PASS information

Title	Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol RGD-77425).
Protocol version identifier	Protocol amendment 2
Date of last version of protocol	09 July 2014.
EU PAS register number	ENCEPP/SDPP/4282
Active substance	butoconazole (test drug); clotrimazole, miconazole, nystatin, metronidazole (therapeutic controls); celecoxib, diclofenac, ibuprofen, indomethacin, naproxen, rofecoxib; carbamazepine, isotretinoin, lithium, valproic acid (active controls and confounding factors).
Medicinal product	all approved products in Hungary containing the above active substances
Product reference	the relevant gynecology products are not centrally authorized.
Procedure number	not applicable (MAH initiated study)
Marketing authorisation holder(s)	Gedeon Richter Plc.
Joint PASS	No
Research question and objectives	The primary objective is to evaluate butoconazole treatment as a potential risk factor for teratogenicity and/or spontaneous abortion in a population-based retrospective study in Hungary, based on National Health Insurance Fund Administration Database (OEP database) records. Secondary objectives: to evaluate therapeutic controls as risk factors in the same analyses, for comparative purposes. To collect epidemiologic data on all outcomes of butoconazole exposed pregnancies. To evaluate the effect of butoconazole and clotrimazole on birthweight.
Country(-ies) of study	Hungary
Principal investigator	Dr. Nándor Ács Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary

Marketing authorisation holder(s):

Marketing authorisation holder(s)	Gedeon Richter Plc. 19-21 Gyömrői út, Budapest 1103, Hungary phone: +36 1 432 7433 email: horvathbea@richter.hu
MAH contact person	Beáta Horváth MD, PhD

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2. List of abbreviations

95% CI	95% confidence interval
AFP	Alpha-fetoprotein
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body Mass Index
BNO	The Hungarian adaptation of the ICD classification system
CA	Congenital anomaly
CHMP	Committee for Medicinal Products for Human Use
DOT	Days of therapy (based on the PUPHA list as published by the OEP)
EMEA	European Medicines Evaluation Agency
ENCePP Checklist	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	Ectopic pregnancy
ET	Elective termination without foetal defect
ET_FD	Elective termination with foetal defect
EU PAS register	European Post-authorization study register
FDA	Food and Drug Administration
GYEMSZI	National Institute for Quality- and Organizational Development in Healthcare and Medicines
GYEMSZI-OGYI	National Institute for Quality- and Organizational Development in Healthcare and Medicines- National Institute of Pharmacy
HBCS	
HCAR/ HCCSCA	Hungarian Congenital Abnormality Registry / Hungarian Case-Control Surveillance of Congenital Abnormalities databases
ICD	International Classification of Diseases
LB	Live birth without cong. anomaly
LB FD	Live birth with cong. anomaly
LMP	Last menstrual period
MAH	Marketing Authorization Holder
N	Number
NHIF	National Health Insurance Fund
NIHD /OEFI	National Institute for Health Development / Országos Egészségfejlesztési Intézet
NSAID	Non-steroidal anti-inflammatory drugs
OENO	Hungarian classification system for medical interventions in inpatients and outpatients
OEP	National Health Insurance Fund (Hungarian abbreviation)
OEP database	National Health Insurance Fund Administration Database
OGYI	National Institute of Pharmacy
OR	Odds ratio

OTC	Over the Counter
PASS	Post-authorization safety study
PL/SQL	Procedural Language/Structured Query Language
Rx	drug prescription
SA	Spontaneous abortion
SB	Stillbirth without foetal defect
SB_FD	Stillbirth with foetal defect
SD	Standard deviation
TAJ Number	Social security identification number (a unique, 9-digit identification number for each insured person at the National Health Insurance Fund in Hungary)

3. Responsible parties

The study is planned as a scientific collaboration of Gedeon Richter Plc (MAH of a butoconazole product in Hungary), RxTarget Kft (contract research organiser in the field of OEP data request and analysis), the National Institute for Health Development (responsible for the HCAR / HCCSCA databases), together with clinical experts Nándor Ács MD, PhD, med habil (Principal Investigator), and Zoltán Kaló MSc PhD (consultant expert). Key responsibilities of the involved parties are tabulated below, and a more detailed description is provided in the main text of the protocol (Section 9). In Protocol Amendment 2, two additional partners have been joined the research team: Syreon Research Institue Ltd. (responsible for the preparation of protocol amendment 2 and the final report), and Gábor Kovács MD, PhD (paediatric expert of Syreon Research Institute). The contract with the National Institute for Health Development has been terminated and could not be extended due to the shortage of research capacity at NIHD at present.

Name	Address	Responsibilities	Contact person
Gedeon Richter Plc.	19-21 Gyömrői út, 1103 Budapest, Hungary	Study sponsorship, study planning and financing, project management.	Beáta Horváth MD, PhD Head of Unit, Strategic Analysis Unit, Medical Strategy and Coordination Department, Gedeon Richter Plc. 32 Gyömrői út, Budapest 1103, Hungary. phone: +36 1 432 6418 email: j.pitter@richter.hu
RxTarget Kft.	10 Bacsó Nándor út 5000 Szolnok, Hungary	Participation in study planning and reporting, programming data analysis, OEP correspondence.	György Rokszin MD. CEO, RxTarget Ltd. 10 Bacsó Nándor út, Szolnok 5000, Hungary phone: +36-70-372-1201 email: rokszin.gyorgy@rxtarget.hu
National Institute for Health Development (HCAR / HCCSCA databases)	2 Nagyvárad tér 1096 Budapest, Hungary	Participation in study planning. Research contract terminated before drawing conclusions in the final report..	Csáky-Szunyogh Melinda Head of the Hungarian Congenital Abnormality Registry, National Institute for Health Development, 2 Nagyvárad tér, 1096 Budapest, Hungary phone: +36-1-4288-229 email: csszunyogh.melinda@ oefi.antsz.hu
Nándor Ács MD, PhD, med. habil.	78/A Üllői út, 1082 Budapest, Hungary	Principal Investigator Consultant Expert in Gynecology. Participation in study planning and in drawing	Nándor Ács MD Second Department of Obstetrics and Gynecology, School of Medicine, Semmelweis University 78/A Üllői út, 1082 Budapest, Hungary

		conclusions in the final report.	
Zoltán Kaló MD, MSc, PhD	ELTE Társdadalomtudományi Kar, H-1518 Budapest, Pf. 32	Consultant Expert in clinical research. Participation in study planning, and in drawing conclusions in the final report.	Zoltán Kaló MD, MSc, PhD Eötvös Lóránd University, Institute of Economics, Health Economics Research Centre Building B, 1/A Pázmány Péter sétány, 1117 Budapest, Hungary
Syreon Research Institute Kft.	119 Thököly street, Budapest 1146, Hungary	Writing of protocol amendment 2 and the final report.	János G. Pitter MD, PhD Principal researcher, Syreon Research Institute Ltd. Phone: +36 20 454 7887 Email: janos.pitter@syreon.eu
Gábor Kovács MD	119 Thököly street, Budapest 1146, Hungary	Participation in the planning of Protocol Amendment 2 and in drawing conclusions in the final report.	Gábor Kovács MD Senior researcher, pediatrician Syreon Research Institute Ltd. Phone: +36 70 430 4644 Email: gabor.kovacs@syreon.eu

4. Abstract

Butoconazole use in pregnancy: population-based case-control studies on adverse pregnancy outcomes in Hungary (study protocol No. 77425)

Rationale and background: Vaginal yeast carriage is frequently occurring in pregnancy. Pharmacotherapy of genital fungal infections during pregnancy may prevent against preterm birth. However, pharmacotherapy itself may pose a risk to the developing foetus (increased risk of spontaneous abortions or foetal defects / congenital anomalies). Butoconazole belongs to a therapeutic class which contains drugs considered safe in pregnancy, as well as drugs which must be avoided in pregnancy. Although butoconazole is administered locally, small amounts of the drug were shown to be adsorbed from the vaginal mucosa. The available non-clinical and clinical data on butoconazole safety in pregnancy is not conclusive. As butoconazole is on the market in Hungary from 2004, the available records in the relevant medical databases allow for a retrospective, large-scale analysis of the risk of adverse pregnancy outcomes in butoconazole exposed pregnant women.

Research question and objectives: The primary objective is to evaluate butoconazole treatment as a potential risk factor for teratogenicity and/or spontaneous abortion in a population-based database analysis study in Hungary, based on National Health Insurance Fund Administration Database (OEP database) records. Secondary objectives: to evaluate therapeutic controls (clotrimazole, miconazole, nystatin, metronidazole) as risk factors in the same analyses, for comparative purposes; and to collect epidemiologic data on all outcomes of butoconazole exposed pregnancies. The effect of butoconazole and clotrimazole on birthweight is also investigated.

Study design: a population-based database analysis of all reported pregnancy outcomes, with case-control studies on the risk of spontaneous abortion and teratogenicity. For the birthweight analyses in Amendment 2, a quasi randomised study design is selected with logistic regression analyses.

Population: all reported pregnancy outcomes reported to the OEP database from 01 January 2005 to 31 December 2011, excluding pregnancies without sufficient identification data on live birth offspring. Cases exposed to other drugs / other risk factors are not excluded from the study. Instead, a range of potential confounding factors is included in the statistical models.

Variables: The investigated pregnancy outcomes include ectopic pregnancy; spontaneous abortion; elective termination (foetal defects); elective termination (no foetal defects or unknown); stillbirth with foetal defects; stillbirth without foetal defects; live birth with congenital anomaly; live birth without congenital anomaly. Birth weight in live births is analysed both as a binary (low birthweight / normal birthweight) and as a continuous variable. Drug exposure time periods include the following time periods: Before conception; First trimester; After first trimester; During all pregnancy; Unknown. For the analysis of teratogenic effects, separate analyses for the 1st month, 2nd month, 3rd month, 2nd + 3rd month are also included.

Data sources: OEP database records.

Study size: based on national birth statistics, the OEP database is expected to contain about 1 100 000 pregnancy outcomes in the relevant time period (including about 670 000 live births).

Data analysis: logistic regression models for the case-control studies on spontaneous abortion and teratogenicity risk, and for the quasi-randomised study on low birthweight. Descriptive statistics for all types of pregnancy outcomes.

Milestones: Final protocol submission to GYEMSZI-OGYI for study approval was planned for June 2013. GYEMSZ-OGYI approval occurred in 29th October 2013. Final report of study results is planned to be finalized in the fourth quarter of 2015.

5. Amendments and updates

No.	Date	Section of study protocol	Amendment or update	Reason
1	09th July 2014	Cover page	Sponsor contact person changed	n.a.
1	09th July 2014	Section 3	Additional abrevations added to the list	Double-check of the text
1	09th July 2014	Section 3.	Sponsor contact person changed	n.a.
1	09th July 2014	Section 4.	Protocol approval date added	Caused delay in study procedures
1	09th July 2014	Section 5.	Amendment 1 summarized	Protocol amendment
1	09th July 2014	Section 6.	Timelines updated	Delay in study approval and procedures
1	09th July 2014	Section 8.	Active control drugs introduced also in the teratogenicity case-control study Myconazole systemic and local products will be analysed separately. Nystatin systemic and local products will be analysed separately. "Evidence of acute infection / inflammatory disease in the first trimester" is deleted NSAID drugs to be investigated are listed by name	Potential confounders, measures of study sensitivity. Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary. This conflunding factor cannot be identified and investigated. List of the investigated NSAID products missing from the original protocol
1	09th July 2014	Section 9.2.	Children without mother records are excluded	Maternal drug exposure without identified mother can not be analysed.
1	09th July 2014	Section 9.3.	HCAR/HCCSCA sentence deleted; Active control drugs introduced in the teratogenicity assessment; Nystatin systemic and local products will be analysed separately. NSAID drugs to be investigated are listed by name	HCAR/HCCSCA records are not analysed in this study. Active control drugs are potential confounders and measures of study sensitivity; Nystatin systemic products are also available in Hungary. List of the investigated NSAID products missing from the original protocol

No.	Date	Section of study protocol	Amendment or update	Reason
1	09th July 2014	Section 9.5.	Children without mother records are excluded	See above
1	09th July 2014	Section 9.7.	Two alternative analyses (according to the amendment, and according to the original protocol)	Check the sensitivity of the results to the amended methodology.
1	09th July 2014	Section 9.7.2.	NSAID drugs to be investigated are listed by name, Reference to the list of NSAID drugs; Myconazole systemic and local products will be analysed separately. Nystatin local and systemic products evaluated separately.	List of the investigated NSAID products missing from the original protocol; Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary.
1	09th July 2014	Section 9.7.9.	Active control drugs added NSAID drugs to be investigated are listed by name	See above List of the investigated NSAID products missing from the original protocol
1	09th July 2014	Section 9.7.10.	Active control drugs added; Myconazole systemic and local products will be analysed separately. Nystatin local and systemic products evaluated separately. Isotretinoin local and systemic products evaluated separately "Evidence of acute infection / inflammatory disease during the first trimester of pregnancy" is deleted	See above Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary Isotretinoin local and also systemic products are available in Hungary. This conflunding factor cannot be identified and investigated
1	09th July 2014	Section 9.7.11.	Myconazole systemic and local products will be analysed separately. Nystatin local and systemic products evaluated separately.	Miconazole systemic products are also available in Hungary. Nystatin systemic products are also available in Hungary
1	09th July 2014	Section 9.9.	Further limitations and considerations added	All limitations shall be discussed in the final report.
1	09th July 2014	Annex 3.1.	Sub-sections added (Annexes 3.1.1 – 3.1.3.)	See at the subsections below.
1	09th July 2014	Annex 3.1.1.	Additional pregnancy identification approaches introduced	In addition to HBCS codes, additional approaches are also introduced to identify most of the pregnancies / births.

No.	Date	Section of study protocol	Amendment or update	Reason
1	09th July 2014	Annex 3.1.2.	Additional BNO/OENO codes specific to pregnancy outcomes have been identified; Reference to updated redundance / outcome hierarchy rules in Annex 3.1.3.	Double-check of the relevant codes; See Annex 3.1.3.
1	09th July 2014	Annex 3.1.3.	Updated redundance / outcome hierarchy rules, with specific criteria of multiple outcomes from the same pregnancy.	Systematic review and update, with more specific rules and logical check. For justifications, please see the imputed text.
1	09th July 2014	Annex 3.2.	Pregnancy-specific codes added	Pregnancy-specific codes are used for pregnancy identification and for alternative Day 1 estimate in case "late AFP criteria" are fulfilled.
1	09th July 2014	Annex 3.3.2.	NSAID drugs to be investigated are listed by name and ATC codes. Additional BNO/OENO codes added to the confounder factors' criteria.	List of NSAID products missing from the original protocol; Double-check of the relevant codes.
1	09th July 2014	Annex 3.4.	Planned analysis of teratogenic risk	Typing error
1	09th July 2014	Annex 3.4.1.	Active control drugs added; two alternative analyses (according to the amendment, and according to the original protocol)	See above
1	09th July 2014	Annex 3.4.2.	Nystatin systemic and local products will be analysed separately. Active control drugs introduced also in the teratogenicity case-control study. ATC codes were added Additional BNO/OENO codes added to the confounder factors' criteria. BNO, OENO and prescriptional ATC codes for the identification of	Nystatin systemic products are also available in Hungary Active control drugs are potential confounders and measures of study sensitivity; ATC codes missing from the original protocol Double-check of the relevant codes. This conflunding factor cannot be identified and investigated. Acute infections

No.	Date	Section of study protocol	Amendment or update	Reason
			"Evidence of acute infection / inflammatory disease during the first trimester of pregnancy" are deleted	are usually treated by the GP. The mentioned codes are under-documented by the GP to the OEP database
2	17 July 2015	Title page	Date of last version updated; Active controls listed as active substances	administrative update; harmonization of title page with the document
2	17 July 2015	Title page	Additional research objective: To evaluate the effect of butoconazole and clotrimazole on birthweight.	Amendment 1 results raised additional research questions as explained in Annex 3.5.
2	17 July 2015	3. Responsible parties	Syreon Research Institute and Gábor Kovács MD, PhD added; NIHD cooperation stopped	Research capacity reasons from Gedeon Richter and NIHD side
2	17 July 2015	4. Abstract	Additional research objective: To evaluate the effect of butoconazole and clotrimazole on birthweight. Quasi-randomized study design, with logistic regression models. Birth weight will be analysed both as a binary (low / normal birthweight) and as a continuous variable.	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	5. Amendments and updates	Amendment 2 details summarized	Protocol amendment 2
2	17 July 2015	6. Milestones	Date of "end of data collection", "end of data analysis and statistics", and of "final report" have been updated	Additional data and time requirements of planning and conducting Amendment 2 analyses
2	17 July 2015	8. Research questions and objectives	Inclusion of active controls in the adjusted regression model for testing of the formal hypothesis on teratogenic risk has been clarified	Harmonization with Section 9.7.10. and with Annex 3.4.
2	17 July 2015	8. Research questions and objectives	In Amendment 2 congenital anomaly and spontaneous abortion analyses, the propensity score will also include the socioeconomic status of the maternal	Efforts to correct for socioeconomic factors in Amendment 2 analyses

No.	Date	Section of study protocol	Amendment or update	Reason
			residence at micro-region level, and urban /rural status, beyond the previously included variables.	
2	17 July 2015	8. Research questions and objectives	In amendment 2 analyses, the primary endpoint refers to the "al1" EUROCAT definition of congenital anomalies.	The al1 definition is the most inclusive of the multiple alternative congenital anomaly definitions in Amendment 2
2	17 July 2015	8. Research questions and objectives	Secondary objective added: to evaluate the role of butoconazole and clotrimazole in the risk of low birthweight (<2500g).	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.1 Study design	Design summary added for the Amendment 2 birthweight analyses	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.3 Variables	Time periods of pregnancy: risk of low birthweight will be evaluated for first trimester, second trimester, third trimester, and during pregnancy drug exposures.	Beyond first trimester exposures, drug exposure in 2nd and 3rd trimester will also be considered.
2	17 July 2015	9.3 Variables	Drug exposures: the analyses will consider drug exposure as a quantitative parameter (number of DOTs)	Amendment 1 analyses evaluated drug exposure as a binary (yes/no) variable. Drug exposure as a numeric variable will allow more graded conclusions
2	17 July 2015	9.5 Study size	Power calculations for code groups of congenital anomalies have been added to the protocol, and summarized here.	Selection of EUROCAT and custom code groups to be analysed. For justifications, see Annex 3.1.4.
2	17 July 2015	9.7 Data analysis	Logistic regression models on low birthweight has been added, with a quasi-randomized design.	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.7 Data analysis	Results will be reported according to Amendment 1 and Amendment 2	Experience accumulating from ongoing data collection and analysis revealed that the original study protocol failed to identify most mother – offspring pairs. Moreover, pregnancy outcomes were

No.	Date	Section of study protocol	Amendment or update	Reason
				ambiguous in cases with multiple outcome records. Accordingly, the study will not be analysed as planned in the original protocol.
2	17 July 2015	9.7 Data analysis	Overview of planned Amendment 2 changes added	For congenital anomaly analyses, see Annex 3.4.3. For spontaneous abortion analyses, see Annex 3.3.3. For birthweight analysis changes, see Annex 3.5.
2	17 July 2015	9.7 Data analysis	Schematic flowchart of the planned analyses: quasi-randomised study on low birthweight added.	Amendment 1 results raised additional research questions. Rationale and study design are detailed in Annex 3.5.
2	17 July 2015	9.7.2 Spontaneous abortions	Drug exposure: changed from binary to numeric in Amendment 2 analyses	Drug exposure as a numeric variable will allow more graded conclusions
2	17 July 2015	9.7.2 Spontaneous abortions	Crude OR: univariate analyses	clarification of crude odds ratios
2	17 July 2015	9.7.2 Spontaneous abortions	Additional analyses of spontaneous abortion risk have been introduced by Protocol Amendment 2. For details, please see Annex 3.3.3.	Reference to a new section describing the Amendment 2 changes
2	17 July 2015	9.7.8. Live births without congenital anomaly	Add descriptive statistics (mean and SD) on pregnancy duration	To check the credibility of the calculated pregnancy periods
2	17 July 2015	9.7.9. Summary table of pregnancy outcomes	The Summary Table of Pregnancy Outcomes table will be filled both according to Protocol Amendment 1 and Protocol Amendment 2 definitions.	Protocol amendment 2
2	17 July 2015	9.7.9. Summary table of pregnancy outcomes	Layout of the table changed: additional columns for all exposed cases, and for all cases.	Exposition periods are not mutually exclusive (e.g. “during all pregnancy” cases included also in “first trimester” cases)

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015			
2	17 July 2015	9.7.10. Multivariate analysis of drug induced risk of congenital anomalies	Time profile of reporting congenital anomalies after birth: codes belonging to any of the new, alternative CA code groups will be analysed in Amendment 2	Change in definition of congenital anomaly code groups
2	17 July 2015	9.7.10. Multivariate analysis of drug induced risk of congenital anomalies	Time profile of reporting congenital anomalies: births in 2005 will be followed	Typing error in table (2004)
2	17 July 2015	9.7.11. Analysis of birth weight	Additional analyses of low birthweight have been introduced by Protocol Amendment 2. For details, please see Annex 3.5.	Reference to a new section describing the Amendment 2 changes
2	17 July 2015	9.9 Limitations of the research methods	Dilution by high numbers of minor congenital anomalies or irrelevant consitions (e.g. congenital dysplasia of the hip) added as a limitation	Amendment 1 analyses showed a high proportion of minor anomalies among the identified “congenital anomaly” cases
2	17 July 2015	9.9 Limitations of the research methods	Non-relevant codes are intended to be excluded from the analysis of teratogenicity risk by Protocol Amendment 2.	Amendment 1 analyses showed a high proportion of minor anomalies among the identified “congenital anomaly” cases
2	17 July 2015	9.9 Limitations of the research methods	Study results will be reported both per Protocol Amendment 1 and Protocol Amendment 2.	Protocol amendment 2
2	17 July 2015	9.9 Limitations of the research methods	Limitations of the birthweight analyses in Protocol Amendment 2 are discussed in Annex 3.5.	Reference to a new section describing the Amendment 2 changes
2	17 July 2015	13. References	References added in Amendment 2	Update of reference list

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	Annex 1. List of stand-alone documents	ENCEPP checklist update and a MS Excel file "Socioeconomic status of micro-regions.xlsx" added	Protocol amendment 2
2	17 July 2015	Annex 3.1.2. Identification of pregnancy outcomes in the OEP database	Code groups listings: clarification added that these definitions partly do not apply for the Amendment 2 analyses	Alternative definitions introduced in Amendment 2
2	17 July 2015	Annex 3.1.4.	Protocol Amendment 2 changes in the identification of pregnancy outcomes: exclusion of mild cases; exclusion of outpatient cases in sensitivity analyses; analysis by code subgroups. Description and justification of the selected 34 alternative CA code groups to be analysed in Amendment 2	Alternative definitions along the EUROCAT recommendations introduced in Amendment 2, to correct for the unexpectedly high rate of apparent CA cases in Amendment 1 analyses. For details and justifications, see Annex 3.1.4.
2	17 July 2015	Annex 3.2. Determination of gestational age in the OEP database	Allocation of cases to pregnancy exposure periods is not mutually exclusive. E.g. mothers with „During all pregnancy" exposure shall also be counted at exposure in „First trimester" and „After first trimester", and shall be included in the case-control analyses of all relevant exposure periods.	To avoid the fragmentation of patient groups exposed in the critical time periods
2	17 July 2015	Annex 3.3.1. Scientific background – SA analyses	Results will be reported according to Amendment 2 (main analysis) and also according to Amendment 1 (ancillary analysis)	Protocol amendment 2
2	17 July 2015	Annex 3.3.1. Scientific backgroun	Potential confounders added with references (paternal age, paternal smoking)	Updated listing of potential confounders

No.	Date	Section of study protocol	Amendment or update	Reason
		d – SA analyses		
2	17 July 2015	Annex 3.3.3. Amendment 2 changes in SA analyses	In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables are replaced by numeric drug exposure variables (days of therapy). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls; The propensity score will also include the socioeconomic status of the maternal residence at micro-region level, and rural/urban status of maternal residence, beyond the currently included variables. Pregnancies with maternal age <15 years or maternal age >45 years are excluded from the Amendment 2 analyses.	Drug exposure as a numeric variable will allow more graded conclusions. Efforts to correct for socioeconomic factors in Amendment 2 analyses. Outlier maternal ages most probably reflect invalid data in the OEP database, according to RxTarget experience.
2	17 July 2015	Annex 3.4.1. Scientific background – CA analyses	Results will be reported according to Amendment 2 (main analysis) and also according to Amendment 1 (ancillary analysis)	Protocol amendment 2
2	17 July 2015	Annex 3.4.1. Scientific background – CA analyses	Crude OR: univariate analyses	clarification of crude odds ratios
2	17 July 2015	Annex 3.4.3.1. Changes in the	Pregnancies with maternal age <15 years or maternal age >45 years are excluded from the	Outlier maternal ages most probably reflect invalid data in the OEP database, according to RxTarget experience.

No.	Date	Section of study protocol	Amendment or update	Reason
		logistic regression model of CA risk	Amendment 2 analyses (for justification, please see Annex 3.3.3); In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables are replaced by numeric drug exposure variables (days of therapy). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls; The propensity score will also include the socioeconomic status of the maternal residence at micro-region level (see in Annex 3.6), and urban/rural status of maternal residence beyond the currently included variables.	Drug exposure as a numeric variable will allow more graded conclusions. Efforts to correct for socioeconomic factors in Amendment 2 analyses.
2	17 July 2015	Annex 3.4.3.2. Definition of cases and controls	In the Amendment 2 analyses of congenital anomalies, 34 alternative definitions will be applied to cases and controls, driven by EUROCAT guidelines and expected power calculations.	Alternative definitions along the EUROCAT recommendations introduced in Amendment 2, to correct for the unexpectedly high rate of apparent CA cases in Amendment 1 analyses. For details and justifications, see Annex 3.1.4.
2	17 July 2015	Annex 3.4.3.3. Sensitivity analyses	For each alternative definition of cases and controls, 1 main analysis and 8 sensitivity analyses will apply: for 3 alternative estimates of day 1 of pregnancy, combined with the inclusion, or the exclusion of isolated or all outpatient reports.	Sensitivity analyses intend to allow robust conslusions on pregnancy period exposures, and to fine-tune the apparent congenital anomaly rates in the overall population.

No.	Date	Section of study protocol	Amendment or update	Reason
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	A quasi-randomised design is introduced, with the exclusion of pregnancies exposed to butoconazole or clotrimazole prescriptions of non-gynecologists and gynaecologists with inhomogenous prescription patterns.	The rationale behind this patient population restriction is that different patient characteristics within the doctor's practice could underlie patient-specific drug selection decisions in non-homogenous prescription practices
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	Potential between-practice differences in patient characteristics are intended to be controlled for by the inclusion of the following socio-economic proxies in the logistic regression models: - micro-regional development status of the maternal residence (as determined in Annex 3.6); - urban / rural status of maternal residence.	To adjust for potential between-practice differences in socioeconomic status
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	Pre-defined logistic regression models and results table outline for the main analysis and for sensitivity analyses	To correct for the potential confounding effect of the included variables; Sensitivity analyses for robust conclusions.
2	17 July 2015	Annex 3.5 Amendment 2 changes in the analysis of low birthweight	Descriptive statistics will be provided on selected measurable patient characteristics, for patient groups with different socioeconomic status	To check the comparability of butoconazole and clotrimazole exposed pregnancies within the same socioeconomic subgroups
2	17 July 2015	Annex 3.6 Socioeconomic status of	Maternal residence postal codes are linked to micro-regional socioeconomic status through the name of the	Efforts to correct for socioeconomic factors in Amendment 2 analyses.

No.	Date	Section of study protocol	Amendment or update	Reason
		micro-regions in Hungary	corresponding town / village, following the official categories of deprivement status in the relevant time period.	

6. Milestones

Milestone	Planned date
Final study protocol	8 July 2013
Submission for GYEMSZI-OGYI approval	10 July 2013
Registration in the EU PAS Register	10 July 2013
Date of GYEMSZI-OGYI approval	29 October 2013
Start of data collection (OEP)*	20 Januar 2014
End of data collection (OEP)*	30 June 2015
Start of data analysis and statistics	10 Februar 2014
End of data analysis and statistics	31 August 2015
Final report of study results	31 December 2015

*: start and stop date of secondary use of existing data (database research).

7. Rationale and background

The hormonal milieu of pregnancy creates a suitable environment predisposing for the vulvovaginal colonisation of Candida. Vaginal yeast carriage is thus more frequent in pregnancy and increases with increasing periods of gestation (Weisberg, 1986).

Pharmacotherapy of genital fungal infections during pregnancy (especially in the first trimester) was shown to have a preventive effect against preterm birth in the case of clotrimazole, while the limitations of the dataset did not allow the appropriate evaluation of other antifungal drugs (Czeizel et al., 2007).

When treating fungal infections in a pregnant woman, it is very important to select an antifungal agent that, whilst effectively treating the mother, will pose no risk to the developing foetus. Given the multitude of topical azoles available for the treatment of Candida vaginitis, it would seem reasonable to prefer locally applied products instead of the use of systemic antifungals if possible, especially in pregnancy. However, the potential risk of locally applied products can not be excluded since small amounts of imidazoles are absorbed from the human vagina (Fromtling, 1988; Rosa et al., 1987).

Gedeon Richter Plc is the MAH of Gynazol-1, a locally applied butoconazole containing product approved for the treatment of Candida vaginitis. The available non-clinical and clinical data regarding the safety of butoconazole in pregnancy is summarized below.

Non-clinical reproductive toxicity data on butoconazole

Butoconazole nitrate was not mutagenic when tested on microbial indicator organisms. No impairment of fertility was seen in rabbits or rats administered butoconazole nitrate in oral doses up to 30 mg/kg/day or 100 mg/kg/day respectively.

In pregnant rats administered 6 mg/kg/day (3-7 times the human dose, representing a 130- to 353-fold safety margin based on systemic serum levels) butoconazole nitrate intravaginally during the period of organogenesis, there was an increase in resorption rate and decrease in litter size, but no teratogenicity.

Butoconazole nitrate had no apparent adverse effect when administered orally to pregnant rats throughout organogenesis, at dose levels up to 50 mg/kg/day (5 times the human dose based on mg/m2). Daily oral doses of 100, 200, 300 or 750 mg/kg/day (10, 30 or 75 times the human dose based on mg/m2, respectively) resulted in foetal malformations (abdominal wall defects, cleft palate), but maternal stress was evident at these higher dose levels (FDA, 2003).

There were no adverse effects on litters of rabbits receiving butoconazole nitrate orally, even at maternally stressful dose levels (e. g. 150 mg/kg, 24 times the human dose based on mg/m2).

Butoconazole nitrate, like other azole antifungal agents, causes dystocia (abnormal or difficult childbirth) in rats when treatment is extended through parturition. However, this effect was not apparent in rabbits treated with as much as 100 mg/kg/day orally (16 times the human dose based on mg/m2).

In summary, the available non-clinical data raised the concern of adverse effects of butoconazole on human reproduction. According to the assessment of this issue by Gedeon Richter's Toxicology Research Department, the concern is modulated by the following factors:

Factors of increased concern in non-clinical studies	**Factors of decreased concern in non-clinical studies**
- malformations occurred; - effects on more than one stages of reproductive cycle (embriotoxicity, teratogenicity, childbirth complications); - maternal toxicity at teratogenic doses was limited to body weight decrease (a direct effect on foetus can not be excluded); - dose-related effects; - embriotoxic dose in rats < 10x human dose (based on mg/m2 calculations); - class alert (other molecules with similar structure and pharmacodynamics were shown to be teratogenic in animals, and human malformations were also reported, e.g. fluconazole).	- positive findings in rat vs. no signal in rabbit; - the observed malformations in rat (abdominal wall defects, cleft palate) do not reflect a common biological mechanism; - embriotoxic dose in rat at about 130- to 353-fold human dose (based on systemic serum levels).

