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Clinical Study Reports within Cochrane Reviews

Consultation meeting

London, UK
16 May 2019

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Meeting agenda

01 Introduction and meeting objectives

02 Overview of the project 'Interim guidance on how to decide whether to include clinical study reports (CSRs) and other regulatory documents into Cochrane reviews' (MIF 2 Project)

03 Presentations from authors who have used CSRs in Cochrane, or other types of reviews, followed up group discussion

04 Group breakout to discuss how Cochrane could overcome the obstacles and challenges faced by authors and editors

05 Presentation to outline and discuss the proposal for conducting pilots in Cochrane reviews

06 Summary of next steps and closing remarks

To begin - thank you!

Thank you to everyone who is here, and those who were invited and provided feedback on challenges and obstacles in using CSRs

The core planning team: Rachel Churchill, Kerry Dwan, Ella Flemyng, Toby Lasserson, Joerg Meerpohl, Nicole Skoetz, Lesley Stewart, David Tovey

Additional speakers: Tianjing Li, Evan Mayo-Wilson, Lars Jørgensen, Bernd Richter, Karla Soares-Weiser

Note taking: Froeks Kamminga

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Introduction and meeting objectives

Presenter: David Tovey

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On Tamiflu

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Neuraminidase inhibitors review

- Clear rationale for use of CSRs
- Huge project
- Led directly to the MIF project
- Report presented to Scientific Committee

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So. Desirable… but is it feasible for Cochrane?

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What happened next

- Conversation with Juan Erviti
- ‘IQWiG is using CSRs for its summaries and they manage to complete the reviews in 12 weeks’
- Meeting with Beate Wieseler at IQWiG

What happened next

- Meeting with Beate Wieseler at IQWiG
  - Underlined value: risk of bias and selective outcome reporting
  - No selection: ‘we always use CSRs, where available’
  - Learning curve but can data extract from a study in two days ‘on average’
  - Forensic versus ‘standard’ approach
  - Challenge of access

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So, it has got to be worth exploring, right?

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Meeting objectives

1. A needs assessment that builds on the findings of the previous Cochrane-funded project that assessed when clinical study reports (CSRs) would be valuable

2. Reflection on the experiences of individuals and teams that have used CSRs as the basis for reviews and exploration of the practical feasibility of using CSRs in Cochrane

Meeting objectives

3. Explore access and other major obstacles to CSRs, as well as discuss how Cochrane could help overcome these. Consider what on-going support would be needed – non-financial/human and financial

4. Plan potential pilots and begin considering the development of how-to guidance on using CSRs in Cochrane Reviews

Overview of MIF 2 Project

Presenter: Lesley Stewart

CSRs as data source in Cochrane reviews

Interim guidance on how to decide whether to include clinical study reports and other regulatory documents into Cochrane reviews

MIF project report by

Tom Jefferson, Isabelle Boutron, Peter Doshi, Su Golder, Carl Heneghan, Alex Hodkinson, Mark Jones, Carol Lefebvre, Lesley Stewart

Background

- Project funded by Cochrane MIF to explore when it might be most valuable to use CSRs in Cochrane reviews
- Initiated in 2014 (low awareness in Cochrane)
- Report delivered Feb 2018
- Encourages Cochrane to enable the use of CSRs as a main data source

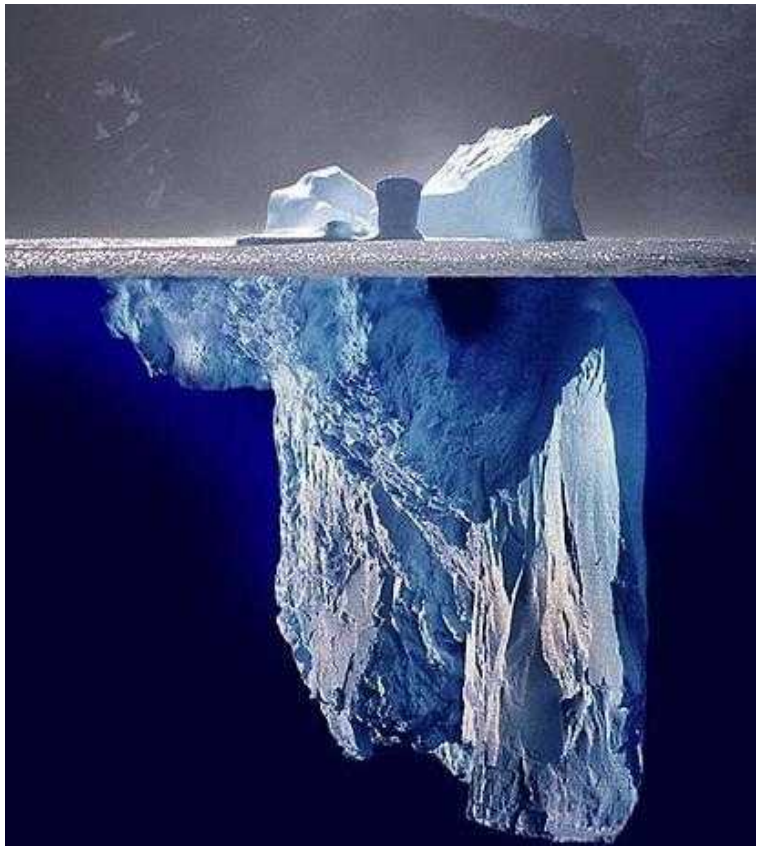
[This meeting responding to report and other developments = MIF project success]

Project objectives

- Describe rationale & current knowledge of practices for including CSRs as data source in systematic reviews
- Develop a **glossary** of licensing and regulatory terminology
- Draft interim guidance on how to **decide when it might be most important (and feasible)** to include CSRs in a Cochrane Review
- Consult with the Cochrane community to solicit views and identify challenges and barriers associated with using CSRs
- Raising awareness
  - Special sessions at Vienna Colloquium
  - Consultation survey
  - Results presented at Korean and Edinburgh Colloquia

Rationale

- Systematic reviews of RCTs play **trusted** role in decision-making
- Most SRs use data extracted from journal publications
- Mounting evidence of selective reporting of clinical trial data
- Commonly leads to overestimate of benefits and underestimate of harms
- Threat to undermine validity of SR
  - if the data are compromised, (no matter how sophisticated and high quality the methods) synthesis may be misleading



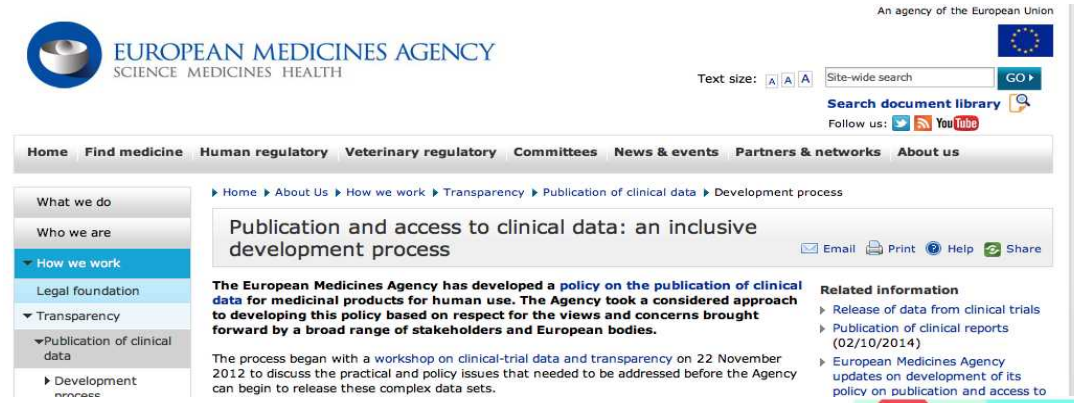
Clinical Study Reports

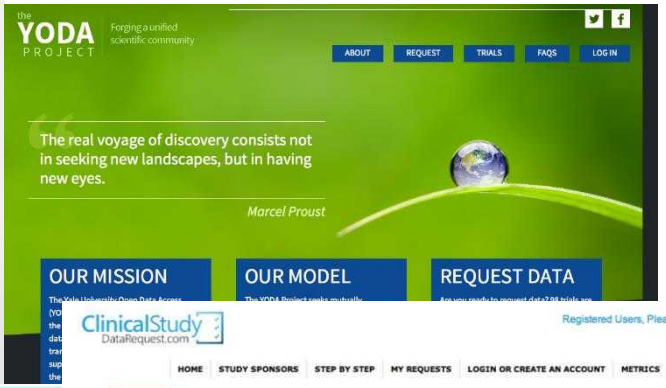
- Documents produced for submission to regulators to obtain a marketing authorisation or license
- By law, provides a comprehensive study record
- Detailed information about planning, execution, and results with large tables, figures, and datasets
- May be very long (hundreds/thousands pages), but often easy to navigate (when all components are in a single file)
- Appendices usually include important study documents: e.g. protocol and amendments, statistical analysis plan and amendments, case report forms, patient information sheets, certificates of analysis, informed consent forms, individual patient listings

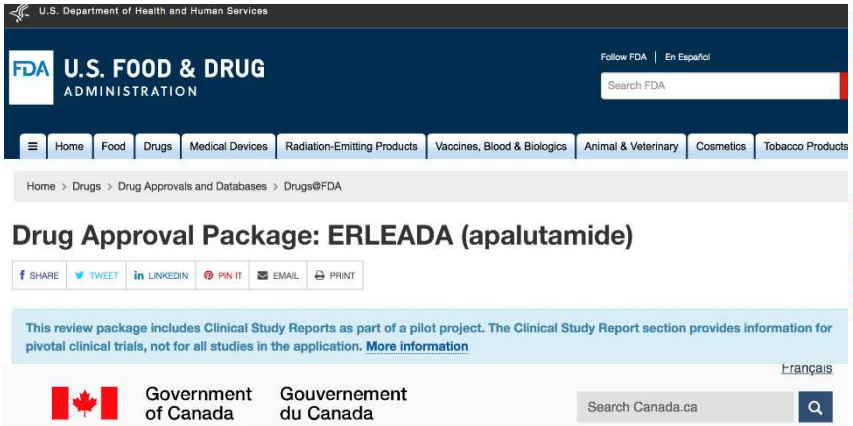
Journal articles

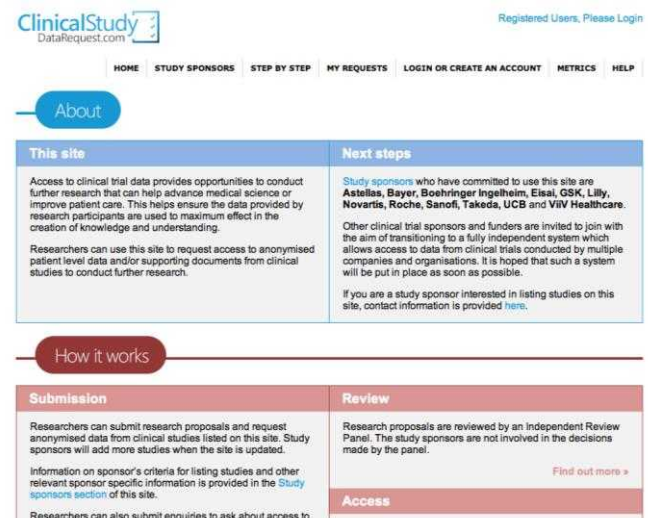
- Journal articles are a main means of communicating clinical trial results in summary form but increasing evidence that articles may be incomplete or biased
- Comparisons of two or more reports of the same trial e.g. journal article versus (CSRs) 19 studies covering over 50 different interventions
  - Gabapentin (Vedula 2009), Reboxetine (Eyding 2010), Tamiflu (Jefferson 2014), rhBMP-2 (Rodgers 2013),Duloxetine (Maund 2014), Olanzapine (Beaumier 2015), Paroxetine and Imipramine (Le Noury 2015), Orlistat (Hodkinson 2016, Schroll 2016)

Increasing availability of CSRs









When to use CSRs: basics

- Available only for drugs or biologics
- Academic trials generally don't produce CSR
- Most reviews would have a mix of trials with & without CSRs
- Some may use only CSRs
  (e.g. Cochrane review of tamiflu)

When to consider use: triggers

Concern about published results & lack of data

- High proportion of trials are industry funded
- High proportion of trials are unpublished
- Known errors or concerns about trial publications
- Important discrepancies between journal publication and registry entry
- Important or standard outcomes not published
- **Concerns about lack of published data on potential harms**
- Post-marketing surveillance has identified safety concerns
- Marketing authorization based on surrogate outcomes

When to consider use: triggers

High value questions

- Budget impact of adopting intervention
- Burden of disease of target population
- Numbers using or likely to use product
- Product new to the market
- New drug class or new mechanism of action
- Important interactions with other drugs
- Prominent claims of safety and/or efficacy advantage
- High degree of media attention

Potential issues

- CSRs may be incomplete
- In some cases may be internally inconsistent
- **BUT** CSRs provide greatest breadth and depth of information compared to journal articles, register data and grey literature
- CSRs often report data on subpopulations provide a source of further analysis
- Wealth of information gives a fuller and more reliable picture of trial strengths and weaknesses, and a more reliable assessment of the benefits **and harms** of the studied interventions

Cochrane community concerns

Project survey identified:

- Understanding of the need to avoid bias
- Enthusiasm for using CSRs
- Lack of knowledge about regulatory documents and terminology
- Considerable concern about knowing ***'how'*** to use CSRs
- Concern about lack of skills
- Need for guidance and training

Personal reflection

- Context of ‘normal’ review CSRs
  - should not add greatly workload
    (not methodological or forensic examination of documentation for inconsistencies which may be justified in some circumstances)
  - should not usually need special skills
- BUT experience shown that access to CSRs for SRs can be problematic
  - mainly not openly available (e.g. CSDR)
  - lengthy process to gain access (many months)
  - legal issues/unsuitable data sharing agreements
  - need for separate agreements with each company

Next steps

Project conclusions

- “Cochrane should consider making regulatory data a preferred source, primarily when the intervention in question is of potential high value and when there is evidence of reporting bias, or both”
- “Cochrane should invest in the infrastructure to make this possible”

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Presentations from authors who have used CSRs in reviews

Presenters: Kerry Dwan, Tianjing Li and Evan Mayo-Wilson, Lars Jørgensen, Bernd Richter, Lesley Stewart

Use of CSRs in the single technology appraisal process (STAs)

Kerry Dwan
Statistical Editor
Cochrane

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Outline

What is an STA?

STA process and using CSRs

Benefits and challenges

Reflections

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STAs

The STA process is designed to provide recommendations, in the form of NICE guidance, on the use of new and existing medicines, products and treatments in the NHS. These include:

- drugs
- medical devices (for example, hearing aids, inhalers, cochlear implants, pacemakers)
- diagnostic techniques (tests used to identify diseases, measure the severity of disease or the progression of disease)
- surgical procedures (for example, repairing hernias).

