

REPORT of the

Multidisciplinary Workshop

Towards A Better Future for Pharmacovigilance in Clinical Trials

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EORTC Headquarters, Brussels

Organised by EORTC and ECRIN



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*on behalf of the “Roadmap Initiative for Clinical
Research in Europe”*



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1. The report and its aim

This report covers the principal discussions and conclusions to emerge from the multidisciplinary workshop entitled “Towards a Better Future for Pharmacovigilance in Clinical Trials” held at EORTC Headquarters in Brussels on 8 February 2010 and organised by EORTC and ECRIN on behalf of the Road Map Initiative for Clinical Research in Europe. This event was financially supported by the European Commission within the FP7 programme (ECRIN-PPI project).

The Road Map Initiative is composed of six pan-European networks. CLINT, which facilitates international stem cell transplantation trials; EBMT, the European Group for Blood and Marrow Transplantation; ECRIN, the European Clinical Research Infrastructures Network; EFGCP, the European Forum for Good Clinical Practice; ELN, the European Leukaemia Network; EORTC, the European Organisation for Research and Treatment of Cancer; ICREL, Impact on Clinical Research of European Legislation.

The main goal of the Road Map Initiative is to work towards suggestions for improvements in potential legislation with the aim of facilitating the performance of clinical research for the benefit of patients and to increase the competitiveness of clinical research on the European level. A series of specialized workshops was held (Single CTA, Co-Sponsorship, Risk-based Approach, Ethical Review, and Pharmacovigilance). Based on those discussions and the resulting reports, a final stakeholder conference will be held on 17 March 2010 with the aim of drafting and submitting a coherent proposal to the European Commission on the way forward for clinical trials in Europe.

2. Introduction

The Directive 2001/20/EC on clinical trials (CTD) defines all the legal requirements with regards to pharmacovigilance in clinical trials in Europe. Article 16 of the CTD requests investigators to report all SAEs immediately to the sponsor, who should maintain detailed records of all AEs which are reported to him. Article 17 requires that each suspected unexpected serious adverse reactions (SUSAR) from all clinical trials on a particular investigational medicinal product must be reported electronically to the European Medicines Agency (EMA) pharmacovigilance database, EudraVigilance Clinical Trial Module (EVCTM). The EMA has to provide Competent Authorities (CA) with access to the data in EVCTM. Sponsors are requested to report on an expedited basis to CA of the concerned member states and to the Ethics Committees (EC) all relevant information about SUSARs. Timelines for reporting are specified: fatal and life threatening SUSARs have to be reported 7 days

from the date of initial report, and an additional 8 days for relevant follow-up. All other SUSARS shall be reported in a maximum of 15 days. Once a year sponsors shall provide CA and EC with a listing of all Serious Adverse Reactions (SARs) and a report of the subjects' safety, the annual safety report (ASR). Following article 18, the EMA has prepared several detailed guidance regarding reports on the collection, verification, and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT 3); on EVCTM (ENTR/CT 4); with Q&As to adverse reactions reporting in clinical trials (Chapter II and V of Volume 10).

Due to the transposition of the CTD at the national level, the process for SUSAR notification as well as the parties to be addressed varies from country to country.

This workshop explored the experiences of the clinical research stakeholders with respect to pharmacovigilance management in clinical trials and examined proposals for a more appropriate pharmacovigilance reporting process in Europe. The ultimate goal was to provide a platform of recommendations, acceptable by all stakeholders, which will be discussed and released during the final Stakeholder Conference in Brussels on 17 March 2010.

The Workshop on Pharmacovigilance in Clinical Trials held On 8 February 2010 was attended by 82 delegates from 15 European countries. All stakeholders were represented: academic clinical researchers, the pharmaceutical industry, clinical research organisations, small and medium size enterprises, ethics committees, patients, national competent authorities, and the European Medicines Agency.

