Implementation of a centralized pharmacovigilance system in academic pan-European clinical trials: Experience from EU-Response and conect4children consortia

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REVIEW ARTICLE

Implementation of a centralized pharmacovigilance system in academic pan-European clinical trials: Experience from EU-Response and conect4children consortia

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Setting-up a high quality, compliant and efficient pharmacovigilance (PV) system in multi-country clinical trials can be more challenging for academic sponsors than for companies. To ensure the safety of all participants in academic studies and that the PV system fulfils all regulations, we set up a centralized PV system that allows sponsors to delegate work on PV. This initiative was put in practice by our Inserm-ANRS MIE PV department in two distinct multinational European consortia with 19 participating countries: conect4children (c4c) for paediatrics research and EU-Response for Covid-19 platform trials. The centralized PV system consists of some key procedures to harmonize the complex safety processes, creation of a local safety officer (LSO) network and centralization of all safety activities. The key procedures described the safety management plan for each trial and how tasks were shared and delegated between all stakeholders. Processing of serious adverse events (SAEs) in a unique database guaranteed the full control of the safety data and continuous evaluation of the risk–benefit ratio. The LSO network participated in efficient regulatory compliance across multiple countries. In total, there were 1312 SAEs in EU-Response and 83 SAEs in c4c in the four trials. We present here the lessons learnt from our experience in four clinical trials. We managed heterogeneous European local requirements

See Appendix D for the members of the EU-Response and c4c safety groups.

For affiliations refer to page 1323

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and implemented efficient communication with all trial teams. Our approach builds capacity for PV that can be used by multiple academic sponsors.

KEYWORDS

clinical trials, drug safety, paediatrics, pharmacovigilance, public health

1 | INTRODUCTION

Conducting large-scale multinational clinical trials is essential both to overcome the challenges in the development of new therapeutic strategies and to learn more about the use of existing medicines. A multicentre collaboration can increase patient enrolment rates and the external validity of the results, thereby generating stronger evidence for unmet medical needs, paediatric and rare diseases, and vaccines, within a shorter period of time. Pharmacovigilance (PV), defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem",[1] is recognized as one of the most critical aspects in drug development.[2] Nevertheless, randomized clinical trials (RCTs) often provide inadequate reporting of toxicity data, especially in paediatrics research, and prospective cohort studies are needed once the drug is licensed.

A robust clinical trial safety department is required to fulfil safety responsibilities, which include the management of adverse events reporting, review and assessment, sites' personnel training, the submission of suspected unexpected serious adverse reactions (SUSARs) and safety issues (whether associated with urgent safety measures or not), the preparation and submission of annual safety reports to regulatory authorities, and risk management-related activities.[3–5] Relatively easily done on a national level,[6] the PV system may become more complex to manage in multi-country trials, in particular for academic sponsors and paediatric research. In the latter, PV activities have to comply with additional paediatric guidelines,[7] requiring, for example, the submission in EudraCT of the final results within 6 months instead of 12 months in adult trials.[8]

Inserm-ANRS MIE has been involved for a few years in different consortia aiming to support European multinational trials, including with academic sponsors outside of our institution. Our PV department was first commissioned to provide a centralized PV system (CPVS) in 2018 for the conect4children (c4c) consortium, a pan-European collaborative paediatric network whose challenging goal is to speed up and facilitate the conduct of high-quality clinical trials in children.[9] The c4c core team scoped the issues and mapped regulatory and practical experience to the needs of a CPVS in paediatrics where safety issues are all the more important.

In early 2020, we were further solicited by the EU-Response network, a Covid-19 trials platform established to cope with the emergence of the pandemic in Europe,[10] to provide our experience and to apply and adapt our process: first in the DisCoVeRy trial, where the CPVS had to be activated urgently within less than a month,[11] followed by the EU-SolidAct trial at the end of the same year.

In this paper, we describe how a unique centralized PV service delegated to conduct the PV activities by multiple sponsors can simplify the hurdles encountered in setting up international clinical trials while fulfilling the stringent safety regulations and guidelines. We propose a series of actions to overcome the main difficulties an academic sponsor might face based on our PV department experiences.

