CIOMS Working Group X

Meta-analysis of safety – thoughts from CIOMS X

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Acknowledgements, conflicts, disclaimer

- Thanks to members of the CIOMS X Wg, especially Jesse Berlin for some slides
- I teach on meta-analysis (as part of pharmaco-epidemiology) at LSHTM and they charge fees!
- I have been ISPE representative at CIOMS Executive
- I have no (other) commercial conflicts
- These views are my own and not necessarily those of the rest of the Working Group

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Outline of talk

- What CIOMS X book – “Evidence Synthesis and Meta-Analysis for Drug Safety” contains
- Key issues in meta-analysis for drug safety
- Meta-analyses of observational data
- Where it will help & where it won’t

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A personal view on CIOMS

- - a unique contribution to worldwide drug safety
- It has possibly had the highest impact to expenditure ratio of any organisation working in drug safety
- It is unique in having worldwide academics & independents as well as regulators and industry (in contrast to ICH) which gives it flexibility and freedom to innovate in patients' interests.

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Contributors

- Editorial group:
  - Brenda Crowe (Chief Editor of the final report, assured the quality of the publication)
  - Jesse Berlin, ScD
  - Tarek Hammad, MD, PhD, MSc, MS, FISPE
  - Bert Leufkens, MD
  - Tongtong Wang, MD, PhD
- Membership included over 30 contributors from industry, academia, and regulatory agencies
- Special appreciation to senior experts outside the WG who during their review made valuable suggestions: Harald Herkner, Peter Lane, Nancy Dreyer, and Julian Higgins
- At CIOMS Drs Gunilla Sjölin-Forsberg and and the late Juhana E. Idänpään-Heikkilä, Ms Karin Holm, Ms Amanda Owden, and Ms Sue le Roux managed the project. Ms Karin Holm, contributing with technical collaboration support and coordination of the editorial work, merits a special thanks

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Why this WG?

- Many recent meta-analyses (Meta-Analysis) have had major impact on clinical or drug regulatory decisions
- Some drugs severely restricted in indication or suspended/withdrawn
- Some have become big issues in the general or medical media
- There is pressure on industry to be carrying out Meta-Analysis as part of drug development
  - pressure may be internal or external
- "Classic" Meta-Analysis has focused on efficacy outcomes
- Meta-Analysis for safety & for the regulatory process has special issues
- More training needed in these issues

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ELSEVIER

Contraception 64 (2001) 125–133

Original research article

Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis☆

Sean Hennessy[a,*], Jesse A. Berlin[a], Judith L. Kinman[a], David J. Margolis[a,b], Sue M. Marcus[a], Brian L. Strom[a,c]

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

THE LANCET

Articles

Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer

*Collaborative Group on Hormonal Factors in Breast Cancer**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

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Table 1. Comparison of Statistical Analyses of 42 Trials Involving Rosiglitazone.*

Test Statistic	Value (95% CI)	
	Myocardial Infarction	Death from Cardiovascular Causes
Data from Nissen and Wolski[1]		
Relative risk	1.27 (0.95–1.71)	1.33 (0.84–2.12)
Odds ratio	1.28 (0.95–1.72)	1.33 (0.83–2.13)
Peto odds ratio	1.43 (1.03–1.98)	1.64 (0.98–2.74)
Risk difference	0.00 (0.00–0.00)	0.00 (0.00–0.00)

CMAJ RESEARCH

Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis

Sonal Singh MD MPH, Yoon K. Loke MBBS MD, John G. Spangler MD MPH, Curt D. Furberg MD PhD

RESEARCH

Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis

Nicolai Haase *physician*[1], Anders Perner *professor*[1], Louise Inkeri Hennings *physician*[1], Martin Siegemund *professor*[2], Bo Lauridsen *physician*[1], Mik Wetterslev *medical student*[1], Jørn Wetterslev *chief physician*[3]

Current problems

- Remember the purposes
- All research requires a plan, and this may include a protocol and a statistical analysis plan
- Slight confusion over nomenclature- what is “Meta-analysis”?
- Statistical issues of combining data
- Scientific issues of combining data
  - e.g. Randomised v observational evidence