3. Current Status of the Safety Reporting Process for Clinical Trials in Europe

Gilles Touraille, EMA, presented the legal framework in relation to safety reporting in the European Economic Area and the detailed guidance. The lack of harmonised implementation across the member states of the safety reporting rules in clinical trials has already been acknowledged by the EMA as a major problem (report of the 'European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive 2001/20/EC and Perspectives for the Future', EMEA/565466/2007, 30-November-2007). The heterogeneous national procedures addressing the safety and monitoring of interventional clinical trials have led to the creation of unnecessary burdens for sponsors by requiring submission of multiple reports to various parties. The use and evaluation of EVCTM data is difficult for the Competent Authorities (CA) or the EMA itself. The signal detection is problematic. The EMA agrees that there is an absolute necessity to streamline the pharmacovigilance reporting system and make better use of available resources and tools in order to improve the analysis of the clinical trials information gathered in EudraVigilance.

According to EMA data in 2009, 140150 cases of SUSARs were reported to EVCTM; only 1% was reported by non-commercial sponsors. The majority of SUSARS were

reported by industry sponsors followed by CA. Some CA must enter data on behalf of academic sponsors who lack the electronic means for doing it.

Workshop participants agreed that while the CTD has clarified the definition of safety events, the way they have to be reported differs significantly from one member state to another. This is caused by the implementation of the CTD into national laws following interpretation by the member states. The lack of harmonised implementation of the CTD is a major problem. National procedures for safety reporting have created unnecessary burdens by duplicating the required work.

In the majority of member states, all SUSAR have to be reported to the CA regardless of their country of origin. Few member states request reporting of SUSARs only related to a trial conducted in that country, or if the SUSARs occurred locally. The same heterogeneity applies to SUSAR notification to ethics committee (EC). Some member states require expedited local SUSAR reports to ECs and periodic listing of SUSAR from foreign countries. Some countries require sponsors to expedite all SUSAR to ECs, while others only require reporting of SUSARs from protocols approved by the ECs which were involved in the approval process. Only periodic safety reporting is required in Denmark. Sponsors must inform investigators immediately about safety issues that could affect the safety of study subjects. The CTD does not provide detailed information, but according to guideline ENTR/CT3 SARs may be aggregated in periodic reporting. Some member states require sponsors to notify all SUSARs to investigators simultaneously with the notification to competent authorities, while other countries accept the period line listing of SUSARs. In addition, a layer of complexity is created by the heterogeneous requirements in terms of the media to be used for safety reporting: electronic versus paper reporting depending on the country and the recipient.

Karin Hedenmalm, Medical Products Agency, Sweden, outlined the CA's current pharmacovigilance activities. A drop in the number of Clinical Trial Authorisation applications has been observed in Sweden since 2005. Fatal SUSARs coming from Sweden are reviewed biweekly. Surprisingly, searches in EVCTM give different results depending on the criteria (EudraCT number, sponsor study number or according to line listing) used for the case search. One half-time person is dedicated just for following the annual safety reports in her institution. Sweden maintains its own ASR database since ASRs are not included in EVCTM. The use of a Data Safety Monitoring Board (DSMB) is imposed by the Swedish competent authority. The presence of a DSMB will be checked as will its way of functioning including the rules for stopping clinical trials, and the membership of the DSMB will also be under scrutiny. In Sweden, DSMBs are requested to interact directly with the CA and the EC.

Chantal Bélorgey, AFSSaPS stressed that CAs need to be informed about SUSARs in order to review the safety development with regard to IMPs and to suspend or prohibit a clinical trial whenever appropriate. CAs do not automatically receive the information they need from EudraVigilance. It is impossible for CAs to check EudraVigilance everyday for new SUSARs. Therefore, CAs have to request sponsors to provide them as well with expedited SUSAR reports, thereby causing the multiple safety reporting experienced by sponsors. One single centralised database would be acceptable if operational. The question is therefore when EudraVigilance will be fully

operational and accessible to CAs and obviating the necessity for them to maintain their own safety database. The roles of ECs and CAs need to be clarified. The content of the Annual Safety Report is not harmonised. Coordination between CAs is needed.

According to Véronique Lamarque from Pfizer, the CTD has improved the pharmacovigilance reporting system since it provided standard definitions. This should offer, in theory, a better protection of the patients especially because the exchange of safety information should be easier between the interested parties. On the other hand, the CTD has partially achieved its original intent because of lack of consistency in the expedited reporting rules and unclear definitions of e.g. IMP.

