Cochrane Methods

Cochrane Scientific Committee

AGENDA

28th February 2018
8pm-10pm UK GMT

AGENDA

DT – David Tovey, Editor in Chief, JC – Jackie Chandler, Methods Co-ordinator

Committee members:

Corinna Dressler (CD)
Research Associate at the Division of Evidence-Based Medicine (dEBM) at the Charité – Universitätsmedizin Berlin, Germany
Donna Gilles (DG)
Senior Researcher, Clinical Performance Mental Health Network, Western Sydney, Australia and editor for both the Cochrane Developmental, Psychosocial and Learning Problems Group and Diagnostic Test Accuracy Review Group.
Julian Higgins (JH)
Professor of Evidence Synthesis at the School of Social and Community Medicine, at the University of Bristol, Bristol, UK, and current Senior Scientific Editor of the *Cochrane Handbook of Systematic Reviews for Interventions.*
AsbjØrn Hróbjartsson (AH)
Professor of Evidence-Based Medicine and Clinical Research Methodology at the University of Southern Denmark, and Head of Research for the Center for Evidence-Based Medicine at Odense University Hospital, which hosts the secretariat of the Cochrane Bias Methods Group.
Ana Marušić (AM)
Professor of Anatomy and Chair of the Department of Research in Biomedicine and Health at the University of Split School of Medicine, Split, Croatia and founder of Cochrane Croatia.
Jane Noyes (JN)
Professor of Health and Social Services Research and Child Health, Bangor University, Wales, UK, lead Convenor of the Cochrane Qualitative and Implementation Methods Group, and a UK Cochrane Fellow.
Tomas Pantoja (TP)
Associate Professor, Family Medicine Department, School of Medicine, Pontificia Universidad Católica de Chile and Editor of the Cochrane Effective Practice and Organisation of Care (EPOC) Group.
Philippe Ravaud (PR)
Professor of Epidemiology, Faculty of Medicine, Head of the Clinical Epidemiology Centre, Hôtel-Dieu Hospital, Paris Descartes University, France and Director of Cochrane France.
Johannes Reistma (JR)
Associate Professor at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands and a member of both the Cochrane Diagnostic Test Accuracy Working Group and the Screening and Diagnostic Tests Methods Group.
Rebecca Ryan (RR)
Research Fellow at the School of Psychology and Public Health, La Trobe University, Australia and Deputy Co-ordinating Editor of the Cochrane Consumers and Communication Group.
Christopher Schmid (CS)
Professor of Biostatistics, founding member and Co-Director of the Center for Evidence Synthesis in Health, Brown School of Public Health, US, Fellow of the American Statistical Association (ASA) and Founding Co-Editor of *Research Synthesis Methods*.
Nicole Skoetz (NS)
Scientific Co-ordinator, Working Group Standard Operating Procedures of the Comprehensive Cancer Centers, Center of Integrative Oncology Köln Bonn, and Co-ordinating Editor Cochrane Haematological Malignancies Group, Department of Internal Medicine, University Hospital of Cologne.
Nichole Taske (NT)
Associate Director (Methodology), Centre for Guidelines, NICE, U

Chairs Ana Marušić and Phillipe Ravaud

AGENDA ITEM	Details and links to documents	Responsibility for item
1) Welcome and apologies received	None received	Chairs & JC
2) Approval of previous minutes	Minutes dated 18th October 2017 – Attachment A and B	Chairs
a) Matters arising	3. **CSC Business matters – Clarifying role of CSC to the wider Cochrane Community** **ACTION 1:** Discussed possible urgent items that might arise from the revisions to the Handbook – none arose so no intermediate action required. **ACTION:** Attached table of contents for V6 of the Handbook as requested by members (apologies this got missed). **ACTION:** No items received from members for the attention of the committee or the Handbook Editors. **ACTION:** Handbook Editors have not identified any methods warranting CSC sign off at this point. **5. Methods for CSC Review - Follow up comments for ROBINS I** **ACTION:** No further update on the development of a competency statement to use ROBINS I, however, competency for complex methods, a wider issue, is under consideration. 7. Special items: a. Research priorities and strategy **ACTION:** Following on from the view that the CSC could not reasonably manage and co-ordinate its own agenda, we have developed processes to filter items to the Committee, see 'Methods for CSC evaluation' process below.	Chairs & JC
3) CSC Business matters	Placing the Scientific Committee in Cochrane's new structures.	DT & JC
4) Submissions	We now manage an open call system. No further submissions received yet. **'Methods for CSC evaluation' process** Following a recent organisational review, a supporting structure for methodologists – the Methods Executive – will take on, the role of filtering methods for implementation and escalation, when appropriate, to the Scientific Committee. This body will also filter	JC

	proposals from the Methods Groups, other methodologists and any submissions received via the online portal.	
5) Methods for CSC Review	**1. Interim guidance on how to decide whether to include clinical study reports and other regulatory documents into Cochrane Reviews.** Attachments C and D **2. Expert panel report on whether using sequential methods to adjust P values is necessary in repeated meta-analyses.** This is an interim report based on two panel meetings, panel members would like further time to finesse a final report. Attachment E and F	Tom Jefferson/Peter Doshi 10minute presentation Chris Schmid on behalf of the panel
6) Methods for CSC sign off and recommendation	None	CSC members
7) Special items:		
a) Research priorities and strategy	Cochrane are developing a Content Strategy, led by David Tovey, to create processes and structures to put in place surveillance and monitoring systems for content developments, and regular audits of stakeholder evidence needs. By content we mean different types of questions, multiple types of data, new methods and how we deliver content to end users and those that make health care decisions. DT will present a verbal update on the status of the Content Strategy.	DT
8) Any Other Business		
9) Meeting schedule	Teleconference – 5th June 2018 @ 12.00pm UK BST Face to Face – 20th September 2018, Edinburgh Colloquium, UK Jan-Feb 2019, May-June 2019, Oct/Nov 2019	JC

Outline of the structure and content for version 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*

No.	Sections and chapters
	About Cochrane reviews This section to be online only, since it is specific to Cochrane and covers many issues that are common across all types of reviews. Key aspects of the content (such as introduction to Cochrane) might be in a preface to the book version.
I	Introduction
II	Planning and logistics of a Cochrane review
III	Reporting a review
IV	Updating a review
	Core methods This section is content for the hardcopy version, online versions may have additional content. Hardcopy version will be concise.
1	Starting the review
2	Defining the review question
3	Developing criteria for including studies
4	Searching for studies
5	Collecting data
6	Estimating and computing effect sizes
7	Assessing risk of bias within and across studies
8	Assessing risk of bias in randomized trials
9	Assessing risk of bias due to missing results
10	Summarizing studies and preparing for the synthesis
11	Analysing data and undertaking meta-analyses
12	Synthesizing findings using non-statistical methods
13	Completing 'Summary of findings' tables and grading the strength of evidence
14	Interpreting results and drawing conclusion
	Specific perspectives in reviews

	This section is content for the hardcopy version, online versions may have additional content. Hardcopy version will be concise. Each chapter here to follow a specific broad structure so that it follows the skeleton of the 'Core methods' section. Areas covered could be (i) background; (ii) formulation of the review; (iii) identifying evidence; (iv) appraising evidence; (v) synthesizing and interpreting evidence; (vi) other issues.
15†	Issues of equity and specific populations
16†	Complex interventions
17†	Network meta-analysis
18†	Adverse effects
19†	Patient reported outcomes
20†	Economics evidence
	Specific types of data This section is content for the hardcopy version, online versions may have additional content. Hardcopy version will be concise. Structure specific to chapter content
21	Variants on randomized trials
22	Individual participant data
23	Prospective approaches to cumulating evidence
24	Non-randomized studies
25	Assessing risk of bias in non-randomized trials
26	Qualitative research and Cochrane reviews
	Other review types This material to be online only, since it is not about intervention reviews.
27	Overviews of reviews
	Methodology reviews

ATTACHMENTS

A – Minutes of 18th October

B – Supplementary document recording results of call.

C - Interim guidance on how to decide whether to include clinical study reports and other regulatory documents into Cochrane Reviews.

D – Supplementary document for interim guidance on clinical study reports.

E – Interim report from Expert panel – Should Cochrane apply error adjustment methods when conducting cumulative meta-analyses.

F – Expert panel background documents

Cochrane Scientific Committee

Teleconference 18th October 2017

Members of the CSC present	
Corinna Dressler (CD)	Present
Donna Gilles (DG)	Present
Julian Higgins (JH)	Present
Asbjørn Hróbjartsson (AH)	Present
Ana Marušić (AM)	Present
Jane Noyes (JN)	Present
Tomas Pantoja (TP)	Present
Philippe Ravaud (PR)	Present
Johannes Reistma (JR)	Present
Rebecca Ryan (RR)	Present
Christopher Schmid (CS)	Present
Nicole Skoetz (NS)	Present
Nichole Taske (NT)	Present
David Tovey (DT)	Present

Other attendees	
Jackie Chandler	Present

Meeting chaired by Philippe and Ana.

1. No apologies all members present.
2. Minutes of the 18th May approved with no amendments.
    a. Matters arising
        i. Reminder to members to complete declarations of interest forms
        ii. Expert panel on cumulative meta-analyses
        We now have a panel with eight members and chaired by CSC member Chris Schmid. Panel members are:
            - Chris Schmid – CSC member and panel Chair, Brown University, US
            - Jo McKenzie – Statistical Methods Group representative, Monash University, Australia
            - Kit Roes – Utrecht University, Netherlands
            - Elena Kulinskaya – University of East Anglia, UK
            - Martin Posch – Medical University of Vienna, Austria
            - Georgia Salanti – University of Bern, Switzerland.
            - Stephen Senn – University of Luxembourg, Luxembourg
            - Jonathan Sterne – Bristol University, UK

        The panel will meet on the 6th December, possibly, with a further meeting in January. Following the evaluation of methods conducted by a Cochrane funded Methods Innovation project, led by Mark Simmonds, a meeting on 13-14th November will discuss project findings and recommendations. The

panel will consider this meeting's output in December. Clarification on CSC's expectations of the panel are:

- Whether there is a problem or not.
- Whether available methods are suitable to address the problem.
- Whether Cochrane should use these methods or not.
- Which method or methods are most suitable and in what circumstances should they be applied?

The expert panel will provide the CSC with their deliberations and recommendations. The CSC membership will make the final decision on recommendations for Cochrane.

