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THERAPIES

CLINICAL PHARMACOLOGY

Overview of literature monitoring practice of clinical trials vigilance units in French institutional sponsors – A study from the REVISE working group

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Summary

Introduction – The evaluation of clinical trial (CT) safety is the main task of CT vigilance units. In addition to the management of adverse events, the units must review the literature to identify

information that may impact the benefit-risk assessment of studies. In this survey, we investigated the literature monitoring (LM) activity of French Institutional Vigilance Units (IVU) from the working group “REflexion sur la VIGilance et la SEcurite des essais cliniques” (REVISE). *Material and methods* – We sent a questionnaire of 26 questions, divided into four themes, to the 60 IVU: (1) Presentation of the IVU and the LM activity; (2) Used sources, queries and criteria for selecting articles; (3) Valuation of the LM and ; (4) Practical organisation.

Results – Of the 27 IVU that responded to the questionnaire, 85% of them carried out LM. This was mainly provided by medical staff to improve general knowledge (83%), to detect Adverse Reactions (AR) not listed in the reference documents (70%) and to detect new safety information (61%). Due to lack of time, staff, available recommendations and sources, only 21% of IVU conducted LM for all CT. On average, units reported four sources: ANSM information (96%), PubMed database (83%), EMA alerts (57%) and the subscription to APM international (48%). The LM had an impact on the CT of 57% of the IVU such as changing the conditions of a study (39%) or suspending a study (22%). *Discussion/Conclusion* – LM is an important but time-consuming activity with heterogeneous practices. According to the results of this survey, we proposed seven ways to improve this practice: (1) Target the highest risk CT; (2) Refine the PubMed queries; (3) Use other tools; (4) Create a decision flowchart for the selection of PubMed articles; (5) Improve training; (6) Value the activity and (7) Outsource the activity.

KEYWORDS

Clinical trials; Patient safety; Safety management; Review Literature

Abbreviations

ANSM: *Agence nationale de sécurité du médicament et des produits de santé*

AR: adverse reaction

ASR: annual safety reports

CRA: clinical research associate

CT: clinical trials

DSMB: data safety monitoring board

EMA: European Medicines Agency

FDA: Food and Drug Administration

FTE: full-time equivalents

IVU: Institutional vigilance units

LM: literature monitoring

LPLV: last patient last visit

MD: medical device

MeSH: medical subject heading

NSI: new safety information

REVISE: REflexion sur la VIGilance et la Sécurité des Essais

SAE: Serious adverse event

SUSAR: suspected unexpected serious adverse reaction

USM: urgent safety measure

Introduction

Vigilance of clinical trials (CT) is an essential activity for the progress of a clinical trial. Its objective is the continuous evaluation of the CT safety, mainly through the immediate notification of serious adverse events (SAE) by the investigator to the sponsor. The IVU, under the sponsor's responsibility, assess the causality of SAE and declare suspected unexpected serious adverse reactions (SUSAR) as well as new safety information (NSI) to the competent authorities [1].

This continuous evaluation also includes a review of the literature. Literature monitoring (LM) is a rigorous ongoing process to ensure regular access to the latest scientific information.

The monitoring strategy passes through different stages: 1) Defining a clear theme and sources; 2) Gathering information using appropriate documentary research tools; 3) Analysing the data in order to eliminate irrelevant data and to collect and classify useful information; 4) Analysing the impact of the selected information and 5) Valuing the results [2].

In clinical research, the LM may relate to a drug, a medical device or an experimental procedure, depending on the type of CT. Its objective is to detect adverse reactions (AR) and other safety information described in scientific publications and communications from competent authorities or other sponsors. Safety information includes inefficiency, new preclinical data, exposure during pregnancy, additional risk reduction measures, etc. LM also helps to analyse new SAE and to identify new risks associated with experimental products or procedures under evaluation [3]. It can thus lead to the adoption of urgent safety measures (USM), including information to be transmitted to the investigators, study document modifications, changes in the care of volunteers and sometimes temporary and/or definitive suspension of inclusions in a study. It is therefore crucial for sponsors to organise a continuous, targeted, structured and relevant LM [4].