What really hurts is that SUSARs are transmitted without any background information and analysis that would enable them to be put in context. Annual Safety Reports do not often provide concise enough safety information. The CTD safety requirements brought additional workload for the sponsor, who has to know and implement national specificities. Additional qualified and administrative staff need to be appointed. V. Lamarque concluded that plenty of safety data, sometimes irrelevant, circulate with variable format and periodicity according to member state. Such data flow is not conducive to the missions and expectations of the concerned parties.

Barry Arnold, AstraZeneca, reported that EFPIA members with their local affiliates structure are able to cope with this complexity. Therefore, this is not a major issue for EFPIA members. However, decisions have to be taken by a company whether to implement a single system (all SUSARs case by case) or two systems (case by case and periodic summary listing depending to the recipient). Some EFPIA members have opted for a single system applied across all member states, i.e., reporting all available safety information to all parties. Many ECs and investigators have complained about the volume of SUSARs and of the uncertain value they generate.

Nathalie Dubois, EORTC, presented the EORTC experience with the safety reporting challenges in investigator-driven clinical trials. The heterogeneity of country-specific procedures, the difficulties for academic sponsors in accessing drug information, the need to train staff in reporting to EudraVigilance Clinical Trial Module (EVCTM) all represent serious hurdles. As opposed to industry, investigator-driven clinical trials portfolios usually involve a variety of drugs for which they are not the owner, and, especially in oncology, there are often multiple treatment modalities such as drug combinations, radiotherapy, chemotherapy or radiation. The decision concerning which safety information must be reported and to whom can be particularly complex. It is difficult for academic sponsors to identify the suitable reference for expectedness, because single Summary of Product Characteristics (SmPC) are only available for centrally registered drugs. For other drugs, national SmPCs exist but differ from country to country, and for older drugs they are simply not available or are difficult to find. Academic sponsors cannot prepare an ASR per drug as requested, because the overall safety information lies with the marketing authorization holder.

Global studies, e.g. transatlantic, are very difficult since the EMA and the FDA speak different pharmacovigilance languages, i.e., they have very different safety reporting requirements. The EORTC has experienced site inspections from MHRA, and the volume of required documentation was considered to be excessive. Surprisingly, MHRA review of the pharmacovigilance aspects was focused on how procedures

were followed rather than on how safety issues were managed. There is doubt concerning the benefit for patients safety resulting from such inspections. For sure the implementation of the CTD has required the adaptation of the internal structure, and a dedicated and trained pharmacovigilance team is definitively not a luxury. The EORTC is compliant, but this permanent adaptation consumes resources, and new challenges still lie ahead.

Lucy Birch from the University of Sheffield reported the investigators' challenges in retrieving data and the complexity of safety reporting. Good collaboration between departments in big institutions and with the sponsor is paramount for proper exchange of information. Data protection requirements make it difficult to get all the necessary data in a timely manner. Responding to sponsor queries can also be burdensome given the sometimes high number of requests and the lack of availability of the principal investigator for the review and signature of queries. Managing the SUSAR inflow is also a challenge. Numerous SUSARs are sent individually under electronic format or on paper, and there is a need to collate them all for the sake of information completeness. This entire workload is highly resources consuming. Investigators need the support of experienced and well organised pharmacovigilance and data management teams.

Peter Schüler, ICON Clinical Research, presented ACRO's experience. Potential under-reporting of relevant safety information should be avoided. In turn, current over-reporting of irrelevant information should be drastically reduced. For that, we need better definition of relevant safety data, clearer guidance for assessing expectedness and relatedness. The reporting needs for placebo cases or underlying diseases should be specified. There should be only one reporting timeline, e.g. 15 working days. It is of importance to improve the exchange of information between stakeholders. Sponsors need regular, e.g. every six months, feedback from EudraVigilance and CAs on the data they submit. Sponsors should have access to EudraVigilance data related to their IMPs. The post-marketing regulation should be expanded to the pre-marketing area. The safety reporting rules should be simplified, and central reporting to EudraVigilance should become the rule. EudraVigilance should be strengthened and data exchange promoted. E2B compatibility across safety databases should be ensured. Only one reporting format should be used (CIOMS I) and in English only. Sponsors and ECs should be allowed to access EudraVigilance for performing signal detection.

