Factors affecting causality assessment of adverse event in clinical trial

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Background & Objective

- Background
  - Adverse Events (AEs) and Adverse Drug Reactions (ADRs) in clinical trials give safety information of the drug
  - Investigators assess causality of AEs when it happens. If relationship between AE and drug cannot be denied, it is recorded as ADR
- Objective
  - Investigate the factors relating to causality assessment in clinical trials

Safety Assessment in Drug Development

Product A

Study B

Study C

<Study A>
- Blind / Open-label
- Study period
- etc

Adverse Drug Reactions

Dr A

Dr B

Dr C

…

Causality assessment

- Observation
- Knowledge
- Information

Adverse Events

- Study drug
- Target disease
- Concomitant disease
- Concomitant drug
- Occasional case
- Other factors

Method & Observation

Method

- Calculated “Causality rate”, defined as follows
  （Unit: MeDRA System Organ Class [SOC]）

$$\frac{\text{Number of ADR}}{\text{Number of AE}} = \text{Causality rate}$$

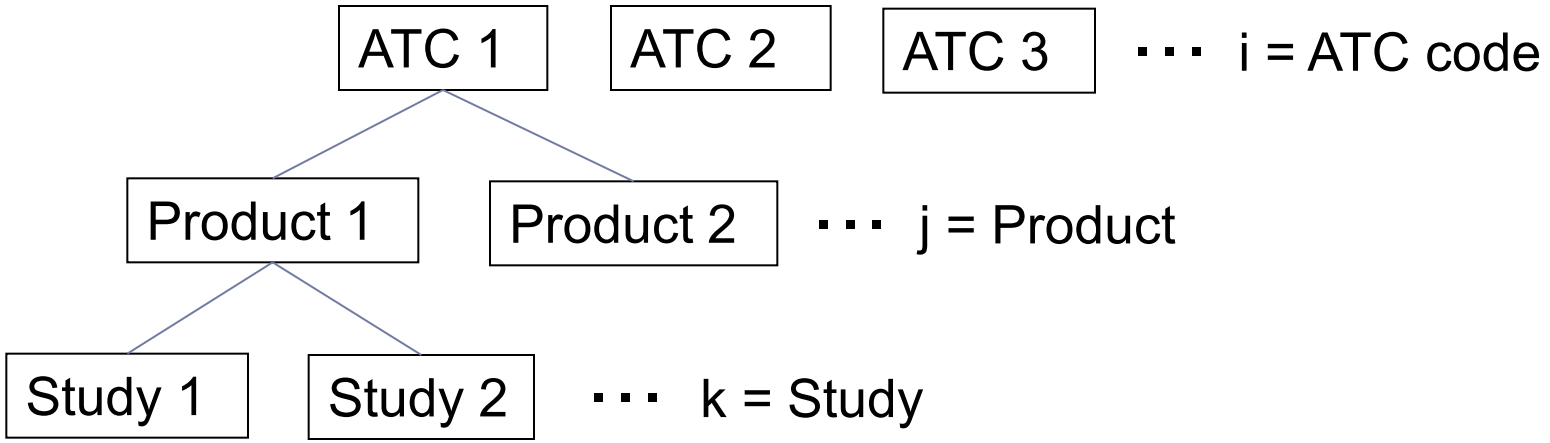
- Investigate the factors which affect causality rate

Observation

- Number of ADRs and AEs (SOC) in clinical study of NMEs approved by PMDA in 2009 and 2010

Analytical Method

Multi level analysis:



Cross random effect：SOC・・・a

$$Y_{ijka} = \beta_0 + \underbrace{\beta_{11} X_{11} + \cdots + \beta_{ij} X_{ij}}_{\text{Explanatory variable}} + \underbrace{\zeta_{ia} + \zeta_{ija} + \zeta_{ijka}}_{\text{Cross random effect}} + \underbrace{\varepsilon_{ijka}}_{\text{Error}}$$

Dependent variable

Exploratory variables

*Dummy variable（No=0, Yes=1）

- **Product**
  - Orphan*, Biologics*, Route of administration
- **Study design**
  - Phase, Patient*, Open-label*, Active comparator*, Placebo*, Number of patient, Study period, Number of arm
- **Study information**
  - AE ratio in clinical trials, AE observed in previous clinical trial*, ADR observed in previous clinical trial*, ADR causality ratio in previous clinical trial
- **Others**
  - Company* (Foreign company = 1, Domestic company = 0), Drug lag