Clinical data on butoconazole in pregnancy

In the pivotal efficacy trials with Gynazol 20 mg/g vaginal cream, 8 unexpected pregnancies occurred (< 1% of 911 enrolled patients), despite investigators' effort to exclude pregnant patients. Only 2 of the 8 women used Gynazol 20 mg/g vaginal cream; both patients carried the pregnancies to term without complications and delivered normal neonates. An additional 2 women received different formulations of sustained release butoconazole vaginal cream for 3 days; 1 of these women delivered a healthy baby, the other elected therapeutic abortion for an unwanted pregnancy. The remaining 4 women received other antifungal imidazoles without any complications.

In a clinical study (IND 17658) 200 pregnant women received butoconazole nitrate intravaginally for 3 or 6 days during the second and third trimesters. It has not been shown that butoconazole causes adverse effects on the foetus. Follow-up reports on infants born to these women have not shown that butoconazole causes any adverse effects (Gedeon_Richter_Plc., 2012).

In a surveillance clinical study of Michigan Medicaid recipients involving 229,101 completed pregnancies conducted between 1985 and 1992, 444 newborns had been exposed to vaginal

butoconazole during the first trimester. A total of 16 (3.6%) major birth defects were observed (17 expected). Specific data were available for six defect categories, including (observed/expected) 4/4 cardiovascular defects, 1/1 limb reduction defects, and 0/1 hypospadiasis. These data do not support an association between vaginal butoconazole use and congenital birth defects. Unfortunately, the study results have not been published, but are cited as „personal communication from F. Rosa, FDA 1993" in a reference textbook (Briggs, 2011).

Recommendations on butoconazole use in pregnancy

In the currently approved Summary of Product Characteristics in Hungary (OGYI/42622/2011, date 17 January 2011) the first trimester of pregnancy is a contraindication, with the following recommendations in pregnancy:

> 4.6 Fertility, pregnancy and lactation
>
> Pregnancy: There are limited amount of data from the use of butoconazole nitrate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Gynazol 20mg/g vaginal cream should not be used during the first trimester of pregnancy, or in women of childbearing potential unless adequate contraception is employed. In the second and third trimester of pregnancy Gynazol 20mg/g vaginal cream should be used only if the potential benefit justifies the potential risk to the foetus.

However, the previously approved Summary of Product Characteristics of Gynazol was less restrictive on it's use in the first trimester, recommending an individual risk-benefit assessment by the treating physician (OGYI 13840/41/2005, date 02 August 2005) (OGYI, 2005). Therefore, it is reasonably expected that a non-negligible fraction of pregnant women were exposed to butoconazole in the first trimester in the investigated time period.

Expected contribution of the current study to the filling of the gaps in current knowledge

This is the first study providing epidemiologic human data on main pregnancy outcomes in butoconazole-exposed women, complying with the requirements of the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005).

The study intends to confirm the results of the F. Rosa study described in (Briggs, 2011) (i.e. to confirm the lack of teratogenic potential of locally applied butoconazole in humans).

In addition, a dedicated case-control analysis is also planned on the risk of spontaneous abortion in butoconazole-exposed pregnancies (first human data in this respect).

The study investigates multiple anti-infective gynecology products in the same setting, allowing a comparative assessment of the butoconazole results. (Previous comparative studies of gynecologic anti-infectives have not included butoconazole in their analyses).

Several high-quality nested case-control analyses have been published previously on the potential teratogenic effects of various drugs and conditions in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA, 1980 - 1996) (Acs et al., 2009a; Acs et al., 2009b; Acs et al., 2010; Banhidy et al., 2007; Banhidy et al., 2011a; Banhidy et al., 2011b; Banhidy et al., 2011c; Czeizel et al., 2004). Drug exposure in these analyses was assessed based on prenatal maternal care logbooks, other medical records, and retrospective self-reported maternal information. Confounding factors of maternal age, employment status, birth order, fever-related influenza or common cold and acute maternal disease, in addition to some drug treatment (e.g. folic acid) were also carefully considered.

In the present study, HCCSCA 1980 – 1996 records are unfortunately not relevant due to the late appearance of butoconazole on the Hungarian market (2004). In the relevant years (2005 – 2013) the available datasets of the case-control surveillance of congenital anomalies (HCCSCA database) do not contain any case with recorded butoconazole exposure (official statement from NIHD based on current HCAR / HCCSCA data search (National_Institute_for_Health_Development, 2013a)). Therefore, the current study is based on the National Health Insurance Fund Administration Database (OEP database). This is the first study with the intention to determine pregnancy outcomes, pregnancy periods, drug exposure, and confounding factors solely from the OEP database. The proposed, OEP-based approach may be useful also for the investigation of other drugs authorised after 1996.

A low birthweight preventive effect of clotrimazole treatment against vaginal candidiasis have been described previously (Banhidy et al., 2009; Czeizel et al., 2004; Czeizel et al., 2007). This is the first study comparing butoconazole and clotrimazole in this respect.

8. Research question and objectives

The study has two co-primary objectives:

- to evaluate butoconazole treatment as a potential teratogenic risk factor in a population-based case-control study in Hungary, based on the OEP database;
- to evaluate butoconazole treatment as a potential risk factor of spontaneous abortion in a population-based case-control study in Hungary, based on the OEP database.

Crude and adjusted odds ratios will be calculated for both of these co-primary objectives, with several sensitivity analyses and several alternative definitions of relevant drug exposure periods. Results of all these analyses will be evaluated together, to allow for robust conclusions. Any positive finding in these analyses will be interpreted in the context of similar findings with therapeutic comparators and with active control drugs. Nevertheless, two formal hypotheses are tested as co-primary endpoints of the study:

Formal hypothesis on teratogenic risk:

- 95% CI of the adjusted* odds ratio of foetal defect/congenital abnormality in pregnancies exposed to butoconazole in the first trimester (vs. not exposed pregnancies) will include the value 1.00 in the main analysis** of teratogenicity risk (Section 9.7.10.).

  **Odds ratio adjusted for: maternal age, local miconazole / systemic miconazole / clotrimazole / local nystatin /systemic nystatin / local metronidazole / systemic metronidazole and/or systemic carbamazepine / systemic isotretinoin / local isotretionin / systemic lithium / systemic valproic acid exposure in the first trimester; and a propensity score of the following: evidence of previous live birth, spontaneous abortion, and/or maternal diabetes in the last 4 years, calendar effect (year and month). In Amendment 2 analyses, the propensity score will also include the socioeconomic status of the maternal residence at micro-region level, and urban /rural status, beyond the previously included variables.*
  ***In amendment 2 analyses, the primary endpoint refers to the "al1" EUROCAT definition of congenital anomalies.*

Formal hypothesis on spontaneous abortion risk:

- 95% CI of the adjusted*** odds ratio of spontaneous abortion in pregnancies exposed to butoconazole (vs. not exposed pregnancies) will include the value 1.00 in the main analysis of spontaneous abortion risk (Section 9.7.2).

  ****Odds ratio adjusted for: maternal age, local miconazole / systemic miconazole / clotrimazole / local nystatin / systemic nystatin / local metronidazole / systemic metronidazole and/or local diclofenac / systemic diclofenac / local naproxen / systemic naproxen / celecoxib / local ibuprofen / systemic ibuprofen / rofecoxib / local indomethacin / systemic indomethacin exposure in the same time period; and a propensity score of the following: evidence of previous live birth, spontaneous abortion, elective termination, infertility treatment, and/or maternal diabetes in the*

last 4 years, evidence of more than one foetus in the current pregnancy; calendar effect (year and month). In Amendment 2 analyses, the propensity score will also include the socioeconomic status of the maternal residence at micro-region level, and urban/rural status, beyond the previously included variables.

Secondary objectives of the study include:

- to evaluate other gynecology anti-infectives (clotrimazole, miconazole, nystatin, metronidazole) as risk factors of teratogenicity for comparative assessment, in the same setting;
- to evaluate other gynecology anti-infectives (clotrimazole, miconazole, nystatin, metronidazole) as risk factors of spontaneous abortion for comparative assessment, in the same setting;
- to evaluate active control drugs in both analyses to assess the sensitivity of the study;
- to collect epidemiologic data on main outcomes of butoconazole exposed pregnancies (in compliance with the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005);
- to evaluate the role of butoconazole and clotrimazole in the risk of low birthweight (<2500g).

Study results are intended to be generalised to the European population.

9. Research methods

9.1. Study design

This study collects human epidemiologic data on main outcomes of butoconazole exposed pregnancies, in compliance with the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP, 2005).

A retrospective analysis is planned, to avoid the time-consuming process of building a pregnancy registry prospectively.

The study includes two case-control analyses for teratogenicity risk and spontaneous abortions, and a low birthweight study with pseudo-random butoconazole and clotrimazole exposure, all with a range of pre-defined confounder factors and sensitivity analyses. For a brief overview, please see the Table below. For more details, please see the indicated Sections of the protocol.

cases	**controls**	**database**	**drug exposure**	**Protocol section**
spontaneous abortions	live births *(live births + stillbirths)*	OEP, 2005-2011.	120 days before index date *(60 or 30 days before index date)* [Index date in cases: date of spontaneous abortion. Index date in controls: 180 days before live birth.]	9.7.2.; Annex 3.3.
foetal defects and congenital anomalies	live births without congenital anomaly *(live births and stillbirths without congenital anomaly)*	OEP, 2005-2011.	1st month, 2nd month, 3rd month, 2nd+3rd month, first trimester, after first trimester *(Day 1 of pregnancy: +2 weeks or -2 weeks)*	9.7.10.; Annex 3.4.

(Italics: sensitivity analyses)

population	**database**	**drug exposure**	**Protocol section**
live births unexposed to butoconazole or clotrimazole; and live births exposed to butoconazole and/or clotrimazole prescribed by gynaecologists with homogenous API selection for the treatment of vulvovaginal candidiasis.	OEP, 2005-2011.	first trimester, second trimester, third trimester, during pregnancy	Annex 3.5.

Rationale to select the case-control design (instead of a retrospective cohort study) for teratogenicity risk and spontaneous abortions:
The case-control study design represent an accepted and recommended approach for the investigation of drug effects on pregnancy outcomes in the postmarketing phase (EMEA/CHMP, 2005). Pregnancy outcomes like ectopic pregnancy, spontaneous abortion, or live birth with congenital anomalies indicate the impairment of normal embryonal /fetal development at different stages and time periods. Therefore, to study a potential drug effect in the OEP database, first the pregnancy outcome and its date must be determined. This information, together with the reported date of obligatory gynecology investigation (AFP screening test) in the case of late pregnancy outcomes is necessary to categorize previous drug exposures according to the relevant time periods of pregnancy (i.e. first/second/third trimester).

Rationale for the design of low birthweight analyses in Amendment 2: shown at Annex 3.5.

The current study is a MAH-initiated, retrospective post-authorization safety study (PASS), based on the analysis of an existing database. In Hungary, the authorized body for the professional and ethical approval of MAH-initiated, national PASS studies is the National Institute for Quality- and Organizational Development in Healthcare and Medicines - National Institute of Pharmacy (GYEMSZI-OGYI). The study protocol has been registered in the EU PAS register before the start of data collection, and the study results will also be submitted once the final study report has been finalised.

9.2. Setting

Persons and place:
All pregnancies and births in Hungary reported to the National Healthcare Fund (OEP) in the investigated time period (see below).

Time period:
All pregnancy outcomes reported to the National Healthcare Fund (OEP) between 01 January 2005 and 31 December 2011 (inclusive). Rationale: Butoconazole became available in Hungary in 2004, and a 1-year follow-up is planned after all pregnancy outcomes (to collect the diagnoses and late reports of congenital anomalies until the age of 1 year). In addition, selected confounding factors will also be evaluated in the last 4 years before all pregnancy outcomes, i.e. from 01 January 2001 the earliest. Rationale: OEP data quality and structure significantly changed over time, not supporting the use of OEP records for the intended purpose in years before 2001.

Selection criteria:
All pregnancy outcome categories (as defined by the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP, 2005)) are included in the study.

Exclusion criteria:
Cases exposed to other drugs / other risk factors are not excluded from the study. Instead, a range of confounding factors is included in the statistical analyses (see Section 9.7). Live births where

the mother's and the child's TAJ number could not be paired to each other in the database will be excluded from the study.

9.3. Variables

Pregnancy outcomes

According to the relevant guideline (EMEA/CHMP, 2005), pregnancy outcomes to be evaluated in the postmarketing phase include the following eight categories:

- ectopic pregnancy
- spontaneous abortion
- elective termination (foetal defects)
- elective termination (no foetal defects or unknown)
- stillbirth with foetal defects
- stillbirth without foetal defects
- live birth with congenital anomaly
- live birth without congenital anomaly

For the technical definitions of these outcomes in the OEP database, please see Annex 3.1. It is expected that the provided definitions cover the vast majority of pregnancies in the relevant time period (an exception is mola hydatiosa which is not investigated in this study, in line with the CHMP guideline (EMEA/CHMP, 2005).

Birth weight data in the OEP database will also be analysed. For more details, please see Section 9.7.11.

Time periods of the pregnancy

According to the relevant guideline (EMEA/CHMP, 2005), all studies should try to address drug exposure in specified time periods of the pregnancy:

- Before conception
- First trimester
- After first trimester
- During all pregnancy
- Unknown

Depending on the pregnancy outcome, different time periods are of particular concern. The analysis of spontaneous abortion in the current study follows the design of a published large-scale study (Rosa 1987), with a drug exposure period of 120 days before index date (where index date is the date of spontaneous abortion in *cases*, and a corresponding date with a similar gestational age in *controls* – for details, please see Section 9.7.2). For the analysis of teratogenic effects, separate analyses for the 1st month, 2nd month, 3rd month, 2nd + 3rd month are also included.

Risk of low birthweight will be evaluated for first trimester, second trimester, third trimester, and during pregnancy drug exposures. For more details and justifications, please see Section 9.7 and Annex 3.2.

Investigated drugs

- butoconazole (test drug)
- clotrimazole, miconazole, nystatin, metronidazole (therapeutic controls)
- diclofenac, naproxen, celecoxib, ibuprofen, rofecoxib, indomethacin (confounding factors and active controls in the spontaneous abortion case-control study);
- isotretinoin, carbamazepine, lithium, valproic acid (confounding factors and active controls in the teratogenicity case-control study).

Note that the current analysis of the OEP database is technically limited to medicinal products with available patient-level records (i.e. non-prescription drugs are not analysed). For the discussion of this limitation, please see Section 9.9.

Two of the therapeutic control drugs (metronidazole, nystatin) are available both in locally administered and systemic formulations (e.g. as oral tablet or as i.v. infusion). In this study, local and systemic formulations will be analysed separately.

Some of the active control drugs are also available both in locally administered and systemic formulations (diclofenac, naproxen, ibuprofen, indomethacin, isotretinoin), which will also be analysed separately.

According to the Original Protocol and Protocol Amendment 1, drug exposure is analysed as a binary parameter (yes/no) based on the evidence of at least one prescription refill in the OEP database in the relevant time periods. The analyses of Protocol Amendment 2 consider drug exposure as a quantitative parameter (prescription refills calculated in DOTs, i.e. days of therapy as declared for all medicinal products in Hungary in the PUPHA list by the OEP). For details, please see Sections 9.7.2., 9.7.10., and Annex 3.5.

Investigated confounding factors

According to a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome (Kallen, 2012), several confounding factors shall also be considered when the effect of maternal drug use on pregnancy outcome is investigated. Confounding factors are partly different for all pregnancy outcomes (e.g. spontaneous abortion, teratogenic effect, ectopic pregnancy). To lower the number of independent variables in the statistical models, most confounding factors will not be analysed separately but will be integrated into appropriate propensity scores. For more details, please see Section 9.7.

9.4. Data sources

Several high-quality nested case-control analyses have been published previously on the potential teratogenic effects of various drugs and conditions in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA, 1980 - 1996) (Acs et al., 2009a; Acs et al., 2009b; Acs et al., 2010; Banhidy et al., 2007; Banhidy et al., 2011a; Banhidy et al., 2011b; Banhidy et al., 2011c; Czeizel et al., 2004). Drug exposure in these analyses was assessed based on prenatal maternal care logbooks, other medical records, and retrospective self-reported maternal information. Confounding factors of maternal age, employment status, birth order, fever-related influenza or common cold and acute maternal disease, in addition to some drug treatment (e.g. folic acid) were also carefully considered.

In the present study, HCCSCA 1980 – 1996 records are unfortunately not relevant due to the late appearance of butoconazole on the Hungarian market (2004). In the relevant years (2005 – 2013) the available datasets of the case-control surveillance of congenital anomalies (HCCSCA database) do not contain any case with recorded butoconazole exposure (official statement from NIHD based on current HCAR / HCCSCA data search (National_Institute_for_Health_Development, 2013a)).

Therefore, the current study is based on the National Health Insurance Fund Administration Database (OEP database). The OEP database contains individual data on the insured Hungarian population regarding their (obligatory) national health insurance funded medical service use, including outpatient prescription medicine claims (note that inpatient prescription medicine claims are hardly reported to OEP), and all inpatient and outpatients visits and investigations (except for general practitioner visits). The medical validity of a payer's database may be compromised by financial aspects whenever the reports are compiled by service providers. Nevertheless, the investigated eight pregnancy outcomes are hard endpoints which are clearly distinguishable and are reliably reported in the clinical practice, according to the expert opinion of the Principal Investigator (Nándor Ács MD PhD med habil). Regarding the validity of reports on diabetes (a confounding factor in the analyses), the reports of service use in a sufficiently long period are also considered to be a valid indicator of the disease (for technical definitions, please see Annex 3.3.2. and Annex 3.4.2.). Maternal age, another important confounding factor is considered to be reliable in the OEP database. Prescription claims in the database are also considered sufficiently valid, given that the prescriptions clearly identify the type of drug prescribed, and that patient co-payment level is significant. The question is of course the gap between a claimed prescription and a medicine taken. Another limitation is the lack of information on non-prescription drug use.

It is important to mention that the OEP database does not contain data on the date of the last menstrual period before the pregnancy outcome, therefore the gestational age in this database is determined indirectly, based on the reported date of obligatory gynecology investigations (for details, please see Annex 3.2.).

9.5. Study size

According to national statistics provided by Hungarian Central Statistical Office, the following numbers of pregnancy outcomes occurred in the relevant time period:

	2005	2006	2007	2008	2009	2010	2011	Total
Live birth	97 496	99 871	97 613	99 149	96 442	90 335	88 049	668 955
Foetal death*	17 528	17 847	17 247	17 714	17 885	16 710	17 220	122 151
Termination of pregnancy	48 689	46 324	43 870	44 089	43 181	40 449	38 443	305 045
Total pregnancy outcomes	163 713	164 042	158 730	160 952	157 508	147 494	143 712	1 096 151

**Foetal death in the Hungarian Central Statistical Office statistics include: ectopic pregnancy, spontaneous abortion, stillbirth.*

Altogether almost 1 100 000 pregnancy outcomes occurred in the evaluated time period (of these, 668 955 live births). The total number of foetal deaths was around 122 000 (including ectopic pregnancy, spontaneous abortion, and stillbirth cases). It is expected that most of these cases are included in the OEP database. Accordingly, the size of the current study is similar to a recently published population-based analysis in Denmark (1 221 546 pregnancy outcomes, (Nybo Andersen et al., 2000)) and is about one order of magnitude larger than the largest published study on other gynecology anti-infectives (104 339 pregnancies, (Rosa et al., 1987). The single published human study on butoconazole investigated 229 101 completed pregnancies and found no increased risk in women with first-trimester butoconazole exposure (Briggs, 2011).

No formal sample size calculation was performed for the current study. To maximize the power and to avoid selection bias, all pregnancies in the relevant time period are included (where the mother-children TAJ number pairs could be established in the database). The expected size of the study is considered to be adequate, i.e. similar or larger than previous published studies on adverse drug effects in pregnancy.

In the congenital anomaly case-control study, code groups to be analysed in Amendment 2 were determined based on the expected power of the planned analyses. For details, please see Annex 3.1.4. Exact statistical power calculation will be conducted and reported for all Amendment 2 congenital anomaly analyses in the study report, based on true patient numbers and exposure data.

9.6. Data management

The screening and processing of individual–level data in the OEP database will be performed directly by OEP personnel, running of PL/SQL scripts provided by RxTarget Kft. The scripts will analyse inpatient, outpatient and prescription drug usage records, linked to each other via

individual TAJ numbers of the patients. All statistical and analytical processing of the data will be done on OEP servers, including all intermediate tables and listings.

In agreement with the data protection standards of the OEP, no individual-level data but only aggregated group statistics and statistical model results will be available to non-OEP personnel. Descriptive statistics will not be provided on groups smaller than 10 patients.

Inductive statistical results will be generated using the following statistical software, installed on OEP computers:

- R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

9.7. Data analysis

The planned analyses comprise descriptive statistics of drug exposure in pregnancies with different pregnancy outcomes, analysis of birth weight in unexposed and drug-exposed pregnancies, and case-control studies on spontaneous abortion and congenital abnormalities considering a range of confounding factors and sensitivity analyses. Logistic regression models on low birthweight has been added in Protocol Amendment 2, with a quasi-randomized study design. A schematic flowchart of these analyses is presented below, while a detailed description is provided in Sections 9.7.1. – 9.7.11 and in Annexes 3.1. – 3.5.

Additional analyses introduced with Protocol Amendment 1

Protocol Amendment 1 introduced additional measures to identify as many pregnancies as possible in the OEP database, and also supplemented the definitions of pregnancy outcomes with relevant BNO/OENO codes which were missing from the original study protocol. For this reason, according to Amendment 1, all descriptive statistics and statistical analyses described in the protocol (including the pre-specified sensitivity analyses) were planned to be conducted in two ways:

- Analyses according to Amendment 1 (main analysis);
- Analyses according to the original / unamended protocol.

Experience accumulating from ongoing data collection and analysis revealed that the original study protocol failed to identify most mother – offspring pairs. The original protocol could not match the transient and permanent social security numbers of the investigated children, resulting in the loss of medical follow-up of about 440 000 live births. Moreover, the exact hierarchy of rules for redundant and conflicting pregnancy outcome codes has not been defined in the original protocol, making pregnancy outcomes ambiguous in cases with multiple outcome records. Accordingly, the study will not be analysed as planned in the original protocol. Instead, all

descriptive statistics and statistical analyses (including the sensitivity analyses) will be conducted in two ways:

- **Analyses according to Amendment 2 (main analysis);**
- **Analyses according to Amendment 1 (ancillary analysis).**

In addition to the extension of the study population and clarification of outcome definitions, Protocol Amendment 1 introduced the following major changes into the analysis:

- Inclusion of active control drugs into the regression analyses of spontaneous abortion and teratogenicity risk;
- Removal of a confounding factor ("evidence for acute infection / inflammatory disease during the first trimester of pregnancy") from the regression models due to insufficient data in the OEP database;
- Separate analysis of systemic and local nystatin, miconazole, and isotretinoin products;
- Specification of NSAID products invstigated in the study.

Additional analyses introduced with Protocol Amendment 2

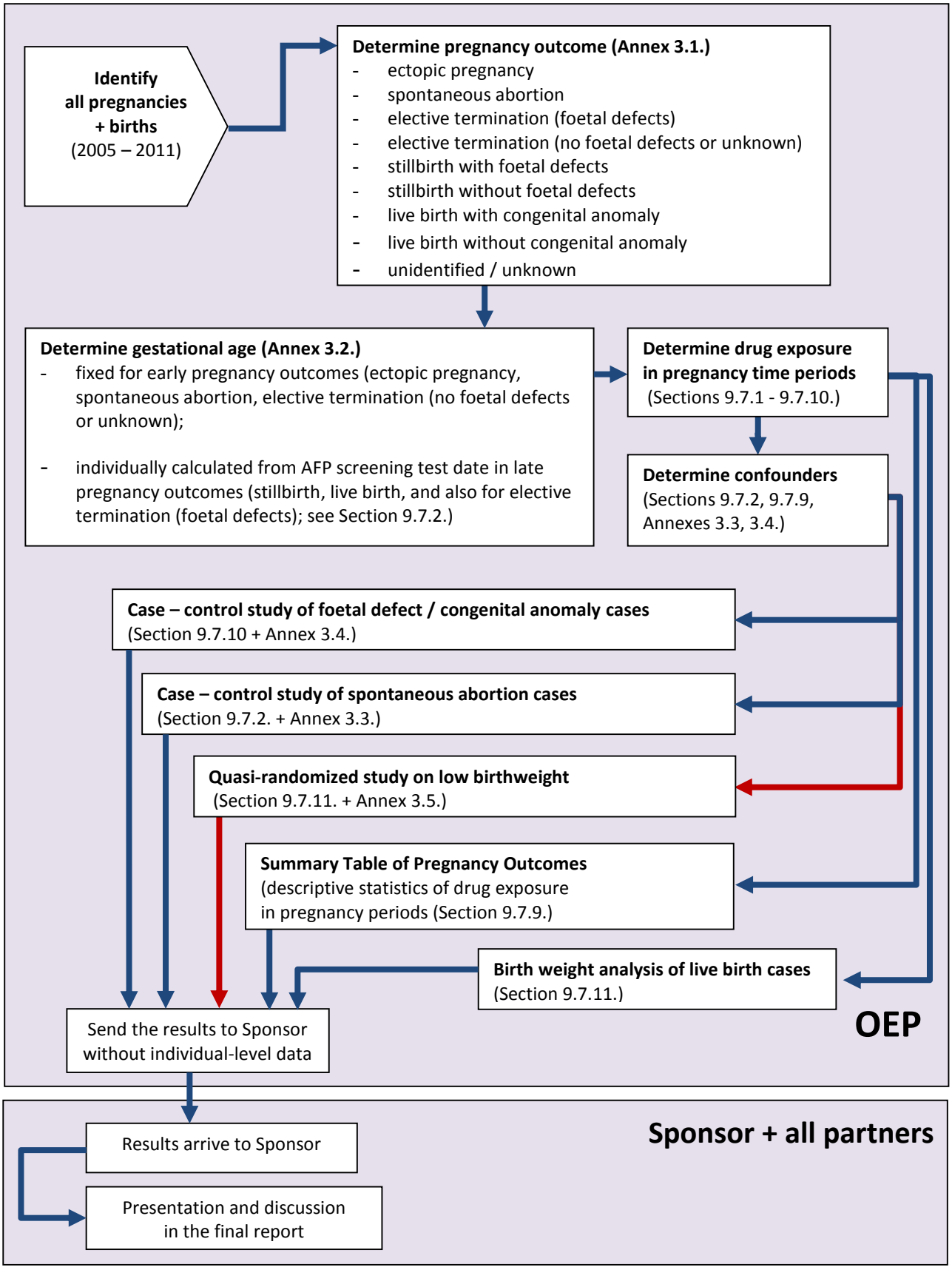
Protocol Amendment 2 was planned based on the preliminary findings of Amendment 1 data analysis. These preliminary findings revealed the following issues, needing the adaptation of the research plan:

1. The rate of live births with congenital anomalies was found to be unexpectedly high, both in the drug-exposed and in the unexposed pregnancies. According to the applied criteria, about 35 – 40% of the evaluated births were classified as congenital anomaly cases (irrespective of drug exposure). This rate is about ten times higher than the previously published 3-5% malformation rates in Hungary (Acs et al., 2010; National_Institute_for_Health_Development, 2013b). The observed difference could be explained by the over-inclusive definitions applied in this study. Please see Annex 3.4.3 for the relevant Amendment 2 changes, with details and justifications of the new criteria of congenital anomaly definitions.

2. The analysis of spontaneous abortions did not find an increased risk for butoconazole, and even a protective effect was found in some sensitivity analyses. However, the protective effect of clotrimazole was more pronounced, and this benefit seemed to be associated with different usage patterns (more patients with repeated administration of clotrimazole than butoconazole). In the Amendment 2 analyses we intend to quantitatively investigate the effect of drug exposure (prescription refills expressed in DOTs), instead of the binary (yes/no) exposure analyses in Protocol Amendment 1. For more details and justifications of the new analyses, please see Annex 3.3.3.

3. The descriptive analysis of low birthweight newborns showed an apparently increased risk in butoconazole exposed pregnancies, while the rate of low birthweight babies was not increased and even slightly lowered in clotrimazole exposed pregnancies. These descriptive analyses were not controlled for potential confounders. The most important potential confounders of low birthweight can not be captured in the OEP database, therefore a quasi-randomized exposure analysis is planned in Protocol Amendment 2. For details and justifications of the new analyses, please see Annex 3.5.

Schematic flowchart of the planned analyses:



9.7.1. Ectopic pregnancies

Ectopic pregnancies will be identified based on the technical definitions of pregnancy outcomes as provided in Annex 3.1.

To investigate a potential drug effect on the relative rate of ectopic pregnancies, drug exposure around the time of implantation is of particular concern. Implantation typically occurs on days 21 to 26 of pregnancy, i.e. until the 12th day after ovulation (Papp, 1999).

Ectopic pregnancy is typically diagnosed after 7 (SD 2) weeks of amenorrhoea (Tay et al., 2000) which refers to weeks 6-10 of pregnancy. The gestational age of ectopic pregnancies is hardly documented in payers' databases and registries. In a previous retrospective analysis in Denmark comprising 1 221 546 pregnancy outcomes, the gestational age of recognised ectopic pregnancies was set as 8 weeks at diagnosis in all cases (Nybo Andersen et al., 2000).

Ectopic pregnancies with a refilled prescription of the investigated drug in the potentially relevant time period, i.e. in the last 8 weeks before the reported outcome will be considered to be „drug exposed". The timing of drug exposure in drug-exposed cases will be classified as a „unknown" due to the inevitable mix of „before conception" and early „first trimester" exposures in this analysis.

The results of the analysis of ectopic pregnancies will be presented in the Summary Table of Pregnancy Outcomes as shown in Section 9.7.9, separately for all tested drugs. These results will be interpreted in the context of alternative pregnancy outcomes (i.e. relative frequency of ectopic pregnancy).

There are several known risk factors of ectopic pregnancy, including previous ectopic pregnancy, history of pelvic inflammatory disease, tubal damage from infection or surgery, a history of infertility, treatment for in vitro fertilisation, increased age, smoking. Previous female sterilisation and current use of an intrauterine contraceptive device are also risk factors when patients with ectopic pregnancy are compared with pregnant controls (Tay et al., 2000). However, no further statistical analysis is planned on this pregnancy outcome beyond the collection of frequency data on drug-exposed and unexposed ectopic pregnancies, because the available non-clinical and clinical data do not raise concerns about any association between butoconazole use and ectopic pregnancy.