LM uses two types of method [5,6]:

- The classic method also called Pull method, which consists of directly searching for information. It involves several stages, including the creation of a search profile by identifying one's needs and choosing one's sources, the manual and regular resumption of the search and finally the evaluation of the relevance and quality of the information obtained. This involves, for example, occasional searches of the PubMed® database for the evaluation of an SAE. The advantage of this method is that the information is more relevant

and does not require any subscription. This more targeted monitoring reduces the amount of irrelevant information. However, it requires more research efforts (going to websites, relaunching the research) and its main risk is the implementation of an irregular LM.

- In the second method, known as Push, the user has access to information automatically pushed according to preferences and predefined criteria. Automating the monitoring process saves time while providing up-to-date information but it generates results that are too voluminous and long to process. It therefore requires judicious use of information search tools on the web such as databases (PubMed[®] queries), newsletters (Regional Pharmacovigilance Centre, APM international), mailing lists (Agence nationale de sécurité du médicaments et des produits de santé [ANSM] and Food and Drug Administration [FDA] alerts) and RSS feeds (European Medicines Agency [EMA]). RSS feeds are text files containing the titles of the latest articles posted by a website and links to them [7].

In the fields of biology and medicine, PubMed[®] is the main search database used to create automated alerts or occasional searches [8]. Creating a PubMed[®] query using the thesaurus medical subject heading (MeSH) is a tool for making PubMed[®] searches more precise and relevant.

In our survey, we wanted to evaluate LM practices within French IVU via the REVISE working group "*REflexion sur la VIgilance et la Sécurité des Essais*". The French working group created in 2007 to address the implementation of the European Clinical Trials Directive (2021/20/CE) among non-industrial sponsors, currently comprises 60 IVU. This includes university hospital vigilance units, vigilance units from regional cancer centres, non-university hospitals and national agencies (e.g. national agency for research on AIDS and viral hepatitis, Pasteur Institute, French blood establishment and health service of the Army) [9].

This work also aims to identify the factors limiting the implementation of effective LM in order to suggest measures for improving practices at a national level. Indeed, the only available recommendations on good LM practices come from the EMA's « **Guideline on good pharmacovigilance practices** », which is intended for marketing authorisation holders [10].

Material and methods

Material

This study is the result of a national survey of REVISE group members through a questionnaire of 26 questions.

The data collected were: (1) Presentation of the IVU and number of full-time equivalents (FTE); (2) Practical organisation of the LM; (3) Choice of CT with LM carried out; (4) Objectives of the LM; (5) Sources used and types of configured alerts; (6) Criteria for selection/non-selection of articles and (7) Impact and valuation of the LM.

Method

The GIRCI Grand Ouest group and the REVISE group coordinators first validated the questionnaire. The survey includes data collected between 11 August 2020 and 27 September 2020.

Results

Presentation of the units

Of the 60 IVU represented in the REVISE group, 27 responded to the questionnaire, which corresponds to a response rate of 45%. Most of the IVU (74%) work in university hospitals (Table 1). On average, the teams consisted of 2.24 FTE.

Thirteen institutions responded to a question on the number of ongoing studies. They were responsible for the vigilance of 45 studies on average [5; 153]. The number of ongoing studies and studies with LM and the number of FTE were not correlated (Table 2).

Practical organisation of the literature monitoring activity

Twenty-three units conducted LM (85%) and almost all of the IVU (89%) carried out an occasional bibliographic search when writing a protocol or annual safety reports (ASR), when an SAE is difficult to analyse or for a meeting of a data safety monitoring board (DSMB) or another scientific committee (Fig. 1).

In the majority of cases, medical staff carried out the literature monitoring: 87% pharmacist and 9% physician. To a lesser extent (17%), a clinical research associate (CRA) or a pharmacy student (9%) carried it out. Two institutions answered that the pharmacovigilance officer realised the LM without specifying the status. For six IVU (26%), only one person, usually the pharmacist or physician in charge of vigilance performed the LM. For 11 IVU (48%), several people in the team realised the LM; in this case, either each vigilant responsible for a portfolio of studies performed the LM of the portfolio or the LM of all studies is realised in turn or, the LM of each study is carried out by the person writing the ASR.

Regarding the frequency, IVU performed the LM activity daily for 39%, weekly for 9%, monthly for 9% or quarterly for 4%. The remaining 39% did not perform the LM activity regularly. Regarding the time devoted to this activity, 74% of the IVU that carried out LM spent less than 5 hours per week. Only one IVU devoted between 5 and 10 hours per week to this activity. The other five IVU did not answer this question.

