Advantages and problems with pregnancy registries: observations and surprises throughout the life of the International Lamotrigine Pregnancy Registry‡

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Abstract

Purpose—The International Lamotrigine Pregnancy Registry monitored for a signal of a substantial increase in the frequency of major congenital malformations associated with lamotrigine exposures in pregnancy over an 18-year period. Key methodological lessons are discussed. Methods The strengths and weaknesses of the Registry were assessed using quantifiable methodological and operational parameters including enrollment, completeness of exposure and outcome data reporting, and lost to follow-up. The choice of comparator groups and stopping rules for registry closure were critically evaluated.

‡The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention

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CONFLICT OF INTEREST
S.S. is a consultant to INC Research, the Coordinating Center for the Registry.
M.C., J.M. and J.W. was previously employed by, and owns sharesin, GlaxoSmithKline.
J.C., R.L. and M.Y. served as unpaid member of the Scientific Advisory Board for the International Lamotrigine Pregnancy Registry.
P.T. was employed by the sponsor of lamotrigine at the time of registry initiation and is now employed by RTI International, a not-for-profit research organization, and was not compensated for contributing to this manuscript.

ETHICS STATEMENT
The Registry was granted IRB approval from Western IRB (WIRB®), which included a waiver of informed consent with anonymous enrollment.
Results—The reliance on voluntary reporting was associated with a clustered geographical distribution of registered pregnancies. The enrollment rate increased over time with new approvals and indications for lamotrigine and publication of interim data. Reporter burden was minimized through a streamlined data collection approach resulting in a high level of completeness of exposure and primary outcome data. Lost to follow-up rates were high (28.5% overall) representing a major limitation; incentives to increase the completeness of reporting failed to reduce rates. A lack of an internal comparator group complicated data interpretation; but external comparisons with multiple external groups allowed an assessment of consistency of outcome data across multiple data sources. A lack of a priori closure criteria prolonged the life of the Registry, and consideration of regulatory guidelines on this subject is encouraged at the time of conception of future registries.

Conclusions—A successful pregnancy exposure registry requires ongoing flexibility and continuous re-assessment of enrollment, recruitment, and retention methods and the availability of comparison data, throughout its lifecycle.

Keywords
pregnancy; registry; lamotrigine; birth defects; methodology; pharmacoepidemiology

INTRODUCTION

Regulatory authorities encourage the establishment of pregnancy registries to monitor medication safety in pregnancy when exposure in women of childbearing age is expected to be common, yet these studies are not without challenges.\textsuperscript{1,2} Anti-epileptic drugs (AED) are often the subject of such monitoring because of the large number of women of childbearing age with epilepsy\textsuperscript{2–5} and the dangers posed by uncontrolled seizures to the mother and fetus if medication is discontinued during pregnancy.\textsuperscript{6} The emergence of a new generation of AEDs in the early 1990s, following an older generation of anticonvulsants with evidence of teratogenic potential,\textsuperscript{5–10} stimulated the establishment of several AED pregnancy registries in the early 1990s. The International Lamotrigine Pregnancy Registry, started in 1992 by Burroughs Wellcome, was one of the first registries established to monitor the safety in pregnancy of one of these new AEDs, LAMICTAL™ (lamotrigine). The primary objective was to monitor for signals of a substantial increase in the frequency of major congenital malformations (MCMs). This paper reviews key methodological lessons from the Registry over its 18 years.

REGISTRY DESIGN

The Registry’s methods are described elsewhere.\textsuperscript{11–13} Briefly, this international, voluntary registry enrolled women who had taken at least one dose of lamotrigine during pregnancy. Health care providers (HCPs) enrolled women anonymously and also provided follow-up data. Enrollment early in pregnancy was encouraged, but not required, to capture first trimester exposures and to avoid enrollment based on knowledge of pregnancy outcome from prenatal testing. Exposure and pregnancy details were collected at enrollment. Information about pregnancy outcome, particularly the presence of an MCM, was collected around the pregnancy due date. An MCM case was defined as any live or stillborn infant, or...
electively terminated fetus, of any gestational age with a major structural or chromosomal abnormality diagnosed before 6 years of age; however, the Registry primarily captured major defects that were external, recognizable in the delivery room and/or symptomatic shortly after birth. Rather than enrolling a control group, the Registry’s results were descriptively compared with data from population-based cohorts and from cohorts of women exposed during pregnancy to AED monotherapy.