An STA is based on a review of clinical and economic evidence principally provided by the manufacturer or sponsor.

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Evidence Review Group (ERG)

The ERG is an independent academic group that reviews the manufacturer or sponsor's evidence submission. The ERG may also prepare some additional analyses. The ERG is normally commissioned by the National Institute for Health Research – Health Technology Assessment Programme.

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STA time line

ERG receives STA – 2 weeks to read and produce any queries

Manufacturer – 2 weeks to respond

ERG – 4 weeks to produce a critique of the manufacturers submission

Total 8 weeks

Sent CSRs electronically for manufacturer's trials or requested during clarification process

CSR contents

Varied depending on manufacturer

Full report on trial

- Protocol
- SAP
- Analyses
- Economic analysis
- Case report forms
- Table of individual adverse events


LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)
STA REPORT
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)
Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive
STA REPORT
2012-2015
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)
Dabrafenib for treating unresectable, advanced or metastatic BRAFv600 mutation-positive melanoma [ID605]
induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer

Nintedanib for previously treated locally advanced or metastatic non-small cell lung cancer

Direct evidence from one phase III RCT

- CSR available

Multiple treatment comparison (4 trials)

- No CSR

Indirect comparisons

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Benefits of CSRs

- Ability to check data included in the meta-analyses or network-meta-analyses
- Reduces selective reporting

Challenges

- **The length of CSRs**
- **Short timing of STA process**

If document is a pdf then it should be searchable

Reflections

Use CSRs as a data source in Cochrane reviews

Protocol should describe how discrepancies between data sources will be dealt with

- i.e. will the CSR be the primary data source?
- Consider dates of all documents

Access to CSRs of all studies included in a review could be an issue, including length of time to obtain them

- Check appendices to CSRs too!

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Using CSRs in Cochrane Reviews

Tianjing Li, MD, PhD

Evan Mayo-Wilson, MPA, DPhil

Center for Clinical Trials and Evidence Synthesis

Take home message

- It can take a long time to get CSRs and other company reports
- Using CSRs takes about as much expertise, and more time, compared with journal articles
- CSRs include the most information about design, risk of bias, and outcomes
  - CSR identify and mitigate reporting bias
- The most (only?) reliable and usable information about harms comes from CSRs and IPD
- Protocols should include methods / plans to address outcome multiplicity, harms, discrepancies across sources

Background: Multiple Data Sources (MUDS) Study Design

- Two case studies:
  - Gabapentin for neuropathic pain (21 trials, 6 CSRs)
  - Quetiapine for bipolar depression (7 trials, 4 CSRs)

- Participants & investigators masked

- Placebo-controlled, parallel RCTs

- Comprehensive searches for published and unpublished data

Mayo-Wilson, 2015. DOI: 10.1186/s13643-015-0134-z OA

CSRs hard to obtain

BMJ 2015;351:h4169 doi: 10.1136/bmj.h4169 (Published 25 September 2015)

thebmj

ANALYSIS

Are manufacturers sharing data as promised?

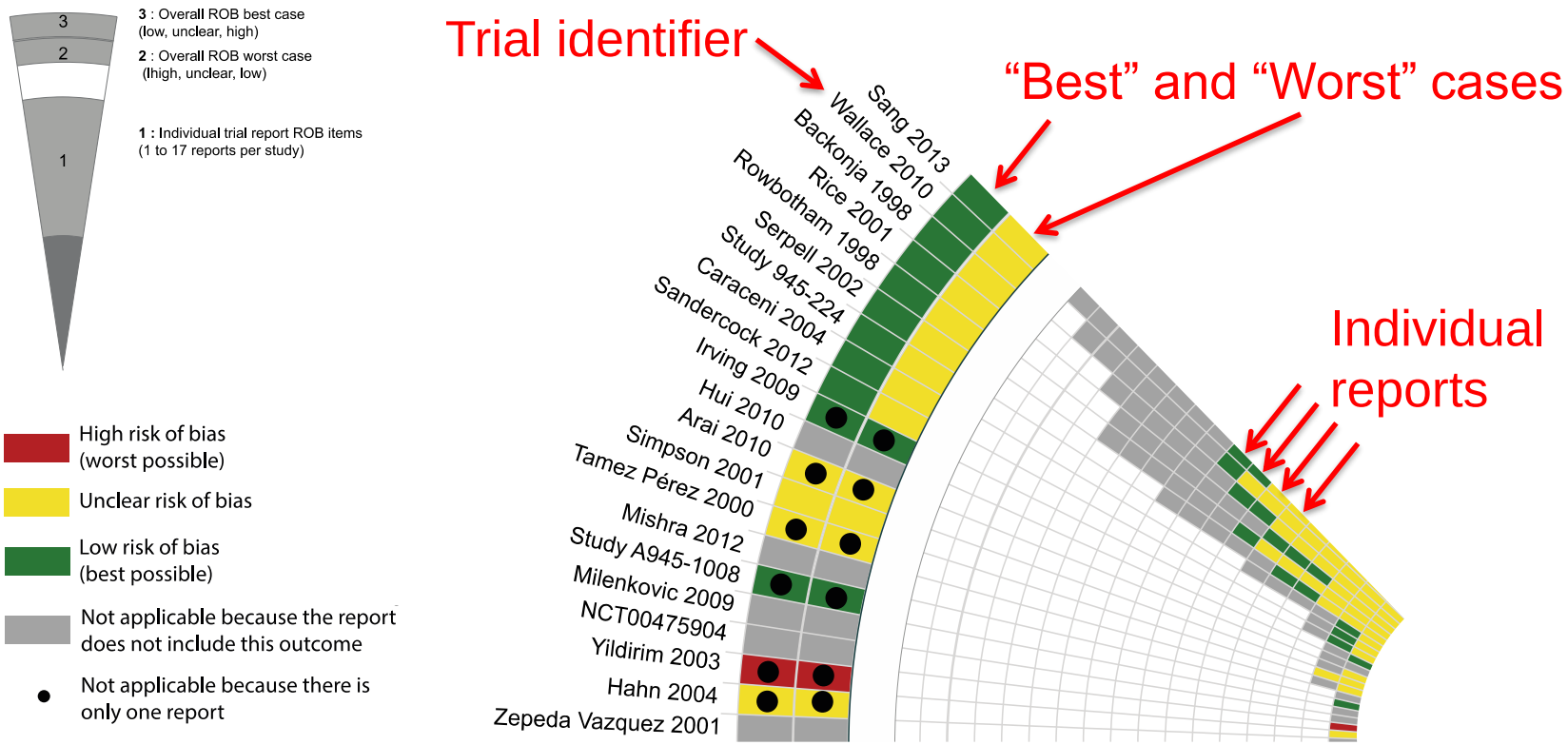
The drug industry's rhetoric over transparency of clinical trial data may not be reflected in practice

Evan Mayo-Wilson *assistant scientist, Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA*, Peter Doshi *assistant professor, University of Maryland School of Pharmacy, Baltimore*, Kay Dickersin *professor, Center for Clinical Trials and Evidence Synthesis, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health*

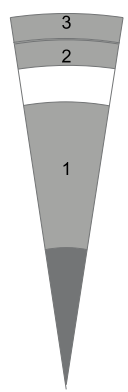
Over the past two years drug and device manufacturers have been among the most vocal contributors to the discussion about transparency of clinical trial data. In 2013 GlaxoSmithKline

that relatively few results have been released to independent groups, and it is unclear whether new policies are leading to more and different types of analyses and publications.

CSRs include more information for ROB assessment



CSRs include more information for ROB assessment



3 : Overall ROB best case
(low, unclear, high)

2 : Overall ROB worst case
(lhigh, unclear, low)

1 : Individual trial report ROB items
(1 to 17 reports per study)

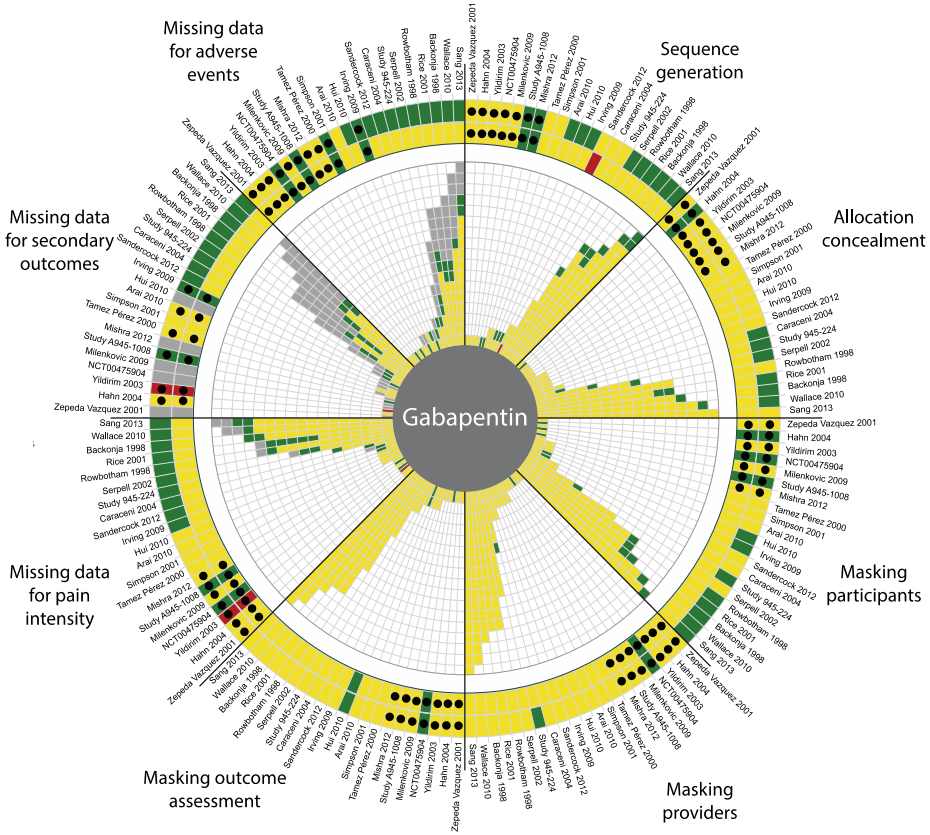
High risk of bias
(worst possible)

Unclear risk of bias

Low risk of bias
(best possible)

Not applicable because the report does not include this outcome

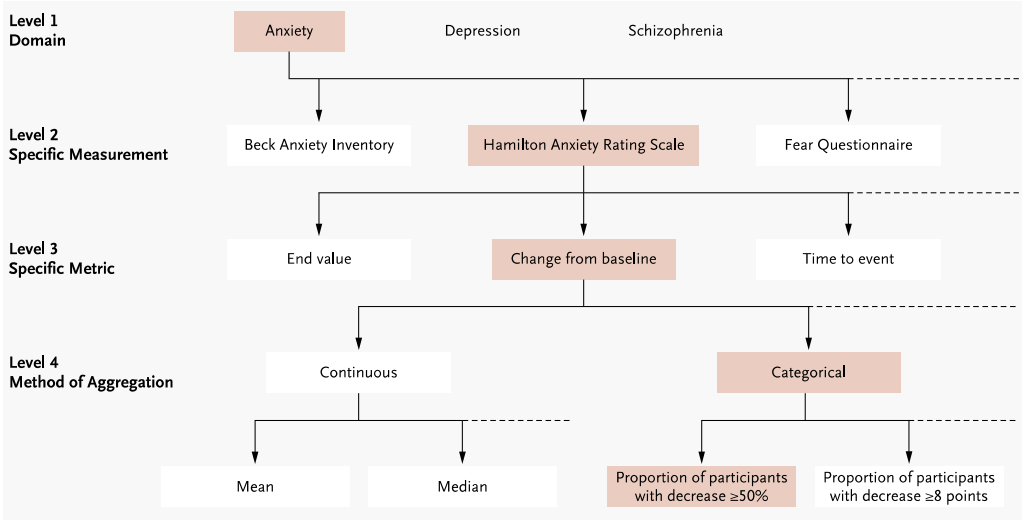
Not applicable because there is only one report

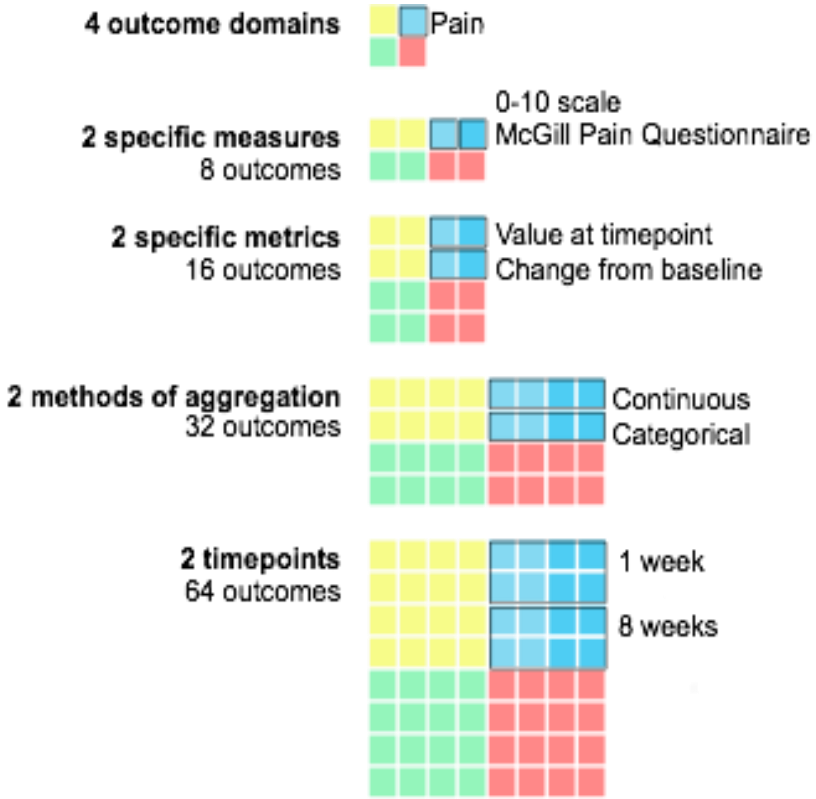


Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007

CSRs include more outcomes and results

Elements of an outcome on ClinicalTrials.gov





Zarin, 2011. DOI: 10.1056/NEJMsa1012065
Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007

Multiple analyses lead to *multiple results for the same outcome*

Analysis population	Handling missing data	Methods of analysis
Participants eligible to be included in the analysis (e.g., people who took one dose, everyone randomized)	Methods to account for missing data, including missing items and missing cases (e.g., multiple imputation, last observation carried forward)	Statistical methods, including analysis model, procedures (e.g., transformations, adjustments), and covariates included in the analysis

