A comparative study between investigator safety data and a pharmacovigilance database: a key role of the pharmacovigilant in the relevancy of clinical trial publications

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BACKGROUND

Safety assessment of an investigational medicinal product is an essential requirement of a clinical trial, and the Consolidated Standards of Reporting Trials group has produced recommendations to improve the communication of pharmacovigilance (PV) data in scientific publications.
However, little data is published as to the quality of reporting.

OBJECTIVES

To compare safety data of a clinical study reported in a published article and in the sponsor's PV database.

METHODS

Selection of article

- Randomly selected among studies in a PV database
- Compared 2 drugs in term of efficacy (not safety primary outcome)

Data extraction

Cases of serious adverse events (SAEs) were extracted:
- from the sponsor's PV database
- from the scientific publication related

SAE using are coded using MedDRA® dictionnary

Analyse

SAEs were compared with regards to:
- **Frequency**
- **System Organ Class (SOC)**
- **Seriousness criteria**
- **Outcome**
- **Causality with treatment**

RESULTS

- Frequency and SOCs were compared (501 patients were randomised in this study)

Article (Number of patients)			PV Database (Number of patients)			PV Database (Number of SAEs)		
60 patients at least one SAE*			78 patients at least one SAE*			Total of 136 SAE		
MedDRA SOC	**Drug A**	**Drug B**	**MedDRA SOC**	**Drug A**	**Drug B**	**MedDRA SOC**	**Drug A**	**Drug B**
Cardiac disorders	2	5	Cardiac disoders	2	5	Cardiac disoders	2	5
Infections / infestations	4	2	Infections / infestations	6	4	Infections / infestations	6	5
Nervous system disorders	3	0	Nervous system disorders	3	2	Nervous system disorders	3	2
Injury and poisoning	4	2	Injury and poisoning	14	11	Injury and poisoning	19	13
Neoplasms	1	1	Neoplasms	2	1	Neoplasms	2	1
Surgical and medical procedures	5	0	Surgical and medical procedures	5	0	Surgical and medical procedures	5	0
Gastrointestinal disorders	3	5	Gastrointestinal disorders	2	5	Gastrointestinal disorders	2	7
Eye disorders	2	5	Eye disorders	2	6	Eye disorders	4	8
Any other SOC	10	11	General disorders and administration site conditions	15	9	General disorders and administration site conditions	17	9
			Renal / urinary disorders	1	0	Renal / urinary disorders	1	0
			Respiratory disorders	5	4	Respiratory disorders	8	7
			Vascular disorders	1	3	Vascular disorders	1	3
			Social Circumstances	0	1	Social Circumstances	0	1
			Psychiatric disorders	0	2	Psychiatric disorders	0	2
			Investigations	1	0	Investigations	1	0
			Metabolism and nutrition	0	1	Metabolism and nutrition	0	1
			Reproductive system and breast disorders	0	1	Reproductive system and breast disorders	0	1

Difference in number of patients between clinical and PV databases

In the SOC injury, there were 3.5 times more patients who presented an SAE in the PV database with Drug A, and 5.5 times more with Drug B. (In PV database, drug administrator errors and incorrect storage of drugs were retained as SAEs)

Difference between number of patients and number of SAEs *

A patient may have presented multiple SAEs in the same SOC→ Bias regarding safety data because the amount of SAEs is important to assess safety of an investigational medicinal product.

SAE/SOC omitted in publication

In the article the author regroups the other SOCs together but the PV database details the SOC repartition. Of note, 18 SAEs regarding drug administration errors and incorrect storage of drug are flagged with the MedDRA term «no adverse effect » in the PV database which is in the General SOC.

***A patient may have multiple SAEs**

- Data regarding seriouness criteria, outcome and causality were not displayed in the article (excepted deaths) but available in the PV database:

Seriousness Criteria	Number of SAEs			
	Arm Drug A		Arm Drug B	
Death	**3**	**(4,2%)**	**3**	**(4,6%)**
Life Threatening	**2**	**(2,8%)**	**2**	**(3,1%)**
Hospitalisation or prolongation of existing Hospitalisation	37	(52%)	41	(63,1%)
Persistent or significant Disability / Incapacity	0	(0%)	0	(0%)
Congenital Anomaly / Birth defect	0	(0%)	0	(0%)
Other medically important condition	29	(40,8%)	19	(29,2%)
Total	71	100%	65	100%

Outcome	Number of SAEs			
	Arm Drug A		Arm Drug B	
Fatal	**3**	**(4,2%)**	**3**	**(4,6%)**
Recovered with sequelae	7	(9,9%)	10	(15,4%)
Recovered without sequelae	57	(80,2%)	50	(76,9%)
Not recovered	4	(5,6%)	2	(3,1%)
Total	71	100%	65	100%

- Of the 136 SAEs, 32 were related either by the investigator or by the sponsor to the investigational medicinal product of this study (drug A or drug B). These 32 SAEs were related to 24 patients.
- In the Arm « Drug A », 2 deaths were reported in the article, whereas 3 were found in the PV database.
- 4 life-threatening SAEs were reported in PV database

DISCUSSION- CONCLUSION

- A number of SAEs and all characterising data (eg seriousness criteria, outcome, causality) were omitted in the restitution of safety data.
- This discrepancy between the data demonstrates that more reconciliations should be made between clinical database and sponsor database. A good collaboration between investigator and sponsor is important to improve the quality and the reliability of safety data.
- The presentation of safety elements wasn't developed according the same methodology and expertise of the vigilant sponsor.

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