9.7.2. Spontaneous abortions

The analysis of spontaneous abortions follows the methods described by Rosa et al (Rosa et al., 1987) for clotrimazole, miconazole, nystatin and other gynecology anti-infectives, i.e. comparisons to normal delivery cases, with the following modifications:

Main analysis of spontaneous abortions	
definition of cases	All spontaneous abortions in the OEP database in the tested time period (2005-2012). For the technical definition of spontaneous abortion, please see Annex 3.1.
definition of controls	Live births with at least 180-day history of the mother in the OEP database before delivery in the relevant time period. For the technical definition of live births (including live births with / without congenital anomaly), please see Annex 3.1.
index date	in cases: reported date of spontaneous abortion. in controls: reported date of live birth minus 180 days.
drug exposure criteria	Prescription claims (Rx) in the first trimester defined as a 120-day period before index date. - Amendment 2 analyses: number of prescribed doses (numeric) - Amendment 1 analyses: 0 / at least 1 prescriptions (binary)

In addition, the following sensitivity analyses are planned, to test the robustness of the results:

Sensitivity analyses of spontaneous abortions	
analysis ID	**Alterations from the main analysis**
Spontab_sensitivity_1	drug exposure period narrowed to 60 days before index date
Spontab_sensitivity_2	drug exposure period narrowed to 30 days before index date
Spontab_sensitivity_3	controls include all live births and stillbirths
Spontab_sensitivity_4	index date for controls: reported date of delivery minus 200 days; in addition, cases and controls must have at least one OEP-reimbursed service 70-250 days before index date. (Replication of the published sensitivity analysis of the Rosa study).
Spontab_sensitivity_5	cases and controls restricted to pregnancies with reported AFP screening test. Drug exposure criteria: prescription claim (Rx) in the last 16 weeks before reported date of AFP screening test.
Spontab_sensitivity_6	cases also include pregnancies without identified pregnancy outcome (see Section 9.7.9.). In cases without identified pregnancy outcome, index date is defined as the date of the last pregnancy-related condition/intervention* plus 30 days.

**Pregnancy-related conditions/interventions are listed in Annex 3.2. at the criteria of „late AFP reporting" pregnancies.*

The main analysis and the sensitivity analyses will include the following test variables:

- Exposure to gynecology anti-infectives within the drug exposure period
  - butoconazole (yes/no)
  - miconazole (local) (yes/no)
  - miconazole (systemic) (yes/no)
  - clotrimazole (yes/no)
  - metronidazole (local) (yes/no)
  - metronidazole (systemic) (yes/no)
  - nystatin (local) (yes/no)
  - nystatin (systemic) (yes/no)

- Maternal age at index date (in 5-year intervals, as a nominal parameter).

- Exposure to non-aspirin NSAIDs within the drug exposure period
    - diclofenac (local) (yes/no)
    - diclofenac (systemic) (yes/no)
    - naproxen (local) (yes/no)
    - naproxen (systemic) (yes/no)
    - celecoxib (yes/no)
    - ibuprofen (local) (yes/no)
    - ibuprofen (systemic) (yes/no)
    - rofecoxib (yes/no)
    - indomethacin (local) (yes/no)
    - indomethacin (systemic) (yes/no)

*List of all relevant NSAID product ATC codes is provided in Annex 3.3.2.

The analyses will also take efforts to consider other confounding variables, integrated into an appropriate „propensity score". For details and justifications, please see Annex 3.3. Note that some potential confounding factors (including age at menarche, gestational age, maternal education, maternal marital status, alcohol use, smoking, caffeine use, illicit drug use, body mass index, social class) will not be included in the models because of the lack of adequate data in the OEP database. However, it is not expected that these factors are associated with both the pregnancy outcome and drug exposure (Clark et al., 2011). For justifications of the planned analysis, please see Annex 3.3.

The indication treated may also be a confounding factor. It is medically plausible that vaginal fungal infections represent an independent risk factor for spontaneous abortion themselves, and/or may occur more frequently in women carrying other risk factors for spontaneous abortion (e.g. malnutrition, systemic antibiotic drug treatment, or promiscuity). The included therapeutic controls clotrimazole, miconazole, or nystatin are especially important in this respect: any elevation of the risk of spontaneous abortions in butoconazole exposed pregnancies will be interpreted in the context of the same risk in pregnancies exposed to therapeutic controls. Note that in a previous clinical study, increased risk of spontaneous abortion was reported for clotrimazole (OR 1.34, 95% CI 1.1 – 1.7) and miconazole (OR 1.36, 95% CI 1.1 – 1.6), and this apparently elevated risk could be drug-related or indication related.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model will be applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome (Kallen, 2012). The logistic regression model is a regression method to predict outcome (e.g. rate of congenital malformations) as influenced by one or more confounding factors. Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for example, presence or absence of a malformation (Kallen, 2012).

For all analyses, odds ratios with 95% confidence intervals will be calculated (both as crude and adjusted values) as shown below.

Variable	Controls N=	Cases N=	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	N (%)	N (%)	1.00	1.00	1.00
butoconazole	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Type of non-aspirin NSAIDs					
none	N (%)	N (%)	1.00	1.00	1.00
diclofenac (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
diclofenac (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
naproxen (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
naproxen (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
celecoxib	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ibuprofen (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ibuprofen (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
rofecoxib	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
indomethacin (local)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
indomethacin (systemic)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal age at index date					
15-19	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
20-24	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
25-29	N (%)	N (%)	1.00	1.00	1.00
30-34	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
35-39	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
40-45	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

*Crude OR: univariate analyses; Adjusted (1): adjusted for all test factors and confounders which are presented in the table; Adjusted(2): in addition, also adjusted for all other investigated confounder factors (the latter have been integrated into a single propensity score before adjustment).

Separate tables will be presented for the main analysis and for all sensitivity analyses, as specified by Protocol Amendment 1 and Protocol Amendment 2.

In addition, the number of spontaneous abortions from the main analysis will be included in the Summary Table of Pregnancy Outcome, separately for all tested drugs. The timing of drug exposure in drug-exposed cases will be classified as „unknown", due to the inevitable mix of first trimester, second trimester and „before conception" exposures in this analysis (for more details on the Summary Table, please see Section 9.7.9).

Additional analyses of spontaneous abortion risk have been introduced by Protocol Amendment 2. For details, please see Annex 3.3.3.

9.7.3. Elective termination (no foetal defects or unknown)

Cases with elective termination (no foetal defects or unknown) will be identified in the OEP database according to the technical definitions described in Annex 3.1.

Similarly to the Rosa study (Rosa et al., 1987), those elective terminations with a refilled prescription of the investigated drug in the last 120 days before the reported outcome will be considered to be „drug exposed". The timing of drug exposure in drug-exposed cases will be classified as „unknown" due to the inevitable mix of first trimester, second trimester and „before conception" exposures in this analysis.

The number of elective terminations (no foetal defects or unknown) will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. For more details, please see Section 9.7.9.

Beyond the collection of frequency data on drug-exposed and unexposed elective terminations, no further statistical analysis is planned on this pregnancy outcome.

9.7.4. Elective termination (foetal defects)

Cases with „elective termination (foetal defects)" will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before elective termination due to foetal defects, the first day of pregnancy will be determined as follows:

analysis ID	First day of pregnancy
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, in line with Annex 3.2.

In cases without a reported AFP test in the last 26 weeks before outcome, the gestational age at elective termination due to foetal defects will be assumed to be 14 weeks in the main analysis, and also in sensitivity analyses 1-3 and 5. For justifications, please see Annex 3.2. In an additional

sensitivity analysis (CA_sensitivity_4), cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis.

The number of elective terminations due to foetal defects in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Elective terminations due to foetal defects (together with stillbirths with foetal defects, and with live births with congenital anomalies) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies. The details of this analysis is described in Section 9.7.10.

9.7.5. Stillbirth with foetal defects

Cases of stillbirth with foetal defects will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before stillbirth, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before stillbirth will be assumed to have the average gestational age of "stillbirth with foetal defects" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of stillbirths with foetal defects in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Stillbirths with foetal defects (together with elective terminations due to foetal defects, and with live births with congenital anomalies) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies. The details of this analysis are described in Section 9.7.10.

9.7.6. Stillbirth without foetal defects

Cases of stillbirth without foetal defects will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before stillbirth, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before stillbirth will be assumed to have the average gestational age of "stillbirth without foetal defects" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of stillbirths without foetal defects in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Stillbirths without foetal defects (together with live births without congenital anomalies) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies, as part of the control group in a sensitivity analysis. The details of this analysis are described in Section 9.7.10.

9.7.7. Live birth with congenital anomaly

Cases of live birth with congenital anomaly will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before the outcome, the first day of pregnancy will be determined as follows:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus 135 days
CA_sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Section 9.7.2. and Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before live birth will be assumed to have the average gestational age of "live birth with congenital anomaly" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for

CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of live births with congenital anomaly in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Live births with congenital anomaly (together with elective terminations due to foetal defects, and with stillbirths with foetal defects) will also be included in a multivariate analysis of the risk of drug induced congenital anomalies. The details of this analysis are described in Section 9.7.10.

9.7.8. Live birth without congenital anomaly

Cases of live birth without congenital anomaly will be identified in the OEP database according to the technical definitions described in Annex 3.1.

In cases with a reported AFP test in the last 26 weeks before the outcome, the first day of pregnancy will be determined as follows:

analysis ID	First day of pregnancy
main analysis	{AFP reported date} minus 121 days
sensitivity_1	{AFP reported date} minus 135 days
sensitivity_2	{AFP reported date} minus 107 days

In pregnancies with late AFP reports alternative Day 1 estimates may be allowed, as specified in Annex 3.2.

Cases without a reported AFP test in the last 26 weeks before live birth will be assumed to have the average gestational age of "live birth without congenital anomaly" cases with reported AFP screening test in the relevant period in the main analysis and in sensitivity analyses, except for CA_sensitivity_4 where cases and controls without a reported AFP test in the last 26 weeks of pregnancy will be excluded from the analysis. For justifications, please see Annex 3.2.

The number of live births without congenital anomaly in the main analysis will be included in the Summary Table of Pregnancy Outcomes, separately for all tested drugs. Drug exposure periods will be analysed based on the calculated first day of pregnancy. For more details, please see Section 9.7.9.

Live births without congenital anomaly will be included in a multivariate analysis of the risk of drug induced congenital anomalies as the control group. The details of this analysis are described in Section 9.7.10.

In addition, Amendment 2 of the protocol introduces descriptive statistics (mean and SD) on pregnancy duration in live birth controls without congenital anomaly in the main analysis and in the sensitivity analyses. The intention of this protocol supplement is to check the credibility of the calculated pregnancy periods.

9.7.9. Summary Table of Pregnancy Outcomes

The layout of the Summary Table of Pregnancy Outcomes as defined by the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP, 2005) is applied in this study, with the following modification: the number of not exposed cases is also included, to illustrate the distribution of outcomes in the unexposed population.

Separate tables will be provided for all of the investigated drugs / drug groups (butoconazole, clotrimazole, miconazole, nystatin, metronidazole; diclofenac, naproxen, celecoxib, ibuprofen, rofecoxib, indomethacin, ; carbamazepine, isotretinoin, lithium, valproic acid).

In these tables, the eight investigated pregnancy outcomes will be included according to the specifications provided in Sections 9.7.1 – 9.7.8. In brief: data from sensitivity analyses will be omitted; and drug exposure period will be specified as „unknown" for cases of ectopic pregnancy, spontaneous abortion and elective termination (no foetal defects or unknown). The Summary Table of Pregnancy Outcomes table will be filled both according to Protocol Amendment 1 and Protocol Amendment 2 definitions.

Exposure is defined as a prescription refilled in the indicated time period. Time periods in the table refer to the following gestational periods:

Time period	**Gestational days**
Before conception	last 30 days before day 1 of pregnancy
First trimester	days 1 – 84
After first trimester	after day 84
During all pregnancy	both in days 1-84 and after day 84
Unknown	any exposure in pregnancy (i.e. the time period ranging from minus 30 days before pregnancy to the date of pregnancy outcome) which can not be clearly sorted to any of the above categories.
No exposure	no exposure in the time period ranging from minus 30 days before pregnancy to the date of pregnancy outcome

The layout of the Summary Table is shown below:

Pregnancy outcome	retrospective cases (number)							
	timing of **{drug name}** exposure in pregnancy (as per Protocol Amendment {1 or 2})							
	Before conception	**1st trimester**	**after 1st trimester**	**during all pregnancy**	**unknown**	**all exposed cases**	**not exposed cases**	**all cases**
Ectopic pregnancy					{exposed No.}	{exposed No.}	{not exposed No.}	{total}

Spontaneous abortion					{exposed No.}	{exposed No.}	{not exposed No.}	{total}
Elective termination (no foetal defects or unknown)					{exposed No.}	{exposed No.}	{not exposed No.}	{total}
Elective termination (foetal defects)	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{exposed No.}	{not exposed No.}	{total}
Stillbirth with foetal defects	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{exposed No.}	{not exposed No.}	{total}
Stillbirth without foetal defects	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{exposed No.}	{not exposed No.}	{total}
Live birth with congenital anomaly	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{exposed No.}	{not exposed No.}	{total}
Live birth without congenital anomaly	{exposed No.}	{exposed No.}	{exposed No.}	{exposed No.}		{exposed No.}	{not exposed No.}	{total}
Unidentified / unknown outcome					{exposed No.}	{exposed No.}	{not exposed No.}	{total}

{exposed No.}: Number of cases belonging to the indicated time period
{not exposed No.}: Number of cases not exposed in any of the indicated time periods.

Unidentified / unknown outcome: there are several reasons which can lead to the lack of identified pregnancy outcome in the OEP database, including e.g. the use of private healthcare services in Hungary, the use of healthcare services in other country, or missed reporting of an occurred pregnancy outcome (e.g. a non-documented early spontaneous abortion). Among these, spontaneous abortion is the medically most important situation. Therefore, all cases without identified outcome will be assumed to be spontaneous abortions in a sensitivity analysis of the spontaneous abortion case-control analysis (see Section 9.7.2.).

In „unidentified / unknown outcome" cases, the timing of drug exposure will be categorized as „unknown" if there is a relevant prescription claim (Rx) in the last 90 days *before* and/or in the first 30 days *after* the date of the last report indicating an ongoing pregnancy. Without prescription claim in the indicated period, the timing of drug exposure will be categorized as „none".

Relative frequencies (%) of the eight investigated pregnancy outcomes will also be calculated and plotted vs. other drugs/drug groups:

- in the first trimester
- after first trimester
- during all pregnancy

- any time during pregnancy*

*: any time during pregnancy: sum of cases exposed before conception, in the first trimester, after the first trimester, during all pregnancy, and unknown.

9.7.10. Multivariate analysis of drug induced risk of congenital anomalies

The intention of the study is to evaluate the total (neonatal + foetal) risk of congenital anomalies in the offspring of mothers who were exposed to the tested drugs. All pregnancy outcomes in these analyses will be identified based on the technical definitions of pregnancy outcomes as provided in Annex 3.1. The following analyses are planned as per Protocol Amendment 1:

<table>
<tr><th colspan="2">Planned analyses of spontaneous abortions (Protocol Amendment 1)</th></tr>
<tr><th colspan="2">Main analysis</th></tr>
<tr><td colspan="2">Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly.
Controls = Live birth without congenital anomaly
Day 1 of pregnancy = {AFP reported date} minus 121 days; in pregnancies with late AFP reports an alternative Day 1 estimate will be applied (as specified in Annex 3.2.).</td></tr>
<tr><th colspan="2">Alterations from the main analysis in sensitivity analyses</th></tr>
<tr><td>CA_sensitivity_1*</td><td>Day 1 of pregnancy = {AFP reported date} minus 135 days</td></tr>
<tr><td>CA_sensitivity_2*</td><td>Day 1 of pregnancy = {AFP reported date} minus 107 days</td></tr>
<tr><td>CA_sensitivity_3*</td><td>Controls = live births without congenital anomaly, stillbirths without foetal defect</td></tr>
<tr><td>CA_sensitivity_4*</td><td>Cases and controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from the analysis</td></tr>
<tr><td>CA_sensitivity_5*</td><td>Cases = Stillbirth with foetal defects, Live birth with congenital anomaly.</td></tr>
<tr><td>CA_sensitivity_6*</td><td>Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring:

BNO Q35 cleft palate
BNO Q36 cleft lip
BNO Q37 cleft lip, cleft palate
OENO 52750 Lágyszájpadplasztika
OENO 52751 Keményszájpadplasztika
OENO 52752 Kemény- és lágyszájpadplasztika, egy ülésben
OENO 52753 Szájpadrekonstrukció, előzetes műtét után
OENO 58981 Oldalsó inkomplett ajakhasadék zárása
OENO 58982 Ajak és külső száj plastica, Le Mesurier szerint
OENO 58983 Ajak és külső száj plastica, Millard szerint
OENO 58984 Ferde archasadék (macrostoma) korrekciója
OENO 58985 Ajak- és külső szájplasztika
OENO 58986 Ajakkorrekció ajakplasztika után
OENO 58987 Median ajakhasadék zárása</td></tr>
</table>

CA_sensitivity_7*	Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring: BNO Q7920 exomphalos BNO Q7930 gastroschisis BNO Q7940 prune belly syndrome BNO Q7950 other congenital anomalies of the abdominal wall OENO 55340 Hernioplastica umbilicalis OENO 55350 Reconstructio parietis abdominis OENO 55358 Gastroschisis műtéte OENO 55359 Omphalocele műtéte OENO 55360 Reconstructio parietis abdominis c. implant. OENO 55361 Reconstructio laparoscopica parietis abdominis cum implantate OENO 55369 Reconstructio laparoscopica parietis abdominis cum conversione
CA_sensitivity_8*	Cases = Live birth in 2005, with foetal defect / congenital anomaly reported until the end of 2012; Controls = Live birth in 2005, foetal defect / congenital anomaly not reported until the end of 2012.
CA_sensitivity_9	Cases and controls fulfilling the criteria of „late AFP reporting" (see in Annex 3.2.) are excluded.

** In pregnancies with late AFP reports an alternative Day 1 estimate will be applied, as specified in Annex 3.2.*

Rationale for these sensitivity analyses is provided in Annex 3.4.

Drug exposure in the following periods will be evaluated: first trimester (Nelson and Forfar, 1971; van Gelder et al., 2011), first month (before organogenesis) (Acs et al., 2009a; van Gelder et al., 2011), second month(Czeizel et al., 1999; van Gelder et al., 2011), third month(Czeizel et al., 1999; van Gelder et al., 2011), second and third month (the critical period for congenital anomalies) (Acs et al., 2009b; Banhidy et al., 2007; Czeizel et al., 1999; Kazy et al., 2005), and after the first trimester (Acs et al., 2009b; Kazy et al., 2005).

The main analysis and the sensitivity analyses will include the following test variables:

- Exposure to gynecology anti-infectives in the relevant time periods
  - butoconazole (yes/no)
  - miconazole (local) (yes/no)
  - miconazole (systemic) (yes/no)
  - clotrimazole (yes/no)
  - metronidazole (local) (yes/no)
  - metronidazole (systemic) (yes/no)
  - nystatin (local) (yes/no)
  - nystatin (systemic) (yes/no)

- Exposure to active control drugs in the relevant time periods
  - carbamazepine

- isotretinoin (local)
- isotretinoin (systemic)
- lithium
- valproic acid

- Maternal age at delivery (in 5-year intervals, as a nominal parameter).

The analyses will also consider the following confounding variables, integrated into a single „propensity score":

- Evidence of previous live birth in the last 4 years before the current pregnancy;
- Evidence of previous spontaneous abortion in the last 4 years before the current pregnancy;
- Evidence of maternal diabetes in the last 4 years before or during pregnancy;
- Year of birth;
- Month of birth.

The technical definitions of these confounders are provided in Annex 3.4.

In addition, descriptive statistics will be provided on all counties of Hungary (divided to „village" and „town"), with absolute and relative frequencies of cases and controls in each of these areas.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model will be applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome (Kallen, 2012). The logistic regression model is a regression method to predict outcome (e.g. rate of congenital malformations) as influenced by one or more confounding factors. Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for example, presence or absence of a malformation (Kallen, 2012).

For scientific rationale, justifications, and technical definitions of the planned analyses, please see Annex 3.4.

For all analyses, odds ratio (OR) with 95% confidence intervals will be calculated (both as crude and adjusted values) as shown below. Separate tables will be presented for the main analysis and for all sensitivity analyses.

Variable	Controls N=	Cases N=	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of drugs					
none	N (%)	N (%)	1.00	1.00	1.00
Butoconazole (local administration)					
butoconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

butoconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Miconazole (local administration)					
miconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Miconazole (systemic administration					
miconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Clotrimazole (local administration)					
clotrimazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nystatin (local administration)					
nystatin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nystatin (systemic administration)					
nystatin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (local administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (systemic administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Carbamazepine (systemic administration)					
carbamazepine in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Isotretinoin (local administration)					
isotretinoin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Isotretinoin (systemic administration)					
isotretinoin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lithium (systemic administration)					
lithium in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

Valproic acid (systemic administration)					
valproic acid in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal age at index date					
15-19 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
20-24 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
25-29 years	N (%)	N (%)	1.00	1.00	1.00
30-34 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
35-39 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
40-45 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

(1) adjusted for other drug exposure (as listed in the table) in the same pregnancy period, and for maternal age
(2) in addition, also adjusted for all other investigated confounder factors (the latter have been integrated into a single propensity score before adjustment).

In addition, the time profile of reporting congenital anomalies after birth will also be investigated. All live births reported in the first year of the study (2005) will be followed-up throughout the investigational time period (up to the end of 2012). Late reports of foetal defects / congenital anomalies (see the BNO / OENO codes as specified in Annex 3.1.) will be analysed and summarized as shown below. For Amendment 2 analysis of timing of reporting, only those BNO and OENO codes belonging to at least one of the 34 alternative congenital anomaly groups will be considered.

Time periods	**No. of children with report in this time period or before**	**No. of children with first report in this time period**	**Relevant BNO / OENO codes in children with first report in this time period (list of codes)**
	total number of live births in 2005: N =		
During pregnancy or at pregnancy outcome	(Number)	(Number)	n.a.
1-365 days after pregnancy outcome	(Number)	(Number)	n.a.
In the 2nd year after pregnancy outcome	(Number)	(Number)	{BNO1 BNO2... OENO1 OENO2...}
In the 3rd year after pregnancy outcome	(Number)	(Number)	{BNO1 BNO2... OENO1 OENO2...}
In the 4th year after pregnancy outcome	(Number)	(Number)	{BNO1 BNO2... OENO1 OENO2...}
In the 5th year after pregnancy outcome	(Number)	(Number)	{BNO1 BNO2... OENO1 OENO2...}
In the 6th year after pregnancy outcome	(Number)	(Number)	{BNO1 BNO2... OENO1 OENO2...}

In the 7th year after pregnancy outcome	(Number)	(Number)	{BNO1 BNO2... OENO1 OENO2...}

It is expected that the vast majority of congenital anomalies are reported during pregnancy or in the first year after birth. Nevertheless, a sensitivity analysis (CA_sensitivity_8) is planned to include the late diagnoses / late reports of congenital anomalies (See at Section 9.7.10.).

Additional analyses of teratogenicity risk have been introduced by Protocol Amendment 2. For details, please see Annex 3.4.3.

9.7.11. Analysis of birth weight

There are separate HBCS codes for birth weight categories as follows:

HBCS	Description
15 7110	Újszülött, születési súly 999 g alatt
15 7120	Újszülött, születési súly 1000-1499 g, jelentős műtéttel
15 7130	Újszülött, születési súly 1000-1499 g, jelentős műtét nélkül
15 7140	Újszülött, születési súly 1500-1999 g, jelentős műtéttel
15 715Z	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, súlyos problémával
15 7160	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, közepes problémával
15 7170	Újszülött, születési súly 1500-1999 g, jelentős. műtét nélkül, egyéb problémával.
15 7180	Újszülött, születési súly 2000-2499 g, jelentős műtéttel
15 719Z	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, súlyos problémával
15 7200	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, közepes problémával
15 7210	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, normális újszülött diagnózissal
15 7220	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, egyéb problémával
15 7230	Újszülött, születési súly 2499 g felett, jelentős műtéttel
15 7240	Újszülött, születési súly 2499 g felett, kisebb hasi műtéttel
15 7260	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, közepes problémával
15 7270	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, normális újszülött diagnózissal
15 7280	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, egyéb problémával
15 734Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napot nem meghaladó gépi lélegeztetéssel
15 735Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napnál hosszabb gépi lélegeztetéssel

Note that clotrimazole was shown to have a preventive effect against preterm birth and low birth weight (below 2500g) when administered in the first trimester (Czeizel et al., 2007). Accordingly, this study investigates all gynecology anti-infectives in this respect. The absolute and relative proportions of low birth-weight cases in drug-exposed and unexposed pregnancies will be presented in contingency tables, with pre-planned statistical comparisons (Chi-square test or Fisher's exact test).

Drug = butoconazole		**Low birth weight (<2500g)**		
		Yes*	No**	Total
Drug exposure in the first trimester	Yes	N (%)	N (%)	N (%)
	No	N (%)	N (%)	N (%)
	Total	N (%)	N (%)	N (%)

*HBCS codes 15 7110, 15 7120, 15 7130, 15 7140, 15 715Z, 15 7160, 15 7171, 15 7180, 15 719Z, 15 7200, 15 7210, 15 7220;
**HBCS codes 15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 734Z, 15 735Z

Similar tables will be provided for clotrimazole, miconazole (local), miconazole (systemic), metronidazole (local), metronidazole (systemic), nystatin (local), and nystatin (systemic).

In addition, more detailed descriptive statistics will be provided for all gynecology anti-infectives as shown below:

		Birth weight					
		<1000g	**1000 – 1499g**	**1500 – 1999g**	**2000-2499g**	**>2500g**	**total**
Relevant HBCS codes →		15 7110	15 7120, 15 7130	15 7140, 15 715Z, 15 7160, 15 7170	15 7180, 15 719Z, 15 7200, 15 7210, 15 7220	15 7230, 15 7240, 15 7260, 15 7270, 15 7280, 15 734Z, 15 735Z	
Drug exposure in first trimester	**none**	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	butoconazole	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	clotrimazole	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	miconazole (local)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	miconazole (systemic)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	metronidazole (local)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	metronidazole (systemic)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	nystatin (local)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	nystatin (systemic)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Moreover, all available individual birth weight data reported to the OEP database will be evaluated, as shown below:

		Individual birth weight data in the OEP database			
		Not reported	Reported	Mean	95% CI
Drug exposure in first trimester	none	N (%)	N (%)	... g	... - ... g
	butoconazole	N (%)	N (%)	... g	... - ... g
	clotrimazole	N (%)	N (%)	... g	... - ... g
	miconazole (local)	N (%)	N (%)	... g	... - ... g
	miconazole (systemic)	N (%)	N (%)	... g	... - ... g
	metronidazole (local)	N (%)	N (%)	... g	... - ... g
	metronidazole (systemic)	N (%)	N (%)	... g	... - ... g
	nystatin (local)	N (%)	N (%)	... g	... - ... g
	nystatin (systemic)	N (%)	N (%)	... g	... - ... g
	total	N (%)	N (%)	... g	... - ... g

Additional analyses of low birthweight have been introduced by Protocol Amendment 2. For details, please see Annex 3.5.

9.8. Quality control

The study protocol and all amendments will be submitted to the competent National Authority (GYEMSZI) for review and approval. Ethical review is included in the GYEMSZI approval process according to the Hungarian law. The study will be registered in the EU PAS register before the start of data collection. Any protocol amendments will also be submitted for GYEMSZI approval and will also be registered at EU PAS.

Quality control of data management will be ensured by the qualified personnel and the regulated workflows at OEP. All output tables received from OEP will be included in the final report.

9.9. Limitations of the research methods

Randomised and double blinded studies in pregnant women are feasible only in exceptional cases (where the study is the best interest of both mother and infant), due to ethical considerations (EMEA/CHMP, 2005).

Case control studies identify individuals with a specific outcome (e.g. a congenital malformation), against a control group and assess both groups with respect to previous exposure. The source data of case-control studies in pregnancy can be a birth defect registry or a pregnancy registry.

Different types of registries exist with respect to the timing of data collection: note that retrospective data collection is subject to *recall bias*. Some registries are set up and coordinated centrally by government agencies with obligatory reporting, while other registries (e.g. some industry or academia initiated registries) are based on voluntary reporting. Note that voluntary reporting is subject to *selection bias*.

The data source of the current study is the OEP database. Key features and limitations of this database are summarized below, together with the planned steps to balance the identified limitations.

OEP database	
Key features	**Limitations**
Coverage: The full insured population in Hungary. Covers all national health insurance funded medical service use, including prescription medicine claims, inpatient and outpatients visits and investigations (except for general practitioner visits).	Lack of insurance; private healthcare services; unnoticed pregnancies (e.g. undiagnosed early spontaneous abortions).
Pregnancy outcomes: The investigated eight pregnancy outcome categories are hard endpoints which are reliably reported to the payer's database. Recall bias is low due to the lack of retrospective data collection.	Not reported (minor or major) malformations; not detected early spontaneous abortions; dilution by high numbers of minor congenital anomalies or irrelevant consitions (e.g. congenital dysplasia of the hip (Czeizel et al., 2011)).
First day of pregnancy: Not included in the database. May be estimated from the reported date of AFP screening test (obligatory screening test in pregnancy after the completion of week 16)	Uncertainty of the calculated Day1 of pregnancy.
Exposure data: All prescription refills are recorded in the database prospectively, i.e. there is no retrospective data collection on drug exposure. Recall bias is low (no retrospective data collection).	Non-prescription drugs are not included in the database; inpatient drug use is hardly recorded in the database; Prescription refills do not always mean medicine intake. Potential off-label use of drugs.
Confounder factors: Several confounder factors included (maternal age, confounder drug use, maternal diabetes, in vitro fertilisation, previous pregnancy outcomes in the last 4 years, etc.). Recall bias is low (no retrospective data collection).	No data on some potential confounders (e.g. maternal smoking, acute fever, employment status, pregnancy outcomes more than 4 years before).

The limitations of the OEP database will be balanced by the following approaches:

- In Hungary, almost all women are insured and even the uninsured women receive free healthcare services related to their pregnancy. Lack of insurance is a theoretical selection bias in general, however, in practical aspects it has marginal relevance in Hungary.

- Private healthcare services are not included in the OEP database. However, the use of private healthcare services is restricted to a small fraction of the population in Hungary.
- Pregnancy outcomes are diagnosed and reported to the OEP by medical professionals. The investigated eight pregnancy outcome categories are hard endpoints which are reliably reported to the payer's database. Non-relevant codes are intended to be excluded from the analysis of teratogenicity risk by Protocol Amendment 2.
- Sensitivity analyses with alternative estimates of the first day of pregnancy (±2 weeks) are planned. In addition, several time periods of pregnancy will be investigated in parallel (first trimester, first month, second month, third month, second and third month, and after the first trimester).
- Non-prescription (OTC) drugs are not supposed to have teratogenic / abortive effects, and their use is expected to be balanced between groups. However, a protective effect of some OTC drugs can not be ruled out (e.g. folic acid).
- Inpatient drug use is hardly recorded in the OEP database. However, fungal gynecologic infections are treated in the outpatient setting in most of the cases. Confounder factors e.g. diabetes or in vitro fertilisation are also looked for at the level of BNO, OENO and HBCS codes.
- All butoconazole, miconazole, nystatin, and metronidazole containing products in Hungary are prescription drugs, therefore patient exposure to these compounds is recorded in the OEP database (note that products not insured by OEP are less reliably documented in the database). However, some pharmaceutical formulations of clotrimazole are non-prescription products, with the consequent lack of available patient-level exposure records in the OEP database. Accordingly, the exposure to clotrimazole will probably be underestimated both in cases and in controls. Note that all of the authorized clotrimazole products are locally administered (which do not suggest significant differences in their bioavailability). Moreover, the extent of underestimation of their use is not expected to be different across cases and controls: drug exposure records precede the pregnancy outcome and are not affected by increased awareness in cases / recall bias.
- It is acknowledged that a prescription refill do not always mean medicine intake. However, analysis of prescription refills is an acknowledged and frequently applied approach to monitor patient drug use in the real-life clinical setting. Asking the patients about their drug use would not add to the reliability of prescription refill data, because of the introduction of a substantial source of recall bias.
- Potential confounders without relevant data in the OEP database (e.g. maternal smoking, fever-related influenza or common cold, employment status, use of selected OTC drugs) will not be included in the OEP database analyses. It is not expected that these confounding factors show correlations both with the pregnancy outcomes and with the exposure to gynecology anti-infectives.
- The effect of random error is minimised by the large sample size (almost 1 100 000 pregnancy outcomes expected in the OEP database).