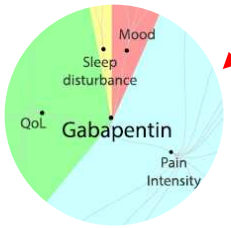
Mayo-Wilson, 2017. DOI: 10.1016/j.jclinepi.2017.05.007

CSRs include more outcomes and results

21 trials

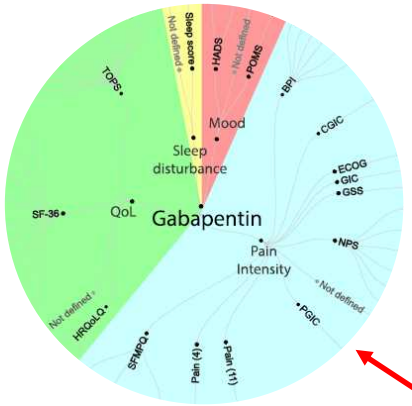
6 with CSRs

4 Outcome domains



Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.05.007

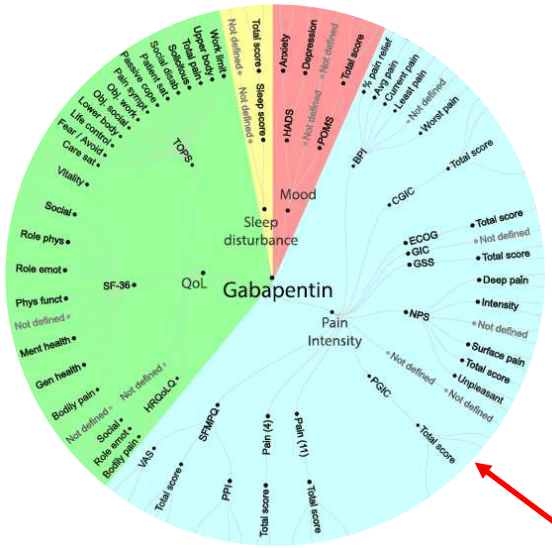
CSRs include more outcomes and results



Multiple measures

Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.05.007

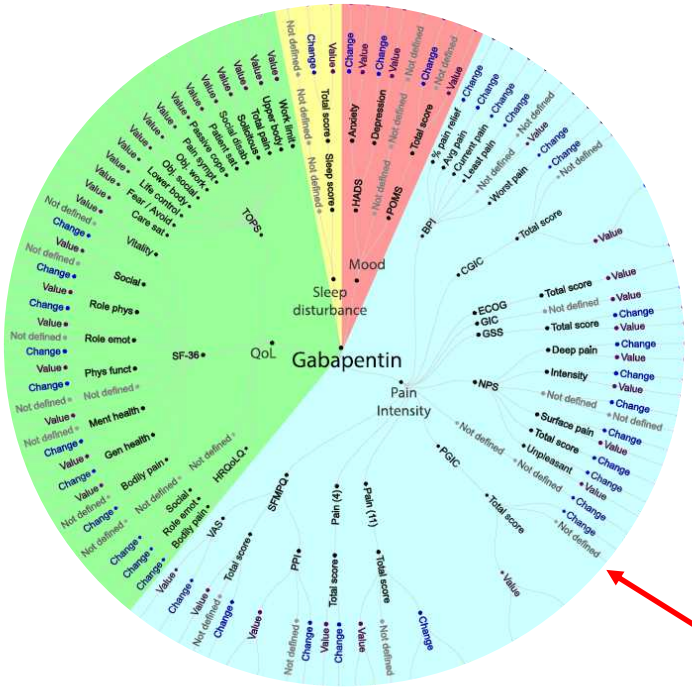
CSRs include more outcomes and results



Multiple totals and subscales

Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.05.007

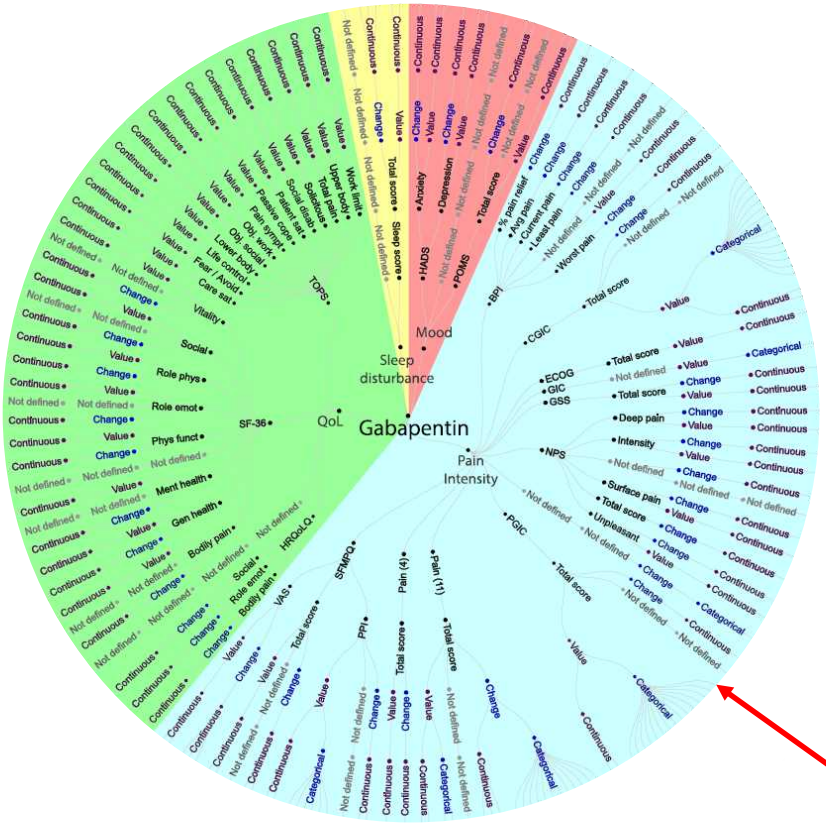
CSRs include more outcomes and results



Multiple metrics

Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.05.007

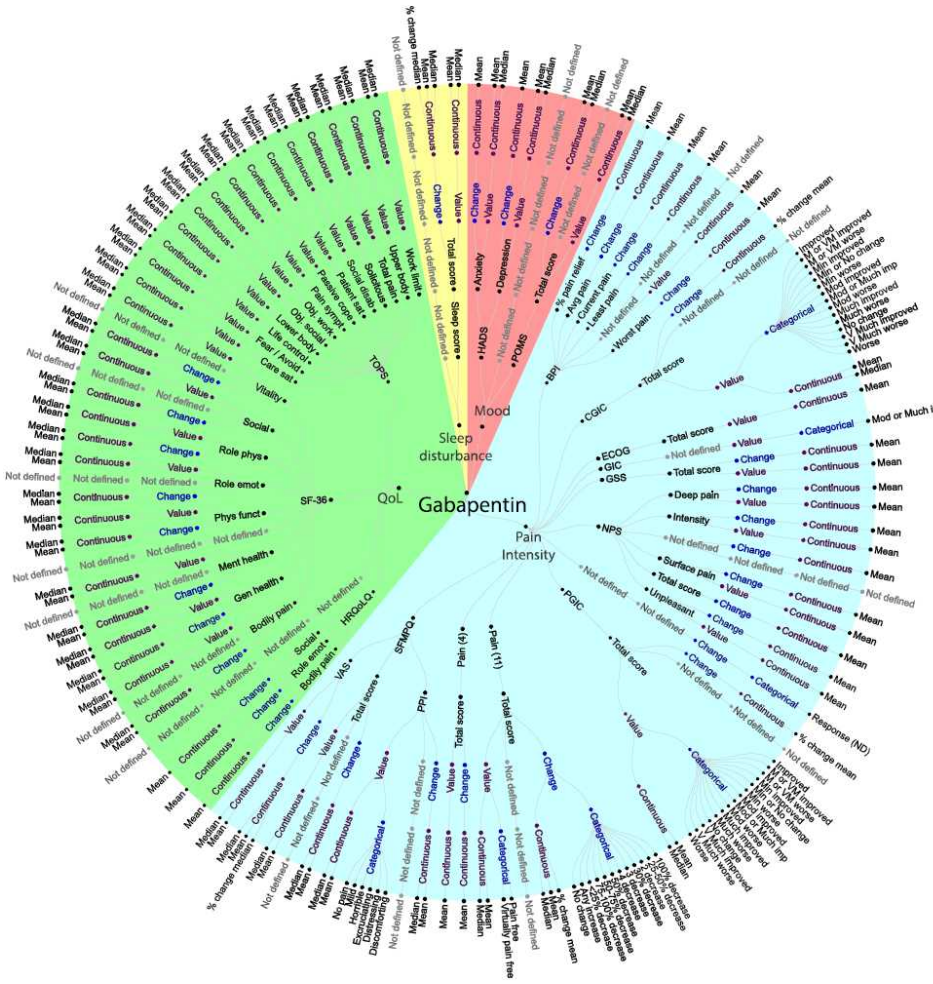
CSRs include more outcomes and results



Multiple methods of aggregation

Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.05.007

CSRs include more outcomes and results



214 outcomes

1230 results

305 (25%) publicly reported

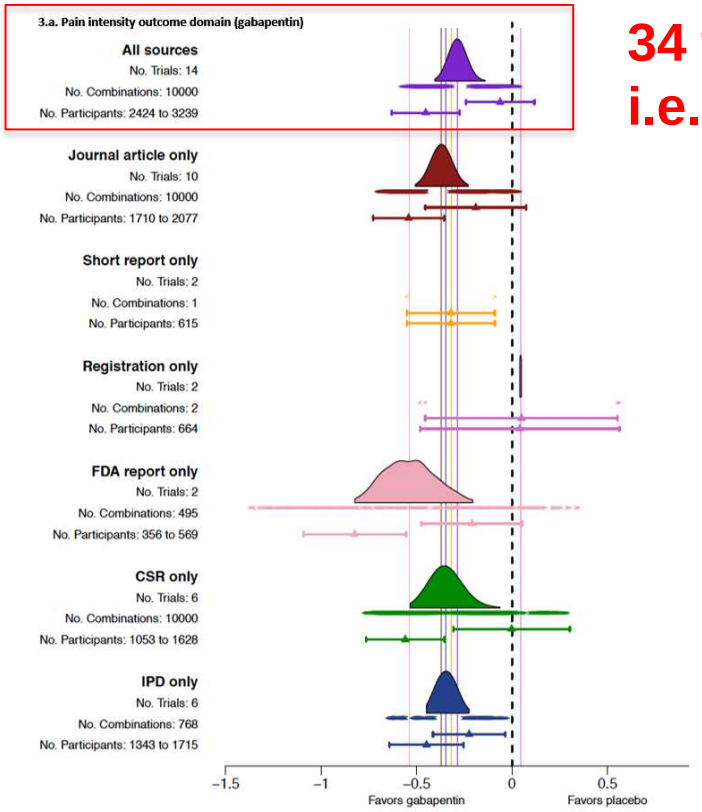
925 (75%) results available only in CSRs

No CSRs for 15/21 trials

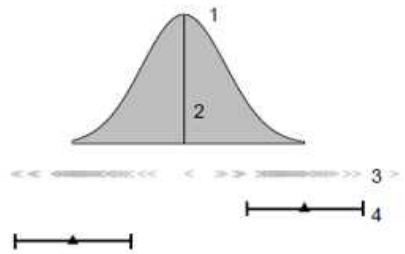
More hidden…

Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.05.007

Implications for meta-analysis: potential for cherry-picking



34 trillion possible meta-analyses of "pain"
i.e., combinations of *the same trials*



Item 1: Histogram showing the distribution of means (SMDs) from meta-analyses using one continuous effect estimate per study (selected at random)
Item 2: Average of the mean effects (SMDs)
Item 3: 95% confidence interval (CI) corresponding to the mean effects (SMDs) in the histogram, including lower (<) and upper (>) limits
Item 4: The smallest and largest possible treatment effect from a meta-analysis (with associated 95% CI) calculated by selecting the most extreme results from any report about each included trial.

Mayo-Wilson, *et al.,* 2017. DOI: 10.1016/j.jclinepi.2017.07.014

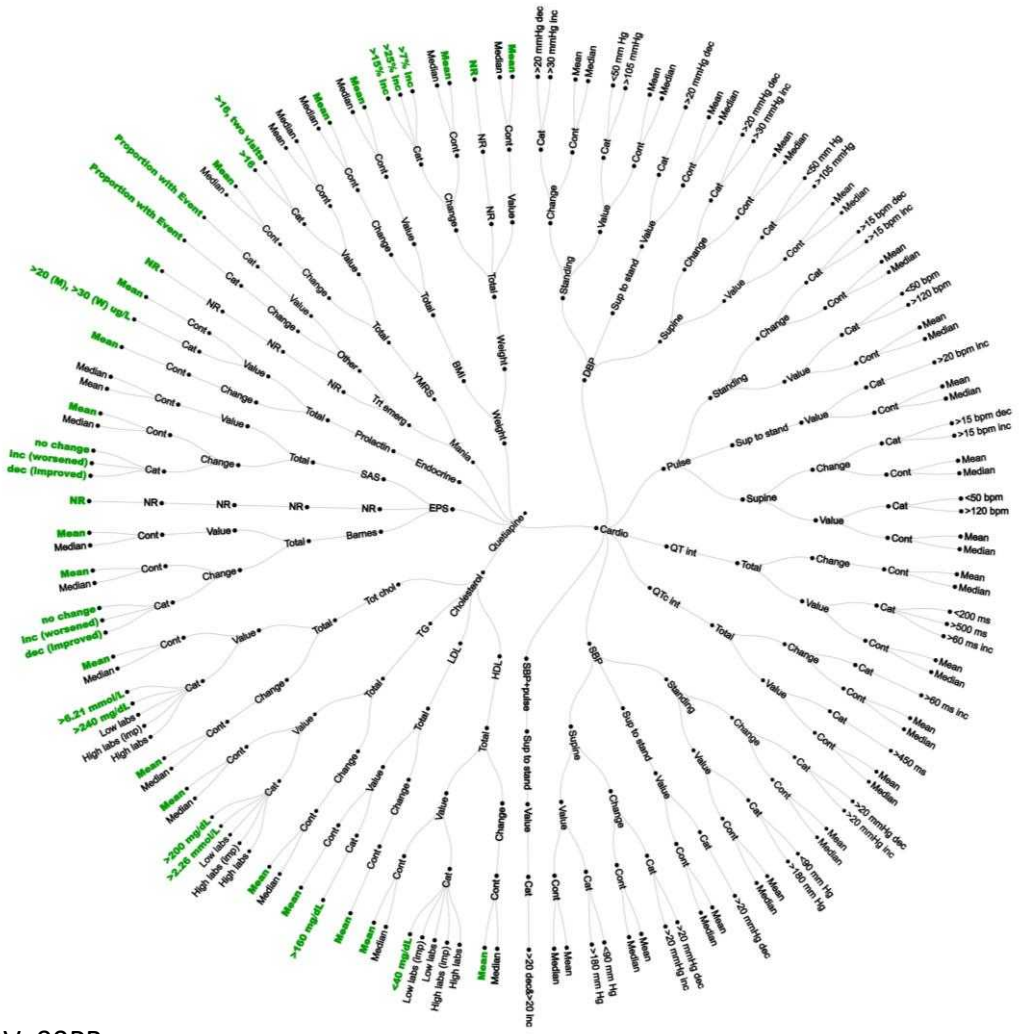
Systematic harms are underreported like benefits