Reports of MCMs were reviewed by the pediatrician on the Registry’s Scientific Advisory Committee in accordance with the case definition and coding schema used by the Metropolitan Atlanta Congenital Defects Program (MACDP), an active population-based birth defects surveillance program. Consistent with the MACDP, minor birth defects were not systematically collected. The distinction between major and minor malformations and its significance is an area of ongoing discussion among experts in the fields of dysmorphology and clinical genetics. In some registries, the MCM case definition includes outcomes with a cluster of two or more minor defects (defects of secondary importance), in the absence of a diagnosed MCM, to increase the sensitivity of registry monitoring and avoid missing a potential signal.

Limiting birth defect ascertainment to the period of just after birth is consistent with the methods used in other registries initiated in the 1990s. In newer registries, infants are typically followed for up to one year of age, which may improve the capture of MCMs diagnosed later in infancy and result in a higher overall rate of MCMs. Infant follow-up requires permission from the parent(s) to contact the pediatric HCP and adds complexity to a voluntary registry.

The Registry closed in March 2010 following the enrollment of 3416 pregnancies from 43 countries. Of those, 2444 had known outcomes and 972 (28.5%) were lost to follow-up (LTFU) (Table 1). The prevalence of MCM following first trimester lamotrigine monotherapy exposure was 2.2% (95% Confidence Interval (CI): 1.6–3.1%) similar to estimates in general population and AED-specific cohorts.

**CHALLENGES TO EXTERNAL VALIDITY**

Although this was an international registry, the majority of exposures were reported from a few countries: 65% from the USA and 20% from Poland, UK, Germany, Sweden, and Denmark. This reporting pattern does not mirror the global pattern of marketing approvals; rather, it likely reflects the benefits of a toll-free telephone number for US enrollments, whereas non-US enrollments were channeled through the Registry sponsor’s local operating companies. A search for pregnancy exposure registries (or cohort or surveillance studies focusing on potential teratogenicity of medications) in the databases of Clinicaltrials.gov and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance reflected a similar pattern. Among 81 pregnancy studies in Clinicaltrials.gov, most were conducted in the USA (n = 51), followed by Europe (n = 18), and other regions with one to three studies each. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance search revealed only four studies (one in the UK and three multinational). It might be surmised that companies required by the Food and Drug
Administration to conduct a pregnancy registry could limit their target population to the USA to minimize financial resources and avoid the somewhat complex and labor-intensive processes required to comply with national data privacy regulations in multiple countries, particularly for rare exposures. Within Europe, it is increasingly possible to harness the existing surveillance infrastructure as many countries now have birth defect surveillance programs, capturing medication exposure, with data provided centrally to EUROCAT for aggregation and evaluation of safety signals.

DIFFICULTIES IN PROJECTING ENROLLMENT

Because of uncertainties around a new medication’s uptake, and future indications, it is challenging to define enrollment targets, estimate the time needed to reach enrollment targets, and develop optimal enrollment methods when initiating a pregnancy registry. Enrollment in this Registry was open to all eligible women whose HCPs were willing to participate. Because of the rarity of exposed pregnancies in the patient population, this study was not site-based with pre-selected investigators. HCPs were informed of the Registry through awareness communications, such as providing a toll-free registry telephone number published in the prescribing information, sending a copy of the bi-annual registry interim report to all HCPs who had enrolled a subject, and including registry information on the FDA listing of pregnancy registries.

During the first years of the Registry, enrollment was low (averaging 40 prospective exposures per year globally) (Figure 1) likely reflecting the initial narrow indication for lamotrigine as adjunctive therapy in adults with partial seizures. Prospective enrollments were defined as pregnant exposed women registered before the outcome of pregnancy was known. To maintain prospective enrollment and avoid bias toward reporting of pregnancies known to have defects, the Registry excluded pregnancies with prenatal diagnosis of a defect at the time of enrollment from the primary analyses. Such pregnancies were classified as retrospective and analyzed separately. By enrolling as prospective women who have had some form of prenatal testing (e.g., ultrasound) that was considered normal, there may be a bias toward normal pregnancy outcomes. Having had a prenatal test that is normal does provide information about the infant’s status and lessens the likelihood that a major abnormality will be identified later or after delivery. A truly prospective enrollment would be a pregnancy for which no testing had been done (normal or abnormal); however, given the high prevalence of prenatal testing, this can be difficult and emphasizes the importance of enrollment early in pregnancy.

