Vaccine Safety
Monitoring, Reporting and Analysis

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Disclaimer

This presentation is based on my own opinion and is not representing the opinion of International Vaccine Institute.

ICH

- **ICH E1 : Extent of Population Exposure To Assess Clinical Safety for Long-Term Treatment of Non-Life Threatening Condition**
- **ICH E2 : Pharmacovigilance, especially,**
  - E2A - Clinical Safety Data Management : Definition and Standard for Expedited Reporting
  - E2B(R3) - Clinical Safety Data Management : Data Elements for Transmission of Individual Case Safety Report
  - E2B(R3)IWG – Implementation Guideline for E2B
  - E2C(R2) – Periodic Benefit Risk Evaluation Report
  - E2D – Post Approval Safety Data Management : Definition and Standard for Expedited Reporting
  - E2E – Pharmacovigilance Planning
  - E2F – Development Safety Update Report
- **ICH E3 : Clinical Study Reports with E3R1**

FDA Guidance for Industry

- Premarketing Risk Assessment
- Safety Reporting Requirements for INDs and BA/BE Studies
- Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Post-approval Clinical Investigations, 2016
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
- Post-marketing Studies and Clinical Trials
- Establishment and Operation of Clinical Trial Data Monitoring Committees
- Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

Contents of Safety Assessment

- Death
- SAE
- Drop out
- Common AE
- Other

Death

- Collect the information on any Death occurring during any time after the first dose of drug or participation of the study, any period of drug exposure, a period of drug toxicity after a subject discontinued drug regardless of causality with drug
- Comparison with death in control group or database of other drugs used in same population
- Collect the information on medical events associated with death and its relatedness to drug

Serious Adverse Event (SAE)

- Any event that results following events regardless of drug relatedness
  - Death
  - A life threatening adverse experience
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant disability /incapability
  - A congenital anomaly or birth defect

- Decision for 'seriousness' by investigator vs. by FDA guidance

- Start to collect when subject sign an informed consent in the clinical trial

- Require brief narratives: CIOMS Form (ICH E3 Structure and contents of Clinical Study report section 12.3.2)
- Suspected Unexpected Serious Adverse Reaction (SUSAR) : Expedited Report to regulatory agency with 15 days only when reasonable causality relationship is established

Other Significant Adverse Event

- Known Adverse Event related with the path way of drug
- Pre-specify in the protocol : Event of Interest

- Marked Hematological or other lab abnormality
- Adverse drop out , dose reduction, significant concomitant therapy
- Potential important abnormality such as single seizure, syncopal episode, orthostatic symptoms

Drop Out from Treatment or Study

- Reason for drop out :
  - Identify the main reason for drop out
  - issue related with reclassification or classification to administrative reason or lost to follow up

- Adverse event associated with (or that cause) drop out
  - Enable to identify the type and frequency of adverse events that subjects can't tolerate and to provide important unexpected adverse reaction
  - Exploration of drop out for Dose response and time dependency
  - Cumulative distribution of time to drop out by treatment group and assessment of drop out pattern are useful

Common Adverse Event

- Collection of AE : Consistency in the development program
  - Treatment Emergent AE : AE occurs starting after the first dose and during the period drug toxicity after the last dose
  - The period of drug toxicity : 30days for the drug with short half-life otherwise 4 times of half life
  - The definition of treatment emergent AE should be specified in the protocol and SAP
  - Approach to eliciting AE : Solicited (List for check up) vs. Unsolicited (Open question)
  - AE includes - Worsening of back ground disease, change in severity of already reported event

- Categories and Preferred Terms :
  - MedDRA coding
  - Use of SMQ (Standard MedDRA query) vs. Individual case review vs. Adjudication

Others

Laboratory Testing

- Consistency in Lab testing procedure for comparability and combinability of study result
  - Method of sample collection and handling
  - The assay method used
  - The reference ranges used
- Unscheduled visit may be included in the database or in the narrative summary for SAE
- Clinically meaningful abnormal lab should be reported as AE
- Toxicity grade : CTC toxicity grading –requirement for clinical symptom

Special Assessment

- Hepatotoxicity
- ECG analysis
- Carcinogenicity
- Immunogenicity
- Withdraw Phenomena/abuse potential
- Human reproduction and Pregnancy data