- Active control drugs are included in the spontaneous abortion case-control study and in the teratogenicity case-control study as measures of study sensitivity.

All together, the planned approach is considered to be suitable to give relevant answers to the research questions. A wider range of confounder factors are considered in the planned analyses than in most published studies in this field, and the planned sensitivity analyses are considered to be adequate to characterise the robustness of the study findings.

Note that all of the statistical analyses, including sensitivity analyses and confounding factors are prospectively defined in the protocol; that the study protocol will be approved by GYEMSZI and registered in the EU PAS Register before the start date of data collection; and that no pilot study was conducted on the reported pregnancy outcomes during the planning of the current study. Study results will be reported both per Protocol Amendment 1 and Protocol Amendment 2.

In the risk assessment of medicinal products on human pregnancy, there are known difficulties with the accurate documentation and validation of cases. Acknowledging the usual uncertainties in the source data, the requested number of pregnancies with prospectively collected, first trimester exposure in the relevant guideline have been inflated to 300 (to exclude a 10x risk of malformations) and to 1000 (to exclude a 2-fold risk of malformations) (EMEA/CHMP, 2006). The current study is expected to include almost 1 100 000 pregnancy outcomes, with a conservative assumption that at least 300 pregnancies were exposed to butoconazole in the first trimester.

Limitations of the birthweight analyses in Protocol Amendment 2 are discussed in Annex 3.5.

9.10. Other aspects

Not applicable.

10. Protection of human subjects

The current study is considered to be in the best interest of the Hungarian population. The scientific quality of the study is ensured by the internationally recognized, Company-independent Principal Investigator and by the strict regulations of PASS studies in the EU.

In the OEP database, the access to individual data will be restricted to authorized personnel, handling the data in strict confidence by their professional standards and legal obligations. No transfer of individual data from OEP will occur by any means. The results provided to the sponsor and other relevant parties will contain group statistics and results only, without individual data.

According to the Hungarian regulation, no informed consent of the registered persons is requested in retrospective studies (23/2002 EüM rendelet, §20/Q).

11. Management and reporting of adverse events/adverse reactions

The Sponsor encourages the OEP and NIHD/OEFI to report any noticed adverse reaction, drug exposure during pregnancy, or congenital anomaly case to the competent authority, as long as this reporting procedure conforms their data management standards and regulations.

The results provided to the Sponsor and other parties will contain group statistics and results only, without individual data. Therefore, the Sponsor can not generate new cases in the Company safety database, and hence, can not report new cases to the competent authorities from this study. Nevertheless, the final report of the study containing the results of all pre-planned analyses will be made available for the competent authorities.

12. Plans for disseminating and communicating study results

Study results will be used for regulatory correspondence (e.g. update of the Summary of Product Characteristics / Patient Information Leaflet) by the Sponsor.

The study will be registered in the EU PAS Register before the start of data collection. Protocol and final report of the study will be uploaded to the EU PAS Register.

Publication of study results is also under consideration. The Sponsor holds the right to the final review and approval of the manuscript of any publication of this study (including the final report) before publication. Authorship of approved publications will be shared across the responsible parties.

13. References

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	1	02 May 2013	ENCePP checklist for study protocols
2	1	17 July 2015	ENCePP checklist for study protocols (Amendment 2)
3	2	17 July 2015	Socioeconomic status of micro-regions_final.xlsx

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for study protocols (Revision 2, amended) has been completed and signed by the Principal Investigator and is attached as a stand-alone document.

Annex 3. Additional information

Annex 3.1. Identification and technical definitions of pregnancy outcomes

Annex 3.1.1. Identification of all pregnancies / births in the OEP database

The following HBCS codes will be used to identify all pregnancies / births (i.e. the relevant mother and/or offspring TAJ numbers) in the OEP database:

HBCS code	Description (in Hungarian)
14 671A	Császármetszés
14 671B	Császármetszés pathológiás terhesség után
14 672A	Nagy rizikójú szülés (kivéve: császármetszés)
14 672B	Nagy rizikójú szülés (kivéve: császármetszés) pathológiás terhesség után
14 673A	Hüvelyi szülés
14 673B	Hüvelyi szülés pathológiás terhesség után
14 673C	Hüvelyi szülés epidurális érzéstelenítéssel
14 673D	Hüvelyi szülés pathológiás terhesség után epidurális érzéstelenítéssel
14 674A	Hüvelyi szülés műtéttel
14 674B	Hüvelyi szülés műtéttel, pathológiás terhesség után
14 675A	Genetikai amniocentézis kromoszómavizsgálattal
14 675B	Chorionboholy mintavétel kromoszómavizsgálattal
14 6760	Egyéb terhességi műtétek
14 677A	Postpartum, post abortum betegségek műtétei
14 677B	Postpartum, post abortum betegségek műtét nélkül
14 6780	Méhen kívüli (ectopias) terhesség műtétei laparoszkóppal
14 6790	Méhen kívüli (ectopias) terhesség műtétei laparotomiával
14 6800	Inkomplett vetélés műszeres befejezéssel 12 hétig
14 681C	Középidős vetélés (spontán és művi)
14 681D	Interruptio aspirációs kürettel 12. hét előtt, altatással
14 6820	Fenyegető vetélés
14 6830	Fenyegető koraszülés
14 6831	Fenyegető koraszülés kezelése Tractocile-vel, a terhesség betöltött 24. hetétől a 33. hetéig
14 6840	Egyéb antepartum betegségek
15 7110	Újszülött, születési súly 999 g alatt
15 7120	Újszülött, születési súly 1000-1499 g, jelentős műtéttel
15 7130	Újszülött, születési súly 1000-1499 g, jelentős műtét nélkül
15 7140	Újszülött, születési súly 1500-1999 g, jelentős műtéttel
15 715Z	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, súlyos problémával
15 7160	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, közepes problémával
15 7170	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, egyéb problémával
15 7180	Újszülött, születési súly 2000-2499 g, jelentős műtéttel
15 719Z	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, súlyos problémával
15 7200	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, közepes problémával
15 7210	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, normális újszülött diagnózissal
15 7220	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, egyéb problémával
15 7230	Újszülött, születési súly 2499 g felett, jelentős műtéttel
15 7240	Újszülött, születési súly 2499 g felett, kisebb hasi műtéttel
15 7260	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, közepes problémával
15 7270	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, normális újszülött diagnózissal
15 7280	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, egyéb problémával
15 7300	Újszülött, áthelyezve 5 napos kor előtt, helyben született

15 7310	Újszülött, áthelyezve 5 napos kor előtt, máshol született
15 7330	Jelentős szív-érrendszeri műtétek újszülött korban
15 7331	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel
15 7332	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel és NO adással
15 734Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napot nem meghaladó gépi lélegeztetéssel
15 735Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napnál hosszabb gépi lélegeztetéssel

In addition to the above listed HBCS codes, the following approaches are introduced in Amendment 1 of the Protocol, to find as many pregnancies / births and mother-child pairs as possible:

Identification of offspring TAJ numbers:

- all newborn TAJ numbers with birth dates between 1st January 2005 and 31th December 2011;

- all transient TAJ numbers of newborns with birth dates between 1st January 2005 and 31th December 2011. Note that transient TAJ numbers are created from the maternal TAJ number with the change of the first digit, and it may be used in health records / prescription claims until the personal TAJ number of the offspring has been declared (typically in the first few days / weeks after birth). Pairwise linkage of transient TAJ numbers to final TAJ numbers is planned based on detailed inpatient and social payment records in the OEP database.

- TAJ numbers where the mother's and the child's TAJ number could not be paired to each other or where there is a discrepancy between the final and the transient TAJ numbers of the child will be excluded from the study.

Identification of TAJ numbers of pregnant women:

- women with BNO or OENO codes specific to **ectopic pregnancy**, reported between 1st January 2005 and 31th December 2011 (list of codes provided in Annex 3.1.2);

- women with BNO or OENO codes specific to **spontaneous abortion**, reported between 1st January 2005 and 31th December 2011 (list of codes provided in Annex 3.1.2);

- women with BNO or OENO codes specific to **elective termination**, reported between 1st January 2005 and 31th December 2011 (list of codes provided in Annex 3.1.2);

- women with BNO or OENO codes specific to the **offspring's fetal malformation / congenital anomaly**, reported between 1st January 2005 and 31th December 2011 (list of codes provided in Annex 3.1.2);

- women with BNO or OENO codes specific to **stillbirth**, reported between 1st January 2005 and 31th December 2011 (list of codes provided in Annex 3.1.2);

- women with BNO or OENO codes specific to **live birth**, reported between 1st January 2005 and 31th December 2011 (list of codes provided in Annex 3.1.2);

- women with BNO or OENO codes **not specific to the outcomes above but specific to pregnancy**, reported between 1st January 2005 and 31th December 2011. The listing of BNO / OENO codes related to pregnancy but not specific to the investigated pregnancy outcomes is provided in Annex 3.2.

Annex 3.1.2. Identification of specific pregnancy outcomes in the OEP database

According to the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP, 2005), pregnancy outcomes to be evaluated in the postmarketing phase include the following eight categories:

- ectopic pregnancy
- spontaneous abortion
- elective termination (foetal defects)
- elective termination (no foetal defects or unknown)
- stillbirth with foetal defects
- stillbirth without foetal defects
- live birth with congenital anomaly
- live birth without congenital anomaly

These mutually exclusive outcomes will be identified in the OEP database based on the following technical definitions below.

BNO codes reported as conditions in the anamnesis (if any) will not be evaluated, and BNO codes reported as potential / unconfirmed diagnoses are also excluded from the study.

Ectopic pregnancy

a) Maternal disease codes (BNO) specific for ectopic pregnancy (in Hungarian)

BNO	Description
O0000	Hasűri terhesség
O0010	Kürtterhesség (tubaris abortus)
O0020	Petefészek terhesség
O0080	Egyéb méhen kívüli terhesség
O0090	Méhen kívüli terhesség, k.m.n.
O8330	Élő magzat szülése hasűri terhességben
P0140	Méhen kívüli terhesség

b) Offspring disease codes (BNO) specific for ectopic pregnancy (in Hungarian)

BNO	Description
P0140	Méhen kívüli terhesség

c) Intervention codes (OENO) specific for ectopic pregnancy (in Hungarian)

OENO	Description
57430	Operatio graviditatis intraabdominalis
57434	Laparoscopos embryo aspiratio
57435	Extrauterin graviditas laparoscopos műtéte
57442	Laparoscopos embryo aspiratio, salpingotomiából
57502	Méhen kívüli terhességbe adott inj., UH vezérléssel
57503	Méhen kívüli terhességbe adott inj., laparoszkópos

d) HBCS codes specific for ectopic pregnancy (in Hungarian)

HBCS	Description
14 6780	Méhen kívüli (ectopias) terhesség műtétei laparoszkóppal
14 6790	Méhen kívüli (ectopias) terhesség műtétei laparotomiával

e) Technical definition of ectopic pregnancy in the current study

Any report of the above maternal disease (BNO) codes and/or foetal disease (BNO) codes and/or intervention (OENO) codes. *(Note that HBCS codes 14 6780 and 14 6790 do not contain additional cases, because some of the listed maternal disease (BNO) codes are obligatory part of them).*

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3..

Spontaneous abortion

a) Maternal disease codes (BNO) specific for spontaneous abortion (in Hungarian)

BNO	Description
O0210	Missed abortion
O03..	Spontán vetélés
O05..	Vetélés egyéb okból
O06..	Vetélés k.m.n.
O3110	Továbbviselt többes terhesség valamely magzat korai vetélése után

Three-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits.

b) Offspring disease codes (BNO) specific for spontaneous abortion (in Hungarian)

BNO	Description
none	

c) Intervention codes (OENO) specific for spontaneous abortion (in Hungarian)

OENO	Description
56903	Missed ab. befejezése
56905	Curettage-incomplett abortus után

d) HBCS codes specific for spontaneous abortion (in Hungarian)

HBCS	Description
14 6800	Inkomplett vetélés műszeres befejezéssel 12 hétig

e) Technical definition of spontaneous abortion cases in the current study

Any report of the above maternal disease (BNO) codes and/or intervention (OENO) codes. *(Note that HBCS code 14 6800 does not contain additional cases, because the listed maternal disease (BNO) codes are obligatory part of this HBCS).*

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Elective termination (foetal defects)

a) Maternal disease codes (BNO) specific for elective termination (in Hungarian)

BNO	Description
O04..	Terhességmegszakitás (művi vetélés szociális vagy orvosi indikáció alapján)
Z6400	Nem kívánt terhességből adódó gondok

Three-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits.

b) Offspring disease codes (BNO) specific for elective termination (in Hungarian)

BNO	Description
none	

c) Intervention codes (OENO) specific for elective termination (in Hungarian)

OENO	Description
56900	Terhességmegszakítás nem orvosi indikációra
5744A	Reductio summae geminorum
5744B	Feticidium electus
57500	Terhességmegszakítás intraamniális gyógyszerrel
57501	Terhességmegszakítás extraamniális gyógyszerrel
57510	Interruptio vacuummal
57520	Interruptio Hegar tágítással, curettage-al
57521	Interruptio laminaria tágítással
57522	Gyógyszerrel végzett interruptio befejezése
57523	Prostaglandin feltöltés, középidős vetélésinductio
57524	Rivanol (1-ezrelékes) feltöltés, középidős vetélésinductio
57525	Oxytocin infusio, középidős vetélésindukció
57526	Többes terhesség reductio
57527	Selectiv foeticid ikerterhességben

d) HBCS codes specific for elective termination (in Hungarian)

HBCS	Description
14 681D	Interruptio aspirációs kürettel 12. hét előtt, altatással

(Note that HBCS code 14 681D does not contain additional cases, because the listed maternal disease (BNO) codes are obligatory part of this HBCS).

e) Maternal disease codes (BNO) specific for foetal defects (in Hungarian) in the Protocol Amendment 1 analyses

BNO	Description
O3360	Veszélyeztetett terhesség téraránytalanságot okozó hydrocephalus miatt
O3370	Vesz.terhesség téraránytalanságot okozó egyéb magzati deformitás miatt
O3500	Vesz. terhesség a magzati közp.idegrendszer fejlődési rendell. miatt

f) Offspring disease codes (BNO) specific for foetal defects (in Hungarian) in the Protocol Amendment 1 analyses

BNO	Description
Q00	Agyvelőhiány és hasonló fejlődési rendellenességek
Q01	Agyvelősérv (encephalocele)
Q02	Kisfejűség
Q03	Veleszületett vízfejűség
Q04	Az agy egyéb veleszületett rendellenességei
Q05	Gerinchasadék (spina bifida)

Q06	A gerincvelő egyéb veleszületett fejlődési rendellenességei
Q07	Az idegrendszer egyéb veleszületett rendellenességei
Q10	A szemhéjak, könnyszervek és szemüreg veleszületett rendellenességei
Q11	Szemhiány, kisszemüség, nagyszemüség
Q12	A szemlencse veleszületett rendellenességei
Q13	A szem elülső szegmentjének veleszületett rendelenességei
Q14	A szem hátsó szegmentjének veleszületett rendellenességei
Q15	A szem egyéb veleszületett rendellenességei
Q16	A fül veleszületett, hallászavart okozó rendellenességei
Q17	A fül egyéb veleszületett rendellenességei
Q18	Az arc és nyak egyéb veleszületett rendellenességei
Q20	A szív üregeinek és összeköttetéseinek veleszületett rendellenességei
Q21	A szívsövények veleszületett rendellenességei
Q22	A háromhegyű és a tüdőverőér-billentyűk veleszületett rendellenességei
Q23	Az aorta- és kéthegyű billentyűk veleszületett rendellenességei
Q24	A szív egyéb veleszületett rendellenességei
Q25	A nagy artériák veleszületett rendellenességei
Q26	A nagyvénák veleszületett rendellenességei
Q27	A perifériás érrendszer egyéb veleszületett rendellenességei
Q28	A keringési szervrendszer egyéb veleszületett rendellenességei
Q30	Az orr veleszületett rendellenességei
Q31	A gége veleszületett rendellenességei
Q32	A légcső és hörgők veleszületett rendellenességei
Q33	A tüdő veleszületett rendellenességei
Q34	A légzőrendszer egyéb veleszületett rendellenességei
Q35	Szájpadhasadék
Q36	Ajakhasadék
Q37	Szájpad- ajakhasadék
Q38	A nyelv, száj és garat egyéb veleszületett rendellenességei
Q39	A nyelőcső veleszületett rendellenességei
Q40	A tápcsatorna felső szakaszának egyéb veleszületett rendellenességei
Q41	A vékonybél veleszületett hiánya, elzáródása, szűkülete
Q42	A vastagbél veleszületett hiánya, elzáródása és szűkülete
Q43	A bél egyéb veleszületett rendellenességei
Q44	Az epehólyag, epevezetékek és máj veleszületett rendellenességei
Q45	Az emésztőrendszer egyéb veleszületett rendellenességei
Q50	A petefészkek, petevezetők és széles szalagok veleszületett rendellenességei
Q51	A méh és méhnyak veleszületett rendellenességei
Q52	A női nemi szervek egyéb veleszületett rendellenességei
Q53	Nem descendált here (cryptorchismus)
Q54	Hypospadiasis
Q55	A férfi nemi szervek egyéb veleszületett rendellenességei
Q56	Határozatlan neműség és pseudohermaphroditismus
Q60	A vese agenesise és egyéb veseállomány csökkenéssel járó elváltozások
Q61	Cystás vesebetegség
Q62	A vesemedence veleszületett, elzáródást okozó rendellenességei és a húgyvezeték veleszületett malformatioi
Q63	A vese egyéb veleszületett rendellenességei
Q64	A húgyrendszer egyéb veleszületett rendellenességei
Q65	A csípő veleszületett deformitásai
Q66	A lábak veleszületett rendellenességei
Q67	A fej, arc, gerinc és mellkas csont-izomrendszerének veleszületett rendellenességei
Q68	A csont és izomrendszer egyéb veleszületett deformitásai
Q69	Számfeletti ujjak (polydactylia)
Q70	Összenőtt ujjak (syndactylia)
Q71	A felső végtag redukciós defektusai
Q72	Az alsó végtag redukciós defektusai
Q73	Nem meghatározott végtag redukciós defektusai
Q74	Egyéb veleszületett végtag-rendellenességek
Q75	Az agy- és arckoponya csontjainak egyéb veleszületett rendellenességei
Q76	A gerinc és csontos mellkas veleszületett rendellenességei
Q77	Csont-porcképződési zavar (osteo-chondrodysplasia) a csöves csontok és gerinccsontok növekedési defektusával
Q78	Egyéb osteo-chondrodysplasiák
Q79	A csont-izomrendszer m.n.o. veleszületett rendellenességei

Q80	Ichthyosis congenita
Q81	Epidermolysis bullosa
Q82	A bőr egyéb veleszületett rendellenességei
Q83	Az emlő veleszületett rendellenességei
Q84	A kültakaró egyéb veleszületett rendellenességei
Q85	Phakomatosisok, m.n.o.
Q86	Veleszületett malformatiós szindrómák ismert külső ok miatt m.n.o.
Q87	Egyéb meghatározott, több szervrendszert érintő malformatiós szindrómák
Q89	Egyéb veleszületett, m.n.o. rendellenességek

Three-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits. Note that maternal reports of unclear anomalies, and offspring reports of chromosomal abnormalities are not analysed in the current study (i.e. the following BNO codes are not analysed: O2830 Antenatalis szűrés során ultrahang-lelet rendellenesség; O2840 Antenatalis szűrés során radiologiai rendellenesség; O2850 Antenatalis szűrés során felfedezett chromosoma és genetikai rendell.; O2880 Antenatalis szűrés során felfedezett egyéb rendellenességek; Q90 Down-szindróma; Q91 Edwards-szindróma és Patau-szindróma; Q92 Egyéb autoszomális, m.n.o. részleges vagy teljes triszómiák; Q93 Az autoszómák m.n.o. monoszómiái és deletiói; Q95 Kiegyenlített átrendeződések és szerkezeti markerek, m.n.o.; Q96 Turner-szindróma; Q97 Egyéb szex-kromoszóma rendellenességek, női fenotipussal, m.n.o.; Q98 Egyéb szex-kromoszóma rendellenességek, férfi fenotípussal, m.n.o.; Q99 Egyéb kromoszóma rendellenességek, m.n.o.).

g) Offspring intervention codes (OENO) specific for foetal defects (in Hungarian) in the Protocol Amendment 1 analyses

OENO	Description
12660	Szívkatéterezés alapvizsgálat
12730	Szívkatéterezés, vénás percután behatolással
12731	Szívkatéterezés, vénás feltárásos behatolással
12740	Szívkatéterezés, vénás transseptális behatolással
12750	Szívkatéterezés, egyéb artériás percután behatolással
12751	Szívkatéterezés, artéria femorális behatolással
12752	Szívkatéterezés, artéria brachiális behatolással
12754	Szívkatéterezés, artériás feltárásos behatolással
12780	Szívkatéterezés-transthoracalis behatolással
50100	Punctio ventriculi cerebri, drain
50216	Cranialis meningocele és encephalocele reconstuctio
50230	Ventriculo-atrialis shunt beültetés
50240	Ventricularis shunt revisioja
50342	Spinalis meningocele és myelocele, reconstructio
50343	Extra-intr.spin.lipomával komb.meningo-myeloc.műtét
50361	Lumbo-peritonealis shunt
52174	Choanalis atresia miatt végzett műtét
52740	Szájüreg plasztikai helyreállítása
52750	Lágyszájpadplasztika
52751	Keményszájpadplasztika
52752	Kemény- és lágyszájpadplasztika, egy ülésben
52753	Szájpadrekonstrukció, előzetes műtét után
52910	Exstirpatio cystae colli lateralis
53114	Tracheostomia
53344	Hörgőfistula zárása izomlebeny plasztikával
53471	Sutura diaphragmae
53472	Reconstructio diaphragmae
53474	Reconstructio diaphragmae, alloplasticaval
53475	Duplicatio diaphragmae
53552	Defectus artef.septi interauric.cordis transvasalis
53829	Coarctatio aortae műtéte /újszülött /
54210	Oesophagostomia cervicalis
54270	Sutura oesophagei p. cervicalis
54271	Sutura oesophagei p. thoracalis
54273	Occlusio fistulae oesophago-trachealis/bronchialis
54274	Cardioplastica
54275	Occlusio fistulae / stomae oesophagei

54541	Duodeno-duodenostomia
54543	Ductus omphaloentericus vagy residuuma eltávolítás
54550	Resectio intestini crassi
54551	Haemicolectomia dextra
54557	Resectio intestini crassi, anastomosis instrument.
54560	Colectomia
54570	Vékonybél anastomosis (bypass)
54581	Ileo-transversostomia
54590	Colo-colostomia
54687	Reconstructio malrotationis intestinorum
54853	Megacolon congenitum definitiv műtéte
54865	Magas/intermediaer recto-analis atresia def. műtéte
5486A	Rectoplastica posterior sagittalis sec.Pena
54965	Reconstr.ani definitiv., alacsony atresia ani miatt
55125	Choledocho-enterostomia
55160	Reconstr. duct. hepatici seu choledochi
55168	Choledochus-cysta eltávolítás, epeút reconstructio
55340	Hernioplastica umbilicalis
55350	Reconstructio parietis abdominis
55358	Gastroschisis műtéte
55359	Omphalocele műtéte
55360	Reconstructio parietis abdominis c. implant.
55361	Reconstructio laparoscopica parietis abdominis cum implantate
55369	Reconstructio laparoscopica parietis abdominis cum conversione
55390	Hernioplastica herniae intraabdominalis
55541	Nephrectomia radicalis
55570	Pyelon plast.et res.pyeloureteralis Andersen-Hynes
55604	Ureteroendoscopos resectio
55621	Ureterotomia, alsó szakasz
55631	Ureter resectio + anastomosis
55650	Ureterocutaneostomia
55671	Anastomosis uretero-ureteralis termino-terminalis
55672	Anastomosis uretero-ureteralis latero-lateralis
55673	Revisio anastomosis ureteris
5567A	Neoimplantatio ureteris sec. Politano – Leadbetter
5567B	Neoimplantatio ureteris sec. Cohen
55784	Húgyhólyag sutura
55820	Húgycső congenitalis billentyű resectioja
55980	Ureterkatéter felvezetés
55983	Ureter strictura katéteres tágítása
55985	Ureterkatéter - dupla J - felhelyezés
56130	Scrotum és tunica vaginalis reconstructio
56240	Orchidopexia
56303	Funiculocele resectio
56310	Mellékhere cysta kiirtása
56330	Epididymectomia
56342	Funiculus és mellékhere reconstructio
56511	Ovarialis cysta eltávolítás (Bonney műtét)
57550	Intrauterin műtétek a magzaton
57553	Magzati defectus intrauterine correctioja
57554	Scalp elektród felhelyezése
58286	Syndactylia csontos szétválasztása, kézen
58400	Amputatio digiti manus
58402	Amputatio digiti manus secondarius
58450	Amputatio digiti pedis
58981	Oldalsó inkomplett ajakhasadék zárása
58982	Ajak és külső száj plastica, Le Mesurier szerint
58983	Ajak és külső száj plastica, Millard szerint
58984	Ferde archasadék (macrostoma) korrekciója
58985	Ajak- és külső szájplasztika
58986	Ajakkorrekció ajakplasztika után
58987	Median ajakhasadék zárása

h) HBCS codes specific for foetal defects (in Hungarian) in the Protocol Amendment 1 analyses

HBCS	Description
none	

i) Maternal intervention codes (OENO) specific for foetal defects (in Hungarian) in the Protocol Amendment 1 analyses

OENO	Description
57550	Intrauterin műtétek a magzaton
57553	Magzati defectus intrauterin correctioja
57554	Scalp elektród felhelyezése

Technical definition of „elective termination (foetal defect)" cases in the Amendment 1 analyses:

The following pregnancy outcomes are considered to be elective termination:

- Report of maternal disease codes (BNO) specific for elective termination, and/or
- Report of intervention codes (OENO) specific for elective termination.

The following pregnancy outcomes are considered to be „elective termination (foetal defect)":

- Elective termination as defined above, and at least one of the following in ± 3 months around the date of elective termination:
    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of offspring intervention codes (OENO) specific for foetal defect; or
    - Report of maternal intervention codes (OENO) specific for foetal defect.

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Elective termination (no foetal defects or unknown)

For the tabular listing of maternal and offspring disease codes and intervention codes specific for elective termination and foetal defect, please see the definition of „Elective termination (foetal defect)" above.

The following pregnancy outcomes are considered to be „elective termination (no foetal defect or unknown)":

- Report of maternal disease codes (BNO) specific for elective termination, and/or report of intervention codes (OENO) specific for elective termination,
  without any of the following reports in ± 3 months around the date of elective termination:

  - Report of maternal disease code (BNO) specific for foetal defect; or
  - Report of offspring disease code (BNO) specific for foetal defect; or
  - Report of offspring intervention codes (OENO) specific for foetal defect; or
  - Report of maternal intervention codes (OENO) specific for foetal defect.

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Stillbirth with foetal defects

a) Maternal disease codes (BNO) specific for stillbirth (in Hungarian)

BNO	Description
O3120	Továbbviselt többes terhesség magzat intrauterin elhalása után
O3640	Veszélyeztetett terhesség intrauterin elhalás miatt
O8340	Darabolásos műtét szülés kapcsán
P95H0	A magzat elhalása nem meghatározott ok miatt
Z3710	Egyszeres halvaszülés
Z3730	Ikerszülés: egy élve és egy halva született
Z3740	Ikerszülés: mindkettő halva született
Z3760	Többszörös ikrek szülése: néhány élve született
Z3770	Többszörös ikrek szülése, mind halva született

Maternal BNO codes reporting more than one stillbirth from the same pregnancy (Z3740, Z3770) will be handled as separate stillbirth outcomes in the analyses.

b) Offspring disease codes (BNO) specific for stillbirth (in Hungarian)

BNO	Description
P95H0	A magzat elhalása nem meghatározott ok miatt

c) Intervention codes (OENO) specific for stillbirth (in Hungarian)

OENO	Description
57341	Magzati koponya perforatioja
57343	Daraboló műtét

d) HBCS codes specific for stillbirth (in Hungarian)

HBCS	Description
none	

e) BNO, OENO and HBCS codes specific for foetal defect (in Hungarian)
See subsections (e) to (i) at the „Elective termination (foetal defect)" definitions.

f) Technical definition of „stillbirth with foetal defect" cases in the Amendment 1 analyses

The following combinations of reports are considered to represent stillbirths with foetal defect:

- Maternal and/or offspring disease codes (BNO) specific for stillbirth, and at least one of the following in the relevant time period (from 6 months before stillbirth, up to 3 months after stillbirth):
    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of offspring intervention codes (OENO) specific for foetal defect; or
    - Report of maternal intervention codes (OENO) specific for foetal defect.

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Stillbirth without foetal defects

a) BNO, OENO and HBCS codes specific for stillbirth (in Hungarian):
see subsections (a) to (d) at the „Stillbirth with foetal defects" definitions.

b) BNO, OENO and HBCS codes specific for foetal defects (in Hungarian):
see subsections (e) to (i) at the „Elective termination (foetal defect)" definitions.

c) Technical definition of „stillbirth without foetal defects" cases in the Amendment 1 analyses

- Maternal and/or offspring disease codes (BNO) specific for stillbirth, without any of the following reports in the relevant time period (from 6 months before stillbirth, up to 3 months after stillbirth):

    - Report of maternal disease code (BNO) specific for foetal defect; or
    - Report of offspring disease code (BNO) specific for foetal defect; or
    - Report of offspring intervention codes (OENO) specific for foetal defect; or
    - Report of maternal intervention codes (OENO) specific for foetal defect.