Enrollment increased at the end of the 1990s following new approvals for lamotrigine, including use as monotherapy for seizure treatment and for bipolar disorder. These approvals also highlighted the need for modified communication strategies to increase awareness of the Registry among different physician groups, for example, among psychiatrists following the approval for bipolar disorder. Increased enrollment also coincided with the first of regular publications of interim results in peer reviewed journals. Awareness efforts were aimed at prescribers, and most of the reporting came from neurologists and to a lesser extent, psychiatrists and obstetric HCPs. Other registries have reported enrollment difficulties of a much greater magnitude despite active awareness.
strategies that include multiple HCP types and venues. Although awareness is critical to enrollment, other factors should be considered including the availability of the target population (e.g., prevalence of the indication among women of childbearing age), the effectiveness of pregnancy avoidance warnings, and varying degrees of risk/benefit for taking a medication during pregnancy in different populations.

The existence of other AED pregnancy registries may have impacted enrollment: several national and international pregnancy registries ran concurrently, monitoring AED safety in pregnancy. These registries included the North American Anti-Epileptic Drug (NAAED) Pregnancy Registry and the International Registry for Anti-Epileptic Drugs in Pregnancy (EURAP). Based on recent reports, the EURAP has enrolled 2568 subjects exposed to lamotrigine monotherapy within 16 weeks of gestation, and the NAAED has enrolled 1562 first trimester lamotrigine monotherapy exposures. Whether there is overlap among women enrolled in these registries remains unclear. Information on concurrent enrollment was sought at the time of enrollment into the Registry; however, these data are difficult to interpret as different registries relied upon different enrollment methods. Hence, an HCP enrolling a patient into the International Lamotrigine Pregnancy Registry may have been unaware that this patient had enrolled herself independently into the NAAED. The various AED registries function independently; therefore, improved communication among them may be useful. However, the identification of double enrollments is complicated by the need to maintain patient anonymity in registries that do not collect identifying information.

VOLUNTARY REPORTING AND DATA QUALITY

The reliance on voluntary enrollment through HCPs prompted the Registry to collect a core, minimal dataset to simplify participation and promote complete reporting, which primarily included data required for assessing the exposure-outcome relationship and the potential for bias. To minimize reporter burden, the Registry contacted the HCP twice: at enrollment and after the estimated date of delivery to assess outcome. At registration, a two-page form was used to collect information on maternal demographics, pregnancy and prenatal testing, and lamotrigine exposure. At followup, after the expected delivery date, a three-page form was used to collect confirmation of exposure and pregnancy outcome information. For pregnancies with MCMs, an additional follow-up contact was available, if needed, to ascertain details of the MCM and presence of risk factors.

Among the 70 outcomes with reported MCMs, additional details were sought for 31 (44.3%). Of these, HCPs for 29 (93.5%) cases provided additional information; however, it was not always meaningful: several indicated that they had lost contact with the patient (8%) or did not have the requested details (7%). At times, the information received did not address the request because the reporter was not the associated obstetrician or pediatrician. This may represent the challenge of a de-centralized health care system. However, contact with multiple HCPs for each mother–infant pair allows for a more comprehensive approach.

Among all prospectively reported pregnancies with known outcomes, data completeness was high among critical variables for the exposure type (polytherapy or monotherapy), earliest
trimester of exposure, lamotrigine dose, maternal age, and gestational age at delivery (Table 1). Data were less complete for maternal race, prenatal testing information, and neonatal anthropometric measurements at follow-up, and these data were not included in the primary analysis. Consequently, data collection could have been further streamlined.