Julian Higgins, Handbook Editor, raised an additional point about the criticality of timelines. A Handbook update is underway with plans to include the output of this work on cumulative meta-analyses following expert panel and CSC recommendations. The February meeting is quite tight anticipating the Handbook's current timeline.

3. CSC Business matters – Clarifying role of CSC to the wider Cochrane Community
DT outlined organisational changes and the role of the CSC within the changing Cochrane infra-structure. In September, the Governing Board agreed a new review production system to create eight high level health topic editorial networks (clustering current CRGs). Senior editors will lead these Networks and constitute a new editorial board that will also include both methods and knowledge translation advisers. He elaborated on the distinctions between the roles of the CSC and the network Editorial Board and how these two new structures fit together. The CSC determines what methods should be used, when they should be used, and when methods should not be used. These decisions are based on the maturity of methods and their empirical support.

The network Editorial Board's responsibility is to ensure the ongoing success of the Cochrane Library and its key products, the CDSR and Central. Much like a journal the Editorial Board will develop strategies to maintain the progress and performance of the Library. This will include the function of the different production teams (including Networks). Therefore, its role is not primarily involving methods, however, there are methodological implications. So, in summary different but complimentary roles. We need further communication in Cochrane to solidify these roles.

Further discussion involved establishing when a methodological issue should come to the CSC. Previously Methods Groups would highlight aspects of methods warranting a policy response. We need to identify processes that filter trivial from controversial methods developments. DT proposed the impact of implementation as another filter, particularly because previous methods were not implemented effectively. Therefore, he proposed a relatively low threshold to provide a stamp of approval. Thus entail a responsibility and impetus to plan implementation involving communications, training and changes to internal systems. So, no further action needed, if easily implemented and uncontroversial.

JH pointed out raised the Handbook was the authoritative guidance on Cochrane methods and therefore, the CSC should endorse Handbook content. Now the CSC is in place we should consider whether any current published guidance is not supported by any CSC members. Members' discussion made the following key points:

- It would help if all members could familiarize themselves with the current Handbook and raise any concerns that might impact on the updated version. However, we are not expected to retrospectively change accepted, well established methods at this stage. Members are asked whether Cochrane is not using the best methods available, in their opinion.
- JH seeks backing from the CSC as the launch of the new version is expected in the last quarter of next year and represents the flagship of Cochrane methods. However, members are not expected to review draft chapters, which are undergoing separate peer review. However, we do ask members highlight areas known to them that might conflict with current or expected practice before publication.
- The next version of the Handbook represents the status of methods at time of publication, thus a baseline, for the CSC. We will produce both a hardcopy and online versions. This version will undergo more regular updating and therefore subsequent refinements are possible in a more agile manner.
- JH with the other editors (including JC) will flag new content deemed necessary for CSC sign off. Overtime processes will develop to align Handbook updates with the CSC agenda programme. JH intimated he has an issue warranting discussion.
- RoB 2.0 and ROBINS I will go into this updated version (V6).
- We will consider future (agile) systems for a wider user (e.g. authors) audience to submit requests for methods or methods review for the Handbook (and CSC). The call suggests this is often an improvement to guidance rather than the method itself.
- JN reminded Cochrane members of the CSC of previous processes where Methods Groups and the Methods Executive would capture the methodological challenges in SRs, and so how will this continue within the new systems.

ACTION: We will use email should any methods issues require urgent discussion for incorporation into the Handbook before our next meeting in February. A meeting will only be called if necessary.
ACTION: Jackie to circulate table of contents for V6 of the Handbook to members.
ACTION: All members are asked to raise issues likely to have implications for the Handbook either now or at a future date.
ACTION: Handbook Editors to identify any methods warranting CSC sign off as soon as possible.

4. Submissions: Please see attached table for summary of discussions and decisions on the six items presented to the Committee for future consideration.
5. Methods for CSC Review - Follow up comments for ROBINS I
   PR conveyed concern expressed to him by a Co-chair of the Cochrane Governing Board regarding the tool's complexity. DT affirmed the Committee's decision to indicate this tool was preferred but not mandated due to the skillset required. The issue is around implementation and the Committee is not expected to revisit their decision. JC noted previous action point requesting Jonathan Sterne to outline the level of competency needed to complete the tool.
   ACTION: JC to contact Jonathan Sterne for an update.
6. Methods for CSC sign off and recommendation - Follow up comments for RoB 2.0
   No further comments
7. Special items:
   a. Research priorities and strategy
      i. Developing future agendas was discussed within the context of discussing the items below.

ii. Future agenda items for consideration and prioritisation:
These items are those identified from current projects that are in process or completed. They were listed to indicate to the CSC likely future agenda items. Key point raised:
- Members felt more information needed on each item to decide on priority or importance for future meetings.
- Further clarification needed on which items were for general endorsement, priority for inclusion in the Handbook or methodological discussion to consider different approaches or empirical basis etc.
- Members want clearer procedures to define and filter items (policy/guidance and scientific questions). Also, specifying action e.g. endorsement, judgement on empirical basis etc. DT added that Cochrane needs to ensure a balanced approach to adopting methods, and how they work within the broader context of Cochrane given there are often specific interests, and decisions are binding.

(a) Intervention Complexity Assessment tool - Jane declared a conflict of interest (Jackie also an author on this work). This item is likely to be incorporated into the Handbook in the complex interventions chapter and not considered contentious.
(b) Guidance for when to include Clinical Study Reports and other regularity data in CR's – the output of this work is important content for the Handbook. CSC review required.
(c) Methods for prognosis reviews and full roll – Specific methods will need review by the CSC, when ready for roll out.
(d) Methods for addressing missing participant data awaiting final guidance – JH reported differences of opinion between project leads and others. If not resolved may require CSC input.
(e) Assessing the quality of evidence and presenting the results of Non-randomised Studies in CR'
(f) Evaluation and validation of the RCT classifier – Discussed issues around whether this warranted review. Discussed as an illustration the RCT classifier. This is a means of identifying RCT's in large datasets and provides evidence of its effectiveness based on its sensitivity and specificity to identify RCT's. Although, results are good and not likely to be contentious, in principle, the CSC would be asked to make a judgement on whether this viable and ready for use.

ACTION: Co-chairs, David and Jackie will discuss and propose processes for filtering items for future agendas.

8. Any Other Business - None
9. Meeting schedule:
Teleconference - 28th February 2018 8pm UK GMT
Teleconference – 5th June 2018 @ 12.00pm UK BST
Face to Face – 16th – 18th September 2018, Edinburgh Colloquium, UK – further information shortly.

Cochrane Scientific Call for agenda items – CSC decisions

Thirteen submissions received – reviewed by Ana, Philippe and David

The following six items were discussed at the CSC meeting on 18th October 2017 and with decisions recorded below.

	Submitted by and title	Aims and objectives	Key features and elaboration
1.	Nicole Skoetz Inclusion of results from searching study registries in Cochrane reviews: completed but not published studies	To give authors guidance how to include completed but not published studies identified in study registries	Currently, there is one section in the Cochrane review called "ongoing trials", but what about all the completed trials authors identified in trial registries? Especially those without any published results, where to report them? Still in the ongoing section? This name is misleading, as some might not be ongoing any more. How do review authors search in trial registries? For the "status" ongoing only? Then they will not identify completed, but not published results. Should review authors include completed but not published trials in "included trials" section? Should review authors impute data for these unpublished trials?
	DT, AM, PR commentary	Advice required on how to proceed Another related question of interest is, in what situations where there are published reports/journal articles as well as data in trial registries, should authors be expected to examine all sources related to a study and comment on inconsistencies? How best to capture data from multiple sources? Also track changes with trials overtime e.g. outcomes How best to manage and to account for discrepancies that occur between sources and approach systematically? Problems with subsequently imputing data, if inconsistent. This covers a broad topic and improved guidance required.	
	CSC decision: Nicole reiterated her key point that "ongoing trials" was not the right classification for trials identified in trial registries that were unpublished but completed. So how should they be classified? JH noted that clearer guidance may assist authors in classifying these appropriately as either awaiting classification (awaiting results) or included studies but with no data. Nicole made a further point, as to whether one should impute data (but no results) to shame authors who leave their work unpublished. In addition, trial registries may also provide data not in the published study report. Therefore, further guidance on managing multiple sources of data required. This is not a matter for the CSC.		

2.	Donna Gilles Meta-analyses of prevalence and risk	To broaden the scope of Cochrane reviews to include the best meta-analytic methods of studies of prevalence and risk	Meta-analysis of prevalence and risk - specific types of reviews. Cochrane does not support meta-analysis of prevalence and risk. This is a growing field and high-quality methods need to be developed. In addition, supporting reviews of prevalence and risk could cover many of the areas which users of Cochrane have identified as gaps in our product.
	DT, AM, PR commentary	Advise on whether a paper outlining challenges and benefits of including this review type should be presented in consultation with the prognosis Methods Group New review type in terms of resourcing requires serious consideration.	
	CSC decision: Cochrane (EiC and the Governing Board) need to decide whether Cochrane should include additional research questions such as prevalence and risk. It becomes a question for the CSC as to whether the methods are ready for application in Cochrane. DT indicated that this could be considered within the Content strategy in development (and whether this would require a Methods Group, if agreed). These research questions are background information rather than directly related to clinical care, although they may become more relevant as personalised medicine becomes a more prevalent focus in health care decision making. This is not currently matter for the CSC and will be considered further in Cochrane's Content Strategy.		
3.	Donna Gilles Meta-regression	To support meta-regression in order to improve the quality of analytic methods particularly in relation to continuous study variables and potentially confounding variables	Meta-regression - all reviews. Because of the lack of available meta-regression software and support, analyses of many large-scale Cochrane reviews inadequately address continuous factors such as dosage and longitudinal follow-up, as well as potential covariates.
	DT, AM, PR commentary	It would help to have a collective view on the importance of this method to encourage its application especially for updates. Meta-regression should be done Currently, RevMan does not support meta-regression. However, should we encourage use of other software, such as R.	
	CSC decision: DG's request addressed the need for better guidance and especially with access to external software e.g. R. Currently there are delays to updating RevMan analysis functions but previously Cochrane did not want to make these complex methods widely available to inexperienced authors. Although, Gert (Information & Knowledge Management) is creating an underlying data structure that should make incorporating statistical methods easier. DG's point is that we should actively encourage the appropriate application of meta-regression for sub group analyses, also needed in network meta-analysis. This is an implementation issue because meta-regression is uncontroversial, however, its		