2 | METHODS

To support our safety responsibilities, the complex safety processes had to be harmonized[12]: Key safety standardized operational procedures (SOPs) were prepared based on the trial specificities and shared to the appropriate actors in the trial. In parallel, we implemented a network of local safety officers (LSOs) to tackle the challenging heterogeneous local safety requirements and thus ensure the CPVS is compliant. Serious adverse event (SAE) processing and assessment were centralized at our department and entered in a unique, secure and validated PV database. When necessary, we ensured that all operational study teams had and maintained proper training throughout the trial. In each trial, the system was adapted either or both to the paediatric-specific regulations, Covid-19 pandemic context and the sponsor (whether Inserm-ANRS MIE or not).

3 | RESULTS

3.1 | Harmonization of the safety processes and communication

The main safety procedures are listed in Table 1. These SOPs proved to be necessary to make sure all PV activities were defined and understood by the multitude of different actors. Our PV department

TABLE 1 Key safety documents and purpose for multi-country trials.

SOP	Safety management plan (SMP)[a]	Safety working instructions for sites (SWI)[a]	Safety communication plan (SCP)	Tasks division log[b]	Pharmacovigilance greenlight checklist
Purpose	Provide an overview of the roles and responsibilities of each actor with clear instructions on operational procedures of safety data management	Intended for the sites only with the purpose to describe the operational procedures the sites and investigators need to follow for the proper collection and reporting of safety data	Describe the communication circuit and roles for all safety aspects, i.e., in case of SUSARs, safety issues, urgent safety measures	Clearly define the tasks and who is responsible for their execution, validation and who should be informed, between the different stakeholders of the trial (sponsor, data and monitoring teams, sites, local safety contacts and industrial partners)	List the administrative and regulatory documents that should be validated and the activities (training, database validation, etc.) that should be done before the start of the trial

[a]See Appendix A: Examples of Summary Plan of a Safety Management Plan and Working Instructions for Sites.
[b]See Appendix B: Example of a PV Tasks Division for a Multi-Country Clinical Trial.