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Live birth with congenital anomaly

a) Maternal disease codes (BNO) specific for live birth (in Hungarian)

BNO	Description
O8000	Koponyavégű, spontán hüvelyi szülés
O8010	Medencevégű hüvelyi spontán szülés
O8080	Egyéb spontán egyes szülés
O8090	Spontán egyes szülés, k.m.n.
O8100	Szülés kimeneti fogóműtéttel
O8110	Szülés üregi fogóműtéttel
O8120	Szülés üregi fogóműtéttel, a koponya forgatásával
O8130	Szülés egyéb és k.m.n. fogóműtéttel
O8140	Szülés vacuum extractióval
O8150	Szülés fogó és vacuum extractio együttes alkalmazásával
O8200	Szülés elektív császármetszéssel, k.m.n.
O8210	Szülés császármetszéssel
O8220	Szülés sürgős császármetszéssel és méheltávolítással
O8280	Egyéb egyes szülés császármetszéssel
O8290	Szülés császármetszéssel, k.m.n.
O8300	Farlehúzásos exctractio
O8310	Egyéb műfogásos szülés farfekvés esetén
O8320	Egyéb, műfogással segített szülés
O8330	Élő magzat szülése hasűri terhességben
O8380	Egyéb egyes szülés meghatározott műfogással
O8390	Egyes szülés műfogással, k.m.n.
O8400	Többes szülés, valamennyi spontán
O8401	Ikerszülés, valamennyi spontán
O8402	Hármas vagy többes szülés, valamennyi spontán
O8410	Többes szülés, valamennyi fogóval és vacuum extractorral
O8411	Ikerszülés, valamennyi fogóval és vacuum extractorral
O8412	Hármas vagy többes szülés, valamennyi fogóval és vacuum extractorral
O8420	Többes szülés, valamennyi császármetszéssel
O8421	Ikerszülés, valamennyi császármetszéssel
O8422	Hármas vagy többes szülés, valamennyi császármetszéssel
O8480	Egyéb többes szülés
O8481	Egyéb ikerszülés
O8482	Egyéb hármas vagy többes szülés
O8490	Többes szülés, k.m.n.
O8491	Ikerszülés, k.m.n.
O8492	Hármas vagy többes szülés, k.m.n.
P0730	Egyéb koraszülött csecsemő
P0731	Egyéb koraszülött csecsemő, 29 betöltött hétnél (203 betöltött napnál) kevesebb gestációs idő
P0732	Egyéb koraszülött csecsemő, 30 betöltött hétnél (210 betöltött napnál) kevesebb gestációs idő
P0733	Egyéb koraszülött csecsemő, 31 betöltött hétnél (217 betöltött napnál) kevesebb gestációs idő
P0734	Egyéb koraszülött csecsemő, 32 betöltött hétnél (224 betöltött napnál) kevesebb gestációs idő
P0735	Egyéb koraszülött csecsemő, 33 betöltött hétnél (231 betöltött napnál) kevesebb gestációs idő
P0736	Egyéb koraszülött csecsemő, 34 betöltött hétnél (238 betöltött napnál) kevesebb gestációs idő
P0737	Egyéb koraszülött csecsemő, 35 betöltött hétnél (245 betöltött napnál) kevesebb gestációs idő
P0738	Egyéb koraszülött csecsemő, 36 betöltött hétnél (252 betöltött napnál) kevesebb gestációs idő
P0739	Egyéb koraszülött csecsemő, 37 betöltött hétnél (259 betöltött napnál) kevesebb gestációs idő
P0800	Óriás újszülött
P0820	Túlhordott újszülött, a terhesség tartamához képest nem nagy súlyú
P1130	Az arcideg szülési sérülése
P1140	Egyéb agyidegek szülési sérülése
P1230	A hajas fejbőr horzsolódása szülési sérülés miatt
P1240	A magzat monitorozása miatt kialakult fejbőr sérülés
P1280	A hajas fejbőr egyéb sérülései
P1290	A hajas fejbőr sérülése, k.m.n.
P1400	Erb-típusú bénulás szülési sérülés miatt
P1410	Klumpke-típusú bénulás szülési sérülés miatt
P1420	A nervus phrenicus bénulása szülési sérülés miatt

P1430	A kari idegfonat egyéb szülési sérülései
P1480	A perifériás idegrendszer egyéb részeinek szülési sérülései
P1490	A perifériás idegrendszer szülési sérülései, k.m.n.
P1520	A m. sternocleidomastoideus sérülése szülési sérülés miatt
P1530	A szem szülési sérülése
P1531	Conjunctiva vérzés szülési sérülés miatt
P1532	Traumás glaucoma szülési sérülés miatt
P1560	A bőralatti zsírszövet necrosisa szülési sérülés miatt
P2200	Az újszülött respiratiós distress syndromája
P2210	Az újszülött átmeneti tachypnoéja
P2280	Az újszülött egyéb légzészavara
P2290	Az újszülött légzészavara, k.m.n.
P2300	Vírus okozta veleszületett tüdőgyulladás
P2310	Chlamydia okozta veleszületett tüdőgyulladás
P2320	Staphylococcus okozta veleszületett tüdőgyulladás
P2330	B-csoportú streptococcus okozta veleszületett tüdőgyulladás
P2340	Escherichia coli okozta veleszületett tüdőgyulladás
P2350	Pseudomonas okozta veleszületett tüdőgyulladás
P2360	Egyéb baktériumok okozta veleszületett tüdőgyulladás
P2361	Congenitalis pneumonia - Haemophylus influenzae
P2362	Congenitalis pneumonia - Kelbsiella pneumoniae
P2363	Congenitalis pneumonia - Mycoplasma
P2364	Congenitalis pneumonia - Streptococcus, egyéb
P2380	Egyéb kórokozók okozta veleszületett tüdőgyulladás
P2390	Veleszületett tüdőgyulladás, k.m.n.
P2400	Meconium aspiratio
P2410	Magzatvíz és nyák aspiratio
P2420	Vér aspiratiója újszülött korban
P2430	Tej és regurgitált táplálék aspiratiója újszülött korban
P2480	Egyéb újszülöttkori aspiratios syndromák
P2490	Újszülöttkori aspiratios syndroma, k.m.n.
P2491	Aspiratios pneumonia újszülöttkorban
P2500	A perinatális időszakban kezdődött interstitialis emphysema
P2510	Újszülött korban keletkezett pneumothorax
P2520	Újszülött korban keletkezett pneumomediastinum
P2530	Újszülött korban keletkezett pneumopericardium
P2580	Egyéb újszülöttkori interstitialis emphysemával kapcs. állapotok
P2600	Újszülött korban keletkezett tracheo-bronchialis vérzés
P2610	Újszülött korban keletkezett súlyos tüdővérzés
P2680	Egyéb újszülött korban keletkezett tüdővérzések
P2690	Újszülöttkori tüdővérzés, k.m.n.
P2700	Wilson-Mikity syndroma
P2710	Újszülöttkori bronchopulmonalis dysplasia
P2780	Egyéb újszülöttkori krónikus tüdőbetegségek
P2790	Újszülöttkorban keletkező krónikus tüdőbetegség, k.m.n.
P2810	Egyéb és k.m.n. atelectasia az újszülöttben
P2820	Cyanoticus rohamok az újszülöttben
P2830	Az újszülött primer alvási apnoéja
P2840	Egyéb apnoe az újszülöttben
P2850	Az újszülött légzési elégtelensége
P2880	Egyéb jellegzetes légzési állapotok az újszülöttben
P2890	Légzési állapot az újszülöttben, k.m.n.
P2900	Szívelégtelenség az újszülöttben
P2910	Újszülöttkori arrhythmia
P2920	Az újszülött hypertoniája
P2930	Perzisztáló foetalis keringés
P2940	Átmeneti szívizom ischaemia az újszülöttben
P2980	Egyéb cardiovascularis rendellenességek az újszülött korban
P2990	Cardiovascularis rendellenesség az újszülött korban, k.m.n.
P3500	Veleszületett rubeola syndroma
P3510	Veleszületett cytomegalovirus fertőzés
P3520	Veleszületett herpesvirus [herpes simplex] fertőzés
P3530	Veleszületett vírushepatitis

P3580	Egyéb veleszületett vírusbetegségek
P3590	Veleszületett vírusbetegség, k.m.n.
P3600	B-csoportú streptococcus sepsis az újszülöttben
P3610	Más és k.m.n. streptococcusok okozta sepsis az újszülöttben
P3620	Staphylococcus aureus okozta sepsis az újszülöttben
P3630	Egyéb és k.m.n. staphylococcusok okozta sepsis az újszülöttben
P3640	Escherichia coli okozta sepsis az újszülöttben
P3650	Anaerobok okozta sepsis az újszülöttben
P3680	Egyéb bakteriális sepsis az újszülöttben
P3690	Újszülött bakteriális sepsise, k.m.n.
P3700	Veleszületett gümőkór
P3710	Veleszületett toxoplasmosis
P3720	Újszülöttkori (disszeminált) listeriosis
P3730	Veleszületett Malaria falciparum fertőzés
P3740	Egyéb veleszületett malaria
P3750	Újszülöttkori candida fertőzés
P3780	Egyéb meghatározott veleszületett fertőző és parazitás betegségek
P3781	Congenitalis varicella
P3782	Congenitalis herpes infectio
P3790	Veleszületett fertőző vagy parazitás betegség, k.m.n.
P38H0	Az újszülött omphalitise enyhe vérzéssel vagy anélkül
P3900	Újszülöttkori fertőző emlőgyulladás
P3910	Újszülöttkori kötőhártya- és könnytömlő-gyulladás
P3911	Conjunctivitis neonatorum - Chlamydia
P3912	Dacryocystitis neonatorum k.m.n.
P3930	Az újszülött húgyúti fertőzése
P3940	A bőr újszülöttkori fertőzése
P3980	Egyéb meghatározott újszülöttkori specifikus fertőzések
P3990	Az újszülött korra jellemző fertőzés, k.m.n.
P5100	Masszív vérzés az újszülött köldökzsinórjából
P5180	Az újszülött egyéb köldökzsinór-vérzése
P5190	Az újszülött köldökzsinór-vérzése, k.m.n.
P5400	Újszülöttkori vérhányás
P5410	Újszülöttkori melaena
P5420	Újszülöttkori végbél vérzés
P5430	Egyéb újszülöttkori gyomor-bél vérzés
P5440	Újszülöttkori mellékvese vérzés
P5450	Újszülöttkori bőrvérzés
P5460	Újszülöttkori vaginalis vérzés
P5480	Egyéb, meghatározott újszülöttkori vérzések
P5490	Újszülöttkori vérzés, k.m.n.
P5700	Magicterus isoimmunisatio következtében
P5780	Egyéb, meghatározott magicterus
P5790	Magicterus, k.m.n.
P5800	Újszülöttkori sárgaság a bőr zúzódása miatt
P5810	Újszülöttkori sárgaság vérzés miatt
P5820	Újszülöttkori sárgaság fertőzés miatt
P5830	Újszülöttkori sárgaság polycythaemia miatt
P5840	Az anyából átjutott vagy az újszülött gyógyszerei okozta sárgaság
P5850	Újszülöttkori sárgaság a lenyelt anyai vér miatt
P5880	Újszülöttkori sárgaság egyéb, meghatározott excesszív haemolysis miatt
P5890	Újszülöttkori sárgaság excesszív haemolysis miatt, k.m.n.
P5900	Koraszüléssel társult újszülöttkori sárgaság
P5910	Epebesűrűsödéses (inspissatiós) syndroma
P5920	Újszülöttkori sárgaság egyéb és k.m.n. eredetű májsejtkárosodástól
P5930	Anyatej-inhibitor okozta újszülöttkori sárgaság
P5980	Újszülöttkori sárgaság egyéb meghatározott okok miatt
P5990	Újszülöttkori sárgaság, k.m.n.
P6100	Átmeneti újszülöttkori thrombocytopenia
P6110	Újszülöttkori polycythaemia
P6120	Koraszülött anaemiája
P6130	Veleszületett anaemia magzati vérvesztés miatt
P6140	Egyéb veleszületett anaemiák, m.n.o.

P6150	Átmeneti újszülöttkori neutropenia
P6160	Egyéb átmeneti újszülöttkori véralvadási zavarok
P6180	Egyéb meghatározott perinatális haematologiai rendellenességek
P6190	Perinatális haematologiai rendellenesség, k.m.n.
P7000	Gestatiós diabeteses anya gyermekének syndromája
P7010	Cukorbeteg anya gyermekének syndromája
P7020	Újszülöttkori diabetes mellitus
P7030	Iatrogen újszülöttkori hypoglycaemia
P7040	Egyéb újszülöttkori hypoglycaemia
P7100	Tehéntej hypocalcaemia újszülöttben
P7110	Egyéb újszülöttkori hypocalcaemia
P7120	Újszülöttkori hypomagnesaemia
P7130	Újszülöttkori tetania calcium- vagy magnézium-hiány nélkül
P7140	Átmeneti újszülöttkori hypoparathyreosis
P7180	A calcium-magnézium anyagcsere egyéb átmeneti újszülöttkori rendell.
P7190	A calcium-magnézium anyagcsere átmeneti újszülöttkori rendell., k.m.n.
P7200	Újszülöttkori struma, m.n.o.
P7210	Átmeneti újszülöttkori hyperthyreosis
P7220	A pajzsmirigyműködés egyéb átmeneti újszülöttkori rendell. m.n.o.
P7280	Egyéb meghatározott átmeneti újszülöttkori endocrin rendellenességek
P7281	Neonatalis transitoricus hypoparathyreosis
P7290	Átmeneti újszülöttkori endokrin rendellenesség, k.m.n.
P7400	Újszülöttek késői metabolikus acidosisa
P7410	Az újszülött dehydratiója
P7420	Az újszülött nátriumháztartásának zavarai
P7430	Az újszülött káliumháztartásának zavarai
P7440	Az újszülött egyéb átmeneti elektrolit-zavarai
P7450	Az újszülött átmeneti tyrosinaemiája
P7480	Egyéb átmeneti anyagcsere zavarok az újszülöttben
P7490	Az újszülött átmeneti anyagcsere zavara, k.m.n.
P75H0	Meconium-ileus (E84.1+)
P7600	Meconium "dugó" syndroma
P7610	Az újszülött átmeneti bélelzáródása
P7620	Tejbesűrűsödés (inspissatio) okozta bélelzáródás
P7680	Egyéb meghatározott bélelzáródás az újszülöttben
P7690	Újszülöttkori bélelzáródás, k.m.n.
P77H0	Enterocolitis necrotisans a magzatban és az újszülöttben
P7800	Újszülöttkori bélátfúródás
P7810	Egyéb újszülöttkori hashártyagyulladás
P7820	Újszülöttkori vérhányás és vérszékelés a lenyelt anyai vér miatt
P7830	Nem fertőzéses eredetű újszülöttkori hasmenés
P7880	Egyéb meghatározott emésztőszervi rendellenességek, k.m.n.
P7890	Az emésztőrendszer újszülöttkori rendellenessége, k.m.n.
P8000	Hidegártalom syndroma
P8080	Egyéb hypothermia az újszülöttben
P8090	Az újszülött hypothermiája, k.m.n.
P8100	Az újszülött környezeti okú túlmelegedése
P8180	Az újszülött hőszabályozásának egyéb meghatározott zavarai
P8190	Az újszülött hőszabályozásának zavarai, k.m.n.
P8300	Sclerema neonatorum
P8310	Újszülöttkori erythema toxicum
P8320	Nem haemolyticus betegség okozta hydrops foetalis
P8330	A magzat, újszülött jellegzetes egyéb és nem meghatározott oedemája
P8340	Az újszülött emlőduzzanata
P8350	Veleszületett hydrocele
P8360	Újszülött köldökpolypusa
P90H0	Újszülöttkori görcsök
P9100	Újszülöttkori agyi ischaemia
P9110	Újszülött szerzett periventricularis cystái
P9120	Újszülöttkori agylágyulás
P9130	Az újszülött cerebralis ingerlékenysége
P9140	Újszülöttkori cerebralis depressio
P9150	Újszülöttkori coma

P9180	Az újszülött agyi állapotának egyéb meghatározott zavarai
P9190	Az újszülött agyi állapotának zavara, k.m.n.
P9200	Újszülöttkori hányás
P9210	Újszülöttkori regurgitatio és felöklendezés
P9220	Az újszülött lassú etethetősége
P9230	Az újszülött alultáplálása
P9240	Az újszülött túltáplálása
P9250	Az újszülött szopási nehézsége
P9280	Az újszülött egyéb táplálási problémái
P9290	Az újszülött táplálási problémája, k.m.n.
P93H0	Reakciók és mérgezések a magzatnak és az újszülöttnek adott szerektől
P9400	Átmeneti újszülöttkori myasthenia gravis
P9410	Veleszületett fokozott izomtónus
P9420	Veleszületett csökkent izomtónus
P9480	Az újszülött izomtónusának egyéb rendellenességei
P9490	Az újszülött izomtónusának rendellenessége, k.m.n.
P9600	Veleszületett veseelégtelenség
P9610	Anyai kábítószer-fogyasztás miatt fellépő újszülötti elvonási tünetek
P9620	Az újszülött kezelésére alkalm. szerektől kialakuló elvonási tünetek
P9640	A terhesség befejeződése, magzat és újszülött
Z3700	Egyszeres élveszülés
Z3720	Ikerszülés
Z3730	Ikerszülés: egy élve és egy halva született
Z3750	Többszörös ikrek szülése
Z3760	Többszörös ikrek szülése: néhány élve született
Z3880	Többszörös ikerszülés, szülés helye, k.m.n.
Z3790	Szülés, k.m.n.

Maternal BNO codes reporting more than one live birth from the same pregnancy will be handled as two (O8400, O8401, O8410, O8411, O8421, O8481, O8491, Z3720, Z3750, Z3760) or three (O8402, O8412, O8420, O8422, O8480, O8482, O8490, O8492) live birth outcomes in the analyses.

b) Offspring disease codes (BNO) specific for live birth (in Hungarian)

BNO	Description
Z3800	Újszülött, szülés kórházban
Z3810	Újszülött, szülés a kórházon kívül
Z3820	Újszülött, egyes, születési hely, k.m.n.
Z3830	Ikerszülött, szülés a kórházban
Z3840	Ikerszülött, szülés kórházon kívül
Z3850	Ikerszülött, szülés helye, k.m.n.
Z3860	Többszörös iker, szülés a kórházban
Z3870	Többszörös ikerszülött, szülés a kórházon kívül
Z3880	Többszörös ikerszülés, szülés helye, k.m.n.

c) Maternal intervention codes (OENO) specific for live birth (in Hungarian)

OENO	Description
57400	Császármetszés – corporalis, longitudinalis
57410	Császármetszés – cervicalis, transversalis
57420	Császármetszés – extraperitonealis
57421	Császármetszés sterilizálással

d) Offspring intervention codes (OENO) specific for live birth (in Hungarian)

OENO	Description
12660	Szívkatéterezés alapvizsgálat
12730	Szívkatéterezés, vénás percután behatolással
12731	Szívkatéterezés, vénás feltárásos behatolással
12740	Szívkatéterezés, vénás transseptális behatolással

12750	Szívkatéterezés, egyéb artériás percután behatolással
12751	Szívkatéterezés, artéria femorális behatolással
12752	Szívkatéterezés, artéria brachiális behatolással
12754	Szívkatéterezés, artériás feltárásos behatolással
12780	Szívkatéterezés-transthoracalis behatolással
50100	Punctio ventriculi cerebri, drain
50216	Cranialis meningocele és encephalocele reconstuctio
50230	Ventriculo-atrialis shunt beültetés
50240	Ventricularis shunt revisioja
50342	Spinalis meningocele és myelocele, reconstruction
50343	Extra-intr.spin.lipomával komb.meningo-myeloc.műtét
50361	Lumbo-peritonealis shunt
52174	Choanalis atresia miatt végzett műtét
52740	Szájüreg plasztikai helyreállítása
52750	Lágyszájpadplasztika
52751	Keményszájpadplasztika
52752	Kemény- és lágyszájpadplasztika, egy ülésben
52753	Szájpadrekonstrukció, előzetes műtét után
52910	Exstirpatio cystae colli lateralis
53114	Tracheostomia
53344	Hörgőfistula zárása izomlebeny plasztikával
53471	Sutura diaphragmae
53472	Reconstructio diaphragmae
53474	Reconstructio diaphragmae, alloplasticaval
53475	Duplicatio diaphragmae
53552	Defectus artef.septi interauric.cordis transvasalis
53829	Coarctatio aortae műtéte /újszülött /
54210	Oesophagostomia cervicalis
54270	Sutura oesophagei p. cervicalis
54271	Sutura oesophagei p. thoracalis
54273	Occlusio fistulae oesophago-trachealis/bronchialis
54274	Cardioplastica
54275	Occlusio fistulae / stomae oesophagei
54541	Duodeno-duodenostomia
54543	Ductus omphaloentericus vagy residuuma eltávolítás
54550	Resectio intestini crassi
54551	Haemicolectomia dextra
54557	Resectio intestini crassi, anastomosis instrument.
54560	Colectomia
54570	Vékonybél anastomosis (bypass)
54581	Ileo-transversostomia
54590	Colo-colostomia
54687	Reconstructio malrotationis intestinorum
54853	Megacolon congenitum definitiv műtéte
5486A	Rectoplastica posterior sagittalis sec.Pena
54865	Magas/intermediaer recto-analis atresia def. műtéte
54965	Reconstr.ani definitiv., alacsony atresia ani miatt
55125	Choledocho-enterostomia
55160	Reconstr. duct. hepatici seu choledochi
55168	Choledochus-cysta eltávolítás, epeút reconstruction
55340	Hernioplastica umbilicalis
55350	Reconstructio parietis abdominis
55358	Gastroschisis műtéte
55359	Omphalocele műtéte
55360	Reconstructio parietis abdominis c. implant.
55361	Reconstructio laparoscopica parietis abdominis cum implantate
55369	Reconstructio laparoscopica parietis abdominis cum conversion
55390	Hernioplastica herniae intraabdominalis
55541	Nephrectomia radicalis
55570	Pyelon plast.et res.pyeloureteralis Andersen-Hynes
55604	Ureteroendoscopos resection
55621	Ureterotomia, alsó szakasz
55631	Ureter resectio + anastomosis

55650	Ureterocutaneostomia
5567A	Neoimplantatio ureteris sec. Politano – Leadbetter
5567B	Neoimplantatio ureteris sec. Cohen
55671	Anastomosis uretero-ureteralis termino-terminalis
55672	Anastomosis uretero-ureteralis latero-lateralis
55673	Revisio anastomosis ureteris
55784	Húgyhólyag sutura
55820	Húgycső congenitalis billentyű resectioja
55980	Ureterkatéter felvezetés
55983	Ureter strictura katéteres tágítása
55985	Ureterkatéter - dupla J – felhelyezés
56130	Scrotum és tunica vaginalis reconstruction
56240	Orchidopexia
56303	Funiculocele resection
56310	Mellékhere cysta kiirtása
56330	Epididymectomia
56342	Funiculus és mellékhere reconstruction
56511	Ovarialis cysta eltávolítás (Bonney műtét)
58286	Syndactylia csontos szétválasztása, kézen
58400	Amputatio digiti manus
58402	Amputatio digiti manus secondarius
58450	Amputatio digiti pedis
58981	Oldalsó inkomplett ajakhasadék zárása
58982	Ajak és külső száj plastica, Le Mesurier szerint
58983	Ajak és külső száj plastica, Millard szerint
58984	Ferde archasadék (macrostoma) korrekciója
58985	Ajak- és külső szájplasztika
58986	Ajakkorrekció ajakplasztika után
58987	Median ajakhasadék zárása
92250	Immunglobulin pótlás (1 egység = 20 ml) újszülöttek ellátása esetén

e) HBCS codes specific for live birth (in Hungarian)

HBCS	Description
15 7110	Újszülött, születési súly 999 g alatt
15 7120	Újszülött, születési súly 1000-1499 g, jelentős műtéttel
15 7130	Újszülött, születési súly 1000-1499 g, jelentős műtét nélkül
15 7140	Újszülött, születési súly 1500-1999 g, jelentős műtéttel
15 715Z	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, súlyos problémával
15 7160	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, közepes problémával
15 7170	Újszülött, születési súly 1500-1999 g, jelentős műtét nélkül, egyéb problémával
15 7180	Újszülött, születési súly 2000-2499 g, jelentős műtéttel
15 719Z	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, súlyos problémával
15 7200	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, közepes problémával
15 7210	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, normális újszülött diagnózissal
15 7220	Újszülött, születési súly 2000-2499 g, jelentős műtét nélkül, egyéb problémával
15 7230	Újszülött, születési súly 2499 g felett, jelentős műtéttel
15 7240	Újszülött, születési súly 2499 g felett, kisebb hasi műtéttel
15 7260	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, közepes problémával
15 7270	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, normális újszülött diagnózissal
15 7280	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, egyéb problémával
15 7300	Újszülött, áthelyezve 5 napos kor előtt, helyben született
15 7310	Újszülött, áthelyezve 5 napos kor előtt, máshol született
15 7330	Jelentős szív-érrendszeri műtétek újszülött korban
15 7331	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel
15 7332	Jelentős szív-érrendszeri műtétek újszülött korban, 5 napot meghaladó gépi lélegeztetéssel és NO adással
15 734Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napot nem meghaladó gépi lélegeztetéssel
15 735Z	Újszülött, születési súly 2499 g felett, jelentős műtét nélkül, súlyos problémával, 5 napnál hosszabb gépi lélegeztetéssel

Note that these HBCS codes may contain additional cases, because the listed maternal disease (BNO) codes are NOT obligatory part of most of these HBCS categories.

f) BNO, OENO and HBCS codes specific for foetal defect (in Hungarian)
See subsections (e) to (i) at the „Elective termination (foetal defect)" definitions.

g) Technical definition of „live birth with foetal defect" cases in the Amendment 1 analyses

The following pregnancy outcomes are considered to be „live birth" cases:

- Report of maternal disease codes (BNO) specific for live birth, and/or
- Report of offspring disease codes (BNO) specific for live birth, and/or
- Report of intervention codes (OENO) specific for live birth, and/or
- Report of HBCS codes specific for live birth; and/or
- Record of offspring personal TAJ number in the OEP database.

The following pregnancy outcomes are considered to be „live birth with foetal defect":

- Live birth as defined above, and at least one of the following reports in the relevant time period (from 8 months before live birth, up to 1 year after live birth):
    - Report of maternal disease code (BNO) specific for foetal defect; and/or
    - Report of offspring disease code (BNO) specific for foetal defect; and/or
    - Report of offspring intervention codes (OENO) specific for foetal defect; or
    - Report of maternal intervention codes (OENO) specific for foetal defect.

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Live birth without congenital anomaly

a) BNO, OENO, HBCS and TAJ codes specific for live birth (in Hungarian)
See subsections (a) to (g) at the „Live birth with foetal defect" definitions.

b) BNO, OENO and HBCS codes specific for foetal defect (in Hungarian)
See subsections (e) to (i) at the „Elective termination (foetal defect)" definitions.

c) Technical definition of „live birth without congenital anomaly" cases in the Amendment 1 analyses

d)

The following pregnancy outcomes are considered to be „live birth without foetal defect":

Live birth as defined above, without any of the following reports in the relevant time period (from 8 months before live birth, up to 1 year after live birth):

- Report of maternal disease code (BNO) specific for foetal defect; and/or
- Report of offspring disease code (BNO) specific for foetal defect; and/or
- Report of offspring intervention codes (OENO) specific for foetal defect; or
- Report of maternal intervention codes (OENO) specific for foetal defect.

In case of multiple pregnancy outcome reports in the same pregnancy (with the same outcome or with different outcomes), specific rules apply as specified in Annex 3.1.3.

Annex 3.1.3. Specific rules for multiple pregnancy outcomes in the same mother

All pregnancy outcomes in the OEP database will be tried to match one and only one of the investigated categories:

- ectopic pregnancy
- spontaneous abortion
- elective termination (foetal defects)
- elective termination (no foetal defects or unknown)
- stillbirth with foetal defects
- stillbirth without foetal defects
- live birth with congenital anomaly
- live birth without congenital anomaly

In pregnancies where **none of these pregnancy outcomes** (as defined above) were reported, the pregnancy outcome will be categorized as **„Unidentified / unknown"**. The planned analysis of pregnancies without identified pregnancy outcome is detailed in Section 9.7.9.

In pregnancies where more than one reported pregnancy outcome are present, specific redundance-removing rules and code hierarchy rules are applied as specified in sections Annexes 3.1.3.1 – 3.1.3.3.

Annex 3.1.3.1. Pregnancies where more than one outcome is allowed

Note that several BNO and OENO codes make plausible multiple pregnancy outcomes from the same pregnancy (e.g. twin pregnancies). These pregnancies will are analysed as two or more separate pregnancy outcomes in the analyses.

Code	Description (in Hungarian)	Multiple oucomes allowed
BNO		
O3000	Ikerterhesség	2 outcome
O3010	Hármas ikerterhesség	3 outcome
O3020	Négyes ikerterhesség	4 outcome
O3080	Többes terhesség egyéb	>2 outcome
O3090	Többes terhesség, k.m.n.	>2 outcome
O3110	Továbbviselt többes terhesség valamely magzat korai vetélése után	SA + ≥1 outcome
O3120	Továbbviselt többes terhesség magzat intrauterin elhalása után	SB + ≥1 outcome
O3180	Többes terhesség egyéb szövődményei	≥2 outcome
O3250	Veszélyezt. ikerterhesség fekvési és tartási rendellenességek miatt	≥2 outcome
O3260	Veszélyeztetett terhesség vegyes fekvés (többes terhességben) miatt	≥2 outcome
O6610	Elakadt szülés az ikrek összeakadása miatt	≥2 outcome
O8330	Élő magzat szülése hasűri terhességben	EP + LB, 1 pregnancy
O8400	Többes szülés, valamennyi spontán	≥2 LB
O8401	Ikerszülés, valamennyi spontán	≥2 LB

O8402	Hármas vagy többes szülés, valamennyi spontán	≥3 LB
O8410	Többes szülés, valamennyi fogóval és vacuum extractorral	≥2 LB
O8411	Ikerszülés, valamennyi fogóval és vacuum extractorral	≥2 LB
O8412	Hármas vagy többes szülés, valamennyi fogóval és vacuum extractorral	≥3 LB
O8420	Többes szülés, valamennyi császármetszéssel	≥2 LB
O8421	Ikerszülés, valamennyi császármetszéssel	≥2 LB
O8422	Hármas vagy többes szülés, valamennyi császármetszéssel	≥3 LB
O8480	Egyéb többes szülés	≥2 LB
O8481	Egyéb ikerszülés	≥2 LB
O8482	Egyéb hármas vagy többes szülés	≥3 LB
O8490	Többes szülés, k.m.n.	≥2 LB
O8491	Ikerszülés, k.m.n.	≥2 LB
O8492	Hármas vagy többes szülés, k.m.n.	≥3 LB
P0150	Ikerterhességből származó magzat vagy újszülött	≥2 outcome
P5030	Vérvesztés az ikertestvérbe (foeto-foetalis)	≥2 outcome
P5050	Magzati vérvesztés az ikertestvér elvágott köldökzsinórján keresztül	≥2 outcome
Z3720	Ikerszülés	≥2 LB
Z3730	Ikerszülés: egy élve és egy halva született	SB + LB
Z3740	Ikerszülés: mindkettő halva született	2 SB
Z3750	Többszörös ikrek szülése	≥3 LB
Z3760	Többszörös ikrek szülése: néhány élve született	SB + ≥2 LB
Z3770	Többszörös ikrek szülése, mind halva született	≥3 SB
Z3830	Ikerszülött, szülés a kórházban	≥2 LB
Z3840	Ikerszülött, szülés kórházon kívül	≥2 LB
Z3850	Ikerszülött, szülés helye, k.m.n.	≥2 LB
Z3860	Többszörös iker, szülés a kórházban	≥3 LB
Z3870	Többszörös ikerszülött, szülés a kórházon kívül	≥3 LB
Z3880	Többszörös ikerszülés, szülés helye, k.m.n.	≥3 LB
OENO		
57526	Többes terhesség reductio	ET + ≥1 outcome
57527	Selectiv foeticid ikerterhességben	ET + ≥1 outcome

Annex 3.1.3.2. Rules of redundance removal

It is expected that pregnancy outcomes will be detected in a redundant way in most pregnancies (because of multiple codes with different coding dates but belonging to the same pregnancy outcome). Redundancy removing rules are specified below.

