The impact of mandatory reporting of non-serious safety reports to EudraVigilance on the detection of adverse reactions

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ROR calculations

Calculation of the ROR is based on a classification of the individual cases in the database into four categories based on two dichotomous variables; this is shown in Table 1.

Table 1. Contingency table for ROR

Medicinal products \ Events	Event R	Not event R
Medicinal product P	a	b
Not product P	c	d

- The value 'a' indicates the number of individual cases that list the suspected medicinal product P and the adverse event R
- The value 'b' indicates the number of individual cases that list the suspected medicinal product P but not the adverse event R
- The value 'c' indicates the number of individual cases that list the adverse event R but not the medicinal product P of interest
- The value 'd' indicates the number of individual cases that do not list the adverse event R or the medicinal product P of interest.

The ROR is computed as (a/b)/(c/d). When no association exists between the reporting of the event R and use of the drug P the ROR would be expected to be around 1.0. An estimate of the statistical variability around this value is calculated based on a commonly used theory for odds ratios that allows a formal lower bound of the 95% confidence interval to be calculated. The rationale for its use is simply that when the statistic is based on few reports it falls further below the point estimate and makes an SDR less likely. Hence it is an intuitive way of incorporating the number of reports on which the disproportionality method is calculated.

Table 2. Proportion of NSRs before and after the legislation by Member State

Country	1 July 2012 - 21 Nov 2017	22 Nov 2017 - End of Study	Country	1 July 2012 - 21 Nov 2017	22 Nov 2017 - End of Study
Austria	47.9	63.9	Latvia	13.7	46.1
Belgium	26.8	65.3	Liechtenstein	12.5	78.9
Bulgaria	2.6	55.2	Lithuania	1.4	63.0
Croatia	65.8	60.8	Luxembourg	1.2	50.0
Cyprus	7.3	67.6	Malta	20.1	56.3
Czech Republic	2.9	47.9	Netherlands	62.8	79.3
Denmark	0.8	63.6	Norway	4.2	67.1
Estonia	27.2	60.5	Poland	7.4	45.0
Finland	1.9	66.4	Portugal	2.9	41.6
France	1.2	57.6	Romania	1.5	54.3
Germany	26.5	70.9	Slovakia	2.2	54.6
Greece	5.6	60.9	Slovenia	1.4	63.5
Hungary	3.1	54.4	Spain	0.9	60.1
Iceland	77.4	72.4	Sweden	1.6	67.6
Ireland	1.5	55.0	United Kingdom	0.9	56.7
Italy	65.1	61.3			

Table 3. Number of ADRs in the reference databases reported in EV

ADRs in reference database	#	%
Total	37,154	
With at least one report in EV	7,256	19.5%
With at least one serious report in EV	7,222	19.4%

Table 4. Performance of signal detection methods in CAPs using the NSRs as a separate group

Methods	Total SDR	True Positive	False Positive	Sensitivity	PPV
ROR_n3 – Only serious	44,826	4,460	40,366	12.0%	9.9%
ROR_n3 – Only non serious	2,163	744	1,419	2.0%	34.4%
ROR_n3 – Serious and non serious (as subgroup)	45,150	4,503	40,647	12.1%	10.0%
ROR_n3 – Serious and non serious together	46,309	4,577	41,732	12.3%	9.9%
ROR_n5 – Only serious	29,527	4,028	25,499	10.8%	13.6%
ROR_n5 – Only non serious	1,254	519	735	1.4%	41.4%
ROR_n5 – Serious and non serious (as subgroup)	29,676	4,054	25,622	10.9%	13.7%
ROR_n5 – Serious and non serious together	30,483	4,143	26,340	11.2%	13.6%

Table 5. Performance of signal detection methods in CAPs using the NSRs as a separate group – post-marketing ADRs

Methods	Total SDR	True Positive	False Positive	Sensitivity	PPV
ROR_n3 – Only serious	24,311	741	23,570	27.5%	3.0%
ROR_n3 – Only non serious	1,253	102	1,151	3.8%	8.1%
ROR_n3 – Serious and non serious (as subgroup)	24,497	746	23,751	27.6%	3.0%
ROR_n3 – Serious and non serious together	25,012	757	24,255	28.0%	3.0%
ROR_n5 – Only serious	16,083	682	15,401	25.3%	4.2%
ROR_n5 – Only non serious	728	65	663	2.4%	8.9%
ROR_n5 – Serious and non serious (as subgroup)	16,157	684	15,473	25.3%	4.2%
ROR_n5 – Serious and non serious together	16,523	693	15,830	25.7%	4.2%

Table 6. Relative risk of SDR when NSRs are included by MedDRA® System Organ Class

SOCs	Risk ratio	N - Only serious	N – Serious and non-serious
Reproductive system and breast disorders	1.135	335	401
Skin and subcutaneous tissue disorders	1.023	3,309	3,571
Vascular disorders	1.019	2,207	2,372
Hepatobiliary disorders	1.016	4,396	4,713
Cardiac disorders	1.013	6,553	7,004
Blood and lymphatic system disorders	1.012	3,715	3,966
Eye disorders	1.008	2,280	2,425
Pregnancy, puerperium and perinatal conditions	1.008	1,222	1,299
Renal and urinary disorders	1.007	3,694	3,924
General disorders and administration site conditions	1.007	2,190	2,326
Gastrointestinal disorders	1.005	5,523	5,855
Respiratory, thoracic and mediastinal disorders	1.004	5,704	6,045
Social circumstances	1.003	207	219
Endocrine disorders	1.002	842	890
Psychiatric disorders	1.000	3,525	3,718
Injury, poisoning and procedural complications	0.995	1,812	1,903
Nervous system disorders	0.994	11,505	12,069
Metabolism and nutrition disorders	0.993	1,926	2,018
Product issues	0.991	66	69
Musculoskeletal and connective tissue disorders	0.990	1,660	1,734
Investigations	0.989	874	912
Congenital, familial and genetic disorders	0.987	1,029	1,072
Infections and infestations	0.986	10,142	10,556
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.983	6,336	6,571
Ear and labyrinth disorders	0.981	450	466
Immune system disorders	0.963	2,778	2,824