Forty-eight percent of the IVU stopped the LM when writing the final ASR and 22% after writing the final report. Other IVU (9%) stopped the monitoring earlier, at the Last Patient Last Visit (LPLV) date. The remaining 21% did not define an end of LM.

Finally, only 35% of the IVU carried out a traceability of the LM activity.

Note that the reasons why four institutions did not monitor the literature are lack of time, lack of personnel and in one case because the coordinating investigator does the monitoring.

Choice of clinical trials with literature monitoring carried out

Among the 23 institutions performing a LM, 83% performed it for all drug CT and only 21% for their entire ongoing CT.

For CT selection criteria, we find:

- For drug trials: the phases of the CT (LM implemented for phases 1 and 2) and the trials for which AR are likely to be reported;
- For medical device (MD) trials: the notion of innovative and easily identifiable MD on PubMed;
- For non-health product trials: the risk of the procedure under evaluation. For example, there is no LM when the procedure under evaluation is a simple blood test.

The limitations raised in setting up LM for all studies were lack of literature sources for MD and non-health product trials and lack of time to extend the search to all drug clinical trials.

Objectives of the literature monitoring

For the IVU that carried out LM, the objectives are the improvement of general knowledge about the subject of the research (83%), the detection of AR not listed in the reference documents of the investigational product/procedure (70%) and the detection of NSI (61%).

Thirteen percent of the IVU also mentioned, in free text, clarifications on the objectives, such as reassessing the benefit-risk balance of the study, informing investigators and patients of a new risk, modifying protocols according to the identification of new risks, conducting an impact analysis and updating associated quality documents.

Used Sources

The Fig. 2. presents the main sources of information used by the IVU. On average, the units report four sources [1; 8].

Regarding access to these sources, 91% of IVU created automatic ANSM alerts and 31% FDA alerts, 35% created PubMed queries and 22% set up RSS feeds. One institution also reported using Med Effect Health Canada queries. Two units (9%) did not create specific alerts or feeds.

PubMed® queries were designed primarily using the MeSH terms "investigational drug name" and "adverse effects" for 6 of the 9 institutions that responded to this question. The other three institutions reported restricting the query to the indication evaluated by the clinical research or performing expanded queries to the therapeutic family for drug studies, or adding "in human" to avoid selecting articles dealing with preclinical studies.

Criteria for selection/non-selection of articles

The selection criteria were articles with relevant AR not reported in the reference documents of the studies (74%), the presence of additional information on AR already known and described (pathophysiological mechanism, severity of the AR, risk factors, etc.) (57%) and articles that provide information on efficacy data against the investigational product (43%).

Among the criteria for not selecting an article, we find a language other than English (61%), *in vitro* studies (48%) and preclinical studies (35%), articles describing a doubtful case report (13%), limited access to the abstract or title (9%) and another therapeutic indication than the indication under study (9%). Finally, 35% of the IVU did not have any criteria for non-selection or did not answer this item.

No IVU had a decision support tool.

Impact and valuation of the literature monitoring

The LM had an impact on 57% of the IVU and led to some USM presented in Fig. 3.

None of the IVU systematically declared an NSI following the detection of an article describing an AR not present in the SmPC. However, 13% of the IVU would declare an NSI if it was an AR with a drug used at the same dosage and in the same therapeutic indication as their clinical trial and if the AR can be extrapolated to the trial population.

Finally, the IVU mainly described the information retained during their literature monitoring in the ASR (57%). Some units also presented the relevant articles during team meetings (9%). For the other IVU, this activity was not valued.

Discussion

Our survey reports a significant involvement of the IVU in LM. This had an impact for nearly half of the units (39%) and led to USM. The LM carried out by the IVU uses both types of monitoring method, Pull and Push, although the main source is the information transmitted by the ANSM. The IVU use the Pull method for occasional research during the evaluation of a complex SAE or the drafting of the ASR. The Push method allows an automation of the search and the implementation of a continuous monitoring and thus the re-evaluation of the benefit-risk assessment of the CT [6].

However, our survey confirms several difficulties encountered by the teams in setting up an efficient and exhaustive monitoring system:

1) **LM is not always applicable to all studies** and IVU often carry out partial monitoring by creating queries for higher risk studies and clinical trials with sources more easily identified in the databases. For MD and non-health product clinical trials, MeSH terms are not easy to find and queries are difficult to automate. Monitoring is often limited to innovative MD and easily identifiable procedures with a higher risk. In view of this, our first recommendation would be to target trials for which it is necessary to carry out an exhaustive LM, i.e the highest risk CT (phase I or II interventional CT, drug CT with less setback in use and innovative MD) and to exclude the CT with a lower risk for patient safety.

