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SAE reporting in the age of digitalisation

The use of electronic data capture (EDC) and electronic case report forms (eCRF) is becoming the gold standard in clinical research. Today, the dream of a paperless (or at least near-paperless) study seems within reach.

Meanwhile, there are EDC systems and eCRF setups available for nearly every budget, whereby rapid access to data and continuous plausibility and completeness checks in particular speak in favour of their application.

When it comes to serious adverse event (SAE) reporting, however, a separate paper-based process is still being used in many studies. The fax machine is regarded as the standard gateway; but the workload for sites and sponsors is high, because one and the same data set must first be put down on paper by hand and then transferred from paper into a database.

Within the scope of digitalisation, electronic SAE (eSAE) reporting is slowly but surely entering the field of clinical research. The ideal workflow allows for the automatic transfer of specific data from the eCRF to the corresponding SAE report so that the physician can meet his statutory reporting duties with just a few clicks. The sponsor receives high-quality and complete data and needs to spend less time on the follow-up (FU).

eSAE – new possibilities are emerging

One almost wants to say: "the sky is the limit", because the technical opportunities that already exist today are very sophisticated and manifold. Every project and every sponsor has special requirements and their own ideas, which means that technical solutions of eSAE reporting are also constantly and rapidly being further developed. The most common requirements for an eSAE reporting solution are:

- Entered SAE data as well as other relevant information from other areas of the eCRF (e.g., medical history) are sent directly to the sponsor's Pharmacovigilance (PV) department in the form of a PDF document from the eCRF.
- Signatures in the eCRF take on the role of the mandatory signature.
- FU information is automatically highlighted in colour in the PDF by the system and is thus easy to find.

In addition, we are seeing an increasing demand for technical solutions that are also able to create additional reports in the regulatory E2B format (ICH HARMONISED TRIPARTITE GUIDELINE) in addition to sending individual PDF SAE reports from the eCRF. Scenarios that create a direct link between the eCRF and the sponsor's safety database are thus conceivable. ICH-E2B is a very extensive and well documented standard for the electronic transmission of SAE reports in XML format. For many years now, this format has been mandatory for sending electronic reports to the FDA and EMA. At the same time, it is also suitable for the exchange of information between eCRF and the safety database.

Arguments in favour of eSAE reporting are clear

The study sites no longer have to fill out forms twice (paper SAE and eCRF form). The sites' motivation to fill out the eSAE form correctly increases, as does the completeness and data quality of the SAE reports.
An automatic visualisation of FU information provides the necessary overview of the current SAE data, which means that cases can be processed more easily and the time needed for processing the case can be significantly reduced. As a result, many (in theory even all) discrepancies can be prevented during the subsequent comparison of the safety database and clinical database (reconciliation). This, in turn, makes it possible to close the database much earlier.

If the SAE data are transmitted in the E2B format (additionally or alone), case handling can be completed even quicker, which is a major advantage in view of the tight regulatory timelines. Furthermore, it also makes it easier to bring together and monitor data from various studies. In times of risk-based quality management, this will become an increasingly important requirement for eSAE reporting.
As a result of electronic data transmission by