	application is an implementation issue and if we require it done we should identify the necessary statistical support. So, this is a matter for the Editorial Board (possibly Governing Board if it impacts on budgets). This is not a matter for the CSC.		
4.	Jayne Tierney Timely and Reliable Evaluation of the Effects of Interventions: A Framework for Adaptive Meta-analysis (FAME)	Aims to develop a prospective approach to Aggregated Data (AD) systematic review that takes all relevant trials into account and allows us to quickly respond and adapt to emerging trial results. The novel Framework for Adaptive Meta-analysis (FAME) allows us to anticipate the earliest opportunity for reliable AD meta-analysis, often years in advance of all trial results being available.	Most systematic reviews of efficacy are retrospective and based aggregate data (AD) from trial reports, meaning they can lag behind therapeutic developments and fail to influence ongoing or new trials. As unpublished and particularly ongoing trials are often overlooked, this can lead to reporting biases, hamper interpretation of meta-analysis results, and means updating is often inefficiently regarded as a separate process. Against this backdrop, unplanned duplication of systematic reviews has flourished. Further information available in Dropbox
	DT, AM, PR commentary	CSC are asked to review this proposal for future agenda discussion. Need to agree the scope of the review as changes.	
	CSC decision: This is a variant on prospective MA. The Handbook chapter is undergoing a revamp to incorporate additional material on "Living systematic Reviews" and IPD. This approach is about keeping on top of accumulating evidence. Jayne will be asked to share this work with colleagues leading on this chapter. JH thinks this is uncontentious and can be incorporated into the Handbook. This is not a matter for the CSC.		
5.	Jayne Tierney Determining when meta-analyses of published time-to-event outcomes reliable enough to form robust clinical conclusions. An evidence-based approach	Currently, it is not clear when meta-analyses of published time-to-event outcomes are reliable enough to form robust clinical conclusions. We aim to provide substantial and systematic empirical evidence on the reliability of meta-analyses based on HRs from published AD in comparison to those from IPD, so as to inform when IPD might be required.	Effects of treatments on time-to-event outcomes are usually measured using a hazard ratio (HR). If HRs are not explicitly reported, they can be calculated or estimated indirectly from other published statistics, or from data extracted from Kaplan-Meier (KM) curves. Each require assumptions that may affect the reliability of aggregate data (AD) meta-analyses including HRs. Further, AD meta-analyses of HRs are at risk of reporting biases, including follow-up bias, which the collection of individual participant data (IPD) may overcome. However, the IPD approach is lengthy, not always feasible and still rare. Therefore, when an answer is needed quickly or until IPD becomes more readily available, we will continue to rely on meta-analysis of published HRs. We aimed to provide

			substantial and systematic empirical evidence on the reliability of HRs derived from published AD and IPD, so as to inform when IPD may be required. Based on an unselected cohort of 18 IPD systematic reviews (238 unique trials), we compared HRs from AD with their IPD equivalents at the trial and meta-analysis level. The IPD represent >80% of eligible trials and ~90% of eligible patients, often with updated follow-up, providing a 'gold standard' with which to compare HRs from AD. Additional information available.
	DT, AM, PR commentary	<u>CSC asked whether leads should submit a paper on providing recommendations as to how to implement and when.</u> It is now possible to calculate data extracted from Kaplan-Meir curves.	
	CSC decision: Authors do not know how to pool time to event data within aggregated datasets. Authors get the direction of effect wrong and don't consider censoring in one arm results in high risk of bias. More advanced guidance is required. NS asked to add a section to the "Collecting data" chapter of the Handbook. This is not a matter for the CSC.		
6.	<u>Rebecca Turner</u> Data-based predictive distributions for between-study heterogeneity	Many meta-analyses contain only a small number of studies, which makes it difficult to estimate the extent of between-study heterogeneity. Bayesian meta-analysis allows incorporation of external evidence on heterogeneity and offers advantages over conventional random effects meta-analysis (Higgins and Whitehead 1996). To assist with implementation of Bayesian meta-analysis, we have provided empirical evidence on the likely extent of heterogeneity in particular areas of healthcare.	Meta-analyses from the Cochrane Database of Systematic Reviews (Issue 1, 2008) were classified according to the type of outcome, type of intervention comparison and medical specialty. The impact of meta-analysis characteristics on the underlying between-study heterogeneity variance was investigated by modelling the study data from all meta-analyses simultaneously. Predictive distributions were obtained for the heterogeneity expected in future meta-analyses. These can be used directly as data-based informative prior distributions for heterogeneity in Bayesian meta-analyses. Between-study heterogeneity was found to be strongly associated with the type of outcome measured in the meta-analysis and somewhat associated with the types of interventions compared. We have published predictive distributions for heterogeneity in meta-analyses of binary

			outcomes (Turner et al. 2012; Turner et al. 2015) and for heterogeneity in meta-analyses of continuous outcomes (Rhodes et al. 2015). In addition, we have proposed accessible methods for implementing Bayesian meta-analysis with informative priors, avoiding the need for specialist Bayesian software (Turner et al. 2015; Rhodes et al. 2016). Using informative priors for heterogeneity would be beneficial in meta-analyses including few studies. These methods could be applied in standard Cochrane reviews.
	DT, AM, PR commentary	Seek a view from the CSC as to whether this should be mandatory or discretionary, and therefore consider the implementation implications.	
	CSC decision: JH conflicted (lead author). Using Bayesian approaches to add prior information provides a better estimate using the random effects MA model and is more robust. Important in DTA reviews with a low number of studies. Specialist approaches will require statistician support. Request paper and presentation for future meeting.		

To the Cochrane Scientific Committee

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

Jefferson T[1], Boutron I[2], Doshi P[3], Golder S[4], Heneghan C[3], Hodkinson A[5], Jones M[6], Lefebvre C[7], Stewart L[8].

1. Editor, Cochrane Acute Respiratory Infections Group
2. Co-convenor, Cochrane Bias Methods Group
3. Author, Cochrane Acute Respiratory Infections Group
4. Co-convenor, Cochrane Adverse Effects Methods Group
5. Researcher, Centre for Reviews and Dissemination, York, UK
6. Deputy Co-ordinating Editor, Cochrane Acute Respiratory Infections Group
7. Co-Convenor, Cochrane Information Retrieval Methods Group
8. Co-convenor, Cochrane IPD Meta-analysis Methods Group

Final Report
February 8, 2018

Summary

The documented presence of reporting bias in biomedical literature of clinical trials is a major threat to the validity and credibility of Cochrane reviews. This interim guidance report outlines the rationale for accessing clinical study reports and other regulatory documents (regulatory data) as a means of addressing reporting bias, and identifies factors that may aid in the decision of whether (or not) to include regulatory data into Cochrane reviews. The guidance includes the origins and current state of regulatory data access, a survey of current systematic reviewers' practices in considering regulatory data for inclusion in reviews, and a glossary (with hyperlinks and screenshots) of terms and nomenclature used in regulatory documents. The glossary will be of considerable practical use to Cochrane authors, given that most lack familiarity.

This guidance does not address how to access, assess and extract regulatory data.

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.

Scope of this document

Recognising the need to widen the scope of data sources for Cochrane intervention reviews beyond journal publications, conference abstracts or trial registry reports, the Cochrane Methods Innovation Fund (MIF) funded a project to produce interim guidance on the circumstances under which clinical study reports and other regulatory documents should be considered for inclusion in Cochrane reviews, either in addition to or instead of data from more traditional sources.

It is important to note that the scope of this project is limited to consideration of 'whether' (or not) to incorporate regulatory data into a Cochrane review and when it might be most important. The project did not intend to address the question of how to use these data sources. The rationale for considering the question of 'whether' was an assumption that not all reviewers would have the resources to incorporate clinical study reports and other regulatory documents into their reviews, and therefore some guidance for prioritization would be helpful. We refer to 'interim' guidance on how to decide whether to incorporate clinical study reports and other regulatory documents into Cochrane reviews, as we have been unable to identify any research evidence in this area.

For those who elect to include clinical study reports and other regulatory documents in their review, the next issue is 'how' to incorporate such data. This project, however, was not funded to address the 'how' question.

Background

Systematic reviews of randomised controlled trials play an important role in decision-making. If properly designed and conducted, they identify, evaluate and summarise complex trial-derived information and provide more reliable and precise estimates of intervention effects than individual studies. Up to now, most systematic reviews have used data extracted from journal publications. In a survey of 348 systematic reviews published in 2014, around three-quarters relied solely on data provided in peer reviewed journals.[1]

Of those that accessed other sources, data from trials registries (such as ClinicalTrials.gov), conference proceedings or contacting authors were the most used. No reviews reported using or attempting to obtain clinical study reports even though the majority of the reviews evaluated drug interventions.[1] A survey of 2184 Cochrane authors also found that contacting 'trialists/investigators,' was one of the most common methods for accessing unpublished data and that data from manufacturers or from regulatory agencies

were rarely obtained.[2]

"Clinical study reports" (CSRs) are documents prepared and submitted to regulators to obtain a license, and represent the most complete synthesis of the planning, execution, and results of a clinical trial. CSRs contain some of the same information as journal papers (i.e. rationale, objectives, methodology, results, discussion/conclusion), but are substantially more detailed with numerous large tables and figures, and datasets not constrained by page limits. A CSR for a single trial may be hundreds, thousands, or even tens of thousands of pages in length and are easy to navigate throughout (when all components are in a single file). CSRs generally contain, as appendices, important study documents including the study protocol and amendments, statistical analysis plan and amendments, case report forms (CRFs), patient information sheet, certificates of analysis, informed consent forms, and individual patient listings among others. CSRs therefore provide more detailed information and complete data than are usually available in journal articles.

"Regulatory documents" is a term we use to refer to any document produced by, or held by, a regulatory agency. Notable types of regulatory documents are CSRs (which are submitted by sponsors) and Medical Officer Reviews (produced by US Food and Drug Administration medical officers) or European Public Assessment Reports (produced by the European Medicines Agency).

(See definitions of the above terms, and others, in the Glossary).

