Minor Protocol Deviation Report

Study: Valproate: risk awareness survey in women of childbearing age (Valproate Survey v2.0)

General Information

Protocol References: P2024/651 / CCB 84062024000442 entitled: "Enquête AFMPS sur la connaissance des risques de tératogénicité du valproate et /'impact des mesures de minimisation des risques chez les femmes en age de procréer"

Agreement from 07-04-2025 till 30-04-2026.

Date of Report: 27-11-25

Investigator Name: Martine Sabbe

Sponsor: Federal Agency for Medicines and Health Products

HMA-EMA Catalogue of real-world data number: EUPAS1000000735

This report describes protocol updates for **logistical and administrative** reasons. These are notified to the Ethics Committee, in the form of a list as stipulated by the procedure on minor deviations of the Ethics Committee of the Hôpital Erasme[1].

Impact Assessment

There is no significant impact on the overall study design, participant safety, or data integrity. Study timelines have been revised due to administrative delays.

These minor deviations pose no risk to the participants nor have any ethical implications.

List of minor deviations and updates

Minor Deviation	Reason for Deviation	Corrective Action
Study was registered in the HMA-EMA Catalogue of real-world data number	As planned.	To be included in the Study Report.
In the definition of the target population, the term	The mutual insurers clarified that patient identification can be	To be included in the Study Report.

[1] https://www.erasme.be/fr/enseignement-recherche/comite-d-ethique/etudes-cliniques/suivi-d-un-projet-d-etude-clinique-ou-aut-0?st

"prescribed" was replaced by **"dispensed**.	performed based on **dispensation** rather than **prescription**.	
The inclusion criterion **"Having received one of the following medicines, all strengths and galenic forms combined, between 01/12/2024 and 31/12/2024"** was corrected to **"Having received one of the following medicines, all strengths and galenic forms combined, between 01/01/2024 and 31/12/2024"**.	This change was made to correct an editorial error; the **look-back period should correspond to one full year**, as was done in the previous survey.	To be included in the Study Report.
The operational definition of **age** was added.	Operational definition needed for selection of patients.	To be included in the Study Report. Age: between 18 and 49 years on 31/12/2024 **—** corresponding to dates of birth between January 1, 1975 and December 31, 2006.
The list of **CNK codes** to be used to select valproate users was added.	Operational definition needed for selection of patients.	To be included in the Study Report. List of CNK codes used to identify valproate-containing medicines: 0003389, 00135806, 00034579, 01085380, 01123694, 03768785, 03768330, 01123686, 00891234, 02455772, 02455798, 02363596, 02363588, 00704429, 00704437, 00704452, 00704460, 00742445, 00742452, 00743864, 00784835, 00784843, 00787390, 00787408, 00810838, 00811174, 00862268, 01585959, 02195626, 02352425, 02352441, 02352458, 02352466, 02455764, 02455780, 02698777, 02698785.

The procedure to be followed by the FAMHP, the CIN and the insurance funds for patient **sampling** as well as the **flow and protection of data** between institutions were simplified and detailed.	Simplification of the procedure to reduce data transfers between institutions (the random selection of the patients will now be carried out directly by CIN-NIC) and to ensure the appropriate number of questionnaires are printed according to language requirements.	Information to be included in the Study Report. The CIN-NIC consolidates patient lists from all mutual insurers and then randomly selects 4,433 numbers: 2,033 for the 18–39 age group and 2,400 for the 40–49 age group. It then provides the FAMHP with the total number of selected patients by language regime to facilitate the printing of questionnaires.
The **time period** during which the survey will remain open was clarified.	Updates required due to administrative delays. Time allowed to respond was slightly extended to include late respondents.	To be included in the Study Report. Expected start: October 2025 Expected completion: December 2025 The survey will remain open for participation until the survey closing date (December 15, 2025), which corresponds to approximately six ten weeks following the distribution of the questionnaires.
Procedures for **data entry** and **quality control** were slightly modified and clarified.	It was assessed that the risk of significant data entry errors is low, given the relatively simple structure of the questionnaire—composed almost entirely of close-ended questions—and the fact that data entry will be performed by trained staff from the Vigilance Division. For this reason, and considering that double entry is a highly time-consuming procedure, an alternative random sampling approach was proposed.	To be included in the Study Report. Data will be entered manually in SurveyMonkey by staff from the Vigilance Division. Quality control will involve a random sampling procedure: 10% of questionnaires will be selected using a random number generator, re-entered, and compared to the original entries to identify discrepancies. The error rate will be calculated as the number of

		discrepancies divided by the total fields checked. Errors will be corrected by cross-checking against the source documents (paper questionnaires). If the error rate exceeds 1%, all errors will be recorded, investigated, and classified to assess potential systematic issues; if necessary, the sample may be expanded and corrective measures implemented. The entire process will be documented in the study report.
Deadlines and milestones were updated.	Updates required mainly due to administrative delays and the extension of the data collection period. Reminders were not planned in the protocol but are presented erroneously in the table of timelines.	Table of timelines and milestones updated and to be included in the Study Report. See **Table 1 Timelines and milestones**
Insurance policy was obtained	As planned.	Information to be included in the Study Report. Insurance number: Ethias 45.510.874
Approval by by the "Comité de sécurité de l'information (CSI) was obtained.	As planned.	Information to be included in the Study Report. Reference: IVC/KSZG/25/106
The questionnaires were revised to reduce the likelihood of inconsistent responses. The option **"Not relevant"** was removed from all questions except Question 12, which concerns the use of contraception.	For Questions 6 to 11, this option was deemed to add little value while increasing respondent burden and the risk of inconsistent responses.	Change implemented in the questionnaire.

Table 1 Timelines and milestones

	2024							2025						
	6	7	8	9	10	11	12	1	2	3	4	5	6	7
Writing/reviewing of protocol	X	X	X	X	X	X								
Development of questionnaire	X	X	X	X										
Pre-testing questionnaire				X	X									
Seeking approval (APD, EC, NIC)							X	X	X	X	X	X	X	
Sampling period														X

Table 2 (continued)

	2025					2026							
	8	9	10	11	12	1	2	3	4	5	6	7	8
Sampling period	X												
Questionnaire Setup and Distribution Preparation Period		X											
Recruitment of respondents			X	X	X								
Data entry and quality control				X	X	X							
Data cleaning and analysis							X	X	X	X			
Writing and reviewing of study report and scientific publication									X	X	X	X	X