LOSS TO FOLLOW-UP

Losses to follow-up in a pregnancy registry can introduce bias if lost cases are more or less likely to have MCMs compared with those completing follow-up. Participants in the International Lamotrigine Pregnancy Registry were classified as LTFU if information on pregnancy outcome was not obtained after multiple contacts. Among enrolled pregnancies, 28.5% (972/3416) were LTFU, varying little between the USA and other countries (data available upon request). Most LTFU cases (79%) were attributable to practices of the participating HCPs: the registering HCP failed to respond to requests for follow-up information (64%), the registering HCP left the practice without providing a forwarding address (8%), and patient could not be identified by the registering HCP (7%). These reflect the limitations of voluntary reporting. Failure of the HCP to identify patients may be related to the administrative complexity of tracking patients anonymously through Registry identification numbers. An additional 19% of LTFU was due to patients no longer being under the care of the registering HCP.

Accepting enrollment directly from women and asking HCPs to obtain informed consent from women so that they can be followed up directly can reduce LTFU.\textsuperscript{43} The Ribavirin Pregnancy Registry reported lower LTFU among enrollments initiated by patients (8.3%) compared with HCPs (24.7%).\textsuperscript{30} Loss to follow-up in the NAAED Pregnancy Registry, which relies solely on direct enrollment by participating women, is approximately 7% among first trimester monotherapy-exposed subjects.\textsuperscript{20} However, it should be noted that this figure does not reflect the potential loss of data from women who refuse to authorize release of medical information for confirmation of selected variables. Up to 30% of women have been reported to refuse authorization within the NAAED Pregnancy Registry, emphasizing the potential for medical record release to impact data accuracy and possibly introduce misclassification.\textsuperscript{42}

In 2004, to decrease LTFU, the Registry introduced a stipend to compensate HCPs for time spent reporting (up to $150 for each completed patient). An analysis examining LTFU for the periods pre-stipend (registry initiation until 1 June 2004) and post-stipend (1 June 2004 until 2 February 2007) showed little impact of the stipend on LTFU: pre-stipend 24.3% (140/576) versus post-stipend 26.8% (184/686). For both periods, the principal reason for LTFU was failure of the HCP to respond at follow-up.\textsuperscript{44} Although it is possible that the stipend could have prevented future increases in LTFU, an examination of the LTFU data in yearly increments showed no substantial changes in the rate or reasons for LTFU. Because of the potential for bias in pregnancy registries, exploring underlying reasons for LTFU and implementing strategies for reducing LTFU should be an ongoing activity in any registry.
INTERNAL OR EXTERNAL COMPARATOR GROUPS?

The choice of comparison data, whether from an internal or external source, is complex. Pregnancy registries enrolling exposures to multiple AEDs have used internal comparator groups including women with epilepsy unexposed to AEDs or exposed to different AEDs.\textsuperscript{17,23,40} While this approach can minimize bias related to differences in enrollment and outcome ascertainment, it does not eliminate confounding by indication. The latter can occur when the differences in MCM risk observed between Registry and comparator groups are related to disease severity or risk associated with other AEDs. Direct statistically based comparisons with groups external to the registry are not without problems and can be influenced by methodological differences including patient selection methods, for example, hospital-based or population-based ascertainment,\textsuperscript{14–16} ascertainment of infant health, MCM case definition, and duration of infant follow-up after birth.

It may, therefore, be useful to compare registry results with those from multiple studies using different methods. Because of a paucity of existing data on AEDs and MCMs at the time of inception of the International Lamotrigine Pregnancy Registry, the Registry protocol specified \textit{a priori} use of the MACDP\textsuperscript{14,15,26} case definition and background data, which had been used by others to place accumulating pregnancy registry data into perspective.\textsuperscript{27,30–32} Later, as more data were published internationally, the Scientific Advisory Committee considered the MCM frequency reported from other cohort studies and AED pregnancy registries, as well as population-based reference data, when reviewing Registry results. The use of multiple reference data sources was particularly important after the approval of lamotrigine for non-epilepsy conditions. This thorough review of cumulative MCM risk was considered sufficient to detect a signal for a substantial increase in the risk of MCMs associated with lamotrigine. Statistical comparisons across studies were avoided because of methodological differences across studies.

Nevertheless, assuming minimal overlapping enrollment across AED registries, descriptive comparisons of reported MCM frequencies across multiple sources may provide a means of assessing the robustness of the Registry data and placing further context around emerging Registry results.