2) **Sources available are very numerous**, and automated monitoring (RSS feeds, creation of PubMed alerts) can bring up hundreds of articles per week, which can drown out the information and consequently lead to difficulties in identifying a potential risk. In a self-assessment of LM practices within the Clinical Trials vigilance unit of the University Hospital of Rennes, the LM had

brought up 102 articles over one week for 19 studies (16 drug CT, 1 MD CT and 2 non-health product CT). We retained only 16% of the articles, which shows that the LM leads to an overwhelming amount of irrelevant information. This requires regular evaluation and cleaning of the data brought up. Thus our second proposal is to refine the PubMed queries by excluding *in vitro* and preclinical studies and articles in another language than English or French, being aware that this can lead to the risk of missing important information.

3) **PubMed® queries are still underused** (35% of IVU). The main difficulty is to find the appropriate MeSH term(s). The MeSH terms mainly used (adverse effect + experimental product) generate a lot of irrelevant information. This is why it is sometimes more judicious to add the indication of the CT. This allows for more targeted monitoring but has the disadvantage of not reporting new AR in another indication than the CT. Moreover, MeSH only queries MEDLINE so PubMed® cannot retrieve references to the most recent articles that do not yet have an associated MeSH descriptor. In addition, computer upgrades can overwrite feeds. For these different reasons, very few IVU automate LM by creating PubMed® queries or RSS feeds. Monitoring is often limited to daily ANSM e-mail alerts and occasional PubMed® searches. One of the respondents proposed the use of other tools such as SCOPUS to create feeds.

4) **LM requires scientific skills and knowledge** of the clinical trial and the product under evaluation. This is why the vigilant (physician or pharmacist) often carries out the LM and more rarely the students/interns. Furthermore, even when a qualified person carries it out, the literature monitoring activity is subjective and the results may not be homogeneous and reproducible between team members. We made this observation during our self-assessment of LM practices by highlighting a difference in the choice of bibliographic references between two reviewers of approximately 12%. Since this observation, the vigilants carry out the literature monitoring of their study portfolio, sometimes helped by well-trained pharmacy students. In addition, the vigilants assess the articles selected by the student to ensure their validity. Following this survey, we created a decisional flowchart to assist in the selection of articles and we are now trying to evaluate this tool.

5) **There are no guidelines or recommendations** available on which IVU can base their work, apart from the EMA's "Guideline on good pharmacovigilance practices", which is intended for marketing authorisation holders [9]. This guideline provides areas for improvement (weekly monitoring by a qualified person, traceability, selection of terms for the construction of the research, criteria for selecting articles, etc.) but is not very transposable for institutional sponsors who do not have the same human and financial resources as an industrial company. Moreover, the

objectives and consequences of LM are not homogeneous from one institution to another. In fact, the same situation, such as the detection of an article with a description of a relevant AR not present in the SmPC, may or may not lead to the declaration of an NSI depending on the IVU. A solution could be to improve LM training within the REVISE group (creation of a working group and drafting of a common guideline).

6) **LM is not a valued activity.** The teams do not track this activity and very rarely exchange the results on the risks potentially identified. The IVU simply describe the information retained succinctly in the ASR without any exploitation or analysis. The objectives of the LM are not formalised, although it can lead to important USM at all stages of a research project. We could value this activity by transmitting the results to the investigators or presenting them in newsletters or during staff meetings.

7) **LM is a time-consuming activity.** Due to a lack of staff despite a constantly increasing activity and in a constantly changing regulatory context, the IVU tend to relegate the literature monitoring to the background. A solution to this problem would be to outsource the activity but again institutional units do not have the means to do so.

The main limitations of this work are:

- the lack of a clear definition of LM which has led to misunderstandings and confusion with regulatory monitoring by some IVU;
- the lack of a question on the use of paying sources (subscriptions to magazines) whose financial cost can be an obstacle for IVU;
- and the lack of data regarding the time spent on LM activities, impeding assessment of a precise description of the time consumption.