Assessing harms

BENEFITS & SYSTEMATIC ADVERSE EVENTS	NONSYSTEMATIC ADVERSE EVENTS
Measured systematically for all participants	Measured if mentioned by participants
Selected *a priori*	Selected based on the results

Systematic

harms are underreported like benefits



http://bit.ly/2Vq90PB

Non-systematic harms are a mess

Nonsystematic adverse events are collected in response to open-ended questions

Anxiety
Abdominal Discomfort
Abdominal Distension
Abdominal Pain
Abdominal Pain Lower
Abdominal Pain NOS
Abdominal Pain Upper
Abdominal Tenderness
Abnormal Dreams
Accidental Overdose
Acne
Acne NOS
Acute Myocardial Infarction
Acute Psychosis
Adnexa Uteri Pain
Aggression
Agitation
Akathisia
Alcohol Intolerance
Alopecia
Altered Visual Depth Perception
Amnesia
Anemia
Anger
Anorexia

Anorgasmia
Aphasia
Aphthous Stomatitis
Appetite Decrease
Appetite Decrease NOS
Appetite Increase
Appetite Increase NOS
Aptyalism
Arthralgia
Arthritis NOS
Arthropod Bite
Arthropod Sting
Asthenia
Asthma NOS
Astigmatism
Ataxia
Atrioventricular Block First Degree
Back Injury
Back Injury NOS
Back Pain
Balance Disorder
Balance Impaired NOS
Bipolar Disorder
Bipolar I Disorder
Bladder Disorder NOS

Visual Disturbance
Vomiting
Vomiting NOS
Weight Decreased
Weight Gain
Weight Increased
Yawning

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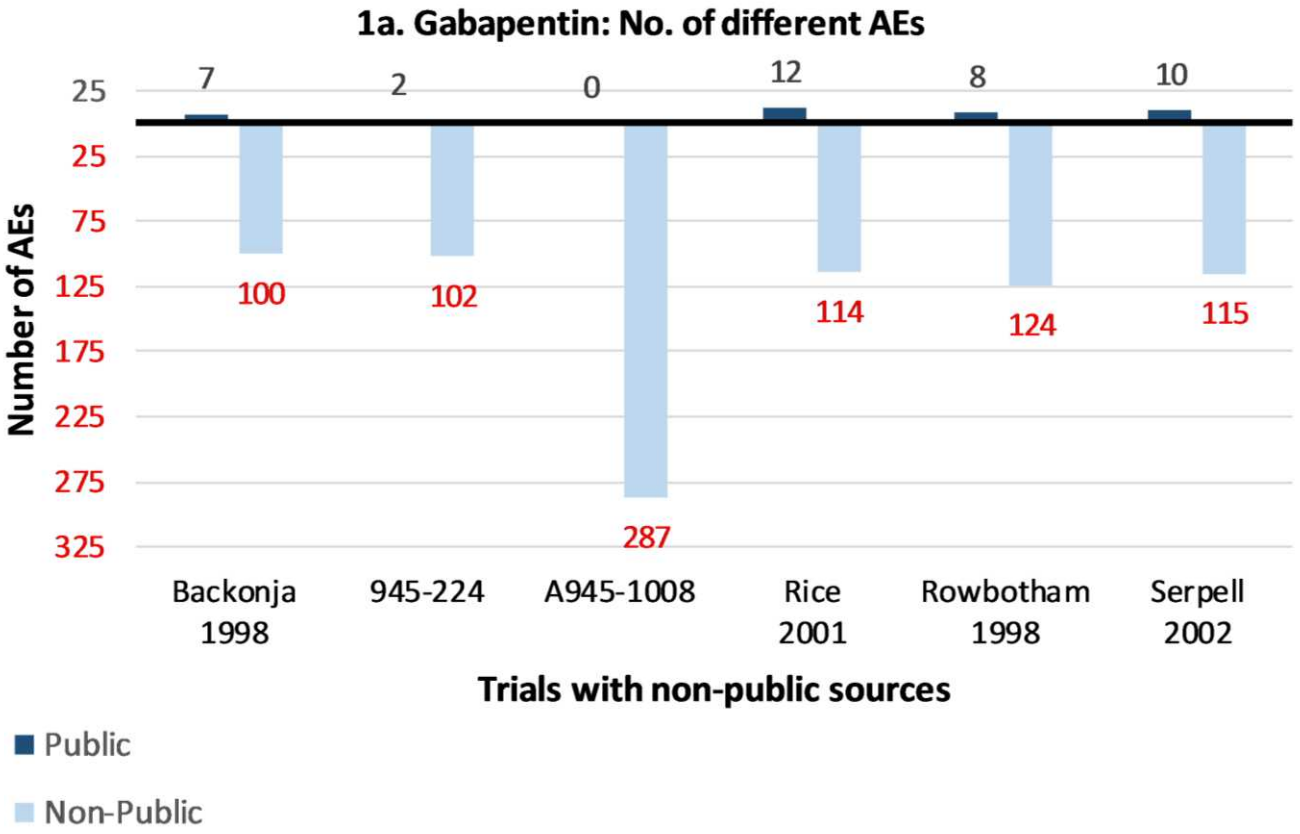
Most non-systematic harms are *never mentioned* publicly



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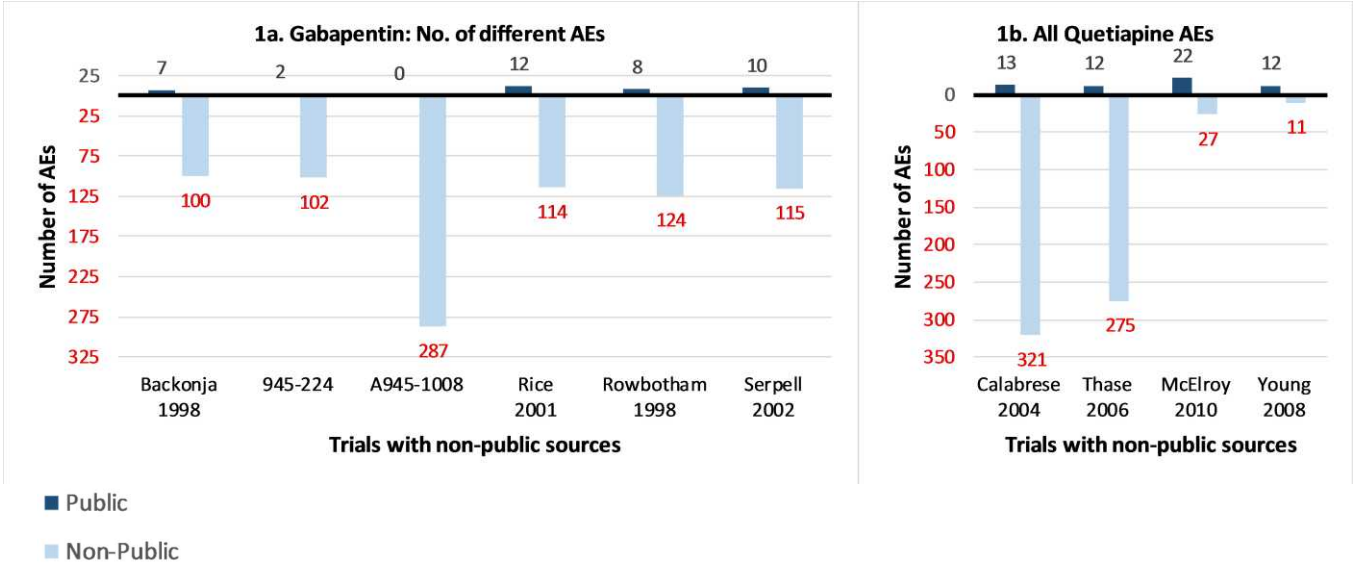

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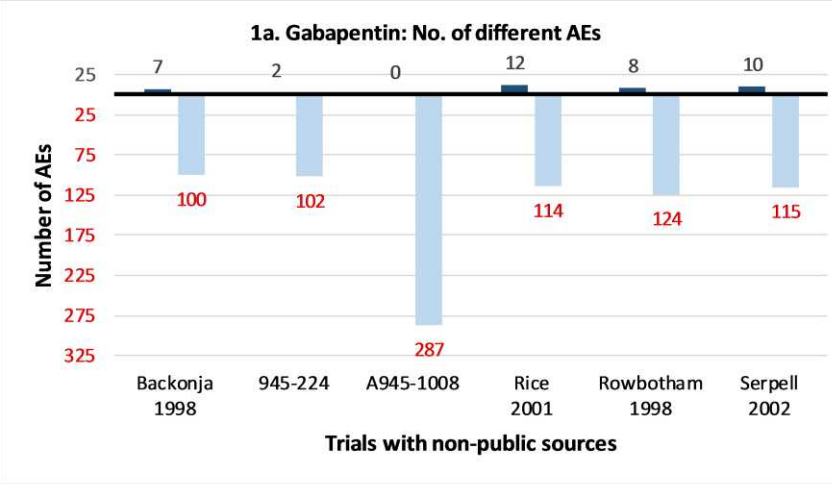
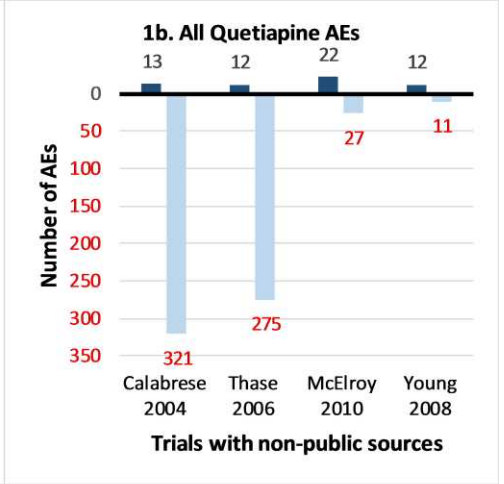
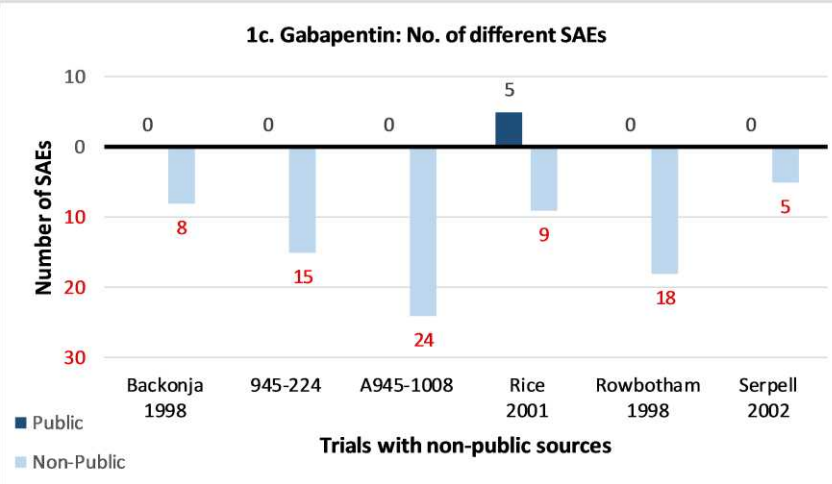
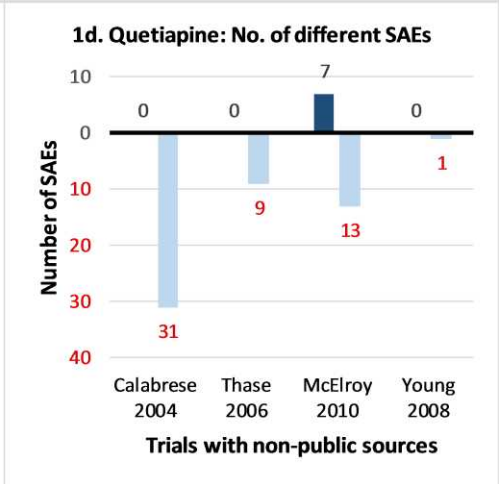








http://bit.ly/2VpiDyf

Multiple selection criteria are used to report non-systematic harms

1) Snapshot

Table 3. Adverse Reactions that Occurred in 2% or more of ARISTADA-Treated Patients and at Greater Incidence than in the Placebo-Treated Patients

2) Prescribing information ("drug label")

ADVERSE REACTIONS

Most commonly observed adverse reaction with ARISTADA (incidence ≥5% and at least twice that for placebo) was akathisia (6.1).