Outcome	Redundance removing rules with justification
ectopic pregnancy („EP”)	Repeated EP codes in the same mother within 12 weeks: a single EP outcome (date = earliest reported date).

	Justification: a biologically plausible interval between two consecutive EP outcomes: at least 12 weeks (4 weeks for regeneration + 8 weeks to detect the second EP)
spontaneous abortion („SA")	Repeated SA codes in the same mother within 12 weeks: a single SA outcome (date = earliest reported date). *Justification: a biologically plausible interval between two consecutive SA outcomes: at least 12 weeks (4 weeks for regeneration + 8 weeks to detect the second SA)*
elective termination without foetal defect („ET")	Repeated ET codes in the same mother within 12 weeks: a single ET outcome (date = earliest reported date). *Justification: a biologically plausible interval between two consecutive ET outcomes: at least 12 weeks (4 weeks for regeneration + 8 weeks to perform the second ET)*
elective termination with foetal defect („ET_FD")	Repeated ET_FD codes in the same mother within 12 weeks: a single ET_FD outcome (date = earliest reported date). *Justification: see at the EP outcome.*
stillbirth without foetal defect („SB")	Repeated SB codes in the same mother within 26 weeks: a single SB outcome (date = earliest reported date). *Justification: a biologically plausible interval between two consecutive SB outcomes: at least 26 weeks (4 weeks for regeneration + 22 weeks pregnancy before the second SB). Note that fetal death before 22 weeks of gestation is categorized as spontaneous abortion in the EMEA guideline.*
stillbirth with foetal defect („SB_FD")	Repeated SB_FD codes in the same mother within 26 weeks: a single SB_FD outcome (date = earliest reported date). *Justification: see at the SB outcome.*
live birth without cong. anomaly („LB")	Repeated LB codes in the same mother within 32 weeks: a single LB outcome (date = earliest reported date). *Justification: a biologically plausible interval between two consecutive LB outcomes: at least 32 weeks (4 weeks for regeneration + 28 weeks pregnancy before the second LB).*
live birth with cong. anomaly („LB_FD")	Repeated LB_FD codes in the same mother within 32 weeks: a single LB_FD outcome (date = earliest reported date). *Justification: see at the LB outcome.*

The relevance of the above biological considerations will be checked by analysing the distribution of time intervals between consecutive reports of the same outcomes. These distributions will be plotted in the final report. It is assumed that redundant codes are temporalily close to each other while the independent pregnancy outcomes are temporally not related. The visual analysis of the inflexion points of the distribution plots might further support the above specified biomedical considerations.

Annex 3.1.3.3. Rules of hierarchy in case of conflicting pregnancy outcome codes

In cases where **different pregnancy outcomes** were reported for the same pregnancy in the below specified time periods, a hierarchy of outcome diagnoses will be applied as follows.

Application sequence	Conflicting pregnancy outcome codes	Approved outcome	Neglected outcome
Rules to be applied before redundancy removal			
1.	elective termination with foetal defect (ET_FD) code and elective termination without foetal defect (ET) code within 12 weeks	ET_FD	ET
2.	stillbirth with foetal defect (SB_FD) code and stillbirth without foetal defect (SB) code within 26 weeks	SB_FD	SB
3.	live birth with cong. anomaly (LB_FD) code and live birth without cong. anomaly (LB) code within 32 weeks	LB_FD	LB
Rules to be applied following redundance removal			
4.	spontaneous abortion (SA) code and ectopic pregnancy (EP) code within 12 weeks	EP	SA
5.	ectopic pregnancy (EP) code and elective termination (ET) code within 12 weeks	EP	ET
6.	ectopic pregnancy (EP) code and elective termination with foetal defect (ET _FD) code within 12 weeks	EP	ET_FD
7.	ectopic pregnancy (EP) code followed by stillbirth with foetal defect (SB_FD) code within 26 weeks	SB_FD	EP
8.	ectopic pregnancy (EP) code followed by stillbirth without foetal defect (SB) code within 26 weeks	SB	EP
9.	ectopic pregnancy (EP) code followed by live birth with congenital anomaly (LB _FD) code within 32 weeks	LB_FD	EP

10.	ectopic pregnancy (EP) code followed by live birth without congenital anomaly (LB) code within 32 weeks	LB	EP
11.	elective termination without foetal defect (ET) code followed by stillbirth with foetal defect (SB_FD) code within 26 weeks	SB_FD	ET
12.	elective termination without foetal defect (ET) code followed by stillbirth without foetal defect (SB) code within 26 weeks	SB	ET
13.	elective termination without foetal defect (ET) code followed by live birth with foetal defect (LB_FD) code within 32 weeks	LB_FD	ET
14.	elective termination without foetal defect (ET) code followed by live birth without foetal defect (LB) code within 32 weeks	LB	ET
15.	spontaneous abortion (SA) code andelective termination without foetal defect (ET) code within 12 weeks	SA	ET
16.	spontaneous abortion (SA) code and elective termination with foetal defect (ET_FD) code within 12 weeks	ET_FD	SA
17.	spontaneous abortion (SA) code followed by stillbirth without foetal defect (SB) code within 26 weeks	SB	SA
18.	spontaneous abortion (SA) code followed by stillbirth with foetal defect (SB_FD) code within 26 weeks	SB_FD	SA
19.	spontaneous abortion (SA) code followed by live birth without congenital anomaly (LB) code within 32 weeks	LB	SA
20.	spontaneous abortion (SA) code followed by live birth with congenital anomaly (LB_FD) code within 32 weeks	LB_FD	SA
21.	elective termination with foetal defect (ET_FD) code followed by stillbirth with foetal defect (SB_FD) code within 26 weeks	SB_FD	ET_FD
22.	elective termination with foetal defect (ET_FD) code followed by stillbirth without foetal defect (SB) code within 26 weeks	SB_FD	ET_FD; SB
23.	elective termination with foetal defect (ET_FD) code followed by live birth with	LB_FD	ET_FD

	foetal defect (LB_FD) code within 32 weeks		
24.	elective termination with foetal defect (ET_FD) code followed by live birth without foetal defect (LB) code within 32 weeks	LB_FD	ET_FD; LB
25.	stillbirth without foetal defect (SB) code and live birth without cong. anomaly (LB) code within 26weeks	SB	LB
26.	stillbirth without foetal defect (SB) code and live birth with cong. anomaly (LB_FD) code within 26weeks	SB_FD	SB; LB_FD
27.	stillbirth with foetal defect (SB_FD) code and live birth with cong. anomaly (LB_FD) code within 26weeks	SB_FD	LB_FD
28.	stillbirth with foetal defect (SB_FD) code and live birth without cong. anomaly (LB) code within 26weeks	SB_FD	LB

Annex 3.1.4. Protocol Amendment 2 changes in the identification of pregnancy outcomes

Protocol Amendment 2 does not change the rules described in Annex 3.1.3, neither on the identification of the following pregnancy outcomes:

- ectopic pregnancy
- spontaneous abortion
- elective termination
- stillbirth
- live birth

However, the identification of cases with fetal defects / congenital anomalies within elective termination, stillbirth and live birth have been amended. The rationale for this amendment was that the rate of live births with congenital anomalies was found to be unexpectedly high, both in the drug-exposed and in the unexposed pregnancies. According to the applied criteria of Protocol Amendment 1, about 35 – 40% of the evaluated births were classified as congenital anomaly cases (irrespective of drug exposure). This rate is about ten times higher than the previously published 3-5% malformation rates in Hungary (Acs et al., 2010; National_Institute_for_Health_Development, 2013b). Dilution of true cases would prevent the detection of drug-related teratogenicity risk signals, therefore we decided to restrict the Amendment 1 criteria for the identification of malformations. The restriction of malformation definitions is approached in three ways: a) exclusion of mild anomalies from all analyses; b) exclusion of outpatient reports in sensitivity analyses; and c) analyses by code subgroups.

Annex 3.1.4.1. Justification for the exclusion of mild cases

It is a common practice in teratogenicity studies to exclude mild anomalies like congenital dysplasia of the hip, congenital inguinal hernia or large haemangioma (Czeizel et al., 2011). The European Surveillance of Congenital Anomalies published an explicite listing of BNO codes for minor anomalies which shall not be reported unless there are co-existing major anomalies (EUROCAT, 2013a). Accordingly, the restricted criteria of congenital anomalies in our study follows the EUROCAT recommendations and exclude all records of minor anomalies listed in **Table 3.1.4.1.A** from the Amendment 2 analyses.

Table 3.1.4.1.A: Excluded minor anomalies in the Amendment 2 analyses.

Q6640	Pes calcaneovalgus
Q6560	Instabil csípő
Q1050	A könnycsatorna veleszületett elzáródása és szűkülete
Q3810	Ankyloglossia
Q5310	Nem descendált here, egyoldali
Q6690	A lábak rendellenessége, k.m.n.
Q8250	Veleszületett, nem daganatos anyajegy
Q6660	A láb egyéb veleszületett, valgus jellegű deformitásai
Q6620	A lábközépcsontok varus állása
Q6550	A csípő veleszületett k.m.n. subluxatiója
Q5250	A szeméremajkak összenövése
Q8990	Veleszületett rendellenesség, k.m.n.
Q6760	Pectus excavatum

Q6800	A fejbiccentő izom veleszületett deformitása
Q5390	Nem descendált here, k.m.n.
Q6680	A láb egyéb veleszületett deformitásai
Q5320	Nem descendált here, kétoldali
Q3140	Veleszületett (gége eredetű) stridor
Q6650	Veleszületett lúdtalp
Q4000	Veleszületett, hypertrophiás pylorus szűkület
Q6540	A csípő veleszületett kétoldali subluxatiója
Q6530	A csípő veleszületett egyoldali subluxatiója
Q6270	Veleszületett vesico-uretero-renalis reflux
Q8330	Járulékos mellbimbó
Q7530	Nagyfejűség (macrocephalia)
Q6630	A lábak egyéb, varus jellegű veleszületett rendellenességei
Q6770	Pectus carinatum
Q1800	Kopoltyúív eredetű üreg, sipoly, tömlő
Q6740	A koponya, arc és állkapocs egyéb veleszületett rendellenességei
Q6780	A mellkas egyéb veleszületett deformitásai
Q1810	Fül előtti üreg és tömlő
Q1700	Járulékos fül
Q7600	Rejtett gerinchasadék (spina bifida occulta)
Q1030	A szemhéj egyéb veleszületett rendellenességei
Q1890	Az arc és nyak veleszületett rendellenessége, k.m.n.
Q3820	Nagynyelvűség (macroglossia)
Q1790	A fül veleszületett rendellenessége, k.m.n.
Q6700	Arc- aszimmetria
Q5300	Ectopiás here
Q6100	Veleszületett solitaer vesecysta
Q3200	A légcső falának veleszületett lágyulása
Q2700	A köldökverőér hiánya vagy hypoplasiája
Q6750	A gerinc veleszületett deformitása
Q1750	Elálló fülkagyló
Q4300	Meckel-gurdély
Q1740	A fül helyzeti rendellenessége
Q6670	Boltíves láb (pes cavus)
Q1820	A kopoltyúív egyéb rendellenességei
Q6850	A láb hosszú csontjainak veleszületett, k.m.n. görbülete
Q4010	Veleszületett hiatus-hernia
Q6840	A sípcsont és szárkapocscsont veleszületett görbülete
Q6730	Ferdefejűség (plagiocephalia)
Q7650	Nyaki borda
Q2610	Perzisztáló bal véna cava superior
Q5270	A szeméremtest egyéb veleszületett rendellenességei
Q4320	A vastagbél egyéb veleszületett működési rendellenességei
Q1730	Egyéb módon szabálytalan alakú fül
Q6720	Hosszúfejűség (dolichocephalia)
Q6330	Hyperplasiás és óriás vese
Q7520	Hypertelorismus
Q1720	Kisfülűség
Q5230	Imperforált szűzhártya
Q6830	A combcsont veleszületett görbülete
Q1020	Veleszületett szemhéjbefordulás
Q1850	Kisszájúság
Q1350	Kék színű ínhártya

Annex 3.1.4.2. Justification for the exclusion of outpatient cases

Congenital anomalies are typically severe, requiring hospitalization and complex medical treatment. Inpatient records of congenital anomalies are considered to be more reliable than

reporting of disease codes indicative for congenital anomalies in the outpatient setting. However, there are severe anomalies (e.g. polydactylia) which do not always require hospitalization. To balance between the advantages and disadvantages of the exclusion of outpatient reports from the analyses, we plan to include both inpatient and outpatient cases in the analyses; except for two sensitivity analyses where isolated outpatient reports (in patients with a single outpatient report of a relevant disease code), or all outpatient reports (in patients without inpatient report of a relevant disease code) will not be considered as indicative for congenital anomaly cases.

Annex 3.1.4.3. Analysis by code subgroups

Ideally, congenital anomaly studies should not focus on overall anomaly rate but should consider all unique anomalies as well as their potential combinations, since a) known teratogenic drugs induce specific congenital anomalies without affecting other anomaly rates and overall congenital anomaly rate; and b) most known teratogen drugs lead to congenital syndromes with a characteristic pattern of unique congenital anomaly types (Banhidy et al., 2005). However, this theoretical approach is hardly feasible due to the high number of relevant codes and their potential combinations. Calculating with 171 anomaly specific BNO codes, 14 535 dual and 818 805 triple code combinations could rise. For comparison, the available dataset in this study includes ~493 000 live births with an expected overall number of 14 800 – 24700 congenital anonaly cases (assuming a 3-5% congenital anomaly rate). Systematic investigation of free anomaly combinations is not the practice in the scientific literature and will not be implemented in this study.

The separate investigation of unique codes indicative for congenital anomalies is compromised by their low incidence and sometimes by the use of alternative codes with synonymous content, which issues are typically overcome by the analysis of homogenous code groups instead of unique codes. The European Surveillance of Congenital Anomalies published a recommended sub-groupping of ICD-10 based BNO codes specific for congenital anomalies (EUROCAT, 2013b). This grouping system consists of a general analysis (“all anomalies”), separate analyses by organ systems (e.g. “nervous system”, “congenital heart defects”, etc), and subgroups of codes within organ systems (e.g. “ventricular septum defect” and “atrial septum defect” within congenital heart defects). For the listing of EUROCAT code groups, please see **Table 3.1.4.3.B**. Note that chromosomal abnormalities (EUROCAT subgroups al88-93) are not investigated in this study.

In this study, all EUROCAT organ system code groups will be evaluated (al2, al10, al15, al17, al34, al101, al40, al49, al52, al58, al61; see on **Figure 3.1.4.3.A**). In addition, EUROCAT code subgroups within organ systems will also be evaluated where >80% statistical power is expected (al97, al21, al22, al55, al59, al66, al67, al81; see **Table 3.1.4.3.B**). The statistical power estimates in this protocol amendment are based on the annual number of the relevant BNO codes in the OEP database in 2005 (**Table 3.1.4.3.B**). Power estimations were aimed to show an at least 2x increase in the rate of congenital anomalies, assuming an 1:500 case:control ratio and 0.5% butoconazole exposure among pregnancies (butoconazol exposure was 0.55% and 0.28% in the first trimester and in the 2nd-3rd month, respectively). For code groups, the number of unique code reports were

added together, neglecting possible co-reporting of codes within the same patient. This simplification may lead to overestimation of case numbers and statistical power – which is a conservative assumption in the study planning phase. Under these assumptions, the annual number of cases required for 80% power was 288, and for 90% power was 514. Exact statistical power calculation will be conducted and reported for all Amendment 2 congenital anomaly analyses in the study report, based on true patient numbers and exposure data.

Statistical power estimation was also applied to all unique congenital anomalies included in any of the EUROCAT code (sub)groups. Individual anomaly codes with >80% estimated power will also be investigated separately (Q383, Q639, Q623, Q649, Q638, Q621; see on **Figure 3.1.4.3.A**).

A custom code group merging the EUROCAT al67 subgroup ("Hip dislocation and / or dysplasia") with BNO code Q659 ("congenital deformity of hip, unspecified") will also be analysed, since Q659 was frequently reported and is closely related to the al67 EUROCAT code group. This custom code group is marked as RG12.

In addition, custom subgroups complementer to the above analyses within organ system code groups will also be investigated (RG01, RG03, RG10, RG11, RG13, RG14, see on **Figure 3.1.4.3.A**).

Beyond the above analyses, special coonsiderations apply to two further congenital anomaly definitions (al100, and RG04), as detailed in Annex 3.4.3.2.

In total, the Amendment 2 congenital anomaly case-control analyses will apply the following 33+2 alternative definitions of congenital anomalies (**Table 3.1.4.3.A**). For the listing of relevant ICD-10 codes, see **Table 3.1.4.3.B**.

Table 3.1.4.3.A. Alternative definitions of congenital anomalies in the Amendment 2 analyses.

Number of alternative definitions	Description	Group IDs	Source
1	All anomalies pooled	al1	EUROCAT
11	Organ systems	al2, al10, al15, al17, al34, al101, al40, al49, al52, al58, al61	EUROCAT
8	EUROCAT subgroups within organ systems, with adequate statistical power	al97, al21, al22, al55, al59, al66, al67, al81	EUROCAT
1	custom subgroups within organ systems	RG12	custom

6	individual codes with adequate statistical power	Q383, Q639, Q623, Q649, Q638, Q621	custom
6	complementer subgroups within organ systems	RG01, RG03, RG10, RG11, RG13, RG14	custom
In summary: 33 alternative definitions of congenital anomalies for standard analyses			
+1	*Special considerations: persistent ductus arteriosus in term babies*	al100	EUROCAT
+1	*Special considerations: abdominal wall defects incl. intervention codes*	RG04	custom

For the details of Amendment 2 analyses of congenital anomalies, please see Annex 3.4.3.

Table 3.1.4.3.B. Description of congenital anomaly code groups in Amendment 2 analyses

ID	(Sub)group name	Included codes*	Sum of code reports in the first year at OEP in 2005**	Assumed stat. power*** to detect a 2x odds ratio in the 2005-2011 period	Analysis of this (sub)group in Amendment 2	First year reports as % of reports in the first 8 years in the OEP database
EUROCAT al1	**ALL ANOMALIES**	Q-chapter, D215, D821, D1810, P350, P351, P371	>30000	>> 90%	YES	97.5%
EUROCAT al2	**Nervous system**	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07	2095	>90%	YES	100%
EUROCAT al3	Neural tube defects	Q00, Q01, Q05	28	<< 80%	*as part of al2*	100%
EUROCAT al4	Anencephalus and similar	Q00	0	<< 80%	*as part of al2*	100%
EUROCAT al5	Encephalocele	Q01	0	<< 80%	*as part of al2*	100%
EUROCAT al6	Spina bifida	Q05	28	<< 80%	*as part of al2*	100%
EUROCAT al7	Hydrocephalus	Q03	131	<< 80%	*as part of al2*	100%
EUROCAT al8	Microcephaly	Q02	64	<< 80%	*as part of al2*	100%
EUROCAT al9	Arhinencephaly / holoprosencephaly	Q041, Q042	0	<< 80%	*as part of al2*	100%
EUROCAT al10	**Eye**	Q10-Q15	145	<< 80%	YES	100%
EUROCAT al11	Anophthalmos / microphthalmos	Q110, Q111, Q112	0	<< 80%	*as part of al10*	100%
EUROCAT al12	Anophthalmos	Q110, Q111	0	<< 80%	*as part of al10*	100%
EUROCAT al13	Congenital cataract	Q120	36	<< 80%	*as part of al10*	100%
EUROCAT al14	Congenital glaucoma	Q150	10	<< 80%	*as part of al10*	100%
EUROCAT al15	**Ear, face and neck**	Q16, Q17, Q18	61	<< 80%	YES	100%
EUROCAT al16	Anotia	Q160	0	<< 80%	*as part of al16*	100%
EUROCAT al17	**Congenital Heart Defects**	Q20-Q26	4821	>90%	YES	95.3%

EUROCAT al97	Severe CHD	Q200, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q234, Q251, Q262	259	~80%	YES	100%
EUROCAT al18	Common arterial truncus	Q200	0	<< 80%	*as part of al17, al97, and RG01*	n.a.
EUROCAT al19	Transposition of great vessels	Q203	19	<< 80%	*as part of al17, al97, and RG01*	100%
EUROCAT al20	Single ventricle	Q204	0	<< 80%	*as part of al17, al97, and RG01*	n.a.
EUROCAT al21	VSD	Q210	792	>90%	YES	98.5%
EUROCAT al22	ASD	Q211	2104	>90%	YES	90.6%
EUROCAT al23	AVSD	Q212	85	<< 80%	*as part of al17, al97, and RG01*	100%
EUROCAT al24	Tetralogy of Fallot	Q213	39	<< 80%	*as part of al17, al97, and RG01*	100%
EUROCAT al25	Triscuspid atresia and stenosis	Q224	0	<< 80%	*as part of al17, al97, and RG01*	n.a.
EUROCAT al26	Ebstein's anomaly	Q225	0	<< 80%	*as part of al17, al97, and RG01*	n.a.
EUROCAT al27	Pulmonary valve stenosis	Q221	185	<< 80%	*as part of al17 and RG01*	100%
EUROCAT al28	Pulmonary valve atresia	Q220	18	<< 80%	*as part of al17 and RG01*	100%
EUROCAT al29	Aortic valve atresia/stenosis	Q230	40	<< 80%	*as part of al17, al97, and RG01*	100%
EUROCAT al30	Hypoplastic left heart	Q234	10	<< 80%	*as part of al17, al97, and RG01*	100%
EUROCAT al31	Hypolastic right heart	Q226	0	<< 80%	*as part of al17, al97, and RG01*	n.a.
EUROCAT al32	Coarctation of aorta	Q251	48	<< 80%	*as part of al17, al97, and RG01*	100%
EUROCAT al33	Total anomalous pulm venous return	Q262	0	<< 80%	*as part of al17, al97, and RG01*	n.a.

EUROCAT al100	PDA as only CHD in term infants (GA +37 weeks)	Q250	709 (including preterm births)	>90%	as part of al17; and in a separate model considering gestational age and co-reported conditions	98.6%
custom RG01	Congenital heart defects, other	al17 codes not belonging to al21, al22, al97, al100.	957	>90%	YES	100%
EUROCAT al34	**Respiratory**	Q30-Q34	370	80-90%	YES	89.8%
EUROCAT al35	Choanal atresia	Q300	24	<< 80%	*as part of al34*	100%
EUROCAT al36	Cystic adenomatous malf of lung	Q3380	12	<< 80%	*as part of al34*	100%
EUROCAT al101	**Oro-facial clefts**	Q35-Q37	276	~80%	YES	100%
EUROCAT al102	Cleft lip with or without cleft palate	Q36, Q37	187	<< 80%	*as part of al101*	100%
EUROCAT al103	Cleft palate	Q35	89	<< 80%	*as part of al101*	100%
EUROCAT al40	**Digestive system**	Q38-Q45, Q790	1226	>90%	YES	88.8%
EUROCAT al41	Oesophageal atresia with or without tracheaoesophageal fistula	Q390-Q391	34	<< 80%	*as part of al40 and RG03*	100%
EUROCAT al42	Duodenal atresia or stenosis	Q410	17	<< 80%	*as part of al40 and RG03*	100%
EUROCAT al43	Atresia or stenosis of other parts of small intestine	Q411-Q418	10	<< 80%	*as part of al40 and RG03*	100%
EUROCAT al44	Ano-rectal atresia and stenosis	Q420-Q423	68	<< 80%	*as part of al40 and RG03*	100%
EUROCAT al45	Hirschsprung's disease	Q431	30	<< 80%	*as part of al40 and RG03*	100%
EUROCAT al46	Atresia of bile ducts	Q442	11	<< 80%	*as part of al40 and RG03*	100%

EUROCAT al47	Annular pancreas	Q451	0	<< 80%	*as part of al40 and RG03*	n.a.
EUROCAT al48	Diaphragmatic hernia	Q790	47	<< 80%	*as part of al40 and RG03*	100%
custom Q383	Digestive system, "Other Congenital Malformations Of Tongue"	Q383	847	>90%	YES	85.0%
custom RG03	Digestive system, other	al40 codes excluding Q383	347	80-90%	YES	100%
EUROCAT al49	**Abdominal wall defects**	Q792, Q793, Q795	21	<< 80%	YES	100%
EUROCAT al50	Gastroschisis	Q793	0	<< 80%	*as part of al49*	n.a.
EUROCAT al51	Omphalocele	Q792	0	<< 80%	*as part of al49*	n.a.
custom RG04	Abdominal wall defects, and/or disease indicative interventions	Q792, Q793, Q795; OENO 55340, 55350, 55358, 55359, 55360, 55361, 55369	21	<< 80%	analysed in a separate model, with longer patient follow-up (3 years)	6.0%
EUROCAT al52	**Urinary**	Q60-Q64, Q794	4201	>90%	YES	96.4%
EUROCAT al53	Bilateral renal agenesis including Potter syndrome	Q601, Q606	0	<< 80%	*as part of al52 and RG10*	n.a.
EUROCAT al54	Renal Dysplasia	Q614	26	<< 80%	*as part of al52 and RG10*	100%
EUROCAT al55	Congenital hydronephrosis	Q620	239	~80%	YES	100%
EUROCAT al56	Bladder exstrophy and / or epispadia	Q640, Q641	12	<< 80%	*as part of al52 and RG10*	100%
EUROCAT al57	Posterior urethral valve and / or prune belly	Q6420, Q794	0	<< 80%	*as part of al52 and RG10*	n.a.

custom Q639	Congenital malformation of kidney, unspecified	Q639	1407	>90%	YES	94.2%
custom Q623	Other obstructive defects of renal pelvis and ureter	Q623	705	>90%	YES	100%
custom Q649	Congenital malformation of urinary system, unspecified	Q649	680	>90%	YES	91.9%
custom Q638	Other specified congenital malformations of kidney	Q638	380	80-90%	YES	96.7%
custom Q621	Congenital occlusion of ureter	Q621	243	~80%	YES	100%
custom RG10	Urinary, other	al52 codes, except for Q620, Q639, Q623, Q649, Q638, Q621	927	>90%	YES	98.6%
EUROCAT al58	**Genital**	Q50-Q52, Q54-Q56	664	>90%	YES	83.9%
EUROCAT al59	Hypospadia	Q54	503	>90%	YES	98.1%
EUROCAT al60	Indeterminate sex	Q56	0	<< 80%	*as part of al58 and RG11*	n.a.
custom RG11	Genital, other	al58 excluding al59	161	<< 80%	YES	57.9%
EUROCAT al61	**Limb**	Q65-Q74	19255	>90%	YES	99.3%
EUROCAT al62	Limb reduction	Q71-Q73	49	<< 80%	*as part of al61 and RG13*	100%
EUROCAT al63	Upper limb reduction	Q71	38	<< 80%	*as part of al61 and RG13*	100%
EUROCAT al64	Lower limb reduction	Q72	11	<< 80%	*as part of al61 and RG13*	100%
EUROCAT al65	Complete absence of a limb	Q710, Q720, Q730	0	<< 80%	*as part of al61 and RG13*	n.a.
EUROCAT al66	Club foot – talipes equinovarus	Q660	238	~80%	YES	95.6%

EUROCAT al67	Hip dislocation and / or dyspasia	Q650-Q652, Q6580, Q6581	14307	>90%	YES	99.4%
EUROCAT al68	Polydactyly	Q69	127	<< 80%	*as part of al61 and RG13*	100%
EUROCAT al69	Syndactyly	Q70	166	<< 80%	*as part of al61 and RG13*	100%
custom RG12	Hip dislocation and / or dyspasia, including "congenital deformity of hip, unspecified"	al67 code(s) and/or Q659	18397	>90%	YES	99.4%
custom RG13	Limb, other	al61 excluding Q660, Q650-652, Q6580, Q6581, Q659	620	>90%	YES	100%
	Other anomalies / syndromes					
EUROCAT al104	Skeletal dysplasias	Q7402, Q77, Q7800, Q782-Q788, Q8716	76	<< 80%	*as part of RG14*	100%
EUROCAT al75	Craniosynostosis	Q750	81	<< 80%	*as part of RG14*	100%
EUROCAT al76	Congenital constriction bands / amniotic band	Q7980	11	<< 80%	*as part of RG14*	100%
EUROCAT al79	Situs inversus	Q893	0	<< 80%	*as part of RG14*	n.a.
EUROCAT al80	Conjoined twins	Q894	0	<< 80%	*as part of RG14*	n.a.
EUROCAT al81	Congenital skin disorders	Q80-Q82	365	80-90%	YES	96.6%
EUROCAT al82	Teratogenic syndromes with malformations	Q86, P350, P351, P371	0	<< 80%	*as part of RG14*	n.a.
EUROCAT al83	Fetal alcohol syndrome	Q860	0	<< 80%	*as part of RG14*	n.a.
EUROCAT al84	Valproate syndrome	Q8680	0	<< 80%	*as part of RG14*	n.a.
EUROCAT al86	Maternal infections resulting in malformations	P350, P351, P371	0	<< 80%	*as part of RG14*	n.a.

EUROCAT al105	Genetic syndromes + microdeletions	Q4471, Q6190, Q7484, Q751, Q754, Q7581, Q87, Q936, D821 Exclude: Q8703, Q8704, Q8706, Q8708, Q8724, Q8726	66	<< 80%	*as part of RG14*	100%
EUROCAT al108	Sequences	Q606, Q6410, Q794, Q7980, Q8703, Q8708, Q8724, Q8980	55	<< 80%	*as part of RG14*	100%
custom RG14	Other anomalies/syndromes, other	any code(s) of al75-76, al79-80, al82-84, al86, al104-105, al108 subgroups	295	~80%	YES	100%

*Minor anomalies listed in Table 3.1.4.1.A are always excluded; **The sum of codes may overestimate the number of cases (multiple codes could be reported from the same case); ***Assumptions: reports in subsequent calendar years belong to new cases; annual OEP reporting rate in 2005 represents the 2005-2011 period; case:control ratio 1:500; butoconazol exposition ratio 0.5% among pregnancies (butoconazol exposure was 0.55% and 0.28% in the first trimester and in the 2^{nd}-3^{rd} month, respectively).