Only half of the members of the REVISE group responded to the questionnaire, which may be respondents more aware of and more involved in LM. However, the collective design, coupled to the geographic and size dispersion of the responding units, still warrants a representative picture of the academic situation in France. Moreover, our results were discussed inside the REVISE group on several occasions.

Following this survey, we created a decision flowchart to assist in the selection of articles. This tool is under evaluation to determine the sensitivity and specificity in the selection of relevant

articles and to ensure that it reduces inter individual variability. Furthermore, it would also be important to know the sources that may lead to the declaration of NSI and the setting up of USM. This will be the subject of a future study.

Conclusion

Literature monitoring is an activity that contributes to the evaluation of the benefit-risk assessment and helps maintain the safety of a clinical trial. This is why, although time consuming, this activity is essential. This work has shown a great heterogeneity in the implementation and traceability of literature monitoring due to lack of time, staff, training and available recommendations on which to base this activity, this in a context of increasing activity and constant evolution of the regulatory framework for clinical trials. One of the major challenges is to value and optimise this activity by targeting studies and adapting the means available to each IVU (resources, tools, etc.), making LM easier, more effective and more likely to be undertaken.

Author contributions

AP conceived the questionnaire, analysed the data and wrote the paper. DF conceived the questionnaire and analysed the data. CL and CM conceived the questionnaire and participated in the writing of the paper. SD, PO, EB, LPSP, SR and AJ reviewed the final manuscript.

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Disclosure of interest

The authors declare that they have no conflict of interest.

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Legends of figures

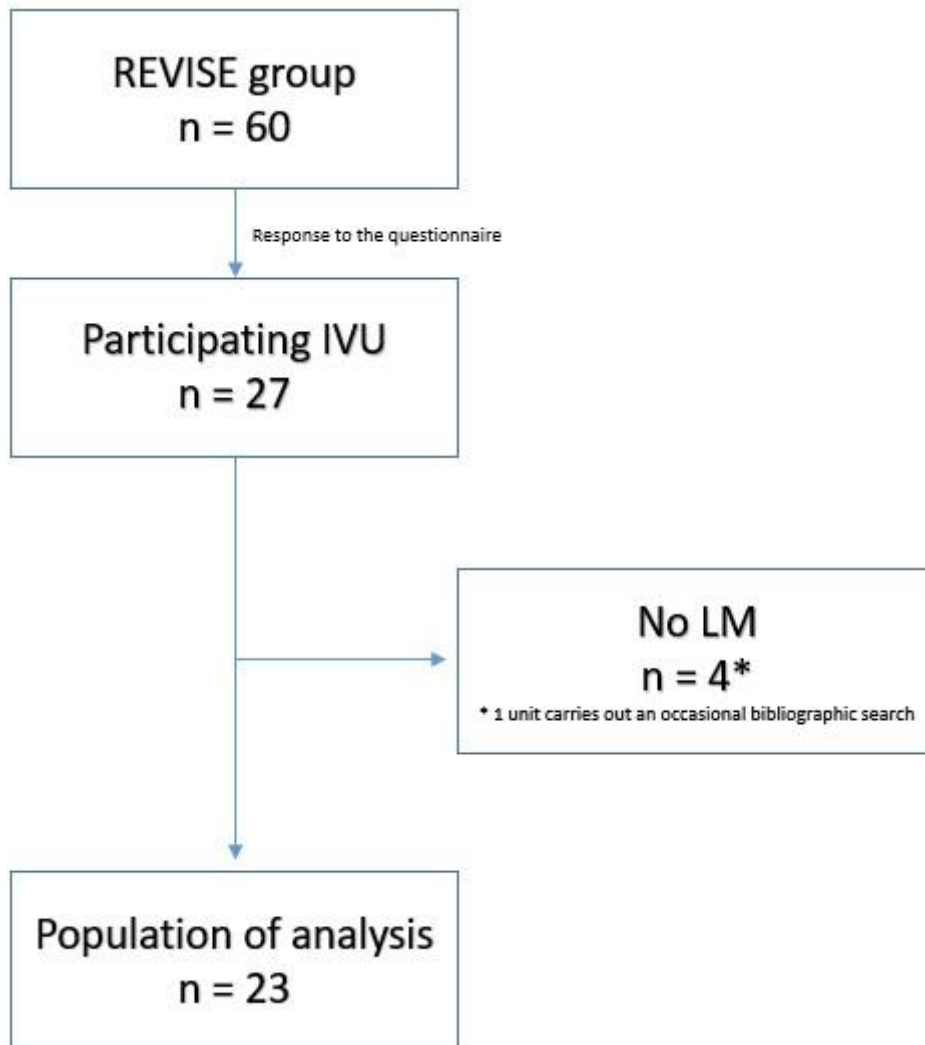


Figure 1. Flow chart of the survey population

IVU: institutional vigilance units; LM: literature monitoring; REVERSE: *REflexion sur la VIGilance et la SEcurité des essais cliniques*.