DECISIONS SURROUNDING CLOSURE OF REGISTRY

Regulatory guidelines\textsuperscript{1} advise pregnancy registry discontinuation if (i) sufficient data accumulate to meet the scientific objectives, (ii) poor recruitment or high LTFU result in insufficient data to meet objectives, or (iii) alternative methods of data collection become possible or preferable. Discontinuation criteria should be defined \textit{a priori} in the study protocol. Registry closure criteria were not pre-specified for this Registry. Contemporary registries typically set a goal of enrolling a specific sample size, often between 300 to 500 pregnancies, based on 80% power calculations aimed to detect a twofold to threefold increase in all MCMs relative to a comparator risk.\textsuperscript{30,31,34} This is sufficient for the objective of detecting a substantial increase in the frequency of MCMs.

The lack of \textit{a priori} closure criteria may have contributed to the Registry’s 18-year duration. However, with the enrollment of over 1000 first trimester lamotrigine monotherapy
exposures and increasingly narrow confidence intervals, the Scientific Advisory Committee considered the Registry had met its primary objective to detect a substantial increase in the frequency of all MCMs. Further confidence resulted from the stability of the MCM frequency estimate during the second half of the Registry’s lifespan (Figure 2), the precision of the estimate, and the 95% confidence interval (1.6–3.1%), at closure.

Over time, the sample size became large enough to observe small numbers of specific malformations potentially signaling an elevated risk, but the lack of precision complicated interpretation. Because a teratogen is likely to increase the frequency of specific or specific combinations of MCMs rather than all MCM types together, it is important to continue to use other methods to monitor for potential risks that a pregnancy registry could not detect. The Scientific Advisory Committee therefore recommended continued monitoring through case control surveillance within the EUROCAT network where cases and controls can be identified, and lamotrigine pregnancy exposure can be ascertained.

Whether the Registry could have ended earlier may be debatable. One could argue that if the Registry’s aim is to detect a signal for major teratogenicity, this was achieved well before the Registry closed. Table 2 illustrates the sample size needed to detect, with sufficient power (both 80% and 90% calculated), various increases (1.5-fold, 2.0-fold, and 2.5-fold) in the frequency of MCMs under various assumptions of background MCM frequencies. For 80% power to detect a doubling in the frequency of all MCMs, a sample size of 502 is needed if baseline frequency of MCM is 2.8%, and 873 exposures are needed if baseline frequency of MCM is 1.6%. Protocol-driven sample size goals with stopping rules are essential to creating a balance between the collection of safety information and the manufacturer’s resource commitment.

CONCLUSIONS

During the 18 years of the International Lamotrigine Pregnancy Registry, much was learned about the strengths and weaknesses of its design. Since its inception in 1992, the science of conducting pregnancy exposure registries has expanded, and methodologies have generally become more complex. To be successful, the lifecycle of a registry requires flexibility and continuous re-assessment of enrollment, recruitment, and retention methods and the availability of comparison data.

ACKNOWLEDGEMENTS

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The authors are very grateful to Paige Churchill, project manager for the best part of 10 years, who ensured the smooth running of the Registry until very close to its end. We also thank Susan King-Zeller who ensured that the end was indeed smooth.

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21. UK Epilepsy and Pregnancy Register. Available at: www.epilepsyandpregnancy.co.uk/ [18 April 2014]


KEY POINTS

- Operating an international pregnancy registry involves considerable logistical challenges that may impact enrollment and external validity; therefore, the efficiency of future pregnancy registries might be maximized by concentrating efforts on a smaller number of countries.

- Data collection in a pregnancy registry should be limited to a core, minimal dataset to simplify participation and promote complete reporting. The minimal dataset should focus on data required for assessing the exposure-outcome relationship and the potential for bias.

- Loss to follow-up can be high in pregnancy registries and may not be addressed through monetary compensation for the reporters’ time.

- The choice of comparison data for a pregnancy registry, whether from an internal or external source, is complex. Descriptive comparisons of reported MCM frequencies across multiple sources may provide a means of assessing the robustness of the Registry data and placing further context around emerging Registry results.