The current volume of information generated by the flow of SUSARs is not manageable by ECs according to Xavier Carné, Hospital Clinic Barcelona. Usually, ECs are not able to make use of those data. ECs do not act as signal identifiers, since safety signal detection by ECs is very rare and might happen only in phase I trials. Definitively, ECs cannot adequately screen safety information based on single case SUSARs since they lack the overall safety information on a particular IMP. The dedication, education, and professionalism of ECs vary widely. Accreditation and auditing of ECs is not happening in the majority of EU countries at this time. ECs need to be professionalized, accredited, and members should be compensated for their time.

Safety reporting requirements should follow a risk-based approach. ECs should receive SUSAR reports only for the studies for which they are responsible and should

receive periodic safety reports for the other studies. J Pleiner reported that the numbers of SUSARs have increased dramatically in his EC at the Vienna University, and this has caused a dramatic increase in workload. This is supported by ICREL data. Definitely, ECs do not have the appropriate resources for playing an active role in safety reporting and detection of new adverse effects. Responsibilities need to be clarified. ECs access to EudraVigilance would be nice, but for whom and for what purpose?

What happens after data are entered into EudraVigilance? Exploiting such a huge volume of information surely presents a challenge. Safety data are not often specifically designed for safety signal detection purposes. The tools for analyses are being developed by EMA and are not yet available. In addition, there is a considerable problem concerning the quality of the data, and neither the EMA nor the CA and EC have the means to validate SUSARs. C Bélorgey, AFSSaPS, reported that her agency is receiving all SUSARs on IMPs tested in France: 50,000 SUSARs were received in 2009 and only about 10% of reported SUSARs are usable. Too many are not SUSARs but are expected SARs. The leading cause is the over-reporting of SUSARs by the sponsors. The fear of legal consequences of under-reporting is ever present. Sponsor motivation lies therefore with compliance with rules rather than with the protection of the patient.

The purpose of the SUSAR reporting is to identify unexpected trends. Are we reporting the right thing? It was agreed that it is rare that single SUSARs can provide significant signal. It is only a piece of data that needs to be put in perspective. The medical assessment that could make more sense of SUSARs is impossible because of the tight reporting timelines and the workload placed on the shoulders of the sponsor and investigators. Only aggregate data could lead to action. Interventions from CAs on the basis of SUSARs are reported to be very rare. For instance, the MHRA is relying more on annual safety reporting than on SUSARs.

We are in a poor situation: an obsession with data collection but lacking a clear goal and therefore very little use of the data collected at such great expense. This is a big waste summarised David Haerry, European Aids Treatment Group.

The current challenge is to determine how we can optimize the safety databases so that we can make the best use of SUSARs and ensure that all SUSARs are reported in practice. Regular and reliable entering of data needs to be improved, there is too much redundancy in the current system as the same information must be entered into multiple forms, and the rules for entering information into the EudraVigilance database need to be tightened.

EudraVigilance remains a one way database, and its public benefit stills needs to be demonstrated. To this end, the clinical research community expects EMA to highlight the forms and the methods on how EudraVigilance could be used to improve patient safety and support the other clinical research stakeholders by providing valuable information on class of agents helping preparation of European wide safety recommendation. It is suggested that EMA should give insight into the process and timelines by which EudraVigilance will serve as a source of information that could improve patients' safety.

In conclusion, we are facing a multilayer problem:

- The capacity of investigators and sponsors to access and assess safety information needs to be improved. Over-reporting and false SUSARs should be prevented.
- CAs: should put the focus on the quality and the relevance of the safety information rather than on sponsor compliance with reporting process.
- The safety information (SUSARs, new safety issues) sent to ECs should be adapted to their needs and better defined.
- There is a general need for a centralised and accessible safety database with adequate analysis tools. This will help avoid duplication of reporting and allow the use of this huge amount of data.

4. Proposals for a more appropriate safety reporting process in clinical trials.

The main question is how can we reduce the volume of safety data flow and improve its quality without compromising the protection of trial participants?