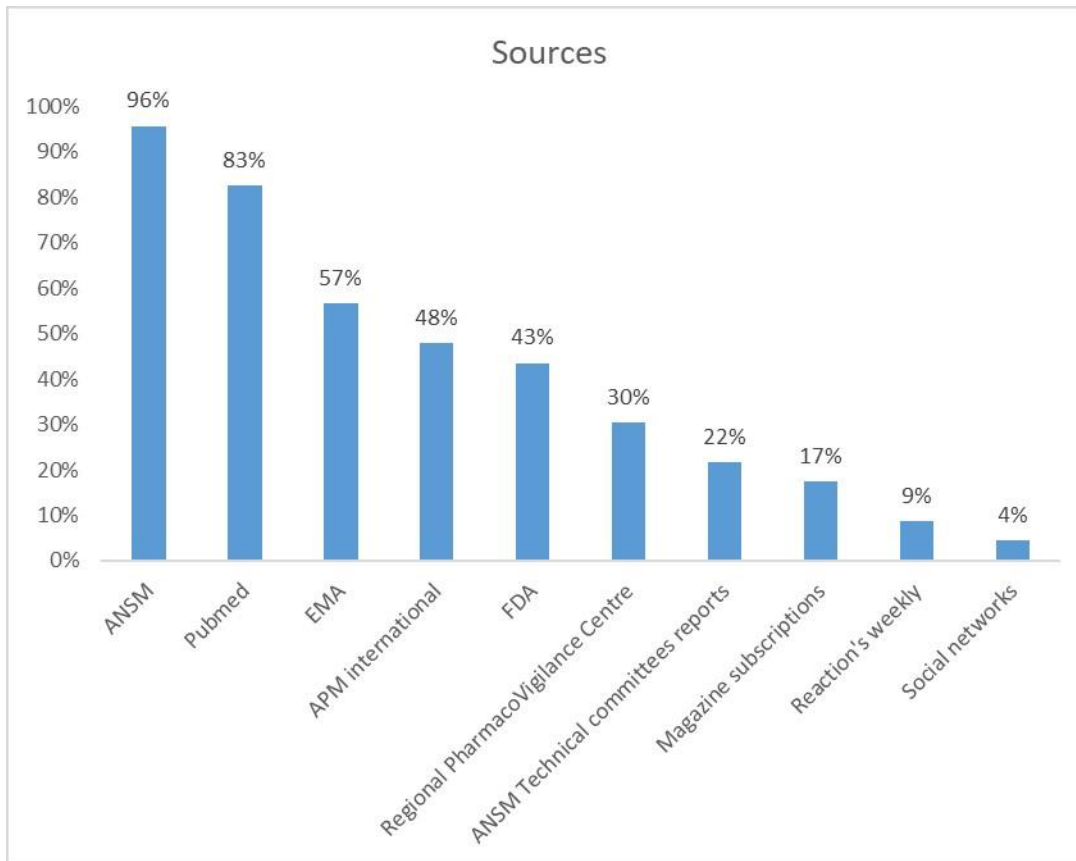


Figure 2. Sources used for the literature monitoring.

ANSM: Agence nationale de sécurité du médicament et des produits de santé; FDA: Food and Drug Administration; EMA: European Medicines Agency