3) Trial registration (NCT01469039)

Frequency Threshold

Threshold above which other adverse events are reported	5%

4) Journal article (Meltzer *et al.*, 2015)

Treatment-emergent adverse events occurring in ≥2% of patients in the aripiprazole lauroxil treatment groups are reported in Table 2. The most common TEAEs occurring in >5% of patients in the aripiprazole lauroxil groups were insomnia, akathisia, headache, and anxiety. Akathisia was the only TEAE with an incidence of ≥5% in each aripiprazole lauroxil group that was at least twice the rate of placebo (11.6%, 11.5%, and 4.3%). The majority (>75%) of all akathisia episodes occurred before the second injection,

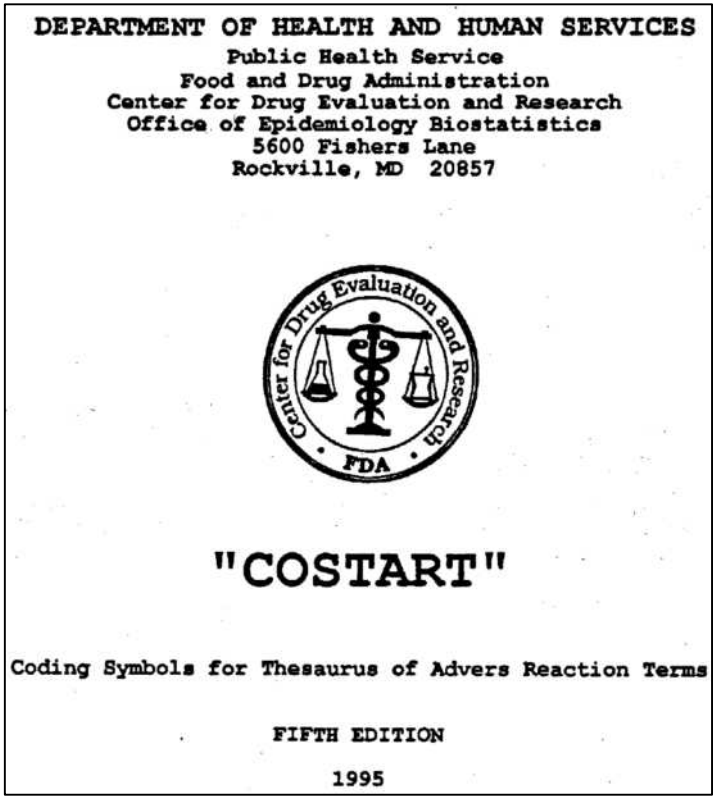
Table 2. Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥2% of Aripiprazole Lauroxil–Treated Patients, Safety Population

	Aripiprazole Lauroxil		
Preferred Term (%)	441 mg (n=207)	882 mg (n=208)	Placebo (n=207)
Any TEAE	58.9	57.2	62.3
Insomnia	9.7	12.0	11.6
Akathisia	11.6	11.5	4.3

http://bit.ly/2E6fJZ5

Implications of grouping harms for synthesis

Nonsystematic harms can be organized and "grouped" for analysis



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Epidemiology Biostatistics
5600 Fishers Lane
Rockville, MD 20857

"COSTART"

Coding Symbols for Thesaurus of Advers Reaction Terms

FIFTH EDITION

1995

WBB PtC Contact FAQs Downloads

MedDRA Medical Dictionary for Regulatory Activities

Search the site

Welcome to MedDRA

In the late 1990s, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed MedDRA, a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans... (more)

Multilingual Access 中文 Čeština Nederlands English Français Deutsch Magyar Italiano 日本語 Português Español

MedDRA Training

14 November 2018 London, United Kingdom Face-to-Face Training - Coding with MedDRA class

15 November 2018 London, United Kingdom Face-to-Face Training - MedDRA: Safety Data Analysis and SMQs

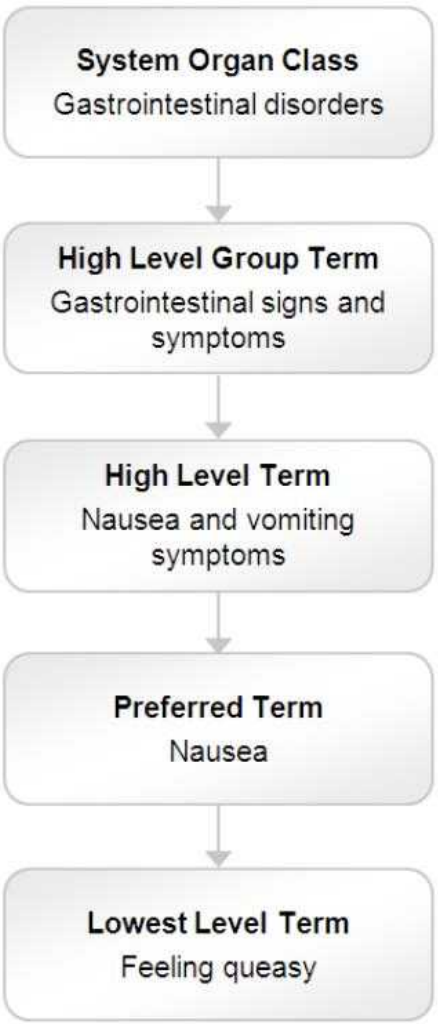
20 November 2018 Lyon, France Face-to-Face Training - Coding with MedDRA

21 November 2018 Lyon, France Face-to-Face Training - MedDRA: Safety Data Analysis and SMQs

U.S. Food and Drug Administration (FDA). Coding Symbols for a Thesaurus of Adverse Reaction Terms 5th Ed. 1995. https://bioportal.bioontology.org/ontologies/COSTART

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Introductory Guide MedDRA Version 17.0. 2014. https://www.meddra.org/sites/default/files/guidance/file/intguide_17_0_english.pdf

Nonsystematic harms can be organized and "grouped" for analysis



27 System Organ Classes

MedDRA

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

Conclusions for harms

Using journal articles in SRs: Junk in, junk out

Table 3.—Most Frequently Reported Adverse Events*

Preferred Terms	Gabapentin (n = 84)	Placebo (n = 81)	*P* Value†
Dizziness	20 (23.8)	4 (4.9)	<.001
Somnolence	19 (22.6)	5 (6.2)	.004
Headache	9 (10.7)	3 (3.7)	.13
Diarrhea	9 (10.7)	7 (8.6)	.79
Confusion	7 (8.3)	1 (1.2)	.06
Nausea	7 (8.3)	4 (4.9)	.54

*Data are number (percentage).
†Data were calculated using the Fisher exact test.

Collected systematically or non-systematically?

Number of events per person?

Grouped or not?

Reporting threshold?

Duration? Severity? Serious?

Definitions consistent across sites within trials and across trials?

Conclusions

- Obstacles: Time, time, time
- How did we overcome the obstacles: Funding and a plan
- Feasibility in Cochrane reviews
  - Use of CSRs might not be feasible without time, funding, and a plan
  - For harms, RCTs about a specific health condition may be *very* limited
  - Reconsider whether all Cochrane reviews can reliably assess harms without CSRs (junk in, junk out) and summaries across conditions / indications
- Use of CSRs affected our conclusions about efficacy, harms, and risk of bias

Cochrane

Lars Jørgensen
Rigshospitalet; Nordic Cochrane

Trusted evidence.
Informed decisions.
Better health.

Clinical Study Reports within Cochrane Reviews Consultation Meeting

London, 16 May 2019

Bernd Richter
Coordinating Editor Cochrane Metabolic and Endocrine Disorders Review Group
Institute of General Practice, Medical Faculty of the Heinrich-Heine University
Düsseldorf, Germany

IQWiG Institute for Quality and Efficiency in Health Care

Medicine put to the test

As an independent scientific institute, IQWiG examines the benefits and harms of medical interventions for patients. We provide information about the advantages and disadvantages of examination and treatment methods in the form of scientific reports and easily understandable health information.

Search

(i.e. Projects, Documents ...)

search

Latest news

Press Releases

Current commenting procedures (Hearings)

Calls for tenders advertised

Apalutamide in prostate cancer: indication of considerable added benefit

2019-05-02 Symptomatic progression is significantly retarded by this drug. This advantage clearly outweighs the disadvantages presented by some side effects.

» read more

How NNTs can be graphically illustrated in network meta-analyses

2019-04-25 In the Journal of Clinical Epidemiology, an international team of authors discusses the possibilities and limitations of graphical representations of statements on absolute effects.

» read more

Ribociclib in advanced breast cancer: survival advantages, accompanied by severe side effects

2019-04-15 Study indicates longer overall survival of postmenopausal women. However, there is a higher frequency of severe diseases of blood and lymphatic system. Overall, added benefit not proven

Background & context

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Biotechnologisch hergestellte Wirkstoffe bei rheumatoider Arthritis

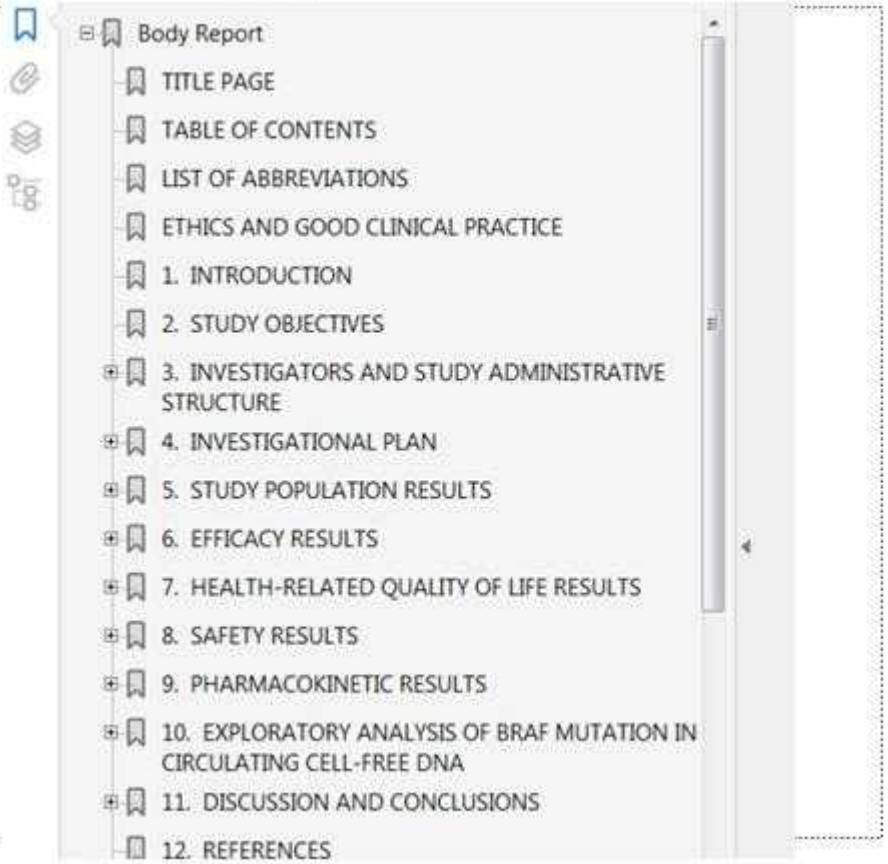
Vorbericht (vorläufige Nutzenbewertung)

Auftrag: A16-70
Version: 1.0
Stand: 30.05.2018

- 120 studies (30% IIT)
- 320 full publications for 101/120 studies (84%)
- Study registers: 159 entries for 96/120 studies (80%)
- .. with results for 69/120 studies (58%)
- CSR: 80/120 studies (67%) & 80/84 spons. Studies (95%)

Don‘t worry

Be happy



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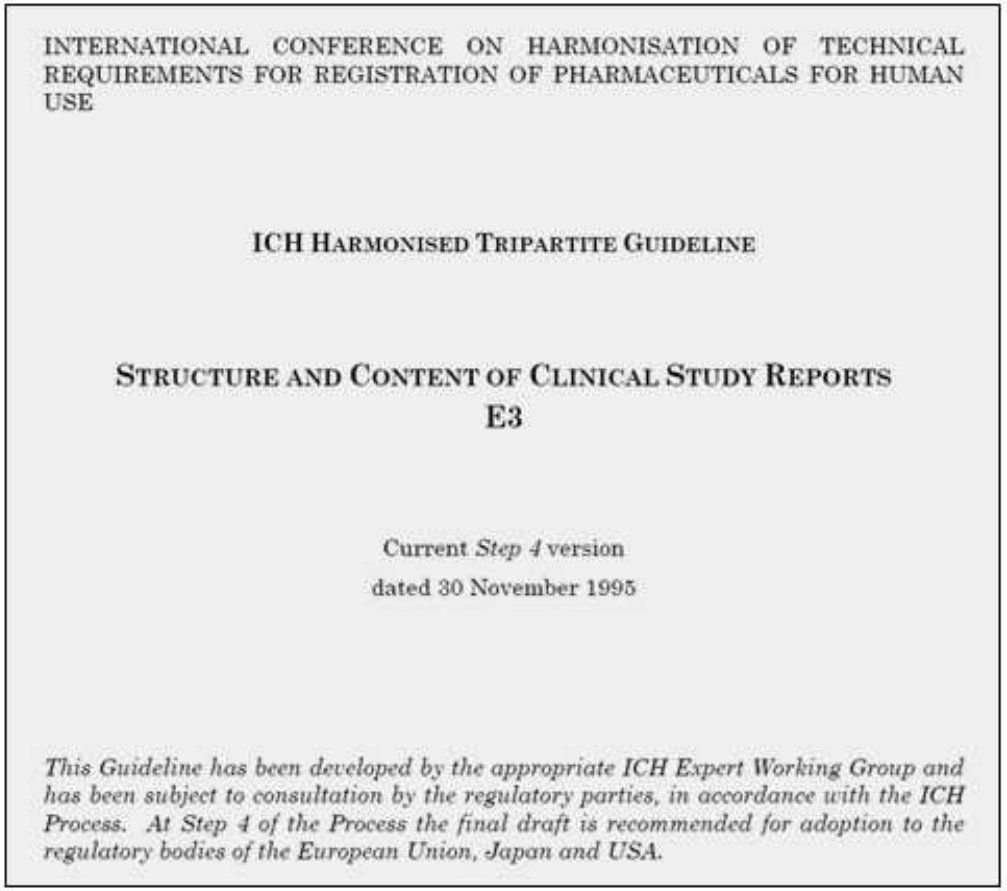
ICH E3 Guideline for CSRs



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
E3

Current *Step 4* version
dated 30 November 1995

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

- describes format and content of CSRs
- in effect since 1996 (Europe, US, Japan)
- core report + appendices
- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

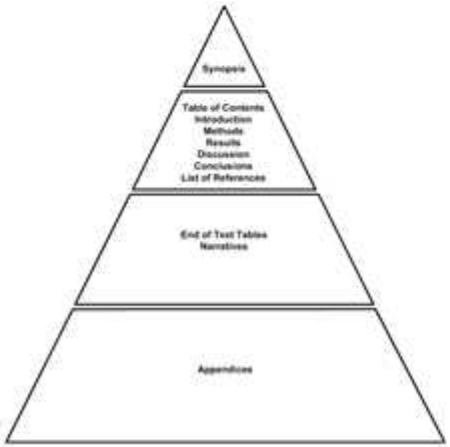
With permission (Beate Wieseler, IQWiG Germany)

How to access a CSR

Help for orientation

Study methods

Study results



Synopsis

Table of Contents (TOC)
TOC for tables
Introduction
Methods
Results
Discussion and Overall Conclusions
List of References

TOC for tables
End of Text Tables
(Narratives)

Appendices
Protocol
Protocol amendments
Case Report Form
Statistical analysis plan
(TOC for tables)
(Summary tables)
(TOC for listings)
(Patient data listings)

With permission (Beate Wieseler, IQWiG Germany)

Synopsis

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Introduction
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List of References

End of Text Tables
Narratives

Appendices

Synopsis

Table of Contents
Introduction
Methods
Results
Discussion and Overall Conclusions
List of References

End of Text Tables
Narratives

Appendices
Study information
- Protocol and protocol amendments
- Sample CRF
- List of IECs or IRBs
- Signature of principal investigator
- List of patients recieving drugs from specific batch
- Randomisation scheme
- Audti certificates
- Documentation of statistical methods
- Documentation of inter-laboratory standardisation methods
- Publications based on the study
- Important publications referenced in the report

Patient data listings
Case report forms
Individual patient data listings (US archival listings)

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EUROPEAN MEDICINES AGENCY

Clinical data

Help | My Account

Site wide search | Search

Home | Find Clinical Data | About

Logged in with an EMA account

You are signed in as **Bernd Richter**.