Monitoring

Within Clinical Trial

- Event of Interest, other significant AE or list of solicited AE should be pre-specified in the protocol
- Review and discuss of SAE and its CIOMS report with PI
- Periodic review safety data for any safety signal
  - Any trends of safety lab or ECG
  - Seriousness, Severity and relatedness – Request for further information and discuss with PI
  - Adequacy of MedDRA coding : Consistency
  - Duplicated reporting
  - Missing data in AE : Start date, ongoing flag, outcome
- Drop out of treatment or study for the rate and reason
- Establish Data Monitoring Committee (DMC) and review unblinded safety data
- The study of cause specific event or mortality requires the adjudication of event

In Development Program

- Develop an integrated safety database while phase 3 is on going
  - Standardization of safety related CRF
  - Standardization of Lab
  - Update of MedDRA version

- Develop a Program Safety Analysis Plan (PSAP) and implement
- Review Periodic Aggregate Safety Report for any safety signal based on PSAP in overall development program
- Literature review of safety information on the same study population, in the development program from other drug in the same pathway

Reporting

Unless Specified

- Report Treatment Emergent Safety Data (AE, ADR, SAE, EOI, Lab, …) in all for safety including CSR, DSUR,
  - Definition of Treatment Emergent AE should be specified in the protocol, SAP and method section of all document for safety
- Report Narratives for Death and SAE
- Summary vs. List
  - Outliers : Comprehensive list including drug start date and stop date or other concomitant medication use
  - Aggregated trend in group, subgroup and time point : Summarize in table (when event occurs in more than 1% of study population or more 2 or 3 subjects)
  - Subject Incidence vs. Exposure adjusted subject incidence
  - Event rate vs. Exposure adjusted Event rate

Subject Incidence

- the frequency of subjects that the clinical event occur within a given time period

- Subject Incidence =# of subjects with the clinical event / total # of subjects (x %)
  - assumption that all subject is followed up for the same period of time
  - acceptable when relatively short exposure (or follow up time) with low drop out
- Exposure adjusted subject incidence = # of subjects with the clinical event / total follow up time from all subject (XX % per person-year) :
  - assumption of constant hazard rate per given period of time
  - useful when significantly different duration of exposure (or follow up time) among subjects or different drop out in groups

- A classification of rarity of AE based on subject incidence
  - Very common (if ≥ 10%)
  - Common (if ≥ 1% and < 10%)
  - Uncommon (if ≥ 0.1% and < 1%)
  - Rare (if ≥ 0.01% and < 0.1%)
  - Very rare (< 0.01%) and not previously reported

Mathematical Note on Approximation of Exposure Adjusted Subject Incidence

Under exponential distribution,

- t- year incidence is $1 - S(t) = 1 - \exp(-\lambda t) \approx \lambda t$ when λ is small
- One –year incidence or yearly incidence rate is approximated by λ, though strictly speaking, it should be $1 - \exp(-\lambda)$
- t –year incidence is approximated by λt, though strictly speaking it should be $1 - \exp(-\lambda t)$
- what actually exposure adjusted subject incidence is λ , hazard rate, not one- year incidence though they are close to each other when λ (and t) is small

Event Incidence (Event Rate)

- the frequency of given clinical events that occurred within a given time period
- useful to evaluate the disease or symptom that recurrence is important such as fracture of osteoporosis, exacerbation of respiratory infection
- clinically justifiable counting rule need to be established before unblinding

- Exposure adjusted Event Incidence = # events / total follow up time for all subjects
  - Assumed constant event rate : $\mu(t) = \lambda t$
  - Exposure adjusted even incidence rate per year is exactly λ

Analysis

Analyses in Safety Assessment (I)

- **Identification of Common and Drug Related AE**
  - Comparison of incidence rate in treatment group to one in control group
  - Multiplicity adjustment of comparison
  - Underpowered for statistically valid detection of small difference even under reasonable correction for multiplicity
  - Evidence of causality : minimum rate in population and consistent difference from control across studies
- **Exploration for dose or time dependency**
  - Higher dose than a label dose may be tested in early phase
  - Display of incidence of drug reaction over dose
- **Exploration for demographic interaction, drug disease and drug-drug interaction**
  - Issue related with subgroup analysis : multiplicity
  - Subgroup analysis in safety is exploratory
  - Pre-specification of subgroup
  - Reproducibility in other study
  - Use of interaction test : significant level of 0.1 instead of 0.05 *