Various working groups were set up by EMA and CTFG for providing harmonised solutions to identified problems. CAs agree that reporting rules should be simplified and harmonised requirements in all member states should be applied. The duplication of safety reporting efforts by sponsors should be avoided. SUSAR collection and assessment should be improved in order to help CAs fulfilling their responsibilities. Assessment work should be shared between CAs. The electronic population of EudraVigilance should be optimised and linked with EudraCT data. CAs need automatic transmission of relevant SUSARs together with appropriate telematic support including efficient signal detection methods. Multiple assessments should be avoided and responsibilities better defined including the modalities of information to ECs. ECs should have access to EVCTM. A risk-based approach could be implemented and SUSAR reporting limited to “high risk” clinical trials. It is also recommended to define standard content and format for ASRs and to organise a single repository at the EU level, e.g. EVCTM. The CTFG subgroup dedicated to pharmacovigilance will issue guidance in 2010 to improve the harmonisation and the simplification of safety reporting.

Industry sponsors insist that safety assessment should be optimised by the full, or at least the partial, centralisation by EMA in collaboration with CAs and ECs. The revision of the CTD should lead to reduction of bureaucracy and simplify safety reporting procedures. Before the implementation of a new regulation and/or the revision of the existing CTD, any efforts should be encouraged towards improving clarification, harmonization, especially with regards to SUSARs reporting and interpretation of the IMP amongst national legislation. It is recommended that sponsors should be involved in the guidelines revision.

EFPIA proposes the amendment of the CTD requesting that SUSARs should be communicated to ECs and PIs only as ASRs and not linked to expedited notification to CAs. Collated data and summary reports of the safety profile should complement

expedited SUSARs. The scope of the ASR should be clarified. CTD and ENT/CT3 should be amended to require SUSAR notification to CAs only.

In order to fulfil their mission, ECs would prefer to receive aggregated data through periodic reports except for local phase I for which expedited SUSAR are necessary. ECs should have access to EudraVigilance. Training should be made available for employees and members of ECs.

Academic sponsors recommend all type of SUSARs to be reported electronically to CAs via EudraVigilance which implies that all the CAs have to be connected to EudraVigilance. They also recommend granting ECs with access to EudraVigilance. Investigator should be provided only with ASRs. The capacity of academics to register SUSARs should be improved. Academic sponsors are requesting that there be only one reference EC per country. EC single opinion should really become reality. DSMBs should play a more active role in the safety assessment, but independent, qualified and trained members are necessary. On the ground of accumulated safety data, a DSMB may recommend the termination of a clinical trial for preserving patients' safety.

In conclusion, there was general agreement among stakeholders on:

- EudraVigilance is the corner stone of the ideal safety reporting system and should therefore be strengthened and fully operational.
- Simplified and harmonised SUSAR reporting process:
 - o Sponsors should report expedited SUSAR reports only to EudraVigilance. CAs would then be automatically notified. ECs should have access to EudraVigilance.
 - o No expedited reporting to ECs and PIs. They should receive ASRs with risk/benefit analysis and line listing of SUSARs and SARs.
- Signal detection on EudraVigilance data should be possible.
- The role of DSMBs should be strengthened. They should unblind the SAEs to identify SUSARs and report them.

Faculty

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| Barry Arnold | ASTRAZENECA, UK |
| Chantal Bélorgey | Agence Française de Sécurité Sanitaire des Produits de Santé, FR |
| Delphine Bertram | Hospices Civils de Lyon, FR |
| Lucy Birch | University of Sheffield, UK |
| Gonzalo Calvo | Hospital Clinic Barcelona, ES |
| Xavier Carné | Hospital Clinic Barcelona, ES |
| Brian Davis | Medicines and Healthcare products Regulatory Agency, UK |
| Jacques Demotes, | ECRIN, INSERM, FR |
| Nathalie Dubois | European Organisation for Research and Treatment of Cancer, BE |
| David Haerry | European AIDS Treatment Group, BE |
| Karin Hedenmalm | Medical Products Agency – Sweden, SE |
| Ingrid Klingmann | Pharmaplex, EFGCP, BE |
| Véronique Lamarque | PFIZER, FR. |
| Françoise Meunier | European Organisation for Research Treatment of Cancer, BE |
| Johannes Pleiner | Vienna Medical School, AT |
| Peter Schüler | ICON Clinical Research, DE |
| Gilles Touraille | European Medicines Agency, EU |