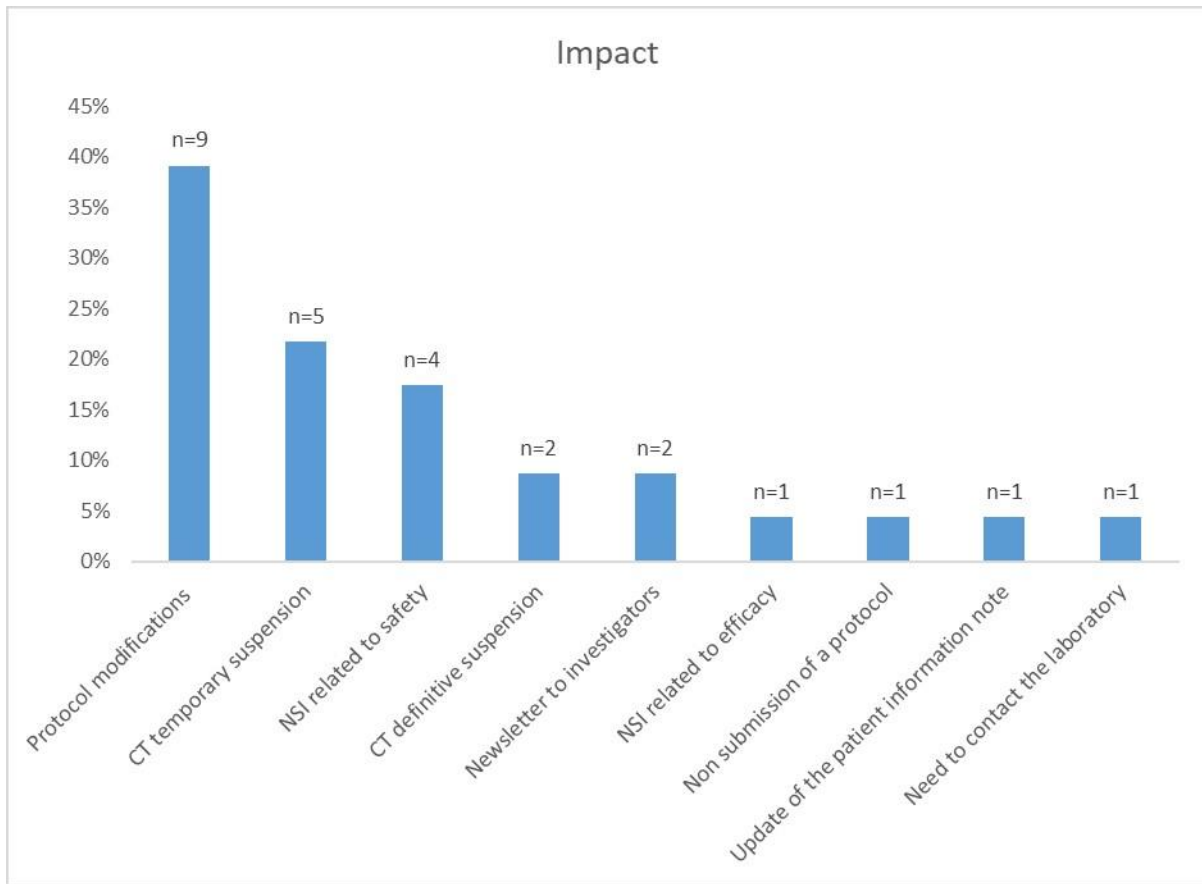


Figure 3. Impact of the literature monitoring

CT: clinical trial; NSI; new safety information

Table 1. Distribution of institutional vigilance units (IVU) participating to revise working group and to data source for the present survey.

Sponsor type	IVU in REVISE group		Participating IVU	
	<i>n</i>	%	<i>n</i>	%
University hospital	27	45	20	74
Non-University hospital	8	13	2	7.5
Other ^a	25	42	5	18.5
Total	60	100	27	100

a

Private or semiprivate health care institution, non-profit organisation.
REVISE: REflexion sur la Vigilance et la Sécurité des Essais

Table 2. Repartition of full-time equivalent (FTE), number of ongoing clinical trials and number of clinical trials with literature monitoring (LM).

IVU	Sponsor type	Numbers of FTE	Numbers of ongoing studies	Studies with LM (%)
1	UH	3.4	50	NK
2	UH	2.0	25	25 (100%)
3	UH	0.8	16	3 (19%)
4	UH	2.3	70	NK
5	UH	3.0	100	NK
6	Private institution	0.6	30	14 (47%)
7	UH	1.5	15	NK
8	UH	3.9	5	NK
9	UH	6.2	153	NK
10	UH	1.3	11	NK
11	UH	2.0	68	32 (47%)
12	Cancer Center	1.0	10	10 (100%)
13	UH	2.7	32	19 (59%)

NK: not known; UH: University Hospital.