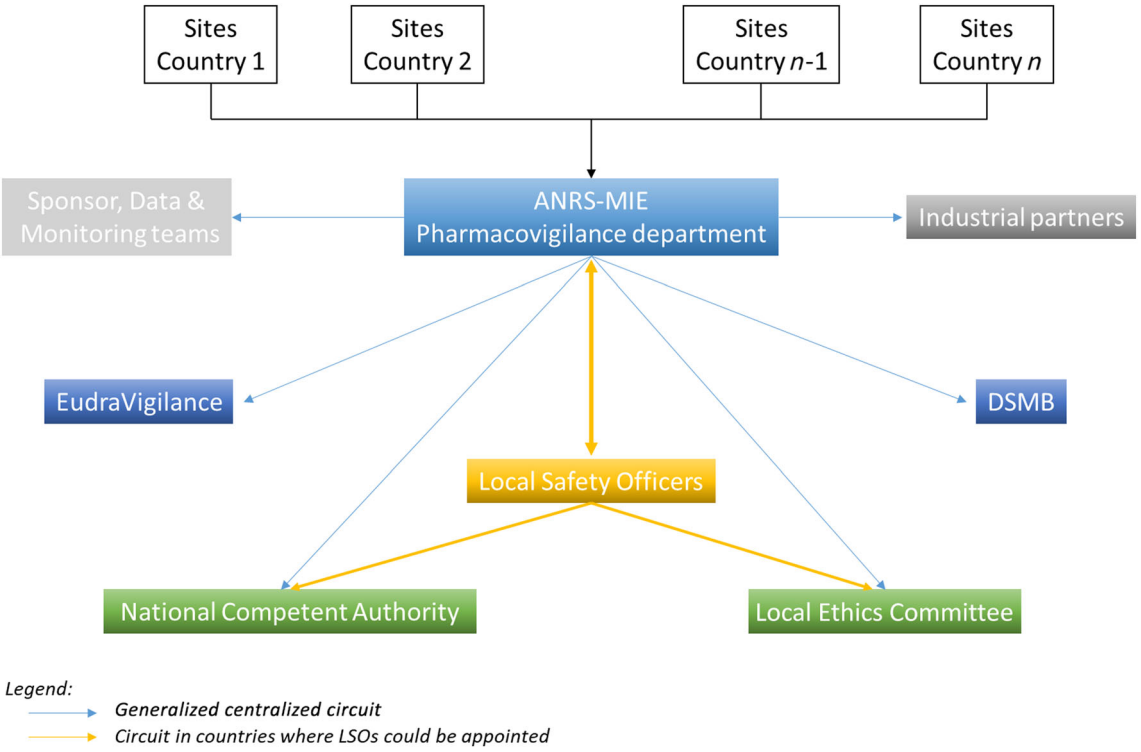

FIGURE 1 Communication process for safety data exchange and reporting between the different stakeholders of the CPVS.

participates actively in multiple and cross-cutting activities, including the review and/or preparation of all safety-related areas (such as the trial protocol design, unblinding process, informed consent form, eCRF setup and validation, safety data exchange agreements [SDEA] with industrial partners, etc.).

Thus, as we are both the main safety contact and an actor for safety in these trials, we worked to establish efficient communication from the very beginning with all stakeholders such as the study teams (sponsor, data, monitoring, sites), the data safety monitoring board (DSMB) and industrial partners, whose efforts had to be coordinated (Figure 1). In particular, the clear allocation of tasks was a key measure of the system. The log of responsibilities and delegation is usually prepared before the study initiation between the different parties. The CVPS allowed more rapid identification of relevant people than is possible for individual academic sponsors. We also made ourselves continuously available for any discussion, clarification or training, whether solicited by the study team members or staff in sites.

3.2 | Regulatory authorities and building up of an LSO network

LSOs were appointed in countries that agreed or had the capabilities to support our local safety submissions on a voluntary basis, and some were independent from the study staff (especially in blinded trials). The rate of LSOs per participating countries differed from trial to trial, ranging from 14% to 85% of 16 participating countries in Covid-19 trials and from 90% to 100% of 19 countries participating in paediatric trials (Table 2). The CPVS allowed the creation of a network of safety contacts for ongoing or further trials.

A crucial responsibility is the local reporting requirements of the national competent authorities (NCAs) and ethic committees (ECs) of the participating countries, which is very complex in Europe (see Appendix C). As some requirements were difficult to identify (e.g., written in local language), when necessary, we contacted the LSO for help or directly the NCA and local EC for countries where no LSO could be appointed. In each consortium trial, we were thus the sole organization responsible for overseeing and ensuring the appropriate safety data submission within the proper timelines and only the CPVS had access to EudraVigilance for safety reporting (Figure 1).

In parallel, the participation of the LSOs in SAE evaluation was encouraged. For example, LSOs could also be involved as a member of the trial safety group (TSG) that we implemented to support discussions about safety issues, the reviewing process being coordinated by the referent person for pharmacovigilance (RPPV) designated in the CPVS. In one of our trials, the LSOs participated in the causality and expectedness assessment of each SAE in their country. If there was no consensus within the TSG, the final decision rested with the Inserm-ANRS MIE PV department.

3.3 | Centralization of SAEs

The centralization of SAE processing in a unique database guaranteed the full control of the safety data by the PV function, avoiding unrecorded, incomplete, misplaced or deleted information, or generation of duplicates, and the continuous evaluation of the risk–benefit profile of the study drugs.

Centralized SAE processing drove the implementation of internal operational procedures to harmonize the safety case processing and coding. The procedures for each trial were adapted to the trial based on: the trial design (e.g., double-blind *vs*. open arms); the investigational medicinal product (IMP)-specific safety profile, such as the need to collect adverse events of special interest (AESIs); and the targeted population and pathology (paediatrics, severe Covid-19 pneumonia).