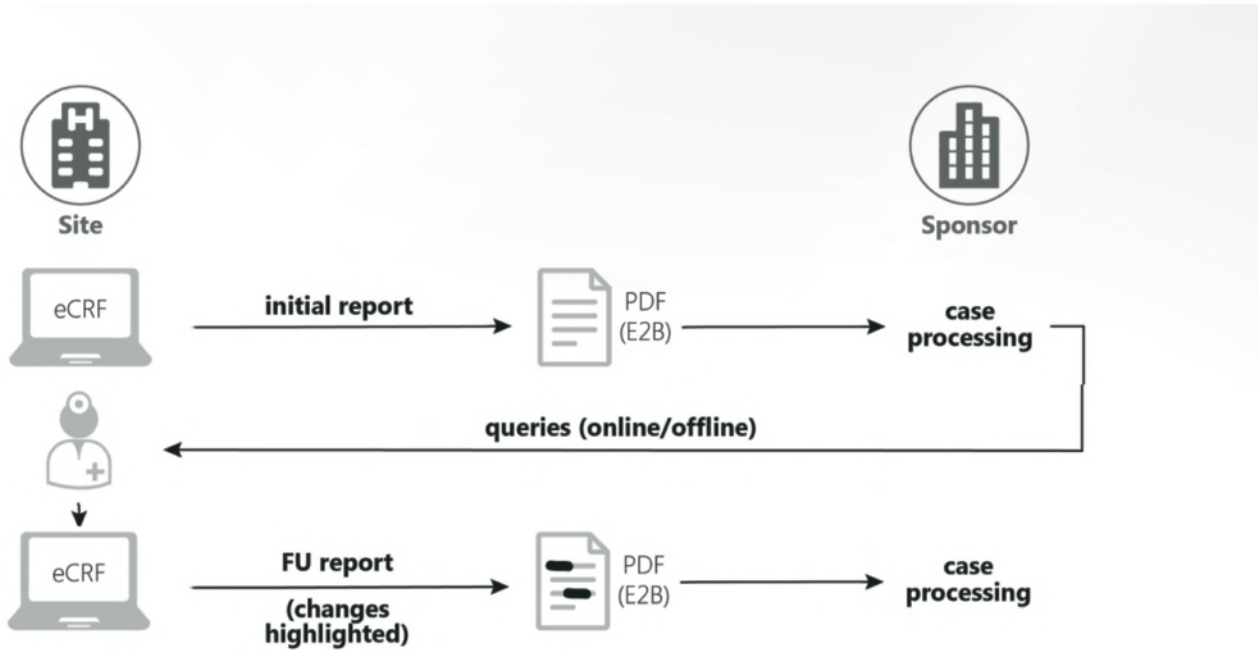

Figure 1: Outline of a typical eSAE reporting workflow

E2B, the data of an SAE are available immediately and can be analysed in a standardised manner. This saves the tedious and error-prone manual data entry into a safety database. In addition, the review is simplified considerably, because the SAE data are no longer only available in a study-dependent or vendor-specific format.

Are there actually any arguments against eSAE reporting?

The most obvious objection arises as soon as a study uses paper-based CRFs. However, there are further potential pitfalls that stem less from the technical aspect than from the workflow of the individual studies.

Every study with an eCRF thus relies on a certain experience and technical affinity of the study staff. The advantages outlined above can only come into effect if the study staff is trained on how to use the eCRF and eSAE tools. The initial training requirement can therefore be greater for an eSAE solution than for a more "classic" SAE reporting by fax.

Even if the reporting is done electronically, the sponsor (or his service provider) must have the necessary staff capacities and competences, for example specialists who monitor the eCRF, process the SAE reports and can instruct the sites on how and where to correct missing or implausible data in the eCRF within the scope of the FU. In this regard, it is very important to have the data quality of the study in mind: primarily, the eCRF is a clinical database - instructions to correct allegedly implausible data may compromise the integrity of the study data in some circumstances.

The blessing of real-time data availability with eSAE reporting can quickly turn into a curse if there are not enough resources available for processing the cases. It is an error believing that an eSAE tool can replace personnel in the PV department. However, it does help employees to process the important information contained in the report rather than having to deal with formal discrepancies and readability issues.

The workflow is the decisive factor

The major challenge of eSAE reporting is thus not so much the technical feasibility, but rather a precise definition of the process in advance. Since we have used classic reporting routes so often, we are of course more familiar with them. Nevertheless, anyone who has ever had to change the fax number on the SAE forms in the middle of an ongoing study will know what problems are associated with workflow changes and uncertainties. This is no different when setting up an eSAE process. A great deal of information must be collected a long time before the start of the study. This is often done under time pressure, because the eSAE tool should logically be set up before data documentation in the eCRF commences. While subsequent changes are possible, they are however generally complicated, because the continuation of the study may not be impeded. *The chart in Figure 1 shows a typical eSAE reporting workflow.*

A well-defined eSAE reporting workflow can be very helpful for meeting the demands of the regulatory reporting duties and can reduce the amount of time and effort invested both for the sites and for the sponsor. As always, the following applies: the technical implementation is only ever as good as the specifications and requirements that were defined beforehand.

The following questions should be answered before starting the process of setting up the eSAE tool in consideration of the sponsor's SOPs and requirements:

- Who can report an SAE - only physicians or also study nurses and study assistants? This is important for the role assignments in the eCRF that define the user permissions.
- Who can sign an eSAE? In what intervals should the reports be signed? Can a report be sent without a signature? Is a signature a

relevant piece of information for the FU that must be actively requested?

- What information must the SAE report contain? Are data from the eCRF (e.g., medical history) to be transmitted in full to the SAE or must the reporting person select the relevant data prior to sending the eSAE? The latter requires the study personnel to actively control the data prior to sending the data.
- What action shall trigger the sending of the report? A click on a corresponding button, the signature or another action entirely?
- After sending an SAE report, what happens to data changes that were made in the eCRF without actively triggering an FU? Which of these changes actually require an FU and how are such cases identified?
- What is the procedure for SAE pages in the eCRF that are only partially completed or not transmitted?
- Shall the physician receive the report as a PDF or should he download it himself? Shall the reporting person receive a confirmation of receipt?
- How can the electronic transmission be guaranteed? SAE reports are frequently sent as an email. How safe is this transmission channel in the age of restrictive and self-learning spam filters?
- How and within what time limits should the query process run? For example, is it assumed that the sites are frequently online and process queries in the system, or should offline communication be set up (e.g., by mail or fax) to notify the sites about queries regarding the SAE?
- Who can make queries in the eCRF? How are CRAs and data management integrated into the process and informed about SAE queries? In this context, redundant or even contradictory queries to the study staff must be avoided at all costs.
- What is the procedure for handling information that is received offline (e.g., when sites send unsolicited information by fax or post)?
- How is the "time zero" of an SAE report defined? When entering an SAE into the eCRF or at the time the eSAE report is sent/received, or maybe even when entering an SAE-like free text somewhere in the eCRF? Additional screening processes and measures must be planned accordingly to avoid jeopardising the internal and regulatory timelines.

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