In late 2010, the European Medicines Agency (EMA) began releasing CSRs of drugs and biologics on request under its Policy 0043.[33,45] In October 2016, the EMA began to release CSRs prospectively under its Policy 0070.[3,4] Policy 0070 applies only to marketing authorisation applications received since 1 January 2015. Documents available from the EMA under this policy normally include the clinical overview, clinical summary, and CSRs of individual trials. Each CSR describes the trial design, conduct and results of analyses including three selected appendices of each CSR: the study protocol, statistical analysis plan, and sample case report forms.[3] In 2017, Health Canada published a report announcing an initiative to publicly release clinical information concerning drugs and devices under an eventual EMA Policy 0070-like mechanism.[6] And in January 2018, the FDA announced that it will publicly release CSRs in a pilot program.[7]

There is an increasing potential for CSRs and other regulatory documents to be considered for inclusion in Cochrane reviews and to alter the way that systematic reviews are conducted in future due to their increasing public availability from a variety of sources.

Not all interventions have regulatory data

At the outset of this project in 2014, we decided to focus on clinical study reports and other regulatory documents relating to pharmaceuticals and biologics for which these documents generally exist. We acknowledge, however, that non-pharmaceutical interventions (such as implantable devices, surgery, rehabilitation, behavioural interventions and diagnostics) are responsible for a large part of healthcare expenditure and that regulatory activity and transparency have been recently increasing in this area, at a slower pace, in particular in the field of devices.

It is important to note that publicly funded trials, even of drugs and biologics, do not usually produce internationally standardised documentation similar to a CSR and are not the focus of this document.

Rationale for the consideration of regulatory documents (including clinical study reports) as sources of data for inclusion in Cochrane reviews

There has been a gradual realisation that sources of evidence historically considered to be reliable (such

as peer-reviewed literature) are affected by reporting bias. Reporting bias generally refers to selective reporting of research depending on the nature and direction of research results. Reporting bias includes publication bias[8–12] and outcome reporting bias,[8–14] among many others.[15]

Studies published in the last decade or so have shed light on reporting biases present in publicly available reports of trials of pharmaceuticals and have highlighted the general lack of transparency that surrounds trial data. Combined, these present a major obstacle in assessing bias in studies included in Cochrane reviews.

Reporting biases can generally only be detected when two or more reports of the same trial are compared: for example, peer-reviewed publications compared with CSRs. In addition to reporting bias, lack of transparency and lack of detail in journal publications may prevent or hinder detailed analyses of data which could be relevant to specific subpopulations potentially benefiting from or being harmed by the intervention.[16] This situation is likely to be the consequence of compressing thousands of pages of text and tables into the historically restricted confines of a printed journal article.[17]

There are indications that CSRs may be incomplete and in some cases may be internally inconsistent between different components of the same CSR.[18] However, a consistent picture emerges when comparing different data sources for the same trial: CSRs provide the greatest breadth and depth of information compared to journal articles, register data and grey literature. Aggregate data on subpopulations are often found in CSRs and can provide a source of further analysis. Such a wealth of information gives a fuller and more reliable picture of trial strengths and weaknesses, as well as a more reliable assessment of the benefits and harms of the studied interventions.

Table 1 contains a selected and illustrative list of studies that have compared different sources of data for the same trial, such as publication vs. CSR or trial register entries vs. publications. Although this is not an exhaustive list of all such studies, it covers more than 50 different interventions and offers glimpses of the ways in which reporting bias affects the biomedical literature.

The studies in Table 1 strongly suggest that discrepancies in the reporting of trials across different sources of data is common. There are limitations to be aware of when interpreting discrepancies. First, different types of trial documents may have very different objectives. CSRs, for example, inform regulators and, by law, provide a comprehensive record of a study. Trials registers, in contrast, are primarily a visible collection of trials and their reporting format is heterogeneous. For example ClinicalTrials.gov does not have a methods section and results can be either absent or incomplete. Under some circumstances (such as for specific funding sources), reporting of trials within trials registers, including the submission of results, is compulsory (but not always adhered to nor adequately policed).[19] Within the United States, there are requirements for National Institutes of Health (NIH) funded research,[20] but in many cases worldwide trial registration is voluntary. The EMA's European Public Assessment Reports (EPARs) and the FDA's Drug Approval Packages are records of regulators' work in assessing a medicine for potential registration and are not primarily meant to provide summaries of trials for reviewing purposes (see Glossary of terms and definitions for taxonomy of regulatory documents). Journal articles are the main means of communicating clinical trial results providing short, accessible summaries of trial findings; but there is increasing evidence that articles may be incomplete or biased. Journal trial articles are readily available and provide relatively short, usually readable, summaries. These qualities are offset by the bias they may introduce and the considerable time and effort expended (sometimes in vain) to clear up discrepancies, contradictions and missing information.

The generalisability of each finding of the studies in Table 1 to the larger population of trials or topic areas that exist is debatable, and it is unclear whether reporting biases are lessening over time. Some journals

have taken steps to limit the bias introduced by the current format of trial reporting, by requiring adherence to CONSORT, by publishing the trial protocol or supplementary online data as an appendix or by requiring data sharing as a condition of publication.[21–23] As it is impossible to squeeze thousands of pages' worth of information into a 10-page publication and the resulting information selection is based on unknown criteria, an alternative solution may be that authors can, where these exist, provide links to the relevant CSR and other summary data (e.g. FDA Drug Approval Packages).

We are aware of three examples of four systematic reviews (a Cochrane review of neuraminidase inhibitors, twin reviews of rhBMP-2, and a review of reboxetine) allowing assessment of contributions of regulatory data compared to the same trial data from published journal articles.[24–27]

In the case of recombinant human bone morphogenetic protein 2 (rhBMP-2), both CSRs and individual participant data were included in the twin reviews,[25,26] while the Cochrane review of neuraminidase inhibitors and the review of reboxetine were based on CSRs.[24] In all cases the conclusions of important aspects of the reviews were changed with access to the more complete data available in the CSRs. Access to the CSRs also provided a deeper understanding of the strengths and limitations of the trial evidence. In the case of the review of reboxetine, the inclusion of CSR data changed the conclusions of the review. and allowed quantification of the exaggeration in favour of the effects of reboxetine compared to placebo (99-115%) and other SSRIs (19-23%).[27] The Cochrane review of neuraminidase inhibitors for influenza also found FDA medical officer reviews to be an important source of data and detail.

As Cochrane reviews are considered to be a gold standard of reliable research synthesis, we need to pay attention to the issue of reporting bias and to address whether, and how to decide when, accessing regulatory data, including CSRs, might offer a solution. The approach, however, is new and unfamiliar to most Cochrane reviewers and at the time of writing, regulatory data are not always immediately available. When available, using such documents involves reviewing very large quantities of information, which is time-consuming and resource intensive. Thus, a framework to help identify where using data from regulatory documents is likely to matter most, and prioritising those reviews which should adopt such an approach, will be helpful for Cochrane groups grappling with how to respond to the increasing availability of these new sources of information.

Current Cochrane practice

To raise awareness of the above issues and to inform our work, we surveyed Cochrane and non-Cochrane authors to gauge how many had considered using regulatory data and how many had actually included them in their reviews. The survey was announced in the Cochrane Digest, and in an email to all Cochrane authors on 10th June 2016. The release intended for authors of non-Cochrane reviews was first advertised on the University of York Centre for Reviews and Dissemination website on the 25th June 2016 and then on the Systematic Reviews journal website. Links to this were also shared via social media. Both surveys were closed on the 19th September 2016 and then the results were combined.

There were 160 respondents who completed the Cochrane (n=153) and non-Cochrane (n=7) surveys combined (Table 2). However, it is not clear how many authors received, opened the digest, or read the invitation to participate. 20/160 (13%) of the respondents had previously requested or used CSRs and other regulatory documents, 7/160 (4%) had considered it, and 133/160 (83%) had never considered it. Data sought by survey respondents were mainly from the EMA and/or the FDA (19 (40%) of the 47 requests made by those previously requesting CSRs in total) and/or directly from pharmaceutical companies (18/47 (38%)). 5/47 (11%) of the requests included non-regulatory data requests to authors of published trials. Amongst the 20 respondents that requested regulatory data, 12 (60%) involved CSRs, five obtained medical and statistical reviews from the FDA and two European public assessment reports (EPARs). The main reasons for accessing CSRs were concerns about reporting biases 11/20 (55%),

outcome reporting bias and publication bias (5/20 - 25%).

Fourteen (70%) of the authors that had used or requested regulatory data, and 6 (86%) authors who only considered regulatory data had faced barriers to access. These were identified mainly as the restricted and limited sharing of trials data, and the time constraints involved in searching and requesting the data.

The survey results in brief show a lack of familiarity with regulatory sources of data, barriers to access and lack of resources to do so. The main rationale for authors seeking regulatory data, however, was minimisation of bias.

The circumstances under which clinical study reports and / or other regulatory documents should be considered for inclusion in Cochrane reviews

Because of unfamiliarity and the additional investment of resources required, we do not consider that Cochrane reviews can be converted immediately to include routine searching for, or inclusion of, regulatory data without a period of preparation and consideration of the consequences of such an action. It may not be necessary for all reviews to adopt such an in-depth approach. It is also important to take stock of current practice. Selection of likely candidate reviews is therefore required.

We were unable to identify any research on the topic of how to decide whether to incorporate clinical study reports and other regulatory documents into systematic reviews, i.e. a rule for determining which reviews would most benefit from the inclusion of such data.

We therefore created an initial list of reasons (or triggers) for seeking and using such data through discussion amongst our group. Our list was a product of our opinion and experience. We then carried out a follow-up targeted survey in which we asked respondents to rate the importance of each criterion in our list. This survey was sent to the 21 (of 27) systematic review authors who had used, requested, or considered using regulatory data in their review and had agreed to participate in a follow-up survey. Fourteen of 21 (66%) provided a response. A description of the criteria are in Table 3 and the results are presented in Figure 1 (where criteria are listed in order of importance).

When authors were asked which criteria were considered most important when considering access to regulatory data (Figure 1), omission and underreporting of trial outcomes and results were the most frequently cited because of likelihood of reporting bias (criteria 10-14,17 and 18). However, the other criteria listed in Figure 1 and Table 3 were also considered important by most authors.

The variables are self-explanatory, reflecting either known or suspected bias in published results or the potential for greatest impact in terms of public health - for example, what are the human costs of acting on biased estimates of effectiveness or harm?

There is no proposed scoring or algorithm for combining criteria to identify priority topics or topic area. The relative importance of criteria listed in Table 3 will depend very much on context, and prioritisation is inevitably a somewhat subjective process.

The authors would be interested in receiving suggestions or reports of experience regarding accessing regulatory data and including such data in systematic reviews. However, as mentioned elsewhere, that this is beyond the scope of this current project.