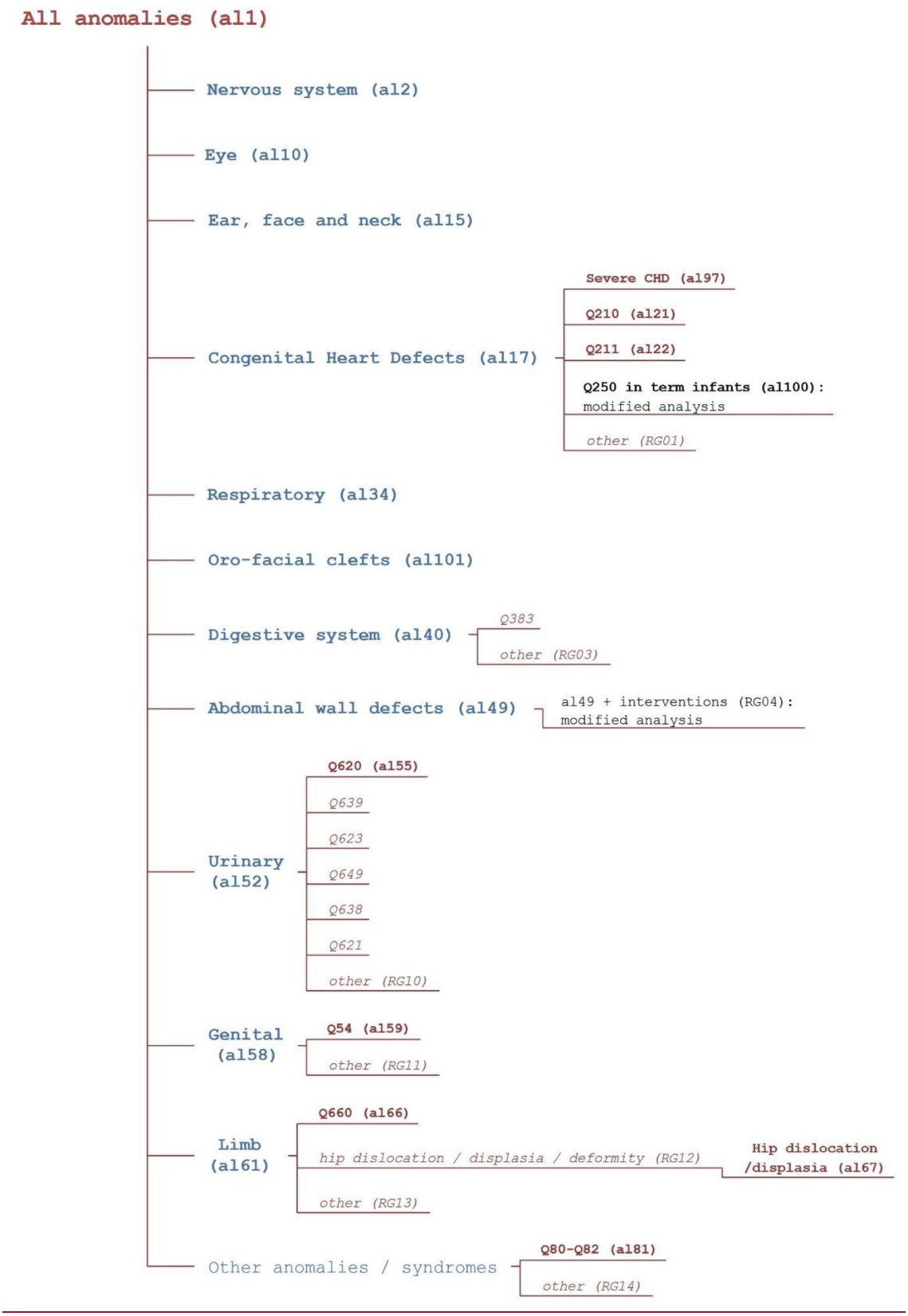

Figure 3.1.4.3.A: Congenital anomaly code groups and subgroups in Amendment 2 analyses. Bold items represent EUROCAT subgroups. For the underlying definitions, please see Table 3.1.4.3.B.

Annex 3.2. Determination of gestational age in the OEP database

Definition of the investigated time periods

According to the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP, 2005), all studies should try to address drug exposure in specified time periods of the pregnancy:

- Before conception
- First trimester
- After first trimester
- During all pregnancy
- Unknown

Therefore, attempts are taken to separately analyse drug exposure as a potential risk factor in these time periods.

Exposure „during all pregnancy" is interpreted as exposure in both the first trimester and after the first trimester; and exposure „before pregnancy" is interpreted as exposure in the last 30 days before Day 1.

Allocation of cases to pregnancy exposure periods is not mutually exclusive. E.g. mothers with „During all pregnancy" exposure shall also be counted at exposure in „First trimester" and „After first trimester", and shall be included in the case-control analyses of all relevant exposure periods.

Cases not exposed to the tested drug in the time period ranging from minus 30 days before Day 1 of pregnancy to the date of pregnancy outcome (unless otherwise indicated in the specific analyses) will be classified as „not exposed".

Determination of the first day of pregnancy in the OEP database

The first day of pregnancy is defined as the first day of the last menstrual period (LMP). This date is not included in the OEP database, therefore the first day of pregnancy is calculated back from the reported date of an obligatory investigation in pregnant women (AFP screening test after 16 completed weeks of pregnancy).

AFP screening test is reported to the OEP database as follows:

OENO code	Description (in Hungarian)
OENO 2662G	AFP meghatározása szérumban
OENO 26670	Alfa-fetoprotein meghatározása szérumban (terhes)

Based on clinical recommendations and expert consultations, biological sample collection for the AFP test in pregnancy and reporting practice to the OEP database show the following temporal pattern:

- typical period of blood sample collection for AFP screening in clinical practice: from Day 106 to Day 136 of pregnancy.

- median day of blood sample collection for AFP screening in clinical practice: Day 120 of pregnancy.

- typical delay between blood sample collection for AFP screening and reported date to OEP in a pilot analysis of 21 pregnancies across Hungary: range -2 to +30 days, mean 2.5 days, median 0 days, interquartile range 0 to +2 days. Accordingly, a 1-day delay will be assumed in the calculations.

Therefore, calculating the first day of pregnancy from the reported date of AFP screening allows a mean estimate of about 120+1=121 days with an inherent uncertainty of about ±2 weeks.

Late reports of AFP sampling were noticed in some cases (up to 30 days in a small-scale pilot analysis). Therefore, the gestational age calculated from the reported AFP date will be overwritten with an ***alternative estimate*** as follows:

Criteria of „late AFP reporting":

the reported AFP date is 97 - 150 days later than the earliest report of any pregnancy-specific condition (BNO) or intervention (OENO).

Calculation of Day 1 in cases / controls with late AFP reporting:

First day of pregnancy = the date of the earliest report of any "pregnancy-specific" condition/intervention, minus 30 days (the latter is the minimal gestational age at diagnosis of pregnancy).

In this context, all of the following condition and intervention codes are considered to be "pregnancy-specific":

- All HBCS, BNO and OENO codes listed in Annex 3.1.1. and Annex 3.1.2.
- Pregnancy-related BNO and OENO codes not specific to pregnancy outcome (as tabulated below)

"Pregnancy-specific" BNO codes not specific to the pregnancy outcome:

BNO	Description (in Hungarian)
N9400	Középidős fájdalom (Mittelschmerz)
O....	any BNO code starting with „O" and not listed as outcome-specific codes in Annex 3.1.2.
P9630	Az újszülött tág koponyavarratai
P9640	A terhesség befejeződése, magzat és újszülött
P9650	Méhen belüli beavatkozások szövődményei, m.n.o.
P9680	A perinatális időszakban keletkező egyéb meghatározott állapotok
P9690	A perinatális időszakban keletkező állapot, k.m.n.
S3762	Terhes méh sérülése
S3767	Placenta sérülése
Z3210	Terhesség, bizonyított
Z33H0	Véletlen észlelt terhes állapot
Z3400	Terhesgondozás első terhesség esetén
Z3410	Egyéb egészségügyi ellátás terhes személynél

Z3480	Terhesgondozás egyéb normális terhességben
Z3490	Terhesgondozás, k.m.n.
Z3500	Terhesgondozás korábbi terméketlenséget követően
Z3510	Terhesgondozás korábbi vetélést követően
Z3520	Terhesség problematikus és terhelő szülészeti előzményt követően
Z3540	Terhesgondozás sokat szült nőnél
Z3550	Terhesgondozás idős (késői) elsőszülőnél
Z3560	Terhesgondozás igen fiatal elsőszülőnél
Z3570	Terhesgondozás szociálisan veszélyeztetett terhesnél
Z3580	Terhesgondozás egyéb veszélyeztetett terhesnél
Z3590	Terhesgondozás k.m.n. veszélyeztetett terhesség esetében
Z3600	Chromosoma rendellenesség szűrése születés előtt
Z3610	Szülés előtti AFP szűrés
Z3620	Születés előtti szűrés magzatvízből
Z3630	Születés előtti UH és egyéb fiz. módszerű szűrés fejl. rendell. iránt
Z3640	Magzati növekedési elmaradás eszközös, ultrahangos szűrése
Z3650	Magzati isoimmunisatio szűrése születés előtt
Z3680	Születés előtti szűrés, egyéb
Z3690	Születés előtti szűrővizsgálat, k.m.n.
Z3900	Szülés utáni ellátás és vizsgálat

"Pregnancy-specific" intervention (OENO) codes not specific to pregnancy outcome:

OENO	Description (in Hungarian)
14780	Chorion biopsia
14781	Chorion biopsia, transvaginalis, UH vezérelt
14782	Chorion biopsia, transabdominalis, UH vezérelt
36140	Terhességi transabdominalis UH vizsgálat
36141	Terhességi transvaginalis UH vizsgálat
44811	Pathológiás terhes folyamatos kórházi gondozása
46010	Első trimesteri terhesgondozói vizit
46020	Második trimesteri terhesgondozói vizit
46030	Harmadik trimesteri terhesgondozói vizit
57200	Kimeneti fogó műtét, episiotomia nélkül
57210	Kimeneti fogó műtét, episiotomiaval
57220	Üregi fogó műtét
57240	Magzati fej forgatása, fogóval
57250	Medencevégű magzat extractioja
57251	Extendalt lábak kifejtése
57252	Felcsapott karok kifejtése
57254	Fej kifejtése
57255	Belső lábrafordítás és extractio
57256	Külső fordítás, extractio nélkül
57260	Fogó alkalmazása a hátul jövő fejre
57270	Egyszerű fartartásos szülés vezetése
57271	Kettőzött fartartásos szülés vezetése
57280	Fej vacuum-extractio
57300	Burokrepesztés
57320	Belső fordítás és extractio
57380	Episiotomia és ellátása
57530	Amniocentesis
57540	Intrauterin transfusio
57551	Magzati vérvétel
57560	Lepényleválasztás
57561	Lepény retentio manuális kiürítése
57580	Resutura dehiscentiae episiotomiae
57581	Gátsérülés ellátása - szülés után

57582	Másodlagosan gyógyuló episiotomia ellátása
57591	Méhűri betapintás szülés után (Bumm kanál)
57593	Uterus űr tamponálása (szülészeti)
82510	Külső fordítás hosszfekvésbe, harántfekvésű magzat
82511	Külső fejrefordítás, medencevégű magzat
82520	Retroflectált terhes uterus kiemelése
82530	Tartási v. forgási rendellenesség korrekció
89610	CTG szülés alatt
89611	CTG terhesség alatt (NST)
89612	CTG terheléses
91318	Diabeteses gravidák, illetve a gestatios diabetesesek időszakos ellenőrzése
92250	Immunglobulin pótlás (1 egység = 20 ml) újszülöttek ellátása esetén
92501	Szülésindítás intraut. gyógyszer adagolással
92510	Szülésindítás iv. gyógyszer adagolással
92530	Szülésindítás im. gyógyszer adagolással
92540	Szülésindítás burokrepesztéssel
92600	Szülés levezetése
92604	Praeeclampsias terhes szülés vezetése, észlelése
94750	Terhesség alatti torna

Note that many of the above conditions / interventions occur in late-stage pregnancy or around childbirth. However, assuming a maximum 60 days delay of late AFP sampling reports in the OEP database, the calculation formula of the alternative Day 1 estimate will rely only on those BNO/OENO/HBCS pregnancy codes which have been reported in the first trimester.

By the introduction of the alternative estimate in late AFP reporting pregnancies, the uncertainty of AFP-based calculation of day 1 is expected to be lowered. Nevertheless, pregnancies fulfilling the criteria of „late AFP reporting" will be excluded from a sensitivity analysis (CA_sensitivity_9).

As an additional measure against the remaining uncertainty, two further sensitivity analyses are included in the protocol with alternative definitions of Day 1 of pregnancy:

analysis ID	**First day of pregnancy**
main analysis	{AFP reported date} minus 121 days
CA_sensitivity_1	{AFP reported date} minus (121+14) days
CA_sensitivity_2	{AFP reported date} minus (121-14) days

Relevant time period of AFP screening tests

AFP screening tests reported after the pregnancy outcome are not considered to be related to the current pregnancy.

AFP screening tests reported more than 26 weeks before the pregnancy outcome are not considered to be related to the current pregnancy. The rationale for the 26-week time period is that most births occur until the completion of gestation week 42 (i.e. not more than 26 weeks later than the earliest recommended time of AFP test).

Handling of pregnancy outcomes with 2 or more reported „AFP date" in the relevant time period

In cases with two or more reported AFP screening tests in the relevant time period, the date of the first AFP test will be taken into account (the second screening test in this time period is interpreted as a confirmatory examination).

Handling of pregnancy outcomes without reported AFP screening test in the relevant time period

- Ectopic pregnancy, spontaneous abortion, elective termination (no foetal defects or unknown): gestational age is not calculated from AFP screening test dates, because these outcomes most frequently precede the completed 16 weeks of gestation. The assumed mean gestational age in these cases is described in Section 9.7.1, together with the planned sensitivity analyses.

- Elective termination due to foetal defects: In cases without a reported AFP screening test in the relevant time period, the gestational age at elective termination will be assumed to be 14 weeks. Rationale: in Hungary, an obligatory ultrasound investigation of pregnant women is scheduled on the 12-13th weeks of pregnancy with the aim of early diagnosis of congenital anomalies. The earliest recommended time of AFP screening test is at the completion of gestational week 16. The assumed gestational age of 14 weeks is a mean estimate of cases with diagnosed anomalies before AFP screening.

- Late pregnancy outcomes (stillbirth and live birth): cases without reported AFP screening tests in the relevant time period will be assumed to have the average gestational age of cases belonging to the same pregnancy outcome with reported AFP screening test dates.

  Foetal defect / congenital abnormality cases and healthy controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from a sensitivity analysis (CA_sensitivity_4) of the teratogenicity case-control study.

Annex 3.3. Case-control study of spontaneous abortions in the OEP database

Annex 3.3.1. Scientific background

According to the terminology of the Guideline on the Exposure to Medical Products During Pregnancy: Need for Post-Authorisation Data, spontaneous abortions are characterised by early foetal death before 22 completed weeks of pregnancy (note that late foetal death after 22 completed weeks of pregnancy is referred to as stillbirth) (EMEA/CHMP, 2005).

Spontaneous abortions in the first 4-5 weeks of pregnancy usually remain unnoticed or are appearing as a slightly delayed and slightly more intensive menses. Accordingly, the exact frequency of spontaneous abortions can not be measured. As a rough estimate, 65-70% of all conceptions are followed by spontaneous abortion (including the symptom-free cases), and about 70% of all spontaneous abortions occur in the first trimester (Papp, 1999).

The rate of diagnosed spontaneous abortion among wanted and diagnosed pregnancies is about 15-20% (Papp, 1999).

The largest published study of drugs approved for the treatment of vaginitis (miconazole, clotrimazole, nystatin, candicidin, aminacrine, metronidazole) as risk factors for spontaneous abortion was a large-scale case-control study based on the Michigan Medicaid dataset, including pregnancy outcomes and prescription claims (Rosa et al., 1987). The study was limited to the time period of 1980 – 1983, and butoconazole was unfortunately not included in this analysis. The study compared the rate of spontaneous abortions to the rate of normal deliveries (with similar gestational age at the comparison), and also to the rate of legal abortions, in separate analyses. Clotrimazole and miconazole exposure in the preceding 120-day period increased the risk of spontaneous abortion (clotrimazole RR = 1.36, 95% CI 1.1 – 1.6; miconazole RR = 1.38, 95% CI 1.2 – 1.5) versus normal delivery, whereas large numbers of exposures to nystatin and aminacrine compounds did not show this association, suggesting that spontaneous abortions are caused by the imidazole agents clotrimazole and miconazole rather than the condition being treated. However, as an alternative explanation, the protecting effect of nystatin and aminacrine against a confounding effect of the treated condition theoretically can not be ruled out. Metronidazole exposure was also associated with an increased relative risk of spontaneous abortion vs. normal delivery (RR = 1.67, 95% CI 1.4 – 2.0). Regarding the comparisons of spontaneous and legal abortion rates, the authors argued that the use of drugs not recommended in pregnancy (like metronidazole) is biased toward more use before planned legal abortions, therefore these comparisons are less easier to interpret (Rosa et al., 1987). The definition of cases, normal delivery controls and drug exposure in the Rosa study are summarized below:

	Definition of cases	**Definition of controls**	**Drug exposure criteria**
Rosa 1987 (Rosa et al., 1987): Michigan Medicaid, 1980-1983			
main analysis	spontaneous abortions (ICD9-634-634.9) in the database (N = 4264)	inpatient deliveries with at least 180-day history in the database (only the first delivery of each women in the evaluated period) (N = 55 736)	Rx in a 120-day period before spontaneous abortion; Rx in a 120 day period, ending 180 days before delivery.
sensitivity analysis	spontaneous abortions (ICD9-634-634.9), with at least one Medicaid-reimbursed service 70-250 days before spontaneous abortion *(to exclude spontaneous abortions with insufficient medical history in the database),* and without delivery diagnosis within 6 months after spontaneous abortion *(to exclude imminent / incipient abortions)* (N = 2326)	inpatient deliveries: with at least one Medicaid-reimbursed service 270-450 days before delivery *(to exclude pregnancies with insufficient medical history in the database),* only the first delivery of each women in the evaluated period (N= 32 944)	Rx in a 120-day period before spontaneous abortion; Rx in a 120 day period, ending 200 days before delivery.

Note that due to the changes introduced in Protocol Amendment 2, all descriptive statistics and statistical analyses (including the pre-specified sensitivity analyses) described in the protocol will be conducted in two different ways:

- Analyses according to Amendment 2 (main analysis);
- Analyses according to Amendment 1 (ancillary analysis).

In the Rosa study, potential confounding factors (indication, obesity, diabetes) were mentioned but not included in the statistical analysis of spontaneous abortion risk factors. n other studies, the most important confounding variables considered were maternal age (Chan et al., 2010; Davanzo et al., 2012; Gissler et al., 2010; Gray and Wu, 2000; Howards et al., 2012; Nakhai-Pour et al., 2010; Nakhai-Pour et al., 2011; Nybo Andersen et al., 2000; Roman et al., 1992; Small et al., 2007; Sozio and Ness, 1998), and history of previous spontaneous abortions (Chan et al., 2010; Gray and Wu, 2000; Nakhai-Pour et al., 2011; Nybo Andersen et al., 2000; Roman et al., 1992; Sozio and Ness, 1998). Other confounding factors were occasionally also included in some studies, including e.g. maternal education (Chan et al., 2010; Davanzo et al., 2012; Roman et al., 1992), alcohol use (Chan et al., 2010; Gray and Wu, 2000; Howards et al., 2012; Roman et al., 1992), current smoking (Clark et al., 2011; de la Rochebrochard and Thonneau, 2002; Gray and Wu, 2000; Howards et al., 2012; Roman et al., 1992; Sozio and Ness, 1998), maternal infertility

(Small et al., 2007), maternal chronic conditions (Nakhai-Pour et al., 2010; Nakhai-Pour et al., 2011), or the use of medications suspected of increasing the risk of spontaneous abortion. Examples for the latter are nonaspirin NSAIDs (Clark et al., 2011; Nakhai-Pour et al., 2011) and antidepressants evaluated by ATC groups (Nakhai-Pour et al., 2010). Place of residence (Davanzo et al., 2012; Gissler et al., 2010; Roman et al., 1992) and calendar effect (in 5-10 year blocks) were also evaluated in some studies (Davanzo et al., 2012; Gissler et al., 2010; Nybo Andersen et al., 2000). Further potential confounders include paternal age above 40 years (de la Rochebrochard and Thonneau, 2002) or paternal smoking(Blanco-Munoz et al., 2009).

Regarding the relevant drug exposure time period before spontaneous abortion, the identified studies show substantial heterogenity (see below).

Study reference	Drug exposure criteria
(Rosa et al., 1987)	in 120 days before index date
(Gissler et al., 2010)	0-3 months before pregnancy
(Nakhai-Pour et al., 2011)	from Day 1 to index date; in 60 days before index date; in 14 days before index date
(Nakhai-Pour et al., 2010)	from Day 1 to index date; in 30 days before index date
(Howards et al., 2012)	in 12 weeks before index date, or: {from day minus 28 to day 91 (4 weeks before pregnancy + 13 completed weeks} (two data sheets)

Accordingly, the main analysis in the current study follows the Rosa study (Rosa et al., 1987), while the planned sensitivity analyses will focus on shorter drug exposure periods (60 days and 30 days before index date). For the list and technical definitions of the selected confounder parameters, please see Annex 3.3.2.

Annex 3.3.2. Technical definitions related to spontaneous abortion cases

Evidence of exposure to drug substances in the relevant time periods will be evaluated in a dichotomous way (yes/no). Any OEP-recorded prescription refill will be handled as evidence of exposure. The following active substances will be analysed:

Gynecology anti-infectives	ATC codes
butoconazole	G01AF15
miconazole (local)	G01AF04, D01AC20; G01AF20
miconazole (systemic)	A01AB09
clotrimazole	G01AF02, D01AC01
metronidazole (local)	G01AF01; D06BX01; G01AF20
metronidazole (systemic)	P01AB01, J01XD01
nystatin (local)	G01AX
nystatin (systematic)	A07AA02
Non-aspirin NSAIDs	**ATC codes**

diclofenac (local)	M02AA15, S01BC03, S01CC01
diclofenac (systemic)	M01AB05, M01AC, M01AB55
naproxen (local)	M02AA12, S01CC01
naproxen (systemic)	M01AE02
celecoxib	M01AH01, L01XX33
ibuprofen (local)	M01AE01, M02AA13
ibuprofen (systemic)	M01AE01, M01AE51, C01EB16
rofecoxib	M01AH02
indomethacin (local)	M02AA23, S01BC01
indomethacin (systemic)	M01AB01

Drug-drug combination medicinal products containing any of the listed active ingredients will be included in the analysis.

Maternal age at index date will be categorized in 5-year groups, handled as a nominal parameter.

In addition, the following confounder factors will be considered, integrated into a single propensity score:

- Evidence of previous spontaneous abortion(s)
  - YES:
    - history of BNO codes specific for spontaneous abortion in the last 4 years before index date (not including the current pregnancy outcome): *O0210, O03, O05, O06, O3110, N96H0, O2620, Z3510* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits), and/or
    - history of OENO codes specific for spontaneous abortion in the last 4 years before index date (not including the current pregnancy outcome): *56903, 56905 ;* and/or
    - report of BNO *N96H0, O2620, or Z3510* in the current pregnancy.
  - NO:
    - lack of evidences specified above

- Evidence of previous elective abortion(s)
  - YES:
    - history of BNO codes specific for elective termination in the last 4 years before index date: *O04, Z6400* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits), and/or
    - history of OENO codes specific for elective termination in the last 4 years before index date: *56900, 5744A, 5744B, 57500, 57501, 57510, 57520, 57521, 57522, 57523, 57524, 57525, 57526, 57527.*
  - NO:
    - lack of evidences specified above

- Evidence of previous live birth:
  - YES:
    - history of BNO, OENO and HBCS codes specific for live birth (for listing, see Annex 3.1.2.)in the last 4 years before index date; and/or

  - any offspring TAJ number recorded in the OEP database belonging to the same mother, in the last 4 years before index date.
- NO:
  - lack of evidences specified above

- Evidence of infertility treatment in the last 4 years:
  - YES:
    - maternal history of BNO codes in the last 4 years before index date: *N9710, N9720, N9780, N9790, N9880, N9890, Z3110, Z3120, Z3130, Z3140, Z3500;* and/or
    - maternal history of intervention OENO codes in the last 4 years before index date: *14703, 16944, 92700, 92701, 92722, 97722, 97723, 97724;* and/or
    - maternal history of HBCS codes in the last 4 years before index date: *13 6530, 13 6540, 13 6550, 13 6560.*
  - NO:
    - lack of evidences specified above

- Evidence of more than one foetus in current pregnancy
  - YES:
    - report of BNO codesin the last 120 days before index date: *O3000, O3010, O3020, O3080, O3090, O3110, O3120, O3180, O3250, O3260, O6610, O8400, O8401, O8402, O8410, O8411, O8412, O8420, O8421, O8422, O8480, O8481, O8482, O8490, O8491, O8492, P0150, P5030, P5050, Z3720, Z3730, Z3740, Z3750, Z3760, Z3770, Z3830, Z3840, Z3850, Z3860, Z3870, Z3880,* and/or
    - report of intervention OENO codes in the last 120 days before index date: *57526, 57527.*
  - NO:
    - lack of evidences specified above

- Evidence of maternal diabetes
  - YES: at least two reports as specified below, separated by at least 30 days, in the last 4 years before pregnancy or during pregnancy:
    - maternal history of BNO codes: *O2400, O2410, O2420, O2430, O2440, O2490; and/or*
    - maternal history of intervention OENO codes: *89010, 89843, 91312, 91313, 91314, 91316, 91317, 91318, 91319, 91320, 91321;* and/or
    - maternal history of prescription refill for drugs belonging to ATC A10.
  - NO:
    - lack of evidences specified above

- year of index date
  - nominal parameter, values from 2005 to 2011.

- month of index date
  - nominal parameter, values from January to December

Annex 3.3.3. Amendment 2 changes in the analysis of spontaneous abortion risk

Amendment 1 results do not indicate significant increase in risk of spontaneous abortions in butoconazole exposed pregnancies (neither in the main analysis, nor in the pre-planned sensitivity analyses). Moreover, a significant protective effect of butoconazole was found in sensitivity analyses 2 and 5. A protective effect of exposure to locally applied metronidazole, miconazole, and nystatin products was also found in a subset of the pre-planned analyses (details will be provided in the final report). The most consistent protective effect was found for clotrimazole, both in the main analysis and in the pre-planned sensitivity analyses.

Interestingly, the exposure of patients to clotrimazole and butoconazole show different time patterns. In the main analysis, we investigated drug exposure in a 120-day period before spontaneous abortion / index date and found 20388 pregnancies exposed to clotrimazole and 5466 pregnancies exposed to butoconazole. When the investigated exposure period was narrowed to the last 30 days of the same 120-day period (in sensitivity analysis 2), the number of butoconazole exposed pregnancies decreased proportionally, to about ¼ of the exposure in the main analysis (1269 pregnancies). In contrast, the number of clotrimazole exposed pregnancies remained disproportionally high (10154 pregnancies, ~ 50% of exposure in the last 120 days). This difference in exposure pattern raises that clotrimazol receiving patients tended to refill more than one prescriptions within the investigated 120-day period. If this was the case, the apparent advantage of clotrimazole could be due to more frequent dosing, i.e. better / longer-term control of fungal vaginal infecions. As alternative explanations, more frequent dosing may be a surrogate of e.g. higher compliance, better socioeconomic status, or recurrent infections (the latter would not explain the advantage of clotrimazole).

To investigate the role of dosing frequency in the protective effect of locally administered gynecologic anti-infectives, Protocol Amendment 2 replaces the current binary (yes/no) parameters of drug exposure in the spontaneous abortion regression models with appropriate numeric parameters (days of therapy, DOTs). Binary data on drug exposure to active control drugs will also be replaced with more graded, numeric exposure data in the Amendment 2 analyses.

Another change in Amendment 2 analyses will be that a proxy for maternal socioeconomic status will be introduced into the propensity score in the logistic regression model. Maternal socioeconomic status will be approximated based on the expected socioeconomic status of the micro-region of her residence. Determination of the micro-regional socioeconomic status of towns / villages in Hungary is described in Annex 3.6.

In addition, county of maternal residence and rural / urban status of maternal residence will also be integrated into the propensity score, to reflect geographic effect as a recognized confounder (Davanzo et al., 2012; Gissler et al., 2010; Roman et al., 1992).

Amendment 1 results indicated that maternal age was outside of the investigated age categories (i.e. the range of 15-45 years) in about 0.1% of pregnancies. Although these extreme values of maternal age may be biologically plausible, the extensive experience of Rxtarget Kft in OEP database analyses suggests that extreme maternal age values are most probably due to incorrect

data entry. Accordingly, the amendment 2 analyses of spontaneous abortion risk will exclude pregnancies with maternal age <15 years or maternal age >45 years).

In summary, Protocol Amendment 2 introduces the following changes in the analysis of spontaneous abortion risk:

- In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables are replaced by numeric drug exposure variables (prescription refills expressed in DOTs). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls;

- The propensity score will also include the socioeconomic status of the maternal residence at micro-region level, and rural/urban status of maternal residence, beyond the currently included variables.

- Pregnancies with maternal age <15 years or maternal age >45 years are excluded from the Amendment 2 analyses.

Annex 3.4. Case-control study of teratogenic risk in the OEP database

Annex 3.4.1. Scientific background

Definition of cases and controls

The intention of the study is to evaluate the total (birth + foetal) risk of congenital anomalies in the offspring of mothers who were exposed to the tested drugs. Accordingly, the group of „cases" is defined in this analysis as the pooled group of the following pregnancy outcomes:

- Elective termination (foetal defects)
- Stillbirth with foetal defects
- Live birth with congenital anomaly

The control group in the main analysis consists of live births without congenital anomaly, similarly to previous studies (Acs et al., 2009b; Acs et al., 2010; Czeizel and Rockenbauer, 1998; Kazy et al., 2005; Nelson and Forfar, 1971), but without matching to confounding factors (see below). In some sensitivity analyses, the control group will be defined as the pooled group of all live births and stillbirths without congenital anomaly / foetal defect (Rosa et al., 1987).

All pregnancy outcomes in these analyses will be identified as provided in Annex 3.1.

In addition, the following sensitivity analyses are planned, to test the robustness of the results:

Planned analyses of teratogenic risk	
Main analysis	
• Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly. • Controls = Live birth without congenital anomaly • Day 1 of pregnancy = {AFP reported date} minus 121 days; in pregnancies with late AFP reports an alternative Day 1 estimate will be applied (as specified in Annex 3.2.).	
Alterations from the main analysis in sensitivity analyses	
CA_sensitivity_1*	Day 1 of pregnancy = {AFP reported date} minus 135 days
CA_sensitivity_2*	Day 1 of pregnancy = {AFP reported date} minus 107 days
CA_sensitivity_3*	Controls = live births without congenital anomaly, stillbirths without foetal defect
CA_sensitivity_4*	Cases and controls without reported AFP screening test in the last 26 weeks before pregnancy outcome are excluded from the analysis
CA_sensitivity_5*	Cases = Stillbirth with foetal defects, Live birth with congenital anomaly.
CA_sensitivity_6*	Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring: BNO Q35 cleft palate BNO Q36 cleft lip BNO Q37 cleft lip, cleft palate

	OENO 52750 Lágyszájpadplasztika OENO 52751 Keményszájpadplasztika OENO 52752 Kemény- és lágyszájpadplasztika, egy ülésben OENO 52753 Szájpadrekonstrukció, előzetes műtét után OENO 58981 Oldalsó inkomplett ajakhasadék zárása OENO 58982 Ajak és külső száj plastica, Le Mesurier szerint OENO 58983 Ajak és külső száj plastica, Millard szerint OENO 58984 Ferde archasadék (macrostoma) korrekciója OENO 58985 Ajak- és külső szájplasztika OENO 58986 Ajakkorrekció ajakplasztika után OENO 58987 Median ajakhasadék zárása
CA_sensitivity_7*	Cases = Elective termination (foetal defects), Stillbirth with foetal defects, Live birth with congenital anomaly, restricted to cases with at least one of the following anomalies / interventions reported in the offspring: BNO Q7920 exomphalos BNO Q7930 gastroschisis BNO Q7940 prune belly syndrome BNO Q7950 other congenital anomalies of the abdominal wall OENO 55340 Hernioplastica umbilicalis OENO 55350 Reconstructio parietis abdominis OENO 55358 Gastroschisis műtéte OENO 55359 Omphalocele műtéte OENO 55360 Reconstructio parietis abdominis c. implant. OENO 55361 Reconstructio laparoscopica parietis abdominis cum implantate OENO 55369 Reconstructio laparoscopica parietis abdominis cum conversione
CA_sensitivity_8*	Cases = Live birth in 2005, with foetal defect / congenital anomaly reported until the end of 2012. Controls: Live birth in 2005, foetal defect / congenital anomaly NOT reported until the end of 2012.
CA_sensitivity_9	Cases and controls fulfilling the criteria of any alternative estimation of Day1 of pregnancy (see in Annex 3.2.) are excluded.