Regulatory compliance was also ensured with the designation of a unique RPPV (especially when ANRS MIE was not part of the sponsor's institution), which avoided missing submissions and assured all safety data were transmitted to the relevant NCAs and ECs.

The majority of SUSARs occurred in France (82% across both consortia) which can be explained by the higher enrolment in this country. According to local requirements, some LSOs were involved in the submission of all SUSARs to local authorities (not only the SUSARs arising in their own country).

The CPVS allowed us to cope more efficiently with the workload with SAE processing, especially in the Covid-19 DisCoVeRy and EU-SolidAct trials in a crisis context (1312 SAEs with 192 SUSARs). In these trials, the rates of SAEs were unpredictable and varied based on the pandemic waves and new country participation. In the c4c consortium, 83 SAEs, including seven SUSARs, were processed taking into consideration the paediatric safety specificities and complications in this population.

3.4 | Safety training

Ongoing and personalized safety training was provided to trial and field staff, including but not limited to LSOs, clinical trial units (CTUs), clinical research associates (CRAs) in charge of monitoring and site staff. We thus completed the good clinical practice (GCP) standards with standalone or trial-specific safety training on safety SOPs, safety-related sections of protocol, MedDRA coding, learned lessons during the clinical trial (e.g., safety issue) and following protocol amendments or SOP updates. This also allowed the sponsor to ensure that each institution understands its role and responsibilities in order to keep the system as efficient as possible.

3.5 | Budget and resources considerations

In total, for our CPVS, three drug safety officers and a manager were necessary for the coordination within the framework of these two consortia, as well as help from consortia stakeholders and support at local level (LSO).

4 | DISCUSSION/HURDLES AND LESSONS LEARNT

After implementing our CPVS in four trials to date, we have listed several hurdles that were encountered.

One of the most challenging issues of PV in a European clinical trial is to fulfil (and thus know) all local requirements for the management of safety data. Despite the EMA's desire to harmonize the reporting via EudraVigilance, requirements are still heterogeneous and local guidelines can be very complex.[13–15] Collecting this multitude of information represents a significant workload at the start of the trial and requires anticipation considering that country regulations may change throughout the trial. A CPVS, working on behalf of multiple sponsors, does this work once, saving resources and reducing the risks to participants and to sponsors.

TABLE 2 Experience of the CPVS per trial (data processed by 30 April 2022).

Consortium	Trial name EudraCT number NCT number	Sponsor (country)	Trial title		Number of recruits by 30 April 2022	Number of countries with LSOs/Total countries[a]	Number of SAEs	Number of SUSARs	Safety issue
conect4children	**TREOCAPA** 2019-004297-26 *NCT04459117*	**Inserm** (France)	Prophylactic treatment of the ductus arteriosus in preterm infants by acetaminophen	Phase II: Open phase to define the minimum effective dose of acetaminophen to close the ductus arteriosus before or at Day 7 in preterm infants of 23–26 weeks of gestation	31	2/2	24	2	1
				Phase III: Blinded phase to define the increase in surviving without severe morbidity at 36 weeks of post menstrual age in preterm infants born at 23–28 weeks of gestation treated with acetaminophen	196	16/16	59	5	
	cASPerCF 2019-004511-31 *NCT04966234*	**Bambino Gesù Children's Hospital—OPBG** (Italy)[b]	Prospective validation and clinical evaluation of a new posaconazole dosing regimen for children and adolescents with cystic fibrosis and *Aspergillus* infection		29	9/10	0	0	0
EU-Response	**DisCoVeRy** 2020-000936-23 *NCT04315948*	**Inserm** (France)	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	Part I—5 open arms in severe Covid-19 forms (closed in January -2021)	1309	4/6	977	140	4
				Part II—1 blinded arm in moderate Covid-19 forms (ongoing since April 2021)	210	11/13	73	7	0
	EU-SolidAct 2021-000541-41 2022-500385-99-00 (CTIS) *NCT04891133*	**Oslo University Hospital** (Norway)	European DisCoVeRy for Solidarity: An Adaptive Pandemic and Emerging Infection	Part 2—Phase 3: 1 blinded arm in severe Covid-19 forms (ongoing since April 2021)	285	2/14[c]	262	45	1

[a]Including France, for which LSO role was fulfilled by the CPVS team.
[b]Early termination of the cASPerCF trial (reason unrelated to safety).
[c]Since end of April 2022, several LSOs have been identified in the EU-SolidAct trial to support PV department with local requirements.