- Closure of the registry should be guided by discontinuation criteria that are defined *a priori* in the registry protocol.
Figure 1.
Cumulative enrollment of prospective cases by reporting period and therapy type, International Lamotrigine Pregnancy Registry, 1999–2009. Note: Yearly reports of lamotrigine exposure prior to 1999 were excluded due to low enrollment numbers. From 1992–1999, the Registry enrolled a total of 200 reports overall (monotherapy and polytherapy).
Figure 2.
Stability of major congenital malformation frequency estimates over time by first trimester lamotrigine monotherapy exposure sample size, International Lamotrigine Pregnancy Registry, 1999–2010. [1] For the purposes of the calculation of risk, an outcome is defined as a live infant with or without a birth defect, or an induced abortion or stillbirth with a birth defect. Spontaneous abortions with or without a defects are excluded. [2] Confidence intervals developed using methods described in Fleiss.36
Table 1


<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall sample sizes</strong></td>
<td></td>
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<tr>
<td>Prospectively enrolled pregnancies</td>
<td>3416</td>
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<tr>
<td>Pregnancies lost to follow-up</td>
<td>972 (28.5)</td>
</tr>
<tr>
<td>Pregnancies with known outcome</td>
<td>2444 (71.5)</td>
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<tr>
<td>Pregnancy outcomes</td>
<td>2492</td>
</tr>
<tr>
<td>Outcomes with MCM (all exposure groups)</td>
<td>87</td>
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<tr>
<td>Outcomes exposed to monotherapy</td>
<td>1817 (72.9)</td>
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<tr>
<td>Outcomes exposed to polytherapy</td>
<td>675 (27.1)</td>
</tr>
<tr>
<td><strong>Completeness of exposure variable reporting</strong></td>
<td></td>
</tr>
<tr>
<td>Total prospectively enrolled pregnancies</td>
<td>2444</td>
</tr>
<tr>
<td>Earliest trimester of exposure</td>
<td>2440 (99.8)</td>
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<td>Exposure dose in earliest trimester of exposure</td>
<td>2357 (96.4)</td>
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<td>Date of LMP or estimated date of delivery</td>
<td>2320 (94.9)</td>
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<tr>
<td>Maternal age</td>
<td>2301 (94.1)</td>
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<tr>
<td>Race</td>
<td>2080 (85.1)</td>
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<td>Prenatal testing in current pregnancy</td>
<td>1429 (58.5)</td>
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<tr>
<td><strong>Completeness of outcome variable reporting</strong></td>
<td></td>
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<tr>
<td>Total pregnancy outcome</td>
<td>2492</td>
</tr>
<tr>
<td>Gestational age</td>
<td>2386 (95.7)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1780 (71.4)</td>
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<tr>
<td>Birth length</td>
<td>1205 (48.4)</td>
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<tr>
<td>Head circumference</td>
<td>658 (26.4)</td>
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</tbody>
</table>

MCM, major congenital malformation.
LMP = first day of last menstrual period.

* Detailed final results available elsewhere.12,13
† Includes 43 sets of twins, one set of triplets, and one set of quadruplets.
Table 2
Sample size needed to detect increases in major congenital malformations frequency from given baseline with given power for a prospective cohort study.*

<table>
<thead>
<tr>
<th>Power (%)</th>
<th>Base MCM frequency † (%)</th>
<th>1.5-fold increase in MCM frequency</th>
<th>2.0-fold increase in MCM frequency</th>
<th>2.5-fold increase in MCM frequency</th>
</tr>
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<tbody>
<tr>
<td>80</td>
<td>1.6</td>
<td>2720</td>
<td>873</td>
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<td></td>
<td>2.0</td>
<td>2175</td>
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<td>1539</td>
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<td>90</td>
<td>1.6</td>
<td>3545</td>
<td>1124</td>
<td>616</td>
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<td></td>
<td>2.0</td>
<td>2835</td>
<td>898</td>
<td>492</td>
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<td></td>
<td>2.8</td>
<td>2012</td>
<td>645</td>
<td>337</td>
</tr>
</tbody>
</table>

MCM, major congenital malformation.

* Numeric results for testing $H_0: P = P_0$ versus $H_1: P > P_0$ using a one-sided Z test with $S(\hat{P})$ to estimate the standard deviation with a continuity. Calculations were based on a target alpha of 0.025, though actual calculated alpha <0.025.

† Baseline MCM frequencies based on general population data. Ranges from 2.1–2.8% depending on whether MCM frequency was determined at birth or up to six years of age, \cite{14,15} and 1.6%–2.2% within first five days of life depending on whether chromosomal and genetic anomalies were included.\cite{16}