Target audience

- Non-statisticians
  - Medical or pharmaceutical or scientific assessors – those who have to read and assess Meta-Analysis reports from various sources
  - For them we will provide a clear description of the basic statistical issues, with warning about the hazards of misuse of statistical methods
- Statisticians
  - Show them key features of the statistical methods, but clarify how assembling the data and asking the right question is at least as important as if not more important than, the details of statistical methods
  - Introduce some important methodological issues
- For everyone
  - Show hoe there is greater uncertainty in the results than are just captured in a single confidence interval
  - Show how interpretation is still required

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Table of Contents

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Chapter 1. Overview and introduction

- The CIOMS X Working Group has deliberately chosen to define “meta-analysis” in this context as:

“The statistical combination of quantitative evidence from two or more studies to address common research questions, where the analytical methods appropriately take into account that the data are derived from multiple individual studies”

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CIOMS X definition of meta-analysis explained

- Should not be constrained only to an activity that follows a systematic literature review
  - Requires careful selection criteria and inclusion of all relevant data
  - Principles may be applied in situations where a single organization owns all of the data for a medicinal product
- Should generally preserve within-study comparisons
  - It is NOT “crude pooling” (adding up numerators and denominators, ignoring “study” stratification)
- Many methods may be appropriate, such as generalized linear models, Bayesian methods and so on, as long as they do not ignore the fact that the data are derived from multiple studies

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Chapter 3. Planning

- 3.1 Preparing the meta-analysis
- 3.2 Definition of population of interest
- 3.3 Definition of outcomes
- 3.4 Evolution of outcomes
- 3.5 Study selection
- 3.6 Study size and small study effects
- 3.7 Multi-arm trials
- 3.8 Risk of bias of the meta-analysis, individual study and overall
- 3.9 Access to combination of individual participant data, summary-level data, or both
- 3.10 Specific issues in meta-analysis of observational studies
- 3.11 Network meta-analysis

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Some elements of the statistical analysis plan

- Primary analysis population (e.g. intention-to-treat, as-treated, or per protocol)
- "One sensitivity analysis (if it is not the primary analysis) should correspond to minimal selection decisions – in other words, using as much data as possible from the original trials and imposing as few opinions of the meta-analysts as possible. Only then does it become obvious what effect these opinions have."
- Handling of missing data at the subject or summary level
- Choice of summary effect measures (e.g. risk difference, odds ratio, or risk ratio)
- Any subgroup analyses to be performed
- Handling of sparse data or zero event trials

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Chapter 4. Analysis and Reporting

- Measures of treatment effect
- Considerations for the choice of the appropriate statistical model (esp. for rare events)
- Advantages and disadvantage of Bayesian approaches
- Considerations regarding:
  - Multiplicity
  - Heterogeneity and meta-regression
  - Sensitivity analyses
- Finally, the chapter provides a proposed checklist for reporting of meta-analysis of drug safety

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Ch 5. Interpretation of results

- Thought process for evaluating the findings of a meta-analysis beginning with first impressions, followed by a more thorough evaluation of the methodology, the fit with other evidence, and implications of the findings for potential subsequent regulatory actions
- Results should be put into context with other available information on the benefits and risks of the product and that appropriate experts should be involved in the review
- Probably the key chapter

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More context

- Combining evidence on AEs, *where these were not the focus of the original studies*, is more challenging than combining evidence on pre-specified benefits
  - Current regulatory guidance is rather sparse
  - Multiple possible outcomes with multiple, possibly imprecise, definitions (other than all-cause mortality)
  - In conjunction with other sources of evidence, such as knowledge about other similar drugs, regulators need to decide whether particular AEs are likely to be associated with drug exposure
  - It is crucial to assess the importance of the harm in the context of benefit-risk of a particular product (but full scale assessment of the benefit-risk balance is beyond the scope of this report)