Advanced search

Browse search

Terms of use

How to find clinical data

Report patient re-identification

Data Protection

Data on this website

This website contains clinical data published under the European Medicines Agency (EMA) policy on the publication of clinical data. The clinical data have been submitted by pharmaceutical companies to support their marketing applications for human medicines under the centralised procedure and have been assessed by the Committee for Human Medicinal Products (CHMP).

EMA is the first regulatory authority worldwide to provide such broad access to clinical data.

For more information on the clinical data on this website, see Clinical data available.

For more information on EMA and its policy

Latest clinical data published

Inovelon (RUFINAMIDE) EMEA/H/C/000660 /II/0037 published 4 December 2018

Ameluz (5-AMINOLEVULINIC ACID) EMEA/H /C/002204/II/0020 published 12 November 2018

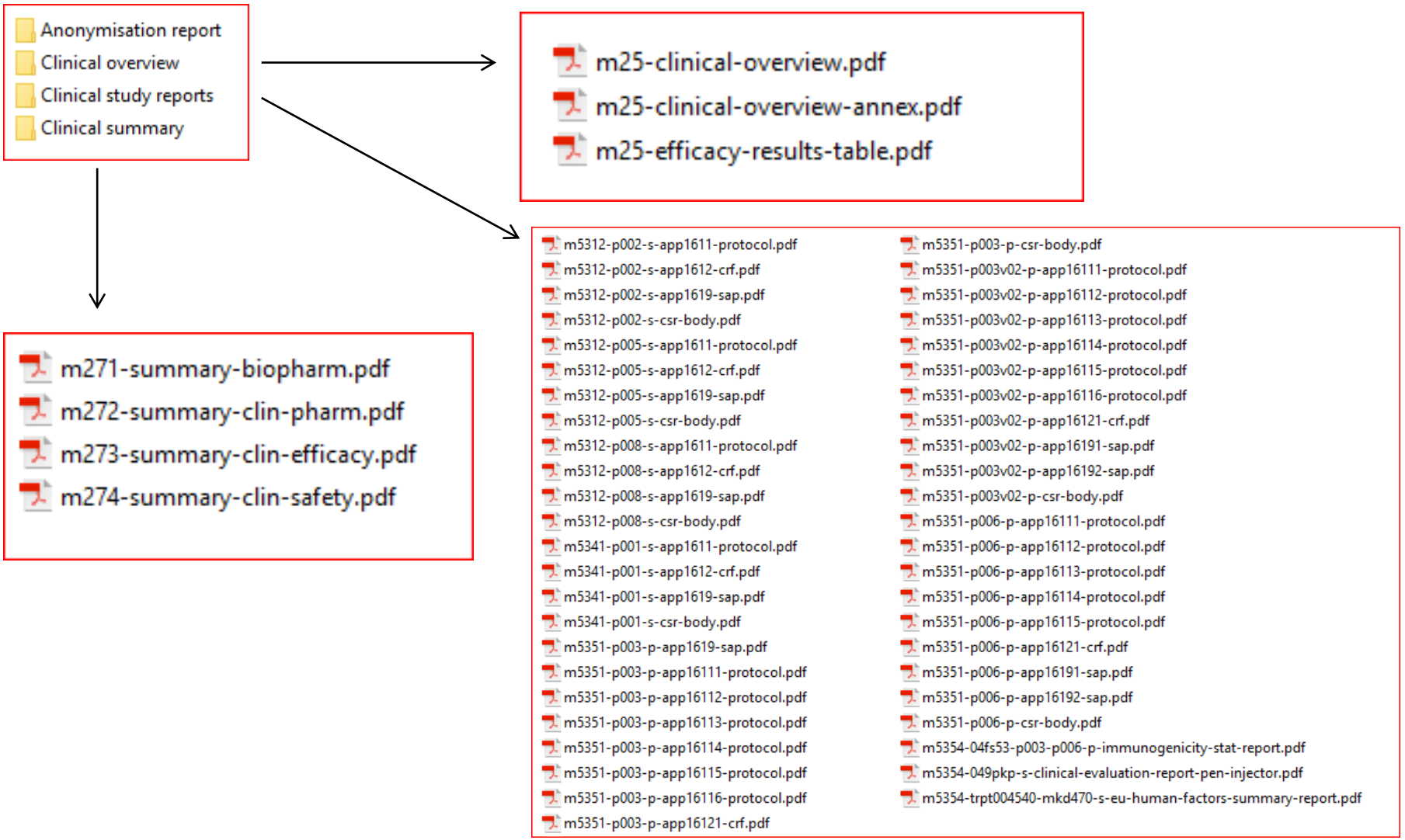
Truxima (RITUXIMAB) EMEA/H /C/004112/0000 published 9 November 2018

Alecensa (ALECTINIB) EMEA/H /C/004164/0000 published 17 October 2018

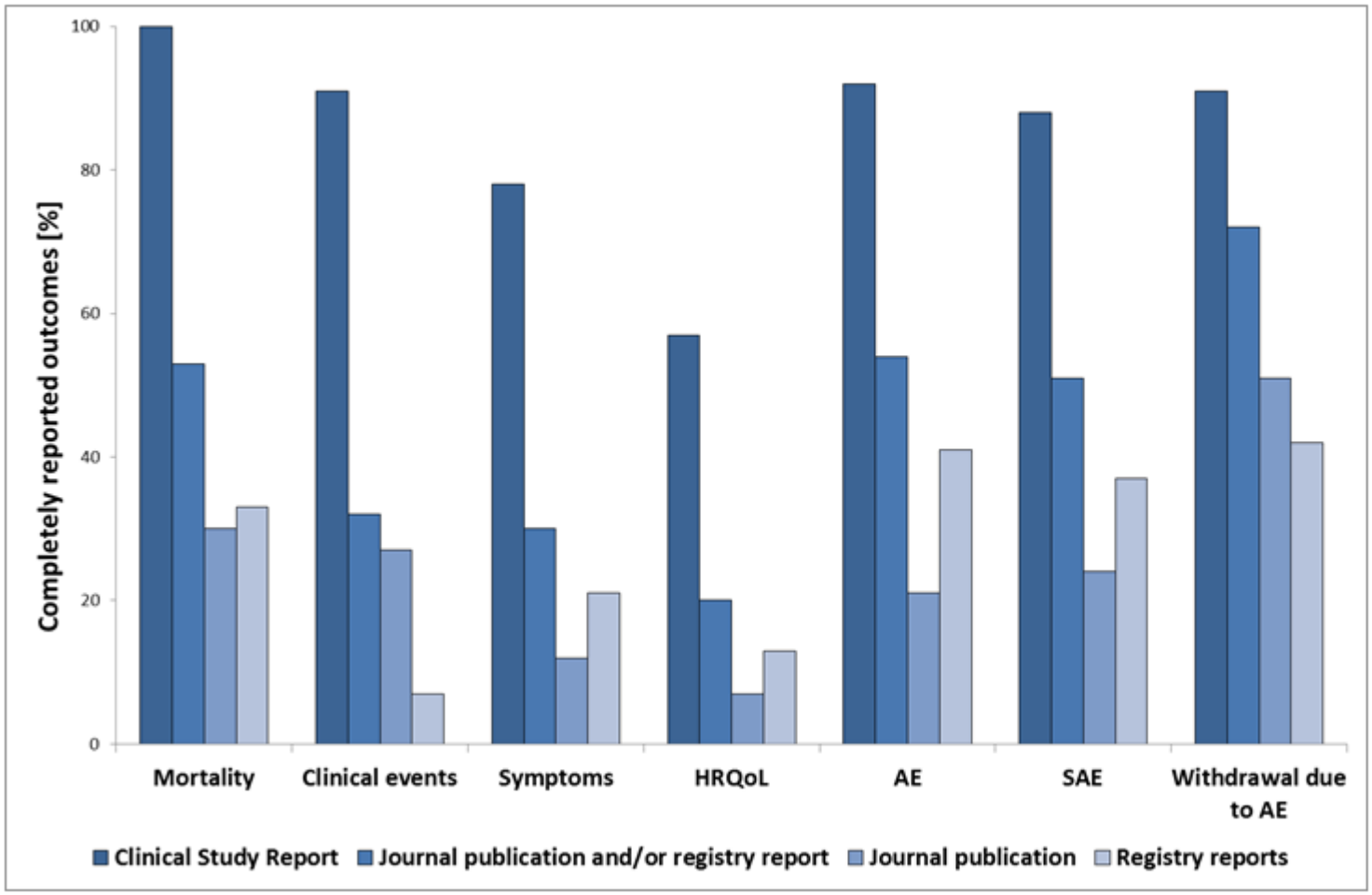
Lucentis (RANIBIZUMAB) EMEA/H/C/000715 /II/0061 published 9 October 2018

Movymia (TERIPARATIDE) EMEA/H /C/004368/0000 published 2 October 2018

Example from a recent EMA report



Information gain from CSRs



Sample 1:
Studies 1989 -2010
(N = 101)

Wieseler B. et al. Plos Med 2013; 10; e1001526

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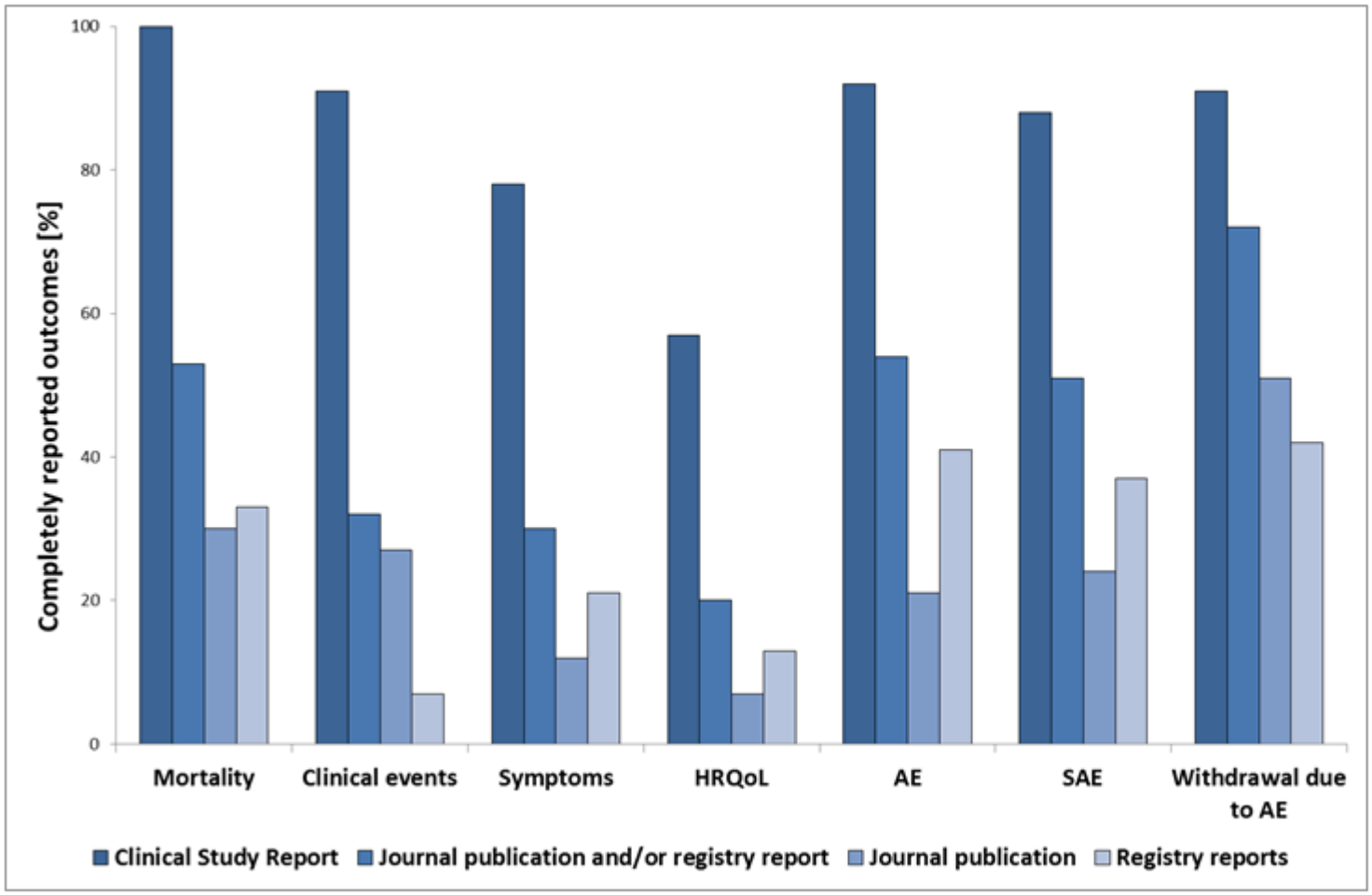
Information gain from CSRs



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Wieseler B. et al. Plos Med 2013; 10; e1001526

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Essential medicines selection

Essential medicines selection
Essential Medicines List and Formulary
Pharmacoeconomics
Selection of medicines in emergencies
WHO Expert Committees
Links
About

22nd Expert Committee on the Selection and Use of Essential Medicines– applications for:

Additional medicines

- Fixed-dose combination antihypertensives - EML
- Bedaquiline - MDR-TB in children - EMLc
- Glecaprevir + pibrentasvir - EML
- Fexinidazole - EML and EMLc
- Sumatriptan - EML
- EGFR tyrosine kinase inhibitors - EML
- Pertuzumab - EML
- Trastuzumab emtansine - EML
- Multiple micronutrient powders - EMLc
- Alteplase - EML
- Diazoxide - EMLc
- Carbetocin - EML
- Dolutegravir + lamivudine + tenofovir DF - EML
- Dabigatran - EML
- Direct oral anticoagulants (DOACs) - EML
- Multiple sclerosis disease modifying therapies - EML and EMLc
- Medicines for multiple myeloma EML
- Escitalopram - EML
- Methylphenidate - EML and EMLc
- Medicines for metastatic prostate cancer - EML
- Pegasparagase - EML and EMLc
- TNF-alfa inhibitors - EML and EMLc
- Tiotropium - EML
- Dolutegravir - EMLc
- Anti PD-1 immune-checkpoint inhibitors - EML
- Aprepitant - EML and EMLc
- Insulin analogues, including biosimilars - EML
- Newly registered antibiotics for EML AWaRe categorization

Essential medicines selection

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Insulin analogues, including biosimilars - EML

22nd Expert Committee on the Selection and Use of Essential Medicines

Drug information:

18.5 Insulin and other medicines used for diabetes

Formulation:

Insulin detemir: injection 100 units/mL
Insulin glargine: injection 100 units/mL
Insulin degludec: injection 100 units/mL

Application prepared by:

Andrea C. Tricco and colleagues

Application for addition of Insulin analogues, including biosimilars - EML
pdf, 3.48Mb

WHO Department comments:

Department of Management of NCDs, Disability, Violence & Injury Prevention - Comments
pdf, 101kb

Public comments:

Health Action International
pdf, 350kb

International Insulin Foundation
pdf, 73kb

Bernd Richter and Bianca Hemmingsen
pdf, 495kb

Jean-Pierre Chanoine
pdf, 500kb

1-15 of 47

Showing results for: Diabetes trials.