The situation with ECs can be even more difficult. While some countries require only centralized submission (main ethics committee), others request regional (local ethics committee) reporting, or both. Even with a local support person, a main difficulty raised by the LSOs was the heterogeneity of formats and modalities (CD-ROM, secured website, e-mail or platform), along with access issues when the sponsor is from a different country. A centralized approach enhances compliance with local requirements while reducing the burden on individual sponsors.

When a CPVS is used, it is essential to implement efficient communication from the start of the trial design discussions and to ensure that all stakeholders take account of the needs of the PV function during the development and implementation of the trial. This challenge affected especially the transversal activities we had to be involved in, which could impact the safety process or regulatory compliance (e.g., unblinding procedure, local SUSARs reporting, safety data exchange with industrial partners, participation in study committees), or the participants' safety (e.g., informed consent form review, IB update's impact analysis)—these hurdles can be mainly overcome using a tasks repartition log. In addition, a confidentiality agreement should be signed with all stakeholders including LSO from a national hub (NH) or CTU to ensure efficient information sharing with the CPVS. While in the EU-Response trials this had to be carried out in a pandemic crisis context; in the c4c consortium, some countries had several local organizations involved in the trial (both a CTU and an NH) with different responsibilities, which increased the complexity and required an effective communication plan between all involved parties.

Finally, the main burden of PV for academic sponsors is operational. Given the number of PV activities in a clinical trial, specialized expertise is required for multinational trials, in particular for paediatric clinical trials for which PV is even more specific. This implies sufficient time to build a PV system with adequate budget and dedicated resources, when poor financial funding and small-sized PV teams are known issues in the public sector. A CPVS removes the startup costs that each sponsor encounters during the setup of a clinical trial. We recommend this expertise should be established outside scheduled trials, with a dedicated budget to ensure sustainability.

5 | CONCLUSION

Our experience in these two distinct European consortia, c4c and EU-Response, has been successful and confirms the value of a CPVS in multi-country trials, in particular in c4c paediatric trials which are perceived as being riskier than other studies. By centralizing the safety data reporting, this system has proved to be both efficient and responsive in a pandemic situation for the two Covid-19 trials we were involved in. This allowed us to cope with the workload that the SAE processing represented in this challenging context, facilitating a focus on the detection of safety signals. Additionally, our system has built capacity for PV across Europe while sharing experiences within all participating European countries, notably thanks to the successful experience of the LSO network.

The new EU Regulation 536/2014,[16] which came into effect in the EU in January 2022, aimed to simplify the conduct of multinational clinical trials and to harmonize the requirements for European countries. Because safety legislation is constantly updated, having LSOs that will support us with their knowledge of local regulatory requirements and their updates is one of the major advantages of our system.

CONTRIBUTORS

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COMPETING INTERESTS

No author declared a conflict of interest in relation to the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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APPENDIX A: EXAMPLES OF SUMMARY PLAN OF A SAFETY MANAGEMENT PLAN AND WORKING INSTRUCTIONS FOR SITES

The following summary tables describe the key points to consider during the writing of the safety SOPs. These summary plans are not exhaustive and should be adapted to the trial in accordance with the protocol, the IMP safety profile and the distribution of tasks.