Discussion

Regulatory documents are a complex and underutilised source of highly detailed data for Cochrane reviews. Although the methodological steps for their inclusion, extraction and analysis are broadly the

same as those with other sources of data, the resource implications of their use are not. For example, resource use for constructing an index of all pharmaceutical comparative studies from multiple sources and reading and extracting data from drug approval packages are 6 months for one whole time equivalent for two drugs of the same class and one vaccine.[24,28] The results of our surveys and our own experience indicate that the use of regulatory documents should be considered, especially when the intervention in question is of potential high value and when there is evidence of reporting bias, or both.

We think that Cochrane should consider making regulatory data a preferred source of data in such circumstances and should invest in the infrastructure to make this possible. This ranges from supporting a regulatory data option in reviews of pharmaceuticals, to training aids on the content and use of such data, to investing in a research programme to identify priorities and limitations of the use of regulatory data.

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Table 1. Examples of studies comparing different sources of data for the same trials.

Reference	Type of study	Intervention comparisons	Source comparison	Take home message
Chan 2004[29]	Cohort study of 102 randomized trials registered with scientific-ethical committees in Denmark, 1994-1995	75% drug trials, 12% counseling/lifestyle trials, 11% surgery/procedure, 2% equipment	Protocols vs publications	"62% of trials had at least 1 primary outcome that was changed, introduced, or omitted." In 40 of 82 trials, pre-specified primary outcomes were not presented as such in the journal publication. In 11 trials, outcomes not pre-specified were reported as the "primary outcome" in the publication. "The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols."
Turner 2008[10]	Review of 74 RCTs for 12 antidepressants reviewed by the Food and Drug Administration, and their corresponding publication (or lack thereof) in the literature	12 antidepressants vs. placebo	Medical officer reviews vs publications	Non-publication and selective reporting occurred frequently, and can change the apparent risk-benefit assessment of drugs. Publicly available medical officer reports are a valuable source of unbiased information about clinical trial design and results.
Eyding 2010[30]	Systematic review of 13 trials. 76% of patient data unpublished: 86% (1946 of 2256 patients) for reboxetine vs placebo and 67% (1760 of 2641 patients) for reboxetine vs SSRIs	Reboxetine for depression vs placebo or vs other SSRIs included in IQWIG HTA report	CSRs vs publications	The addition of unpublished data changed the direction and conclusions of the efficacy and harms analyses. Published data vs full dataset overestimate benefits by 99-115% vs placebo and 19-23% vs other SSRIs.
Jefferson 2012[31]	Cochrane review of 25 trials (15 oseltamivir, 60% unpublished, those published had been ghostwritten and corresponding “authors” had no access to study data)	Neuraminidase inhibitors for influenza vs placebo	CSRs vs publications	Lack of detail in publication and unexplained discrepancies when compared to CSRs led the authors to change methods compared to previous version of the review and include only regulatory data, significantly changing the conclusions of the review.
Coyne 2012[32]	Review of the Normal Hematocrit Trial (NHT) run in the 1990s on 1265 hemodialysis patients with cardiac disease	Epoetin lower (9–11 g/dl) vs higher (13–15 g/dl) doses to increase haematocrit to reduce mortality and improve survival and QoL.	CSR vs publication	“Disclosure of these [CSR] results in the 1998 publication or access to the FDA filed report on the NHT in the late 1990s would likely have led to earlier concerns about epoetin safety and greater doubts about its benefits.”
Wieseler 2012[16]	Systematic review of 29 studies included in 16 HTA reports prepared by IQWIG during 2006-2011	16 different pharmaceuticals mainly for depression and type I and II diabetes	CSRs vs publications vs register entries	CSR consistently reported more information than registers or journal publications.

Wieseler 2013[33]	Systematic review of 101 trials with full CSR available included in 16 HTA reports prepared by IQWIG. The study population is the same as Wieseler 2012 but in this study the authors quantified information gain for patient-relevant outcomes graded from 1 to 4	16 different pharmaceuticals mainly for depression, asthma and type I and II diabetes	CSRs vs publications vs register entries (unclear which trials have been registered where. Also some trials were conducted in the late 1980s)	CSRs reported complete information on 78%-100% of benefit outcomes vs 20% - 53% in combined publicly available sources. The authors estimated 13% publication bias. CSRs reported complete information on 84% - 92% of harm outcomes vs 27% to 72% of combined publicly available sources. 15% NR by publicly available sources for both general harms and withdrawals due to possible harms.
Rodgers 2013[25] **& Fu 2013**[26]	Systematic review of 13 trials and 4 single arms studies (10 and 1 journal published)	Recombinant human bone morphogenetic protein 2 (rhBMP-2) for spinal fusion vs iliac crest bone graft	IPD vs CSRs vs journal publications	Wealth of extra detail from CSRs provided by manufacturer. “Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and underreporting.” Fu et al conclude that “Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and underreporting.”
Doshi 2013[17]	Descriptive review of 78 CSRs	14 different pharmaceuticals and biologics	CSRs vs publications (comparison in size)	The ratio of CSR pages to publication pages for available full CSRs with a corresponding publication (“compression factor”) ranged from 379 to 8805.
Vedula 2013[14]	Review of transparency and accuracy of reporting of the numbers of participants, description of types of analyses, and criteria for including participants in the analysis in 11 published trials	Gabapentin vs placebo for four off-label uses (migraine prophylaxis, treatment of bipolar disorders, neuropathic pain, and nociceptive pain)	CSRs accessed from litigation with their published counterparts (21 trials identified, 11 assessed, 8 trials excluded because unpublished, 1 not randomised, 1 no CSR available)	Probably biggest discrepancies occurred between protocol and publication. Authors conclude “we found that the trial publication was not a transparent, or accurate (presuming that the research report truly describes the facts), record for the numbers of participants randomized and analyzed for efficacy”.
Maund 2014[18]	Review of nine trials in 1999-2001 (7 journal published)	Duloxetine vs placebo	CSR vs publications vs register entries. 1/9 R1 and 9/9 R2	7 S published 2 NS unpublished 1 NS published as S after post hoc analysis not mentioned in the paper Harms 50% and 25% participant reporting inconsistency in 2 trials, 1 death in active arm in unpublished trial; lack of clarity on phase of deaths Suicide NR < 2% in register reports. SAE 3 articles failed to report, register entries unclear
Le Noury 2015[34]	RIAT publication, restoring GSK’s trial 329 run in the 1990s and journal published in 2001	Paroxetine vs placebo & imipramine vs placebo	IPD with CRFs for 34% (93/275) participants and CSR vs publication	Paroxetine was reported as safe and effective in company sponsored ghost written publications. Access to CSR data led the authors to conclude that the drug was no more effective than placebo and was toxic in adolescents. The authors identified 4 outcomes cited in the protocol but not reported in the CSR and publication

Köhler 2015[35]	Systematic review of 15 dossier assessments by AMNOG submitted to IQWIG between 2011 and 2015. The authors assessed completeness of reporting in each document category	15 different drugs including anti HIV and oncology	AMNOG documents: IQWiG dossier assessments and publicly available modules of company dossiers vs non-AMNOG documents: EPARs vs journal publications vs register entries available at market entry date point	"At the time of market entry of a new drug, a substantial amount of information needed for assessment of the corresponding clinical studies and for understanding of the drug's benefits and harms is missing in publicly available European public assessment reports, journal publications, and registry reports (non-AMNOG documents)"
Beaumier 2015[36]	Cochrane review update of 4 CSR (3 journal-published in 4 publications)	Olanzepine vs placebo	CSRs vs publications	Dilution due to different coding of similar events (e.g. – "nervousness", "anxiety" and "agitation"). Long term harms not reported in publications.1 suicide in active arm NR in publication; 1 death in active arm from CV causes identified from FDA drug approval package not reported in either CSR or publication. 2 suicide attempts not reported in active arm in publication and S dose-response with metabolic syndrome NR in a journal publication.
Cosgrove 2016[37]	Review of data considered by regulators for registration vs other data available to them vs publications and comparison of regulatory vs SR process	Vortioxetine vs placebo (4 RCTs) or active comparator (6 studies) for depression	FDA drug approval package (based on 10 short term RCTs) and EMA EPAR (12 RCTs) vs publications. At least 3 studies were unpublished (38% of randomised participants). All unpublished studies showed no difference with comparator*	"Published literature gives the impression that vortioxetine is efficacious, safe, and well tolerated, when in fact the data were not collected or analyzed in a way that provides sound empirical support for this conclusion." Authors note extensive sponsor ties of 8/10 authors of published studies and comment on regulatory practice which focuses on an in-depth analysis of "positive" trials rather than the whole evidence base.
Hodkinson 2016[38]	Exploratory review to assess the reporting of harms in Orlistat trials	Orlistat vs placebo	5 Roche CSRs vs 5 journal publications	Journal publications provided insufficient information on harms outcomes compared to CSRs. Serious adverse events, were not reported or mentioned in the journal publications. Overall, CSRs provide extensive information about harms for study methods, including design, conduct, and analysis of the trial.
Jureidini 2016[39]	Litigation documents vs publication	Citolapram vs placebo	Comparison of 750 documents from the Celexa and Lexapro Marketing and Sales Practices Litigation and publication.	"The published article contained efficacy and safety data inconsistent with the protocol criteria. Procedural deviations went unreported imparting statistical significance to the primary outcome, and an implausible effect size was claimed; positive post hoc measures were introduced and negative secondary outcomes were not reported; and adverse events were misleadingly analysed. Manuscript drafts were prepared by company employees and outside ghostwriters with academic researchers solicited as 'authors"

Schroll 2016[40]	Descriptive review of 7 RCTs to assess the reporting of AEs	Orlistat vs placebo	7 CSRs from Roche vs. Protocols vs. Journal publications	"Study identified important disparities in the reporting of adverse events between protocols, clinical study reports, and published papers. Reports of the trials systematically understated adverse events. Based on the study findings, systematic reviews of drugs might be improved by including protocols and CSRs in addition to published articles".
Mayo-Wilson 2017[41]	Impact assessment to determine whether disagreements among multiple data sources of the same trials affected meta-analytic effect estimates, statistical significance and interpretation	Gabapentin and quetiapine	21 gabapentin RCTs (74 reports, six IPD) and seven quetiapine RCTs (50 reports, one IPD)	"Disagreements across data sources affect the effect size, statistical significance, and interpretation of trials and meta-analyses."