Edit search criteria

CONDITION	DESCRIPTION	START	DISTANCE	STATUS	Select header to sort by column
Diabetes **Diabetes Mellitus, Type 2** **Healthy**	This trial is conducted in Europe. The aim of the trial is to investigate the safety, tolerability, pharmacokinetics (the exposure of the trial drug in the body) and pharmacodynamics (the effect of the investigated drug on the body) of insulin 320 in healthy subjects.	01/06/15	NA	Completed Trials	View details
Diabetes **Diabetes Mellitus, Type 2**	This trial is conducted globally. The aim of this trial is to compare efficacy and safety of insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy in combination with metformin in subjects with type 2 diabetes mellitus.	26/07/15	NA	Completed Trials	View details
Diabetes **Diabetes Mellitus, Type 2**	This trial is conducted globally. The aim of this trial is comparing glycaemic control and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine (IGlar) as add-on therapy to SGLT2i (sodium-glucose cotransporter 2 inhibitors) in subjects with type 2 diabetes mellitus.	23/05/16	NA	Completed Trials	View details

COMPLETED

A clinical trial comparing efficacy and safety of insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy in subjects with type 2 diabetes mellitus

PDF

Layperson Summary

CSR (Clinical Study Report)

Synopsis

TRIAL ID:
NN9068-4185

NCT NUMBER:
NCT02420262

EUDRACT NUMBER:
2014-003621-18

Clinical Trial Report

Trial ID: NN9068-4185

DUAL™ VII - Insulin degludec/liraglutide (IDegLira) vs. basal-bolus therapy

A clinical trial comparing efficacy and safety of insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy in subjects with type 2 diabetes mellitus

Trial Phase: 3b

3 Table of contents for the individual clinical trial

Search for clinical information on drugs and medical devices

From Health Canada

Content and search results on this site are in the language provided by the manufacturer. Access and use of clinical information is governed by the **Terms of Use**.

Drugs | Medical devices

Search content

Search | Reset

Filter by:

Brand name: (Select)

Manufacturer: (Select)

Ingredients: (Select)

Regulatory activity: (Select)

Regulatory decision: (Select)

Decision date: (Select)

Release date: (Select)

Don't see what you're looking for?

Check the list of clinical information releases in progress to see what we're already working on.

Still don't see what you're looking for? You can request clinical information for a drug or a medical device.

Additional information

Additional information on the public release of clinical information.

CSL

CLINICAL STUDY REPORT

A Phase I/III Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study of Recombinant Coagulation Factor VIII (rFVIII) Compared to Recombinant Human Antihaemophilic Factor VIII (rFVIII; INN: octocog alfa) in Subjects with Hemophilia A, and a Repeat PK, Safety and Efficacy Study

CSL627_1001

Investigational product:	Recombinant Factor VIII (rVIII-SingleChain)
Indication studied:	Hemophilia A
Phase:	Phase I/III
Design:	Open-label, multicenter, crossover study
Study dates:	First subject in: 15-Feb-2012 Last subject out: 12-Dec-2014
Coordinating Investigator:	Prof. Dr. med. Ingrid Pabinger Division of Hematology and Hemostaseology Department of Internal Medicine I Medical University Vienna Währinger Gürtel 18-20 1090 Wien Austria

What are the benefits?

- Simple structure, comparable to a publication
- All endpoints reported
- Methodology, possible comparison with study protocol
- Time-specific data for endpoints & participant numbers (see RoB 2.0!)
- No author request necessary
- Easy navigation in pdf files
- Newer documents: direct links to tables, figures etc.

What are the obstacles and challenges?

- Frightening encounter at first sight (antidote: top-down approach)
- Difficult access: currently EMA, Canada (clinical information on drugs), manufacturer sites, IQWiG, (CT.gov)

Reflections

- Should first be piloted & done in-house (CRGs …)
- Near future: highly experienced & enthusiastic review author teams
- Requests, contracts etc. for CSRs: centrally (Cochrane instead of CRGs, authors …)

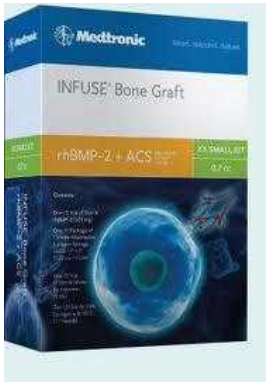
Example systematic review using data from CSRs

Safety and effectiveness of recombinant human bone morphogenetic protein -2 (rhBMP-2) for spinal fusion (principally an IPD-MA)

Centre for Reviews and Dissemination

Lesley Stewart

Context



Bone morphogenetic protein for spinal fusion

- Approved by FDA 2002 (ALIF surgery)
- Published RCTs reported benefits & almost no adverse effects
- Use in US grew rapidly 80% use off-label in cervical spine
- Later observational studies reported AEs
- Review of publications and publicly accessible FDA documents suggested an increased risk of complications and adverse events
- US Senate Finance Committee investigation of publishing practices
- Yale Open Access to Data (YODA) project persuaded manufacturer to deposit CSRs & IPD from all trials for independent scrutiny and re-analysis

the YODA PROJECT

Forging a unified scientific community

ABOUT | REQUEST | TRIALS | FAQS | LOG IN

"The real voyage of discovery consists not in seeking new landscapes, but in having new eyes."

Marcel Proust

OUR MISSION

The Yale University Open Data Access (YODA) Project's mission is to advocate for the responsible sharing of clinical research data, open science, and research transparency. The Project is committed to supporting research focused on improving the health of patients and informing science and public health. The YODA Project can only improve with your feedback. Please share your comments and ideas.

CONTACT US

OUR MODEL

The YODA Project seeks mutually beneficial partnerships with Data Holders, promoting independence, responsible conduct of research, good stewardship of data, and the generation of knowledge in the best interest of society. To participate, each Data Holder must transfer full jurisdiction over data access to the YODA Project.

LEARN MORE

REQUEST DATA

Are you ready to request data? 98 trials are currently available to request as of June 16, 2015.

GET STARTED

YODA

Commissioned two teams to independently re-analyse the Medtronic data
Agreed scope, no restriction on teams' approaches

CRD

- IPD meta-analysis in context of full systematic review
- Adverse events investigation informed also by supplementary analysis of observational studies (aggregate published data)
- Reporting practice investigated by conducting systematic reviews using:
  - aggregate data extracted from trial publications
  - aggregate data extracted from clinical study reports
  - IPD

Research questions

- Is rhBMP-2 a safe and effective intervention in spinal fusion surgery?

- Has academic reporting of industry sponsored trials lacked rigor
  - if so has this undermined the integrity of the publicly available evidence on which clinical decisions are made
  - Would rigorous systematic review of publically available published results reach the same conclusions as systematic review and synthesis of the underlying data reach similar conclusions

EDITORIAL | Annals of Internal Medicine

A Historic Moment for Open Science: The Yale University Open Data Access Project and Medtronic

REVIEW | Annals of

Effectiveness and Harms of Recombinant Human Bone Protein-2 in Spine Fusion

A Systematic Review and Meta-analysis

Rongwei Fu, PhD; Shelley Selph, MD; Marian McDonagh, PharmD; Kimberly Peterson, MS; Arpita Tiwari, MHS and Mark Helfand, MD, MS

Background: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is used as a bone graft substitute in spinal fusion, which unites (fuses) bones in the spine. The accuracy and completeness of journal publications of industry-sponsored trials on the effectiveness and harms of rhBMP-2 has been called into question.

Purpose: To independently assess the effectiveness and harms of rhBMP-2 in spinal fusion and reporting bias in industry-sponsored journal publications.

Data Sources: Individual-patient data (IPD) from 17 industry-sponsored studies; related internal documents; and searches of MEDLINE (1996 to August 2012), other databases, and reference lists.

Study Selection: Randomized, controlled trials (RCTs) and cohort studies of rhBMP-2 versus any control and uncontrolled studies of harms.

Data Extraction: Effectiveness outcomes in IPD were recalculated using consistent definitions. Study characteristics and results were abstracted by 1 investigator and confirmed by another. Two investigators independently assessed quality using predefined criteria.

Data Synthesis: Thirteen RCTs and 31 cohort studies were included. For lumbar spine fusion, rhBMP-2 and iliac crest bone graft were similar in overall success, fusion, and other effectiveness measures and in risk for any adverse e
across interventions (77% to 93% a
anterior lumbar interbody fusion,
nonsignificantly increased risk for r
genital problems. For anterior cervi
associated with increased risk for wo
gia. At 24 months, the cancer risk w

Annals of Internal Medicine | REVIEW

Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion

A Meta-analysis of Individual-Participant Data

Mark C. Simmonds, PhD, MA; Jennifer V.E. Brown, MSc, BA; Morag K. Heirs, MSc, MA; Julian P.T. Higgins, PhD, BA; Richard J. Mannion, PhD; Mark A. Rodgers, MSc, BSc; and Lesley A. Stewart, PhD, MSc, BSc

Background: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is widely used to promote fusion in spinal surgery, but its safety has been questioned.

Purpose: To evaluate the effectiveness and safety of rhBMP-2.

Data Sources: Individual-participant data obtained from the sponsor or investigators and data extracted from study publications identified by systematic bibliographic searches through June 2012.

adverse events. At 24 months, ODI scores were 3.5% lower (better) with rhBMP-2 than with ICBG (95% CI, 0.5% to 6.5%) and radiographic fusion was 12% higher (CI, 2% to 23%). At or shortly after surgery, pain was more common with rhBMP-2 (odds ratio, 1.78 [CI, 1.06 to 2.95]). Cancer was more common after rhBMP-2 (relative risk, 1.98 [CI, 0.86 to 4.54]), but the small number of events precluded definite conclusions.

Limitation: The observational studies were diverse and at risk of

sion: At 24 months, rhBMP-2 increases fusion rates, re-
pain by a clinically insignificant amount, and increases early
gical pain compared with ICBG. Evidence of increased can-
dence is inconclusive.

Funding Source: Yale University Open Data Access

rn Med. 2013;158:877-889. www.annals.org
or affiliations, see end of text.

BMJ

BMJ 2013;346:f3981 doi: 10.1136/bmj.f3981 (Published 20 June 2013) Page 1 of 14

RESEARCH

Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion

OPEN ACCESS

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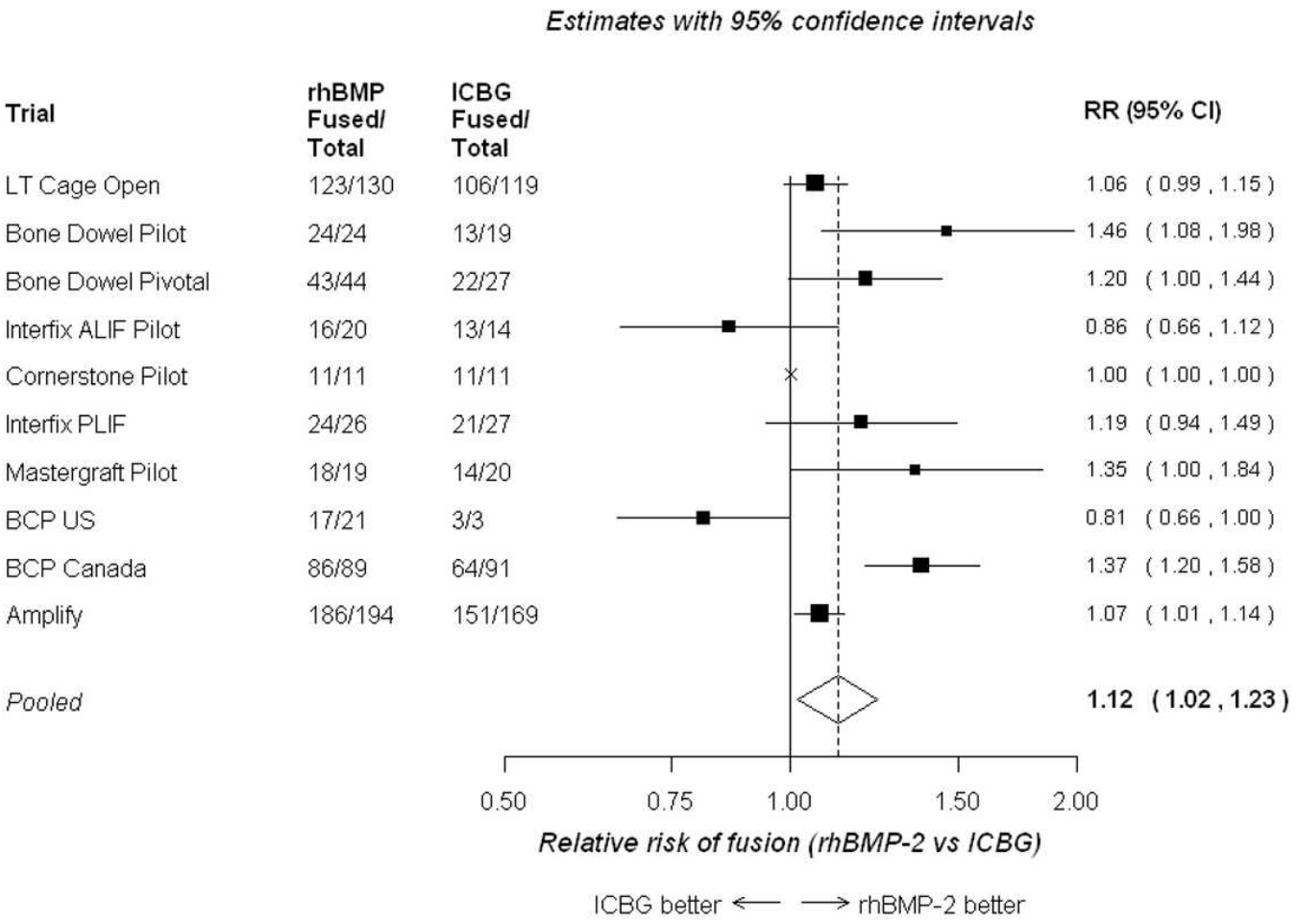
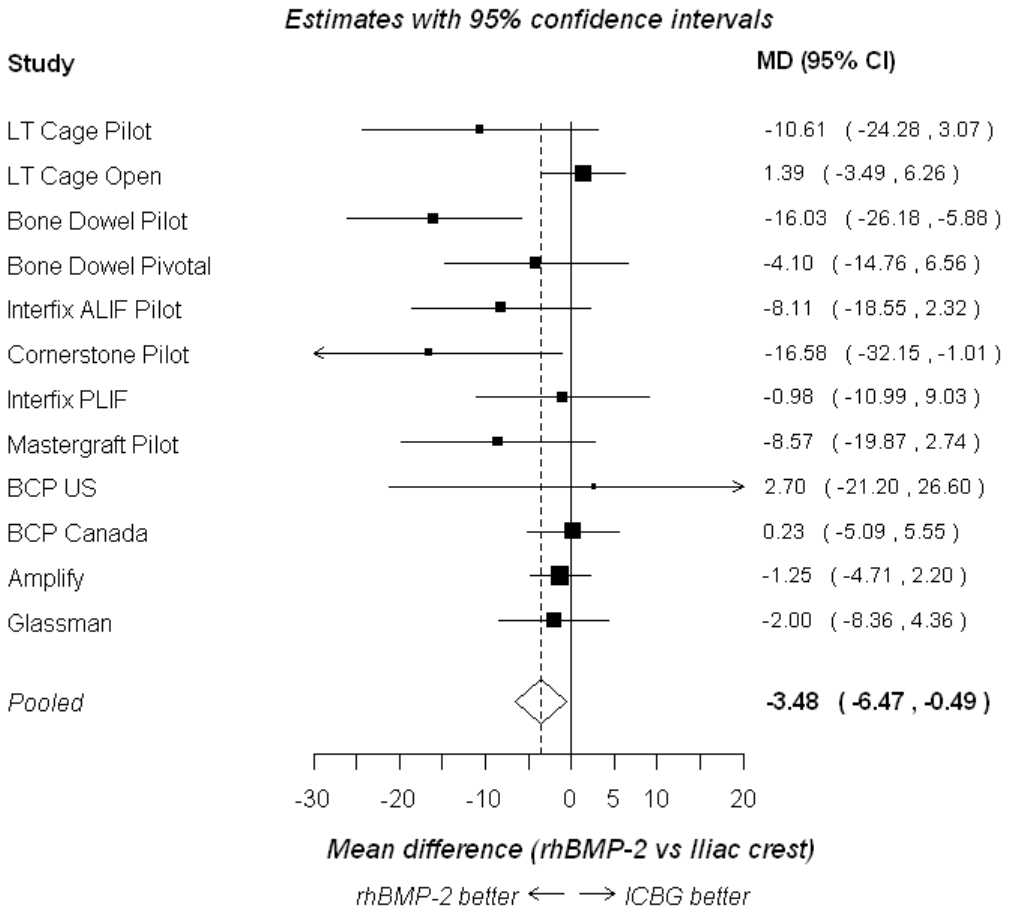
IPD analysis: successful fusion by 2 years