Causality Rate

	Mean	Std. Dev.
System Organ Class		
Blood and lymphatic system disorders	0.49	0.43
Cardiac disorders	0.46	0.40
Ear and labyrinth disorders	0.48	0.46
Endocrine disorders	0.44	0.47
Gastrointestinal disorders	0.42	0.35
General disorders	0.48	0.41
Hepatobiliary disorders	0.42	0.40
Immune system disorders	0.14	0.28
Infections and infestations	0.09	0.22
Injury, poisoning and procedural complications	0.03	0.09
Investigations	0.63	0.34
Musculoskeletal and connective tissue disorders	0.16	0.26
Neoplasms benign, malignant and unspecified	0.30	0.40
Psychiatric disorders	0.40	0.41
Reproductive system and breast disorders	0.28	0.38
Surgical and medical procedures	0.04	0.13
Vascular disorders	0.44	0.43
Eye disorders	0.29	0.38
Metabolism and nutrition disorders	0.49	0.41
Nervous system disorders	0.38	0.39
Renal and urinary disorders	0.49	0.44
Respiratory, thoracic and mediastinal disorders	0.18	0.27
Skin and subcutaneous tissue disorders	0.35	0.36
All ADR	**0.35**	**0.39**

	Mean	Std. Dev.
ATC		
Alimentary Metabolism	0.22	0.31
Anti infective	0.44	0.45
Anti neoplastic	0.62	0.41
Cardiovascular	0.38	0.40
Genitourinary	0.12	0.23
Nervous	0.58	0.38
Respiratory	0.10	0.22
Sensory	0.12	0.28
Route of administration		
Inhalation	0.33	0.42
Eye drop	0.12	0.28
Intravenous injection	0.47	0.42
Nose spray	0.14	0.25
Oral	0.37	0.39
Subcutaneous injection	0.21	0.33
Phase		
Phase I	0.52	0.47
Phase II	0.37	0.40
Phase III	0.30	0.35

*All min is “0” and all max is 1”

Results (1/2)

Base Model : Variables about product, study design, and previous information

	N = 1425	
Variables	**Coef.**	**P>z**
Orphan	0.207	0.063 *
Number of arms	0.024	0.040 **
AE ratio in the study	0.228	0.000 ***
Same ADR observed in previous study	0.202	0.000 ***
Same AE observed in previous study	-0.042	0.066 *
Study period	-0.005	0.087 *

Note: Variables with no statistical significance are not shown

Result (2/2)

Model2: Drug lag and Causality rate in previous study are included

	N = 592	
Variables	**Coef.**	**P>z**
Patient study	0.267	0.070 *
Active comparator	0.125	0.011 **
AE ratio in the study	0.290	0.000 ***
Causality rate in previous study	0.218	0.000 ***
Intravenous injection	0.318	0.089 *

Note: Variables with no statistical significance are not shown

Discussion (1/3)

Variable associated with increase in causality rate

Variables	Possible causes
Orphan	Causality cannot be definitely denied because accumulated data is limited
Active comparator	Investigators consider the possibility of being allocated to active comparator arm
Number of arms	Many number of arms make it difficult to consider which drug is treated. And causality can not be denied
Patient study	Patient study is conducted later stage therefore study drug information is collected more.

Discussion (2/3)

Variable associated with increase in causality rate

Variables	Possible causes
Intravenous injection	AE relating to injection site increase the causality rate
AE ratio in the study	Investigators consider the relationship between AE and drug when they see the AE is frequently observed
Same ADR observed in previous study	Investigators consider causality as positive when same ADR was observed in previous study
Causality rate in previous study	If relationship between AE and drug was affirmed in previous study, causality is considered as positive in current study, too

Discussion (3/3)

Variable associated with decrease in causality rate

Variables	Possible cause
Study period	The longer observation period is, the more causality can be denied; for example AE recovers even though subject continues to be treated with investigational drug
Same AE observed in previous study	Investigator consider ADRs as important (same ADR in previous study does affecting to increase strongly)

Conclusion

- Some factors, e.g. study design and drug information, affect causality rate with statistical significance
- These factors relate to causality assessment in clinical trials.
  - Give information to Investigators' assessment
  - Or indirectly relate to the way of assessment
- Careful interpretation is necessary because causality is assessed by Investigators based on their knowledge and observation and these factors do not affect causality assessment directly

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Conflict of Interest;

We declare that we have no proprietary, financial, professional and any kind of other personal interest of any nature from company or any organization according to COI policy of JSCP