Key:

AMNOG = Arzneimittelmarktneuordnungsgesetz (Germany's Act on reform of the market for medicinal products);
CSR = clinical study reports;
CV = cardiovascular;
IQWIG = Institute for Quality and Efficiency in Health Care, Germany;
NA = Not applicable;
NK = Not known;
NR = Not reported (by the authors);
NS = statistically not significantly different;
QoL = quality of life.
R1 (Registration 1) = in public register;
R2 (Registration 2) = in manufacturer register);
S = statistically significantly different;
SAE = serious adverse events

Table 2: Characteristics of respondents and their experiences with regulatory data

	Requested regulatory data	Considered regulatory data	Not considered regulatory data
Question	**Total no. of responses: n (% of total responses)**		
Should regulatory data be used in Cochrane reviews?	n=20	n=7	n=133
Yes	15 (75)	3 (43)	43 (32)
In some cases	5 (25)	3 (43)	66 (50)
No	0 (0)	0 (0)	17 (13)[β]
Unsure	0 (0)	1 (14)	7 (5)
Rationale for using regulatory data?	n=20	n=7	N/A
Under reporting of harms	3	2	N/A
ORB	11	3	N/A
Publication bias	5	0	N/A
Missing data	2	1	N/A
Other	2*	2**	N/A
Familiarity with the regulatory process for pharmaceutical and biologics?	N/A	N/A	n=133
Yes - detailed understanding	N/A	N/A	8 (6)
Yes - basic understanding	N/A	N/A	83 (62)
No	N/A	N/A	42 (32)[γ]
Awareness of debate for improved access to clinical trial data?	N/A	N/A	n=133

Yes	N/A	N/A	113 (85)***
No	N/A	N/A	20 (15)

N/A: question was not asked in the survey as it was not applicable; ORB: outcome reporting bias

*(1) was a request from a reviewer and, (1) for detailed medical information from manufacturer about the product

**(1) Because of uncertainty in risk of bias assessment domains and (1) based on national Australian guidelines for regulatory approval

[β] Reasons why regulatory data should not be considered: (9) interventions non-pharmacological, (5) lack of guidance on how to include the data and (3) too time-consuming

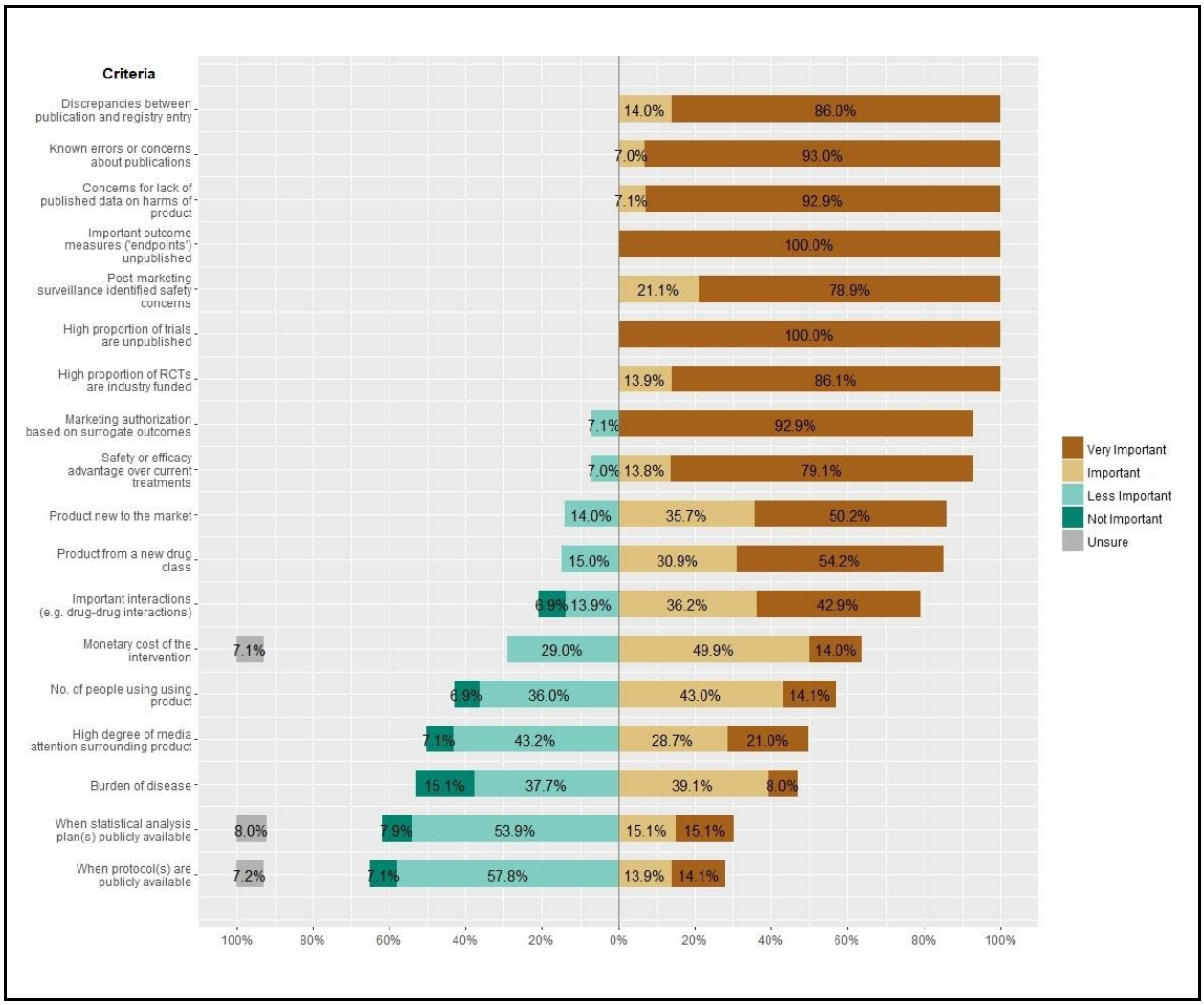
[γ] Reasons why not familiar: (2) Respondents conducted non-pharmacological reviews that do not require familiarity with regulatory data

***(2) respondents mentioned the AllTrials initiative,[42] (2) mentioned the “Tamiflu review”,[24] (1) respondent was involved in the EMA policy 0070 regarding access to clinical trial data in 2014[4] and (1) Ben Goldacre’s Bad Pharma.[43]

Table 3. Criteria for assessing whether to include regulatory data of a drug or biologic in a Cochrane review (not in order of priority)

Criteria	Description of criteria
1	Monetary cost of the intervention on the healthcare budget (i.e. considering both the price of a course and the number of people in the population that are being - or will be treated)
2	Burden of disease of the indication this product is meant to treat/prevent
3	Number of people using or likely to use the product
4	Product new to the market
5	Product from a new drug class or has a new mechanism of action
6	Has important interactions with other drugs (e.g. drug-drug interactions)
7	High proportion of RCTs evaluating this product are industry funded
8	Prominent claims of safety and/or efficacy advantage of this product over currently available treatments
9	High degree of media attention surrounding this product
10	High proportion of trials of this product are unpublished
11	Post-marketing surveillance has identified safety concerns
12	Important or standard outcome measures (also known as 'endpoints') have not been published
13	Concerns regarding a lack of published data on potential harms of the product
14	Marketing authorization based on surrogate outcomes (rather than clinical outcomes)
15	When protocol(s) are publicly available
16	When statistical analysis plan(s) publicly available
17	Known errors or concerns about trial publications of this product
18	Important discrepancies between the journal publication and the trial registry entry

Figure 1: Criteria for considering using regulatory data by order of importance according to 14 authors who had used, requested, or considered using regulatory data



Glossary of terms and definitions for taxonomy of regulatory documents
(Also see supplemental file of screenshots)

Acronyms

- **AusPAR.** See **Australian Public Assessment Report**
- **CRF.** See **Case Report Form**.
- **CSR.** See **Clinical Study Report.**
- **CTD.** See **Common Technical Document.**
- **EMA.** See **European Medicines Agency.**
- **EPAR.** See **European Public Assessment Report**.
- **FDA.** See **Food and Drug Administration.**
- **FOI.** See **Freedom of Information.**
- **FOIA.** See **Freedom of Information Act.**
- **ICF.** See **Informed Consent Form**
- **IMRAD.** See **Introduction, Methods, Results, and Discussion.**
- **IPD.** See **Individual Participant Data.**
- **ISE.** See **Integrated Summary of Effectiveness**
- **ISS.** See **Integrated Summary of Safety**
- **MAA.** See **Marketing Authorization Application.**
- **MOR. See Medical Officer Review**
- **NDA.** See **New Drug Application.**
- **PIL.** See **Patient Information Leaflet.**
- **PSUR.** See **Periodic Safety Update Report.**
- **RAP.** See **Report and Analysis Plan**
- **SAP.** See **Statistical Analysis Plan.**
- **SmPC**. See **Summary of Product Characteristics.**

Terms

- **Advisory Committee documents.** See **FDA Advisory Committee meeting materials**.
- **Aggregate data.** A colloquial term referring to summary data resulting from combining individual level data (e.g. mean age). **Individual listings** data can be combined to form **aggregate data**, but this cannot occur in reverse.
- **Amendments.** May refer to **Study Protocol** amendments or **Statistical Analysis Plan** Amendments, documents that list the various versions and changes made to a protocol over time. Amendments can vary in detail. Sometimes they document the original text, the new text, and the reason for the change.
- **Annotated Case Report Form.** An empty **Case Report Form (CRF)** in which the variable names are noted (annotated) next to fields, indicating how entries were to be recorded in the electronic dataset. Such information can be used to understand how data recorded on CRFs were transformed into an electronic patient level dataset.
    - Example: Zanamivir trial NAI30031, ACRF Contact, PDF p. 6
    - Also see an example in the Screenshots Gallery
- **Appendices.** See **Clinical Study Report Appendices**.
- **Australian Public Assessment Report (AusPAR).** A public assessment report, authored by the Australian regulator Therapeutic Goods Administration, that summarizes the evaluation and considerations of TGA in deciding to approve or not approve a marketing application for a prescription medicine. Whereas one EMA **EPAR** is written for each medicine, an AusPAR is created for a single marketing application, and is not updated following publication. Additional AusPARs are published for generic medicines, major variations and extensions of indications.