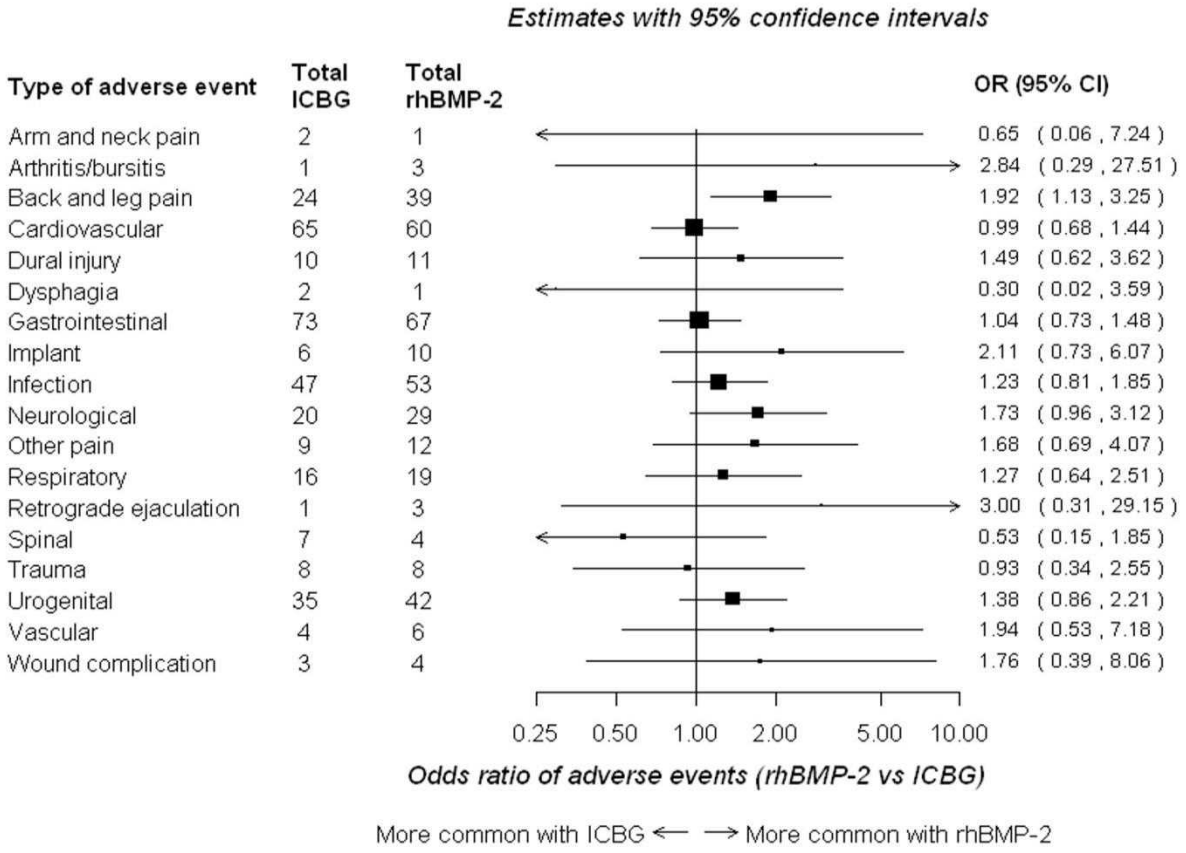
IPD analysis: Oswestry Disability Index at 2 years



Reporting of effectiveness outcomes

- Medtronic trials collected median of 16 effectiveness outcomes (11-18)
- Median of 9 outcomes (range 1-14) reported in individual peer-reviewed publications
- No single abstract or journal article reported all the clinical outcomes known to have been collected in a trial
- **Combining data from all journal publications and conference abstracts could not identify a complete set of outcome data for any study**
- BUT did not appear to be systematic bias in reporting of pain or fusion outcomes
- Systematic review of published data would have reached similar conclusions to IPD review

IPD analysis: adverse events at or after surgery



Reporting of adverse events

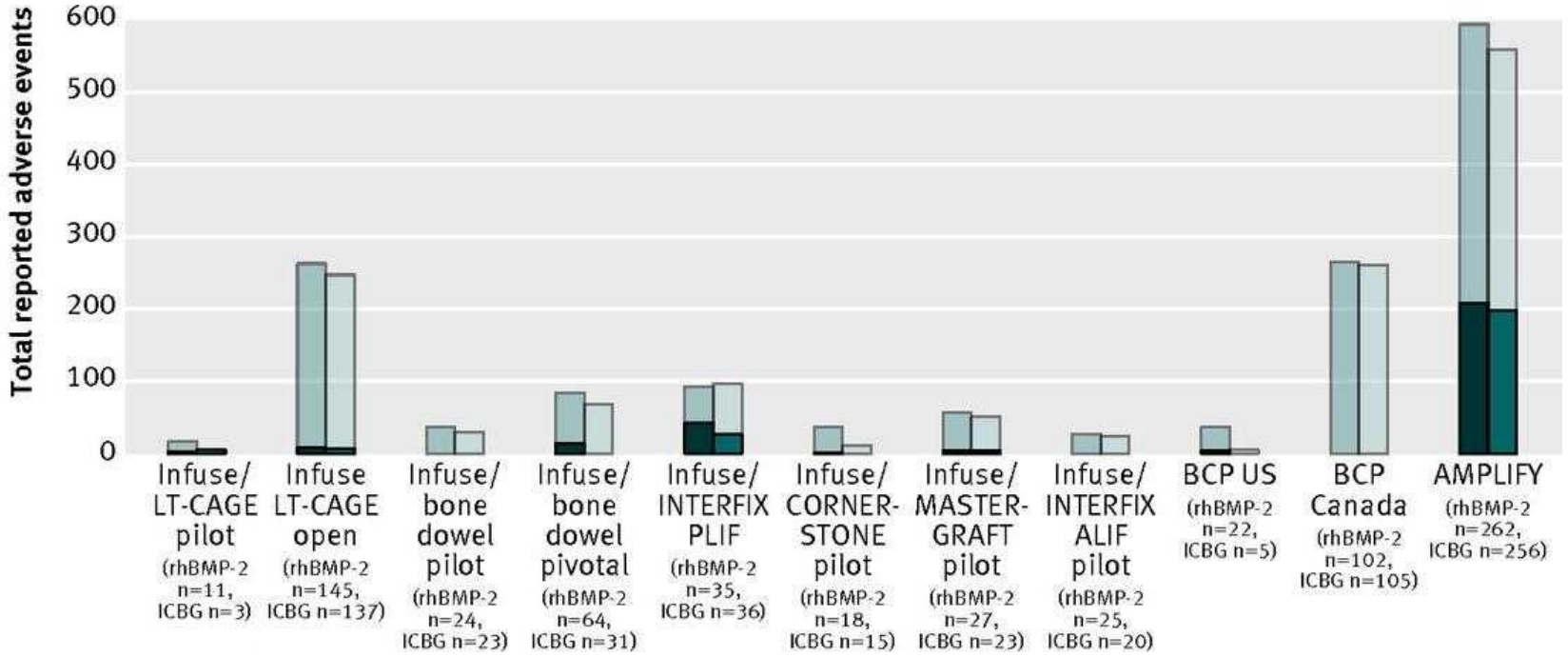
- Complications and adverse events were notably absent from Medtronic trial publications

- Across all known Medtronic RCTs (published & unpublished) 18.5% of adverse events reported somewhere in published literature (19% rhBMP-2, 18% ICBG)

- Across all published Medtronic RCTs 23% adverse events reported somewhere in published literature

- For INFUSE trials 10.5% of collected adverse events have been reported (12% INFUSE, 9% ICBG)

Total number of adverse events reported



rhBMP-2 events (IPD)	263	38	85	93	38	58	29	37	266	593
ICBG events (IPD)	247	31	70	97	13	51	25	6	262	558
rhBMP-2 events (published)	9	0	14	43	2	4	0	4	0	209
ICBG events (published)	8	0	0	27	1	5	0	0	0	198

Reliability of published literature

- Incomplete reporting did not substantially influence meta-analysis of **effectiveness** outcomes

- Complications & adverse events largely absent from publications - across all Medtronic RCTs (published & unpublished) only 18.5% of adverse events reported somewhere in published literature

- Published **adverse event** data was **completely inadequate** and inconsistent. Any systematic review based solely on the publicly available data could not properly evaluate the safety of rhBMP-2

Resource implications

- Study publications were absent, overlapping, duplicated and very time consuming to disentangle & extract data
(even with foreknowledge of clinical trials program)

- **Clinical study reports** were a rich source of data, would not support the more complex analyses possible with IPD, but **permitted more detailed investigation & analysis than from publications alone**

- Team new to CSRs but found them relatively easy to navigate (well structured and consistent) and extract data from

- The IPD and CSR syntheses were less time-consuming than the parallel review of publications !

- But these were provided at the outset of the project so no delays from identifying and requesting data

Grouping challenges/obstacles in using CSRs into themes

Chairs: Ella Flemyng

Group discussion - questions to consider:

1. Are there any other obstacles or challenges that haven't been mentioned yet?
2. Are there any obstacles and challenges listed in Appendix 1 of the Agenda that should be discussed?
3. What do you think the **main** obstacles and challenges are?
4. How would you group them?

Aiming for **five main themes** for discussion this afternoon (*next slide*)

Grouping challenges/obstacles in using CSRs into themes

Do these themes work or do they need changing?

1. Access to CSRs
2. Data sharing agreements
3. Considerations for protocols and implementation of SR analysis plan
4. Assessing and extracting data from a single CSR
5. Using CSRs with other data sources within a single review

These themes were grouped using feedback on challenges and obstacles prior to the meeting (see Appendix 1)

Lunch

12:45-13:30 (45 mins)

Cochrane

Group breakout

Chair: Toby Lasserson

Group breakout to discuss **how Cochrane could overcome** the obstacles and challenges faced by authors and editors:

1. Access to CSRs – Joerg Meerpohl
2. Data sharing agreements – Lesley Stewart
3. Considerations for protocols and implementation of SR analysis plan – Tianjing Li
4. Assessing and extracting data from a single CSR – Nicole Skoetz
5. Using CSRs with other data sources within a single review – Kerry Dwan

Proposal for pilots

Presenter: Toby Lasserson

Pilot

Identification of Cochrane reviews for pilot to reflect three purposes

- *Separate review to **replicate/repeat/reproduce***
- ***Update** an existing review*
- *New review*

Which Networks/CRGs? Which upcoming Reviews?

Proposal for the pilot

- Clinical Study Reports 'Network'/'Working Group'
  - *Interest/expertise not tied to 1 Methods Group*
  - *Sharing experience with different providers*
  - *Role/remit of Methods Support Unit*
- Project managed by Methods Implementation Coordinator (Ella Flemyng)
- Development of a full methods implementation plan (templates now available)

Cochrane

Key questions for evaluation

- Evaluation by authors, CRGs & Network support/editorial teams to address key questions
  - *Guidance needed for teams at start (likely barriers & facilitators)?*
  - *Resources (admin support, contract, time & money)?*
  - *Considerations for protocols (e.g. decision rules on discrepancies, sensitivity analysis)?*
  - *Implications for editorial policy, process & tech?*
  - *Implications for ongoing support/editor/author training?*

- What other questions should we be asking?

Summary of next steps

Chair: Toby Lasserson

Closing remarks

Chair: Karla Soares-Weiser

Thank you!

From the core planning group: Rachel Churchill, Kerry Dwan, Ella Flemyng, Toby Lasserson, Joerg Meerpohl, Nicole Skoetz, Lesley Stewart, David Tovey

If you have any further questions or follow up, please contact Ella Flemyng, Methods Implementation Coordinator (eflemyng@cochrane.org)