SOP Safety Management Plan	The **Safety Management Plan SOP** should adhere to the following plan and include at least the items outlined in bold: 1. Introduction 2. Definitions and Abbreviations *Terms as defined in the protocol.* **3. Responsibilities and Roles** *In accordance with the Tasks Distribution and the Protocol* 3.1 Sponsor *Presentation of the sponsor teams and listing of their tasks related to the safety data management (Impact Analysis of IMP RSI update, SAE management…), further detailed in section 4.* **3.1.1 Sponsor entity** **3.1.2 Inserm-ANRS Pharmacovigilance Department** 3.1.3 Clinical Trial Unit **3.1.4 Local Safety Officer** (if applicable) **3.1.5 Trial Safety Group** (if applicable) 3.2 Investigators *Brief summary of the investigators' main responsibilities, refer to the Working Instructions SOP for further details (shared to all investigators).* 3.3 Trial Committees (not exhaustive list) *List the trial committees with short roles description and refer to the corresponding charters for more details.* **3.3.1 Trial Management Group (TMG)** **3.3.2 Trial Steering Committee (TSC)** **3.3.3 Data Safety Monitoring Board (DSMB)** 3.4 General Communication Circuit *Summary of all communication circuits between the different stakeholders (scheme suggested).* **4. Procedures** *Description of all the safety procedures put in place and applicable to the trial.* 4.1 Notification *Safety data reporting in particular regarding:* • *SAE notification modalities by the investigator (eCRF, paper form), including pregnancy and other trial-related events (e.g., AESI)* • *SAE reception by the sponsor* • *Queries management* *Refer to the Working Instructions for Sites SOP for further details.* 4.2 SAE Assessment by the Sponsor (causality and expectedness) *Clarification of who is responsible for assessment within the sponsor's teams and what should be applied in case of lack of consensus within the TSG. Investigator's assessment method is mentioned in the Working Instructions for Sites SOP.* **4.3 Submission of SUSARs** *Description of all applicable submission of SUSARs with their modalities and timelines: to NCAs, ECs, Investigators, DSMB, industrial partners… and clarification of the responsible actor (LSO, PV department).* 4.4 Safety Data Circuit *Summary of the management of the safety data exchange (scheme suggested).* **4.5 Unblinding Procedure by PV** (if applicable) **4.6 Safety Issue Management (including unanticipated problem)** **4.7 Annual Safety Report** *Example of appendices: List of LSO contacts, Unblinding form by PV…*
SOP Working Instructions for Sites	The **Working Instructions** are meant for sites and shared with all investigators. This SOP should adhere to the following plan and include at least the detailed items outlined in bold: 1. Introduction 2. Definitions *Terms as defined in the protocol.* 2.1 Investigational Medicinal Product(s) 2.2 Events 2.3 Pregnancy **3. Reporting Procedures and Requirements** *Detailed description of the reporting procedures of all events by the investigators in accordance with the SMP SOP and the protocol.* **3.1 Reporting of AE/SAEs, Pregnancies and Special situations** **3.2 Processing and data entry on the SAE Form**

(Continues)

	3.3 Follow-up of reported Serious Adverse Events **3.4 Queries Management** **4. Investigator SAE Assessment** *Assessment method as per protocol and GCPs.* **4.1 Grading of Adverse Events (Severity)** **4.2 Seriousness Assessment** **4.3 Causality Assessment** **5. Unblinding Procedure by Investigator** (if applicable) 6. Contact details *Example of appendices: SAE forms, Stopping rules and Dose adaptations, Manual for SAE form completion, List of AESIs…*

APPENDIX B: EXAMPLE OF A PHARMACOVIGILANCE TASKS DIVISION FOR A MULTI-COUNTRY CLINICAL TRIAL

The following table lists the main safety tasks repartition between a CPVS and other actors involved in a multinational trial. The tasks are not exhaustive (i.e., transversal activities) and should be adapted to the trial.

