

One of the benefits of this dataset is the information that could be investigated, such as birth weight, fetal growth, congenital anomalies, perinatal conditions, etc., for the women over 40 in the dataset. Although the population size is only about 29,000, the information could be studied with a modest degree of power.

One of the feasibility studies being conducted is intended to determine the possible power we have to address certain questions (Feasibility Assessment for Study of Antidepressant Safety During Pregnancy). Table 2 shows the number of mothers linked to infants where there was medication exposure to antidepressants during pregnancy. Studies to date have generally been underpowered, due to small study cohorts. Here, though, there is a substantial population of almost 50,000 babies with exposure to antidepressants. Such patient volumes should allow reasonably powered assessment.

TABLE 2 Exposure to Antidepressants During Pregnancy

Medication	Deliveries
SSRI	**48,633**
TCA	**6,693**
MAOI	**203**
Other	**17,308**
Multiple	**8,876**
No Usage	**957,228**

Conclusion

It is hoped and intended that MEPREP will enable the analysis of compatible data in multi-site studies and improve programming efficiency and accuracy. The Program will be an important resource for the evaluation of birth outcomes associated with medication use during pregnancy, and of patterns and trends in medication use during pregnancy**.**