* page 298, Quantitative Evaluation of Safety in Drug Development, 2015

Analyses in Safety Assessment (II)

➢ Laboratory Test Result

- Descriptive analysis and not for hypothesis testing
- For central tendency : mean change from baseline
- Shift table from normal to abnormal or shift table by toxicity grade from baseline toxicity
- For outlier, comprehensive listing on outlier, especially outliers in more than one variables
- List of subjects with large shift within the normal range
- List of subject having persistent abnormalities

Statistics for Safety Comparison with Control

1. **Risk Difference (RD)**

$$\theta = P_t - P_C$$

2. **Relative Risk (Risk ratio: RR)**

$$\theta = {}^{P_t}/_{P_c}$$

3. **Odds Ratio (OR)**

$$\theta = \frac{{}^{P_t}/_{(1-P_t)}}{{}^{P_C}/_{(1-P_C)}}$$

Where
Pt = incidence in treatment
Pc = incidence in control

Pooled Data vs. Individual Study Data

- Appropriate the pooling of studies in similar design
  - Improve precision
  - important for rare or lower frequency events
  - Formal test for heterogeneity may be useful to assess the appropriateness of pooling
  - Enable to perform drug-demographic, drug-disease interaction in subgroup
  - Pooling can obscure potential meaningful difference between studies
- Individual Study data
  - Different study population and better ascertainment
  - Assess the direction and amount of differences across studies
  - Enable to informally assess the extent of variability and identify outlier
- Crude Pooling vs. Meta Analysis

Techniques for Meta Analysis

➢ Fixed Effect Model *

- Under assumption of a common treatment effect across all individual studies
- An estimate of θ is

$$\hat{\theta} = \frac{\sum \hat{\theta}_i \omega_i}{\sum \omega_i}$$ where ω_i is weight for study *I*

➢ Random Effect Model *

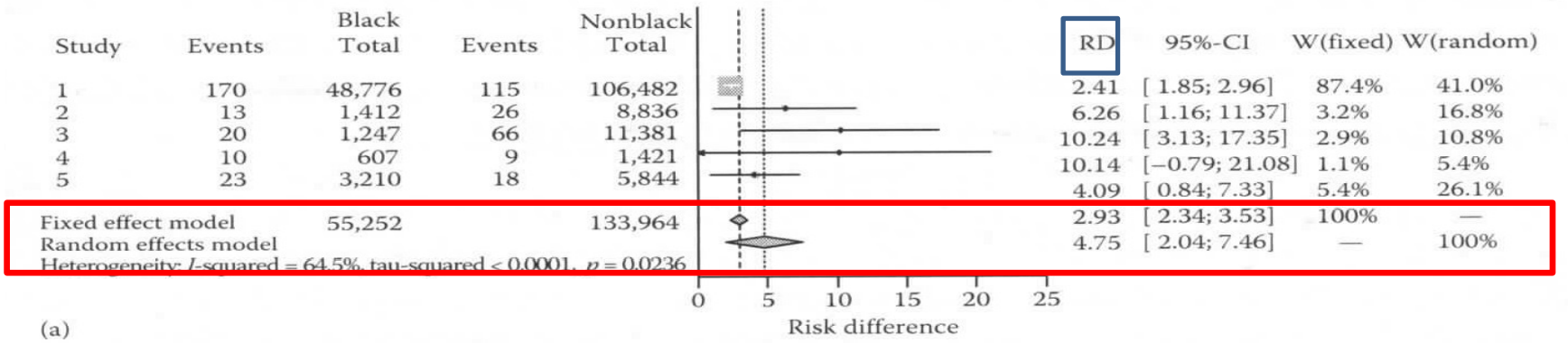
- Under assumption that treatment effects in k studies $(\hat{\theta}_1, \hat{\theta}_2, \ldots, \hat{\theta}_k)$ are independent random samples from a normal distribution N (θ, τ^2) where τ is between study variance

$$\hat{\theta}^* = \frac{\sum \hat{\theta}_i \omega_i^*}{\sum \omega_i^*} \quad \text{Where } \omega_i^* = (\omega_i + \hat{\tau}^2)^{-1}$$