Main safety activities	Sponsor	Pharmacovigilance department	Investigators	CTU / CRA	Local Safety Officers
Recording of AE on the eCRF	I	I	R	M/I	NA
Verification of eCRF completion	NA	NA	R	M/R	NA
MedDRA coding of AE and validation	NA	C/R	NA	IN/R	NA
Recording of SAE/pregnancy/special situations and related FUs on eCRF	I	I	R	M/I	I
Notifying SAE/pregnancy/special situations forms and related FUs to pharmacovigilance department	I	I	R	NA	I
Assessing (causality and expectedness) and reviewing all SAEs and related FUs	I	R	R	I	I
Query resolution	I	IN/R	IN/R	M/I	IN/R
Reporting SUSARs to CA through EudraVigilance + MHRA	R/I	R	NA	I	I
Reporting SUSARs directly to CA (country-specific obligations)	R/I	C/IN/R	NA	I	I
Transmission of SUSAR and line-listing to ECs	R/I	IN/R	NA	I	R/IN
Transmission of SUSAR and line-listing to PI/other investigators	R/I	IN	I	I	R
Reporting SARs (including SUSARs) according to some country-specific requirements	R/I	R/IN	NA	I	R
Safety reconciliation	NA	R	NA	R	NA
Preparing and reviewing DSUR	IN	R/IN/C	NA	IN	IN
DSUR submission to NCA and local EC	R/I	C/R/IN	I	I	R
DSUR submission to DSMB	R/I	C/R/IN	NA	NA	NA
Executive Summary of DSUR transmission to Investigators	R/I	C/R/IN	I	M/I	R
Safety issue—Urgent safety measure	R/I/C	R/IN	I	M/IN	IN
Informing CA of safety issue	R/I/C	R/I?	NA	M/I	IN
Preparing and reviewing the Safety Management Plan	R	R	NA	IN	I
Unblinding procedure	I	IN/C/R	I/IN	R	NA
Sites training	R/I	R	IN	R	IN
LSO training	R/I	R	NA	IN	IN

Key: R, Responsible, C, Coordinate, M, Monitoring, I, Informed, IN, Involved, NA, Not Applicable

APPENDIX C: SUSARs SUBMISSION TO COMPETENT AUTHORITIES BASED ON LOCAL LEGISLATION

Country	CA	SUSAR	Via EMA (EudraVigilance—EVCTMPROD)	Additional CA EudraVigilance ID requested	Other local method specificities
Austria	Austrian Agency for Health and Food Safety	All	X	-	-
Belgium	Federal Agency for Medicines and Health Products (FAMHP)	All	X	-	-
Czech Republic	State Institute for Drug Control	All	X	-	-
Denmark	Danish Medicines Agency	All	-	DKMAEUDRA	-
Estonia	State Agency of Medicines	All	X	-	-
Finland	Finnish Medicines Agency	All	X	-	-
France	National Agency for the Safety of Medicine and Health Products	All	X	-	declarationsusars@ansm.sante.fr
Germany	Federal Institute for Drugs and Medical Devices	All	-	BFARM	-
Greece	National Organization for Medicines	All	X	-	-
Hungary	National Institute of Pharmacy and Nutrition	Only domestic	-	OGYI	-
Ireland	Health Products Regulatory Authority (HPRA)	All	-	-	-
		Only domestic	-	IMBCT	Send an email to HPRA for the first Irish SUSAR
Italy	Italian Medicines Agency	All	X	-	-
Luxembourg	Ministry of Health	All	X	-	-
Netherlands	Healthcare and Youth Care Inspectorate, Ministry of Health, Welfare and Sport	All	X	-	-
Norway	Norwegian Medicines Agency	Only domestic	-	NOMACT	-
Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	All	-	-	urpl@urpl.gov.pl
Portugal	National Authority of Medicines and Health Products	All	X	-	-
		Only domestic	-	-	farmacovigilancia.ec@infarmed.pt
Slovakia	State Institute for Drug Control	Only domestic	X	-	-
Spain	Spanish Agency for Medicines and Health Products	All	X	-	-
		Only domestic (local site)	-	-	Email to Autonomous Communities
Sweden	Swedish Medical Products Agency	All	-	-	-
Switzerland	Swiss Agency for therapeutic Products (Swissmedic)	Only domestic	-	-	susar@swissmedic.ch
UK	Medicines and Healthcare Products Regulatory Agency	All	-	-	ICSR Submissions platform

APPENDIX D: EU-RESPONSE AND C4C SAFETY GROUPS

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