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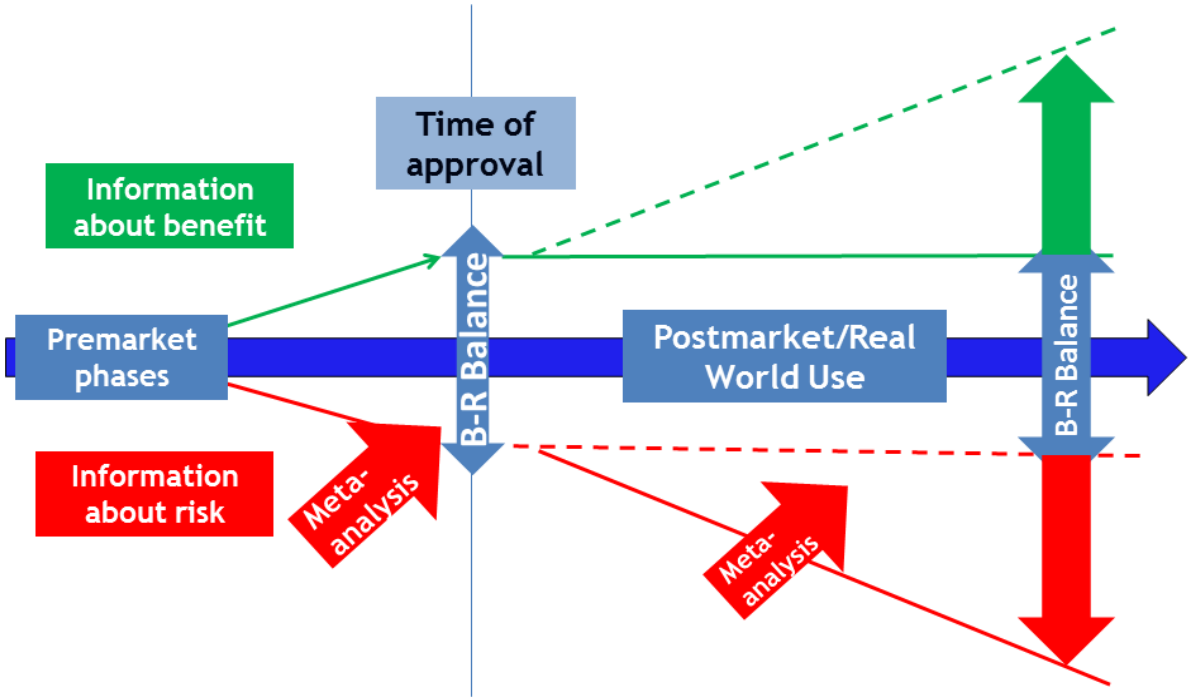
Figure 2.1 Simplified schematic of the role of meta-analysis in assessment of clinical safety data for a medicinal product or class of products



B-R = Benefit-Risk

Meta Analysis of Observational Studies

- In contrast to RCTs, sample size may not be primary problem
- It is possible to repeat bias across studies (HRT & CHD?)
- It will still be done, so regulators must understand strengths and limitations
- Problems are different to those of RCTs, though publication bias is an issue
- Quality of studies is possibly a greater issue
  - May need very careful review of the original studies
- Unintended effects may be more valid
- Some success stories
  - e.g Collaborative groups on hormonal effects on cancers

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Where it will help & where it won't

- **Where the CIOMS monograph will help**
- Education of non-US regulators
  - Need for them to start doing meta-analyses?
- Point out gains and warnings about M-A for safety issues
- Help industry to make better submissions through the whole drug development program
- Caution in interpretation, especially with OS
- **Where it may not help**
- No single suggestion for the best way of doing things
- No recommendations on software
- Not a guideline on reporting

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PRISMA – Guidelines for reporting

- Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *BMJ* 2009; 339:b2535
- Zorzela L, Loke YK et al. PRISMA harms checklist: improving harms reporting in systematic reviews *BMJ* 2016; 352 :i157
- Sterne JAC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919
- Checklist can be found on Equator-network website – "Explanation & Elaboration" papers

  http://www.equator-network.org

Conclusion

- Encourage careful design, conduct, and interpretation of meta-analyses of drug safety
- Encourage registration of protocols
- Encourage good reporting (PRISMA guidelines)
- Encourage critical appraisal
- Buy the book (eVersion available)

http://www.cioms.ch/index.php/publications/available-publications

- Support CIOMS!

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