** In pregnancies with late AFP reports an alternative Day 1 estimate will be applied, as specified in Section 9.7.2. and Annex 3.2.*

Rationale for these sensitivity analyses:

Sensitivity analyses 1, 2, 4, and 9 intends to deal with the uncertainty of the calculation of the first day of pregnancy.

Sensitivity analyses 6 and 7 focus on those congenital anomalies reported in preclinical tests with butoconazole (in a single species, at high doses only): cleft palate, and abdominal wall defects, respectively (FDA, 2003).

Sensitivity analyses 3 and 5 provide alternative definitions of controls and cases, respectively, to test the robustness of the results.

Sensitivity analysis 8 deals with possible late diagnoses / late reports of congenital anomalies.

Note that due to the changes introduced in Protocol Amendment 1, all descriptive statistics and statistical analyses (including the pre-specified sensitivity analyses) described in the protocol will be conducted in two different ways:

- Analyses according to Amendment 2 (main analysis);
- Analyses according to Amendment 1 (ancillary analysis)

Time periods of drug exposure

In this analysis, drug exposure in the following periods will be evaluated:
- first trimester (Nelson and Forfar, 1971; van Gelder et al., 2011)
- first month (before organogenesis) (Acs et al., 2009a; van Gelder et al., 2011)
- second month(Czeizel et al., 1999; van Gelder et al., 2011)
- third month(Czeizel et al., 1999; van Gelder et al., 2011)
- second and third month (the critical period for congenital anomalies) (Acs et al., 2009b; Banhidy et al., 2007; Czeizel et al., 1999; Kazy et al., 2005)
- after the first trimester (Acs et al., 2009b; Kazy et al., 2005)

Confounding factors

In most epidemiological studies, the problem of confounding adds to the uncertainty in conclusions drawn. This is also true for studies on the effect of maternal drug use on birth defect risks. Different methods exist for the control of confounder factors. In a case-control study, this can be done by matching when the controls to cases are selected with, for instance, the same maternal age and other characteristics one wants to adjust for. More common, notably when large datasets are analysed, is to adjust for the confounders in the statistical analysis. The most common way to do this is by using a logistic regression model(Kallen, 2012).

In a recent series of population-based large-scale case-control studies on drug-induced congenital abnormalities in the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) 1980-1996, the following confounding factors have been considered (Acs et al., 2009b; Acs et al., 2010):

Confounding factor	Adjustment method
sex	matched controls
birth week in birth year	
district of parent's residence	
maternal age *(<20year / 20-29year / >29year)*	adjusted odds ratio
birth order *(first delivery / second or more)*	
maternal employment status *(professional-managerial-skilled worker / semi-skilled worker-unskilled worker-housewife / others)*	

fever related influenza and/or common cold *(yes / no)*	
acute maternal diseases of digestive system *(yes / no)*	
other drugs *(yes / no)*	
folic acid use *(yes / no)*	

The most consistently considered confounders in studies of other datasets were maternal age at delivery (Kazy et al., 2005; Nelson and Forfar, 1971; van Gelder et al., 2011) and parity (number of previous live births) (Kazy et al., 2005; Nelson and Forfar, 1971; van Gelder et al., 2011). In addition, the van Gelder study included a wide range of additional confounder factors, typically as binary parameters (history of miscarriages, history of induced abortions, history of stillbirths, pre-pregnancy BMI higher than 25, maternal education >12 years, fever during gestational weeks 0–12, smoking during gestational weeks 0–12, and folic acid use from 4 weeks before pregnancy through week 8 of gestation (van Gelder et al., 2011). Note that there is no available data from the OEP database on some of these potential confounders. Pre-existing diabetes was an exclusion criteria in the van Gelder study, therefore the present study also considers the potential confounding effect of diabetes (see in Annex 3.4.2.).

Some potential confounding factors including maternal employment status, folic acid use, maternal education, and smoking can not be controlled for in the present analysis, because of the lack of adequate data in the OEP database.

Pre-pregnancy body mass index neither can be controlled for in this analysis, because of the lack of adequate data in the OEP database. The mechanism behind the effect of obesity is unclear and a possible explanation is that obesity is associated with an increased risk of diabetes type 2 (Kallen, 2012). The current study will adjust the calculated risks to the confounding effect of diabetes.

The district of the mother's permanent residence is coded in Hungary in a 4-digit system, with around 3600 nominal values. Therefore, this parameter is not included in the regression model. Instead, place of residence will be categorized as „village" or „town" in all of the counties.

The indication treated is not expected to be a confounding factor in the analysis of congenital anomalies, because none of the investigated vaginal candidiasis drugs was associated with increased risk of congenital anomalies in the Rosa study (Rosa et al., 1987). Accordingly, the treated indication itself is not considered to be a confounding factor of teratogenic risk in the present study.

The selected confounding factors with their technical definitions are provided in Annex 3.4.2.

To adjust for the confounder(s) in the statistical analysis, a logistic regression model will be applied, as recommended in a recent review on the problem of confounding in studies of the effect of maternal drug use on pregnancy outcome (Kallen, 2012). The logistic regression model is a regression method to predict outcome (e.g. rate of congenital malformations) as influenced by one or more confounding factors. Logistic regression is used in analyses aiming at risk determinations in a dichotomous situation, for example, presence or absence of a malformation (Kallen, 2012).

For all analyses, odds ratio with 95% confidence intervals will be calculated (both as crude and adjusted values) as shown below. Separate tables will be presented for the main analysis and for all sensitivity analyses.

Variable	Controls N=	Cases N=	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Type of gynecology anti-infectives					
none	N (%)	N (%)	1.00	1.00	1.00
Butoconazole (local administration)					
butoconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
butoconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Miconazole (local administration)					
miconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Miconazole (systemic administration)					
miconazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
miconazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Clotrimazole (local administration)					
clotrimazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
clotrimazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nystatin (local administration)					
nystatin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

nystatin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nystatin (systemic administration)					
nystatin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
nystatin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (local administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Metronidazole (systemic administration)					
metronidazole in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
metronidazole after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Carbamazepine (systemic administration)					
carbamazepine in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
carbamazepine after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Isotretinoin (systemic administration)					
isotretinoin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Isotretinoin (local administration)					
isotretinoin in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
isotretinoin in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

isotretinoin after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lithium (systemic administration)					
lithium in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lithium after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Valproic acid (systemic administration)					
valproic acid in 1st month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in 2nd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in 2nd and/or 3rd month	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid in first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
valproic acid after first trimester	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal age at index date					
15-19 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
20-24 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
25-29 years	N (%)	N (%)	1.00	1.00	1.00
30-34 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
35-39 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
40-45 years	N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

**Crude OR: not adjusted to other drugs or to maternal age; Adjusted (1): adjusted for other drug exposure (as listed in the table) in the same pregnancy period, and for maternal age; Adjusted(2): in addition, also adjusted for all other investigated confounder factors (the latter have been integrated into a single propensity score before adjustment).*

Annex 3.4.2. Technical definitions related to the analysis of teratogenicity

Evidence of exposure to drug substances in the relevant time periods will be evaluated in a dichotomous way (yes/no). Any OEP-recorded prescription refill will be handled as evidence of exposure. The following active substances will be analysed:

Exposure to gynecology anti-infectives in the relevant time periods

Gynecology anti-infectives	ATC codes
butoconazole	G01AF15
miconazole (local)	G01AF04, D01AC20
miconazole (systemic)	A01AB09
clotrimazole	G01AF02, D01AC01
metronidazole (local)	G01AF01; D06BX01
metronidazole (systemic)	P01AB01, J01XD01
nystatin (local)	G01AX
nystatin (systematic)	A07AA02

Exposure to active control drugs in the relevant time periods

Active control drugs	ATC codes
carbamazepine	N03AF01
isotretinoin (local)	D10AD04
isotretinoin (systemic)	D10BA01
lithium	N05AN01
valproic acid	N03AG01

Maternal age at delivery (in 5-year intervals, as a nominal parameter)

Confounding variables as integrated into a single „propensity score”:

- Evidence of previous live birth in the last 4 years before current pregnancy:
  - YES:
    - history of BNO, OENO and HBCS codes specific for live birth (for listing, see Annex 3.1.2.) in the last 4 years before index date; and/or
    - any offspring TAJ number recorded in the OEP database belonging to the same mother, in the last 4 years before index date.
  - NO:
    - lack of evidences specified above

- Evidence of previous spontaneous abortion
  - YES: any of the following reports in the last 4 years before Day 1 of the current pregnancy:

  - history of BNO codes specific for spontaneous abortion: *O0210, O03, O05, O06, N96H0, O2620, O3110, Z3510* (3-digit BNO codes represent all 5-digit BNO codes starting with the indicated 3 digits);
  - history of OENO codes specific for spontaneous: *56903, 56905.*
- NO:
  - lack of evidences specified above

- Evidence of maternal diabetes
  - YES: at least two reports as specified below, separated by at least 30 days, in the last 4 years before pregnancy or during pregnancy:
    - maternal history of BNO codes: *O2400, O2410, O2420, O2430, O2440, O2490; and/or*
    - maternal history of intervention OENO codes: *89010, 89843, 91312, 91313, 91314, 91316, 91317, 91318, 91319, 91320, 91321;* and/or
    - maternal history of prescription refill for drugs belonging to ATC A10.
  - NO:
    - lack of evidences specified above

- year of birth
  - nominal parameter, values from 2005 to 2011.

- month of birth
  - nominal parameter, values from January to December

Annex 3.4.3. Amendment 2 changes in the analysis of teratogenic risk

Amendment 2 changes in the analysis of teratogenic risk include the modification of the logistic regression model, alterations in the definition of cases and controls, and changes in the planned sensitivity analyses.

There is no change in the investigated drugs and in drug exposition windows. Odds ratios with 95% confidence intervals will be calculated (both as crude and adjusted values) and presented in the same tabular outline as shown in Annex 3.4.1.

Annex 3.4.3.1. Changes in the logistic regression model of congenital anomaly risk

Similarly to model changes in the spontaneous abortion risk analyses, the logistic regression model of congenital anomaly risk will be modified in the following way:

- Pregnancies with maternal age <15 years or maternal age >45 years are excluded from the Amendment 2 analyses (for justification, please see Annex 3.3.3);
- In the regression models of the main analysis and all sensitivity analyses, binary (yes/no) drug exposure variables are replaced by numeric drug exposure variables (prescription refills expressed in DOTs). This change is consistently applied for butoconazole as well as for all therapeutic controls and active controls;
- The propensity score will also include the socioeconomic status of the maternal residence at micro-region level (see in Annex 3.6), and urban/rural status of maternal residence beyond the currently included variables.

Annex 3.4.3.2. Definition of cases and controls

In the Amendment 2 analyses of congenital anomalies, 35 alternative definitions will be applied to cases and controls. For justification and details, please see Annex 3.1.4.

For 33 of the 35 alternative definitions (al1, al2, al10, al15, al17, al34, al101, al40, al49, al52, al58, al61, al97, al21, al22, al55, al59, al66, al67, al81, Q383, Q621, Q623, Q638, Q639, Q649, RG01, RG03, RG10, RG11, RG12, RG13, and RG14; for details, please see Annex 3.1.4.), cases will be defined as live birth, stillbirth, or elective termination due to foetal defect with reported ICD codes belonging to the appropriate code groups in the relevant time period (from 8 months before live birth, up to 1 year after live birth; from 6 months before stillbirth, up to 3 months after stillbirth; or in ± 3 months around the date of elective termination).

In these analyses, controls will be defined as live births without any congenital anomaly code (as listed in EUROCAT group al1) during pregnancy or until the age of 1 year.

Special considerations apply to two further alternative definitions (al100, and RG04) as detailed below.

Special considerations for the EUROCAT subgroup al100

This EUROCAT subgroup is called "Persistent ductus arteriosus as only congenital heart defect in term infants (gestational age >37 weeks)". This subgroup will be analysed with the following modifications:

- Cases will be defined as live births,
    - with >37 weeks gestational age, and
    - with a Q250 ICD code in their first year after birth, and
    - without any other congenital heart defect anomaly codes (as listed in EUROCAT group al17) during pregnancy or until the age of 1 year.

- Controls will be defined as livebirths with >37 weeks gestational age, without any congenital anomaly codes (as listed in EUROCAT group al1) during pregnancy or until the age of 1 year.

Special considerations for the custom subgroup RG04

The intention of this custom code subgroup analysis is to focus on abdominal wall defects, a recognized nonclinical safety signal for butoconazole in the rat (see Section 7 of the protocol for details). The relevant EUROCAT code subgroup (al49) includes ICD-10 codes Q792, Q793, and Q795, which codes were hardly reported in the OEP database in 2005. The potentially relevant intervention codes OENO 55340, 55350, 55358, 55359, 55360, 55361, 55369 are not included in EUROCAT definitions but are more frequently reported to the OEP database than the ICD codes belonging to al49. Accordingly, beyond the analysis of al49, a custom subgroup of all these codes have also been formed to analyse the risk of abdominal wall defects (marked as RG12). A time-dependent analysis revealed that the interventions associated with abdominal wall defects were typically reported after the first year (see the last column of **Table 3.1.4.3.B** in Annex 3.1.4). For this reason, the case-control analysis applying the RG12 definition of congenital anomalies will be performed with the following modifications:

- Cases and controls will be restricted to live births with 3-year follow-up data (i.e. only live births in the 2005-2009 period will be included);

- Cases will be defined as live births with at least one ICD-10 or intervention code report belonging to RG12 in the first 3 years after birth;

- Controls will be defined as all other live births with 3-year follow-up data, without any other congenital anomaly codes (as listed in EUROCAT group al1) during pregnancy or until the age of 3 years.

Annex 3.4.3.3. Sensitivity analyses

For each alternative definition of cases and controls, 1 main analysis and 8 sensitivity analyses will apply as follows:

	Day1 of pregnancy = AFP-107 days*	**Day1 = AFP-121 days***	Day1 = AFP-135 days*
all outpatient reports included	Sensitivity analysis 1 (S1)	**Main analysis (M)**	Sensitivity analysis 2 (S2)
isolated outpatient reports excluded	Sensitivity analysis 3 (S3)	Sensitivity analysis 4 (S4)	Sensitivity analysis 5 (S5)
all outpatient reports excluded	Sensitivity analysis 6 (S6)	Sensitivity analysis 7 (S7)	Sensitivity analysis 8 (S8)

**In pregnancies with late AFP reports, an alternative Day 1 estimate will be applied (as specified in Annex 3.2.).*

Given that cases / controls are defined in 33+2 alternative ways and 1 main + 8 sensitivity analyses apply to all definitions, 35 x 9 = 315 separate results tables will be generated and reported. The proper identification of report tables will be supported by result table names including case definitions (one of the 35 code group names as provided in Annex 3.1.4.3) together with analysis type (M or S1-S8).

Similarly to the original protocol, the amendment 2 analyses investigate the time profile of congenital anomaly reporting after birth (see section 9.7.10.). All live births reported in the first year of the study (2005) are to be followed-up throughout the investigational time period (up to the end of 2012). For this purpose, the evaluated BNO and OENO codes are listed in Annex 3.1.2 for Amendment 1 analyses; while only those BNO and OENO codes will be evaluated in Amendment 2 analyses which are included in any of the 35 alternative congenital anomaly code groups (see Annex 3.1.4.3 for details).

Annex 3.5. Amendment 2 changes in the analysis of low birthweight

Preliminary results calculated per Protocol Amendment 1 revealed an apparent increase of low birthweight newborns from butoconazole exposed pregnancies, while clotrimazole exposure was associated with an apparent protective effect against low birthweight. Previously published studies also described a protective effect of clotrimazole against preterm birth (Banhidy et al., 2009; Czeizel et al., 2004; Czeizel et al., 2007). Note that all of the published studies analysed the same 1-2% Hungarian sample.

The descriptive analyses in our study were not controlled for potential confounders. Recognized risk factors for low birthweight include risk factors for intrauterine growth restriction (e.g. maternal cigarette smoking, alcohol and caffeine consumption, caloric intake during pregnancy, maternal height and pre-pregnancy weight, paternal weight and height, parity, history of prior low birthweight infants, maternal cardiopulmonary or renal medical conditions, infant sex and birth order (Kramer, 1987; Ota et al., 2014; Valero De Bernabe et al., 2004)). In developed countries, the far most important factor is cigarette smoking, followed by poor gestational nutrition and low pre-pregnancy weight (Kramer, 1987).

Preterm birth also contribute to elevated risk of low birthweight. Recognized risk factors for preterm birth include pre-pregnancy weight, prior history of prematurity or spontaneous abortion, cigarette smoking, uterine myomas, maternal age, maternal Hb concentration, chronic stress, employment status, maternal periodontitis, acute and chronic maternal diseases, inadequacies in prenatal care, genitourinary infections, infant gender, birth order, and district of mother's residence. (Banhidy et al., 2011b; Bashore et al., 2014; Bulut et al., 2014; Czeizel et al., 2007; Kramer, 1987; Ota et al., 2014; Valero De Bernabe et al., 2004).

Unfortunately, most of the above potential confounders can not be captured in the OEP database. As an effort to exclude any confounding by unmeasurable risk factors, a quasi-randomized study design is planned for the Amendment 2 birthweight analyses: to exclude the possibility of an association between maternal characteristics and the selection of butoconazole or clotrimazole by their gynecologists, the Amendment 2 birthweight analyses will include only unexposed pregnancies, and those pregnancies exposed to butoconazole or clotrimazole prescriptions of doctors with homogenous prescription pattern in the relevant calendar years.

Homogenous prescription pattern of a doctor is defined in the following way:

- the doctor had a valid licence in gynecology, and have prescribed at least 10 doses of (butoconazole + clotrimazole) in total in the relevant calendar year;
- and his/her butoconazole / (butoconazole + clotrimazole) prescription ratio was 0% or 100% in the relevant calendar year.

The rationale behind this patient population restriction is that different patient characteristics within the doctor's practice could underlie patient-specific drug selection decisions in non-homogenous prescription practices. In contrast, patient chracteristics probably did not shape drug selection in practices where all patients received the same (butoconazole or clotrimazole) drug.

Our pilot analyses suggest that a significant fraction of gynaecologist-years with ≥10 annual butoconazole+clotrimazole prescriptions applied a homogenous prescription pattern (**Figure 3.5.A**).

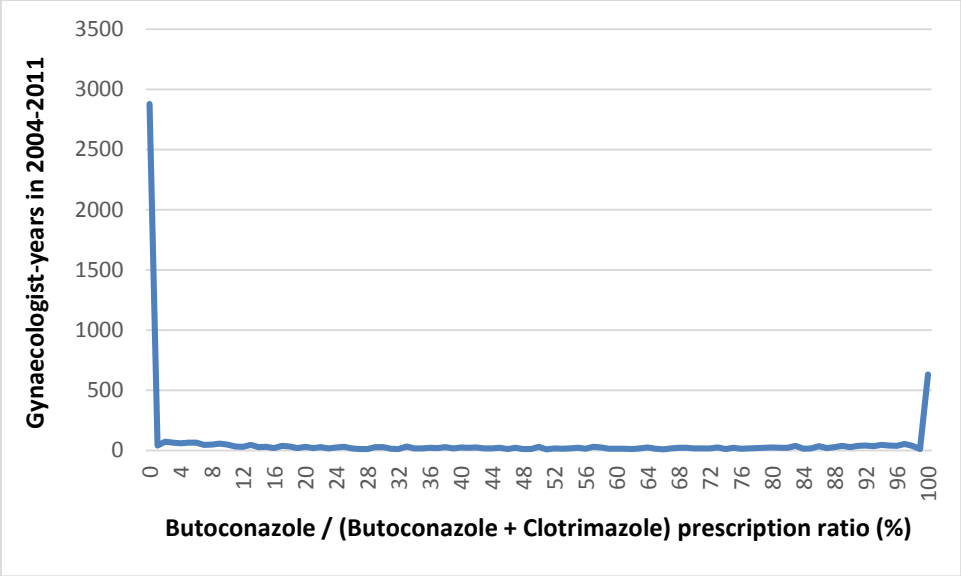

Figure 3.5.A: Histogram of gynaecologist-years in 2004-2011 with different butoconazole / (butoconazole + clotrimazole) prescription ratios. Homogenous prescription patterns are represented by the spikes at 0% and 100%. Only gynaecologist-years with at least 10 (butoconazole + clotrimazole) prescriptions are included in this chart.

Potential between-practice differences in patient characteristics are intended to be controlled for by the inclusion of the following socio-economic proxies in the logistic regression models:

- micro-regional development status of the maternal residence (as determined in Annex 3.6);
- urban / rural status of maternal residence.

The effect of butoconazole and/or clotrimazole exposure on birthweight will be analysed in the below detailed logistic regression models. All included variables are binary (yes / no) in the regression models, with "no" value as the reference case. Pregnancies with multiple / combined butoconazole and clotrimazole exposures are not excluded (unless any of the butoconazole or clotrimazole prescriptions were written by a doctor with not homogenous prescription pattern in the calendar year of prescription).

Main analysis:

$$P_{(\text{birthweight } <2500\text{g})} \sim B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, B_{21}, B_{22}, B_{23+}, C_{21}, C_{22}, C_{23+}, B_{31}, B_{32}, B_{33+}, C_{31}, C_{32}, C_{33+}$$

+ S_{HH}, S_{LHH}, S_{LHH-K}, R;

where B_{1x} and C_{1x} stand for exactly x prescribed butoconazole (B) or clotrimazole (C) therapies in the first trimester; and B_{2x}, C_{2x}, B_{3x} and C_{3x} stand for exactly x prescribed butoconazole (B) or clotrimazole (C) therapies in the second and third trimester, respectively. When x = "3+", three ore more butoconazole and clotrimazole therapies were prescribed in the indicated trimester, respectively. In the birthweight analyses, one refilled butoconazole prescription indicates one butoconazole therapy; while the prescription refill of cotrimazole vaginal tablet (3x or 6x) corresponds to 1 or 2 clotrimazole therapies, respectively. S_{HH}, S_{LHH}, and S_{LHH-K} stand for maternal residence microregional development status characteristics: deprived ("Hátrányos Helyzetű"), most deprived ("LegHátrányosabb Helyzetű"), and most deprived requiring complex interventions ("Komplex programmal segítendő leghátrányosabb helyzetű), respectively (see also Annex 3.6); and R stands for rural status of maternal residence. All included variables are binary (yes / no) variables in the regression model, all with "no" value as the reference case;

Sensitivity analyses:

$P_{(\text{birthweight } <\mathbf{2500g})}$ ~ B_{11+}, C_{11+}
+ S_{HH}, S_{LHH}, S_{LHH-K}, R;

where B_{11+} and C_{11+} stand for at least 1 prescribed butoconazole (B) and clotrimazole (C) therapy in the first trimester, respectively. Note that all included variables are binary (yes / no) in the regression models, with "no" value as the reference case.

$P_{(\text{birthweight } <\mathbf{2500g})}$ ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}
+ S_{HH}, S_{LHH}, S_{LHH-K}, R;

$P_{(\text{birthweight } <\mathbf{2500g})}$ ~ B_{D1}, B_{D2}, B_{D3+}, C_{D1}, C_{D2}, C_{D3+}
+ S_{HH}, S_{LHH}, S_{LHH-K}, R;

where B_{Dx} and C_{Dx} stand for exactly x prescribed butoconazole (B) or clotrimazole (C) therapies during all pregnancy (overall exposition in the 3 trimesters). B_{Dx} and C_{Dx} are binary (yes / no) variables in the regression model, all with "no" value as the reference case;

$P_{(\text{birthweight } <\mathbf{2000g})}$ ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, B_{21}, B_{22}, B_{23+}, C_{21}, C_{22}, C_{23+}, B_{31}, B_{32}, B_{33+}, C_{31}, C_{32}, C_{33+}
+ S_{HH}, S_{LHH}, S_{LHH-K}, R;

$P_{(\text{birthweight } <\mathbf{2000g})}$ ~ B_{11+}, C_{11+}

+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

$P_{(\text{birthweight} <\mathbf{2000g})}$ ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}
+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

$P_{(\text{birthweight} <\mathbf{2000g})}$ ~ B_{D1}, B_{D2}, B_{D3+}, C_{D1}, C_{D2}, C_{D3+}
+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

Birthweight (grams) ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}, B_{21}, B_{22}, B_{23+}, C_{21}, C_{22}, C_{23+}, B_{31}, B_{32}, B_{33+}, C_{31}, C_{32}, C_{33+}
+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

Birthweight (grams) ~ B_{11+}, C_{11+}
+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

Birthweight (grams) ~ B_{11}, B_{12}, B_{13+}, C_{11}, C_{12}, C_{13+}
+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

Birthweight (grams) ~ B_{D1}, B_{D2}, B_{D3+}, C_{D1}, C_{D2}, C_{D3+}
+ S_{HH}, S_{LHH}, $S_{LHH\text{-}K}$, R;

For all of the above analyses, crude and adjusted odds ratios, and patient numbers for all included parameters will be presented in the final report. As an example, **Table 3.5.A** shows the planned format of the main analysis results in the final report. Similar tables will be provided with the results of all sensitivity analyses.

Table 3.5.A: Planned format of the main analysis results in the final report.

Variable	Value	N (%)	OR (95% CI)*		
			crude	adjusted (1)	adjusted (2)
Butoconazole and clotrimazole exposure variables					
B_{11}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{12}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{13+}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{11}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{12}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{13+}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

B_{21}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{22}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{23+}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{21}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{22}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{23+}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{31}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{32}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
B_{33+}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{31}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{32}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
C_{33+}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Socio-economic status indicators					
S_{HH}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
S_{LHH}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
S_{LHH-K}	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
R	no	N (%)	1.00	1.00	1.00
	yes	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)

*Crude OR: univariate analyses; Adjusted(1): adjusted for all variables within the relevant table panel (all butoconazole and clotrimazole exposure variables; or all socio-economic status indicators); Adjusted(2): adjusted for all variables in the table.

To qualitatively check the assumed comparability of butoconazole and clotrimazole exposed pregnancies in the above analyses, descriptive statistics will be provided on the following measurable patient characteristics, for the following patient groups:

	Pregnancies where B_{11+} = yes	**Pregnancies where C_{11+} = yes**	**Pregnancies where B_{D1+} = yes**	**Pregnancies where C_{D1+} = yes**	**Pregnancies where B_{D1+} = no and C_{D1+} = no**
Maternal residence: **rural, S_{LHH-K} = YES**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years	N {%}	N {%}	N {%}	N {%}	N {%}
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **urban, S_{LHH-K}** = YES					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low birthweight (<2500g)	N {%}	N {%}	N {%}	N {%}	N {%}

infant in the last 4 years					
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **rural, S_{LHH} = YES**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years	N {%}	N {%}	N {%}	N {%}	N {%}
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **urban, S_{LHH} = YES**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low	N {%}	N {%}	N {%}	N {%}	N {%}

birthweight (<2500g) infant in the last 4 years					
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **rural, S_{HH} = YES**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years	N {%}	N {%}	N {%}	N {%}	N {%}
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **urban, S_{HH} = YES**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}

evidence of at least 1 low birthweight (<2500g) infant in the last 4 years	N {%}	N {%}	N {%}	N {%}	N {%}
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **rural, not deprived**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years	N {%}	N {%}	N {%}	N {%}	N {%}
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)
Maternal residence: **urban, not deprived**					
number of live births	{N}	{N}	{N}	{N}	{N}
maternal age	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}	{mean, SD}
infant sex: male	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of miscarriage in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}

evidence of at least 1 prior birth in the last 4 years*	N {%}	N {%}	N {%}	N {%}	N {%}
evidence of at least 1 low birthweight (<2500g) infant in the last 4 years	N {%}	N {%}	N {%}	N {%}	N {%}
history of maternal diabetes*	N {%}	N {%}	N {%}	N {%}	N {%}
number of maternal gynecology visits in first trimester**	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)	mean (SD); median (IQR)

*criteria: see at Annex 3.4.2. IQR, interquartile range. ** Definition of maternal gynecology visits: outpatient visit at a gynaecologist; or outpatient visit due to pregnancy-related disease/condition (the relevant codes are listed in Annex 3.2); or hospitalization due to pregnancy-related disease/condition. Hospitalization is calculated as a single gynecology visit, irrespective of hospitalization duration. The maximal number of calculated gynecology visits per day is 1.

Annex 3.6 Socio-economic status of micro-regions in Hungary

Micro-regions of Hungary were systematically characterised and ranked by a complex indicator of socioeconomic status in 2007, based on 31 parameters in 5 major groups (economic, infrastructural, societal, social, and employment characteristics)(2007; Pénzes, 2014). Based on this ranking, 94 of the 174 micro-regions were identified as deprived, of which 47 were classified as "most deprived" and among those, 33 were classified as "most deprived, needing complex intervention".

In 2011, the number of micro-regions increased to 175 when the "Ajkai" micro-region was divided to the "Devecseri" and "Ajkai" micro-regions after an industrial disaster (spill at the alumina plant Magyar Alumínium Zrt. (MAL Zrt.) Ajkai Timfoldgyar, destroying or damaging ~300 houses). The new, "Devecseri" micro-region covered the damaged area and has been classified as "most deprived, needing complex intervention" from 2011.

In the OEP database, postal code is available for the residence of all patients. Maternal residence postal codes were linked to village / town names by the postal code database of Magyar Posta (downloaded from http://www.posta.hu/ugyfelszolgalat/iranyitoszam_kereso, version 19 June 2015).

Village/town names were linked to micro-regions as listed in Appendix 1 of Act XXI of 1996, and Act CXLIX of 2010 (the latter established the newly formed "Devecseri"micro-region). Socioeconomic status of micro-regions was determined as listed in the 311/2007(17th November) Decree of the Hungarian Government. For the time period 2011-2012, the socioeconomic status of the newly formed "Devecseri" micro-region was set to "most deprived, needing complex interventions", along the 116/2011 (7th July) Decree of the Hungarian Government. This isolated mionor change could have marginal relevance in the present study, therefore the socioeconomic status of the micro-regions have been determined based on the 311/2007(17th November) Decree of the Hungarian Government.

The list of postal codes with the corresponding micro-regional socio-economic classifications is provided in a separate MS Excel file.

Micro-regional socioeconomic status of maternal residence is categorized as NH (Nem hátrányos helyzetű / not deprived), HH (hátrányos helyzetű / deprived), LHH (leghátrányosabb helyzetű / most deprived), and LHH-K (leghátrányosabb helyzetű, complex beavatkozást igénylő / most deprived requiring complex intervention). The corresponding binary variables handle these categories as mutually exclusive ones:

Binary variables	Micro-region categories			
	NH	HH	LHH	LHH-K
S_{HH}	no	yes	no	no
S_{LHH}	no	no	yes	no
S_{LHH-K}	no	no	no	yes

S_{HH}, S_{LHH}, and S_{LHH-K} will be introduced into the regression models by the following ways:

- Spontaneous abortion models: S_{HH}, S_{LHH}, and S_{LHH-K} included in the propensity score in the adjusted(2) models;
- Congenital anomaly models: S_{HH}, S_{LHH}, and S_{LHH-K} included in the propensity score in the adjusted(2) models;
- Birthweight analyses: S_{HH}, S_{LHH}, and S_{LHH-K} directly included in the regression models as indicated in Annex 3.5.