- Assume heterogeneity between studies and model it by τ^2
- If τ^2 is small, $\hat{\theta}$ and $\hat{\theta}^*$ are close

* page 303 & 306, Quantitative Evaluation of Safety in Drug Development, 2015

Example : Choice of Metric in Meta Analysis



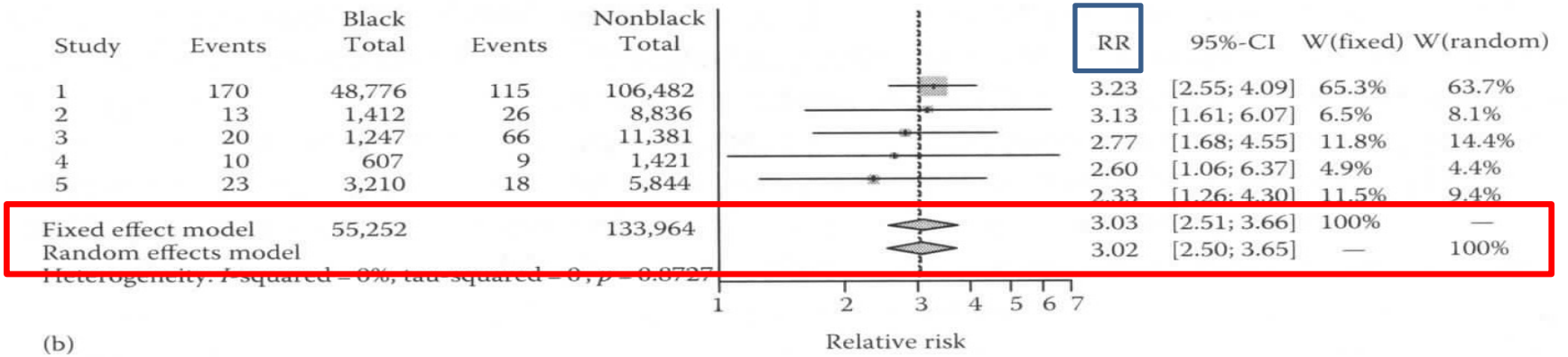
Study	Events	Black Total	Events	Nonblack Total	RD	95%-CI	W(fixed)	W(random)
1	170	48,776	115	106,482	2.41	[1.85; 2.96]	87.4%	41.0%
2	13	1,412	26	8,836	6.26	[1.16; 11.37]	3.2%	16.8%
3	20	1,247	66	11,381	10.24	[3.13; 17.35]	2.9%	10.8%
4	10	607	9	1,421	10.14	[−0.79; 21.08]	1.1%	5.4%
5	23	3,210	18	5,844	4.09	[0.84; 7.33]	5.4%	26.1%
Fixed effect model		55,252		133,964	2.93	[2.34; 3.53]	100%	—
Random effects model					4.75	[2.04; 7.46]	—	100%

Heterogeneity: I-squared = 64.5%, tau-squared < 0.0001, p = 0.0236

0 5 10 15 20 25

Risk difference

(a)



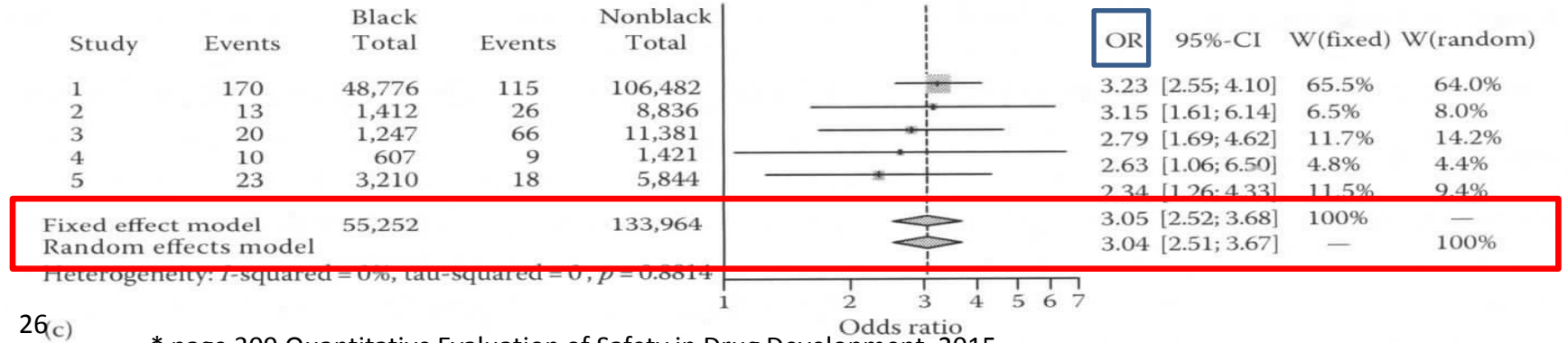
Study	Events	Black Total	Events	Nonblack Total	RR	95%-CI	W(fixed)	W(random)
1	170	48,776	115	106,482	3.23	[2.55; 4.09]	65.3%	63.7%
2	13	1,412	26	8,836	3.13	[1.61; 6.07]	6.5%	8.1%
3	20	1,247	66	11,381	2.77	[1.68; 4.55]	11.8%	14.4%
4	10	607	9	1,421	2.60	[1.06; 6.37]	4.9%	4.4%
5	23	3,210	18	5,844	2.33	[1.26; 4.30]	11.5%	9.4%
Fixed effect model		55,252		133,964	3.03	[2.51; 3.66]	100%	—
Random effects model					3.02	[2.50; 3.65]	—	100%

Heterogeneity: I-squared = 0%, tau-squared = 0, p = 0.8727

1 2 3 4 5 6 7

Relative risk

(b)



Study	Events	Black Total	Events	Nonblack Total	OR	95%-CI	W(fixed)	W(random)
1	170	48,776	115	106,482	3.23	[2.55; 4.10]	65.5%	64.0%
2	13	1,412	26	8,836	3.15	[1.61; 6.14]	6.5%	8.0%
3	20	1,247	66	11,381	2.79	[1.69; 4.62]	11.7%	14.2%
4	10	607	9	1,421	2.63	[1.06; 6.50]	4.8%	4.4%
5	23	3,210	18	5,844	2.34	[1.26; 4.33]	11.5%	9.4%
Fixed effect model		55,252		133,964	3.05	[2.52; 3.68]	100%	—
Random effects model					3.04	[2.51; 3.67]	—	100%

Heterogeneity: I-squared = 0%, tau-squared = 0, p = 0.8814

1 2 3 4 5 6 7

Odds ratio

(c)

* page 309 Quantitative Evaluation of Safety in Drug Development, 2015

In Vaccine

Safety Assessment for Vaccine

- Vaccines are usually administered to healthy persons with expectations as they are safe
- Unlike most of drugs, major population for vaccine is children, and more than 10 million vaccine per year is administered to children less than 1 years old
- Adverse events after vaccinations occur
  - but are generally rare
  - unlikely to be detected in pre-licensure clinical trials
  - post-marketing monitoring of adverse events after vaccinations is essential.
- Post marketing surveillance activity has a shared responsibility between national regulatory and the sponsor
- Purpose to detect the safety signal from much larger and diverse population
- Two categories of AEFI : vaccine (product or quality related) reaction and immunization related error or anxiety
- Know the denominator for post marketing safety event

Vaccine Safety Assessment based on WHO Guidance

Standard Practices

- Observation (20-60 min) after each dose for vaccination
- Collection of solicited sign and symptom recorded daily for 4-7 days after each dose – pre-specify in the protocol
- Unsolicited AE for entire period between dose and/or 4 weeks from the last dose
- SAE or pre-specified AE of interest (AESIs) for at least 6 month after the last dose
- May be allowed to follow up only SAE and AESIs for long term follow up
- For Vaccine with new adjuvants, follow up at least 12 month from the last dose
- Routine lab test may not be necessary

Additional Investigation

- Detection of viremia
- Assessment shedding (quantity and duration)

Summary

- Unless the primary end point of study is a specific safety event of interest, the safety assessment in clinical trial or in development program should be done descriptively rather than based on hypothesis testing

- Setting a well established integrated safety database and developing PSAP to review periodic safety profile at early stage of drug development are keys for the success of the drug development

Thank you