The first AusPAR was published in Nov 2009. Also see **European Public Assessment Report**, **Drug Approval Package**
    - Example: AusPAR for Vytorin
    - Look up other AusPARs here
    - More information here
- **Biologic License Application (BLA).** The regulatory vehicle through which sponsors submit a biologic for possible marketing approval to the **Food and Drug Administration**. The requirements are similar, but not identical, to those of a **New Drug Application**.
- **Blank Case Report Form.** A sample **Case Report Form (CRF)**, of unique pages only, that is, empty forms not yet filled in. One copy of all CRFs used in a trial is typically contained in section 16.1.2 of **Clinical Study Reports** formatted according to the **ICH E3 guidelines**.
    - Example: *Tamiflu (oseltamivir) trial NV18671 PDF page 336-527*
    - Also see an example in the Screenshots Gallery
- **Case Report Form (CRF).** The original paper or electronic forms on which individual participants' data (demographic, efficacy, safety, etc) are recorded during the clinical trial. The forms are typically the most 'raw' form of detailed data available for understanding what happened in a clinical trial, and the data they contain are statistically analysed only after they have been entered into an electronic database of individual patient data. Forms can vary in length, from a few pages to hundreds of pages, and each trial can have multiple forms—for example, for different visits or for the different tests or procedures the participant undergoes.
    - Example: Arthronat trial MA-CT-10-002 PDF pp. 3985-4749.
    - Also see an example in the Screenshots Gallery
- **Centralised procedure.** See **European Medicines Agency (EMA)**.
- **Certificate of analysis.** A short report in a **CSR** describing a chemical analysis and physical appearance of the contents of the medications (including any placebo) used in the clinical trial
    - Example: *Tamiflu (oseltamivir) trial WP16263 page 422-3.*
    - Also see an example in the Screenshots Gallery
- **Clinical Overview.** See **Module 2.5 (Clinical Overview) & Module 2.7 (Clinical Summary).**
- **Clinical Study Report (CSR).** An unabridged report of a clinical study written for regulators following the E3 reporting guidelines developed by the regulatory-industry collaborative effort International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). CSRs represent the most complete synthesis of the planning, execution, and results of a clinical trial. CSRs contain some of the same information as journal articles (i.e rationale, objectives, methodology, results, discussion/conclusion), but are substantially more detailed with numerous large tables and figures, and datasets not constrained by page limits. In addition, CSRs generally contain, as appendices, important study documents including the study protocol and amendments, statistical analysis plan and amendments, case report forms (CRFs), patient information sheet, **certificates of analysis**, informed consent forms, and individual patient listings among others.
    - Example: *Tamiflu (oseltamivir) trial M76001*
    - Also see an example in the Screenshots Gallery
- **Clinical Study Report Appendices. Clinical Study Reports** generally contain numerous appendices. The **ICH E3 guideline** document lists recommended appendices which start in section 16 of the document. These include the **study protocol** and **amendments** (section 16.1.1), **statistical analysis plan** and amendments (section 16.1.9), **blank case report form** (section 16.1.2), blank **informed consent form** (section 16.1.3), randomization scheme and codes (section 16.1.7), audit certificates (section 16.1.8), and patient data listings including discontinued patients (section 16.2.1), protocol deviations (section 16.2.2), adverse event listings for each patient (section 16.2.7), case report forms for deaths, other serious adverse events, and withdrawals for adverse events (section 16.3.1), and individual patient data listings (section 16.4).

- **Clinical Summary.** See **Module 2.5 (Clinical Overview) & Module 2.7 (Clinical Summary).**
- **Common Technical Document (CTD).** The name adopted by the ICH which refers to the way of structuring quality, safety, and efficacy information in support of a **marketing authorization application** (called a **New Drug Application** at the FDA). The CTD format is used by the EMA, FDA and Japanese PMDA. The CTD contains five modules (Modules 1, 2, 3, 4, and 5). **Clinical Study Reports** are contained in Module 5. The **CTD** is depicted by the ICH as a pyramid.
    - See http://www.ich.org/products/ctd.html
    - Also see the pyramid in the Screenshots Gallery
- **Drug Approval Package.** Reviews of clinical study reports and related documents for approved drugs, written by staff from the US Food and Drug Administration (FDA). Drug Approval Packages can be found of the Drugs@FDA website. Drug Approval Packages generally include the approval letter, summary review, medical review, chemistry review, pharmacology review, statistical review, clinical pharmacology biopharmaceutics review and microbiology review. Drug Approval Packages may also include the printed labeling, officer/employee list, office director memo, proprietary name review and administrative documents and correspondence and other reviews. FDA makes similar documents available for biologics under the Center for Biologics Evaluation and Research (CBER) website. Also see: **European Public Assessment Report**, **Australian Public Assessment Report**.
    - Example: Sivextro (Tedizolid Phosphate)
    - Also see an example in the Screenshots Gallery
- **Drug label.** (Also known as prescribing information, product information, labelling, package insert, **summary of product characteristics**) The content of this document varies by regulator, but generally is an official description of a medical product that includes the indication (for what the medicine is used, and in which population), contraindications, adverse events, instructions for safe use, and technical details. Labels may also include information on clinical pharmacology, toxicology, and clinical trials. This information generally has a primary audience of healthcare professionals, and in the United States can be searched for on DailyMed (NIH), the FDA Online Label Repository, and Drugs@FDA. In the EU, drug labels are referred to as the **Summary of Product Characteristics**, and can be searched for on EMA's website (at present, they can be found under the "Product information" tab of the drug's page on EMA's website). Information specifically written for patients is found in Medication Guides, Patient Package Inserts, and Patient Information Leaflets, often found attached to the healthcare professional information.
    - Example: Dalvance (dalbavancin) FDA approved label
    - Example: Xydalba (dalbavancin) EMA Summary of Product Characteristics
    - Also see an example in the Screenshots Gallery
- **Drugs@FDA.** Searchable database of regulatory data maintained by the FDA. Drugs@FDA offers public access to **drug labels**, patient information (cf. **patient information leaflet**), approval letters, **medical officer reports**, **statistical officer reports**, and other elements of the **drug approval package** for drugs approved since 1998. For drugs prior to this date, a **Freedom of Information Act** request is necessary to obtain these documents. A comparable database does not exist for biologics, but similar information is available by searching the "Vaccines, Blood & Biologics" section of FDA's website.
    - Drugs@FDA: http://www.fda.gov/drugsatfda
    - For biologics, look for FDA reviews on the webpage of each individual product. FDA has a webpage that lists of all licensed biologics with supporting documents.
- **EMA Policy 0043.** The **European Medicines Agency** Policy 0043 governs the agency's approach to the retrospective release of certain documents when in the agency's possession. This includes **Clinical Study Reports** (and other parts of the **Common Technical Document** including **Modules 2.5 and 2.7**), **Investigator's Brochures**, and **Periodic Safety Update Reports**. In colloquial terms, it is the agency's **freedom of information** policy. The policy is

dated 30 November 2010, effective from 1 December 2010 and its official title is "European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)."
    - Online here: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf
- **EMA Policy 0070.** The **European Medicines Agency** Policy 0070 governs the agency's approach to the prospective publication of clinical data in the agency's possession. The policy was finalized on October 2, 2014, effective from 1 January 2015 but its implementation is happening in stages, beginning with the publication of **Clinical Study Reports** (Autumn 2016). A second phase (Phase 2) is planned for the future, to cover third party access to **individual participant data**. The official title of Policy 0070 is "European Medicines Agency policy on publication of clinical data for medicinal products for human use."
    - Online here: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf
- **EMA Policy on Publication of Clinical Data.** Also known as the policy on "Clinical Data Publication." See **EMA Policy 0070.**
- **European Medicines Agency (EMA).** Regulatory agency in the European Union responsible for drugs and biologics approved through a centralised procedure. Medicines can also come to market through other non-centralised procedures, such as in a specific individual country or group of countries.
- **European Public Assessment Report (EPAR)**. Not a single document but a collection of regulatory documents describing the evaluation of all medicines granted or refused marketing authorization by the European Medicines Agency. Documents include a lay summary, labelling, package leaflet, summary of product characteristics, a public assessment report for the initial authorization and subsequent major changes, and an overview of procedural steps taken before and after authorization. Some information is published in all official languages of the EU while other documents are in English only, and some are only available online.
    - Example: Olazax (Olanzapine) EPAR
    - Also see an example in the Screenshots Gallery
- **Food and Drug Administration (FDA).** Regulatory agency in the United States responsible for food (including dietary supplements), drugs, biologics, medical devices, radiation-emitting electronic products, veterinary products, and tobacco products.
- **FDA Advisory Committee meeting materials.** The FDA makes use of federal advisory committees in an effort to receive independent advice from outside experts regarding regulatory decision making. Under US law (Federal Advisory Committee Act), meeting materials made available to committee members must be made available to the public at or before the time of the meeting. Meeting materials generally consist of two types: sponsor submitted materials and FDA submitted materials. These materials may contain limited data from clinical trials, but can include data not available elsewhere as well as FDA analyses of data (e.g. pooled analyses or sensitivity analyses). Unlike the Drugs@FDA database, Advisory Committee meeting materials may discuss applications that ultimately are not approved by the FDA, and as such serve as a source of unpublished data. Materials are, however, released to the public subject to the Freedom of Information Act (FOIA), which the FDA interprets as exempting certain types of information from disclosure, and therefore the publicly accessible versions may contain redactions. FDA posts Advisory Committee materials on its website, and generally also posts meeting minutes and a meeting transcript.
    - Advisory Committee meeting materials homepage: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm

    - Example: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm446101.htm
- **Freedom of Information (FOI).** General term that refers to laws or other governmental mechanisms allowing public access to documents held by governments. For discussion relevant to clinical trial data, for the United States see **Freedom of Information Act (FOIA)** and for Europe, see **EMA Policy 0043** and **EMA Policy 0070**.
- **Freedom of Information Act (FOIA).** A United States **freedom of information** law passed in 1967 that gives the public - generally irrespective of citizenship - the right to request records from any US federal agency. Thus far the FDA has generally (but not always) considered clinical trial data to be exempt from release under FOIA.
- **ICH E3 guideline.** A guidance document entitled "Structure and Content of Clinical Study Reports," developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Expert Working Group. They were formalised in 1995 "to assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy [for regulators] to review." Most clinical study reports follow the general structure laid out in the E3 guidelines, which have not been updated since 1995.
    - ICH E3 guideline
- **Individual listings.** A colloquial term referring to a document or electronic dataset which contains data recorded at the level of the individual participant. In **CSR**s, individual listings are provided in section 16.2 (Patient Data Listings), 16.3 (Case Report Forms), and 16.4 (Individual Patient Data Listings). In written documents they generally come in the form of tabular data, but may also appear in other forms, for example as is the case of individual participant **Serious Adverse Events narratives (ICH E3 guidelines** section 12.3.2) and withdrawals. Some journal publications may include individual listings as supplementary online material. Contrast with **Aggregate data**.
    - Example: Paroxetine trial 329
- **Individual participant data (IPD).** Data for each participant in a trial. This contrasts with aggregate or summary data, which is produced by combining data from multiple participants. Individual participant data allows for the replication of all analyses in study reports and exploration of further analyses. IPD generally come in two forms: electronic datasets (that are therefore readily analyzable with software packages) and printed/paper listings (as in the type found in the sections of CSRs that contain **individual listings**).
- **Informed Consent Form (ICF).** An information sheet that is required by law to be provided to potential research participants to enable an informed decision regarding study participation. The information sheet is also accompanied by a form used to document study participants' understanding of the study and consent to participate. Major elements that information sheets should contain include a description of the study purpose, information on the study intervention(s), study procedures, potential side effects, risks and benefits, compensation, and participants' rights.
- **Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS). Integrated summaries of effectiveness data and of safety (harms) data of more than one study, possibly including pooled/meta analyses, prepared for the FDA (**required for **New Drug Applications**, and encouraged for **Biologic License Applications)**. In the harmonized regulatory submission dossier, the **Common Technical Document**, the ISE and **Integrated Summary of Safety (ISS)** might be found in section "5.3.5.3 Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses)." The Summary of Clinical Efficacy (section 2.7.3 of the CTD) and Summary of Clinical Safety (section 2.7.4 of the CTD) were meant to replace the ISE and ISS

- **Integrated Summary of Safety (ISS).** Similar to the **Integrated Summary of Effectiveness**, but instead of clinical efficacy, the focus of an ISS is on safety (harms) of a product. See **Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS)**.
- **Introduction, Methods, Results, and Discussion (IMRAD).** Acronym used to describe the typical structure of a scientific report, that begins with the Introduction section, followed by Methods, Results, and finally a Discussion section. Short reports, such as journal publications of clinical trials, and long reports, such as clinical study reports, are generally both structured similarly to IMRAD.
- **Investigator's brochure.** A document written by a **sponsor** and intended for clinical investigators interested in becoming involved in a study. It summarises the current body of evidence about an intervention under investigation, typically based on preclinical and early phase human studies. The document is periodically updated in light of new information.
    - Example: Rituximab Investigator's Brochure
- **Licence/License.** The formal permission a regulator grants a company to market a medical product in a given territory.
- **Marketing Authorization Application (MAA).** The complete dossier of information submitted to the European Medicines Agency when sponsors seek marketing authorization for a medicine throughout the European Union under the EMA's centralised procedure.
- **Marketing Authorisation Holder (MAH).** (Also often referred to as a 'sponsor' or 'manufacturer'.) The entity granted marketing rights for a given medicine in a given jurisdiction. The EMA uses the term MAH whereas the FDA uses the term "sponsor".
- **Medical Officer Review.** Also known as a "Clinical review" or "Medical review". As one part of the FDA's process for evaluating marketing applications for new medicines (e.g. a New Drug Application or Biologics License Application), a medical officer, usually a physician, performs a review of and prepares a report regarding the clinical aspects of the application. These reports generally contain a listing of clinical studies included in the application and information about the design and results of those trials, including analyses conducted independently by the medical officer and additional commentary. Medical officer reviews are made public under FOIA and are posted to the FDA's website (for drugs, under the Drugs@FDA database and for biologics, by searching the "Vaccines, Blood & Biologics" section of the FDA's website).
    - Example: Gardasil clinical review
    - Example: bevacizumab clinical review part 1
    - Also see an example in the Screenshots Gallery
- **Medical Officer Report.** (Also referred to as a Medical Officer Review) See **Medical Officer Review.**
- **Medical Review.** See **Medical Officer Review.**
- **MedWatch.** The FDA safety information and adverse event reporting program. MedWatch encompasses both materials FDA makes available to the public and healthcare professionals as well as the three pharmacovigilance systems FDA Adverse Event Reporting System (FAERS), Vaccine Adverse Event Reporting System (VAERS), and Manufacturer and User Facility Device Experience Database (MAUDE).
    - Also see new web-based FAERS Public Dashboard
- **Module 2.5 (Clinical Overview) & Module 2.7 (Clinical Summary). Common Technical Document** module section 2.5 contains the Clinical Overview which is an accurate and exhaustive description of the evidence development plan. It contains the product development rationale, overview of biopharmaceutics, clinical pharmacology, efficacy, safety, benefit/risk conclusions, and literature references. The evidence development plan lists the completed, ongoing and planned studies by their study ID (which may or may not correspond to a register identifier). It is an invaluable overview and is relatively short (around 30 pages), and is complemented by Module 2.7, the Clinical Summary, which provides more detail of the same

data (in around 50 to 400 pages), including the Summary of Clinical Efficacy (section 2.7.3) and Summary of Clinical Safety (section 2.7.4).

- **Module 5. Clinical Study Reports** and raw data (for regulators that require or request it) are included in Module 5 of the **Common Technical Document**. There is no space limitation for Module 5.
- **Narratives.** See **Serious Adverse Event narratives**.
- **New Drug Application (NDA).** According to the FDA, "The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S." The application should contain sufficient information for the FDA to make a marketing decision. "The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged." Compare with **Marketing Authorisation Applications** in the European Union. Also see **Biologic License Application**.
- **Patient Information Leaflet (PIL).** (Similar documents in the United States are called the 'patient package insert' or 'medication guide'.) A document, typically a few pages in length, containing written medical information for patients that accompanies approved medicines. Information contained in the leaflet include active ingredient and indication, contraindications, warning and precautions, dosage and administration, possible side effects, storage of the medicine, marketing authorisation holder and manufacturer. Many forms of written medical information are reviewed and approved by regulators. However in the United States, patients may also receive a pharmacy leaflet when picking up a prescription medication. These documents are not regulator approved, but contain information that is similar in scope to official information and is written by third party vendors (not the manufacturer).
    - Example: Xydalba (Dalbavancin) PDF page 22
    - Also see an example in the Screenshots Gallery
- **Periodic Safety Update Report (PSUR).** EMA required pharmacovigilance document prepared by the marketing authorisation holder to provide an up to date evaluation of the benefit-risk-balance of a medicine. PSURs describe the worldwide safety experience with a medicine at a defined time after its authorization. Summarized data on the benefit-risk of a medicine and results of all studies of the medicine, authorised and unauthorised uses, are included.
- **Phamacovigilance.** (Also often referred to as "drug safety"). The science and activities relating to the collection, detection, assessment, monitoring and prevention of adverse effects of medicines. Also see **MedWatch.**
- **Protocol.** Generally refers to a **Study Protocol** document**,** but may also refer to a **Study ID.**
- **Regulatory document.** Colloquial term that generally refers to any document produced by, or held by, a regulatory agency. This may therefore include documents produced by regulators, such as an FDA **Medical Officer Review**, or a document submitted by a sponsor to a regulator, such as a **Clinical Study Report**.
- **Report and Analysis Plan.** See **Statistical Analysis Plan**.
- **Serious Adverse Event narratives**. Clinical Study Reports contain individual participant narratives of serious adverse events (ICH E3 section 12.3.2). They consist of unstructured free text and summarize information relevant to the serious adverse event. Each individual narrative is typically a paragraph to a page long.
    - Example: See PDF p.276 onwards of paroxetine study 329
- **Statistical Analysis Plan (SAP). (Also known as a Reporting Analysis Plan.)** Similar to a **study protocol** but focusing on the statistical methods and definitions to be used for data analysis. Like a **study protocol** any planned or actual changes from the original written SAP should be justified and documented with formal SAP amendments. The **amendments** should be dated.

- **Statistical Officer Review.** Report similar to a **Medical Officer Review**, but written by an FDA statistician. The statistical review may include the statistician's independent analyses using IPD submitted by the sponsor. Available as part of the **Drug Approval Package** on the Drugs@FDA website.
    - Also see an example in the Screenshots Gallery
- **Statistical Report.** See **Statistical Officer Review.**
- **Statistical Review.** See **Statistical Officer Review.**
- **Study ID.** (Sometimes referred to as Study Number. Pharmaceutical companies also often refer to a Study ID as a **Protocol**.) Identifier given to a single trial by its sponsor. Each trial may have multiple identifiers. For example: GlaxoSmithKline's HPV vaccine study 580299/012 (GSK's own ID) is also known as HPV-012 (part of the Cervarix programme) and NCT00169494 (registration ID), and may also be referred to by four known publications of the trial. The IDs may not be immediately reconcilable.
- **Study Protocol.** (Disambiguation: **Protocol**.) A document, written prospectively before recruiting participants into a study, which records the general rules and intended methods of conducting, analysing, and reporting the study. Detailed statistical methods are often recorded in a separate statistical analysis plan document, but the protocol should include the sample size calculation and an overview of the planned statistical analyses. Clinical trial protocols can be tens to hundreds of pages in length. A protocol may be required by the research ethics board, a data and safety monitoring board, or a funding body. Any planned or actual changes from the original written protocol in the conduct and/or analysis should be documented with formal protocol amendments.
    - Example: GSK Paroxetine Study 329 Protocol
    - Also see an example in the Screenshots Gallery
- **Summary Basis of Approval.** A document, according to the FDA, that contains "a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process." (21CFR314.430) Sponsors may draft the Summary Basis of Approval; it may also be written by FDA scientists.
- **Summary of Product Characteristics (SmPC).** Term used in the European Union to refer to the **drug label**. The SmPC describes the properties and the officially approved conditions of use of a medicine, and is intended for use by healthcare professionals. The SmPC is part of the **European Public Assessment Report (EPAR)**.
    - See an example in the Screenshots Gallery
- **Trial Master File (TMF).** A TMF is the collection of documentation that allows the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with Good Clinical Practice to be evaluated. It is also essential to allow the trial to be effectively managed by the sponsor as it allows the appropriate individuals access to the necessary trial documentation. The documentation contained within the TMF should be sufficient to adequately reconstruct the trial activities undertaken, along with key decisions made concerning the trial. Consideration should be given to the TMF being a stand-alone set of documentation that does not require additional explanation from the associated sponsor or site staff.

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Screenshots Gallery

Selected screenshots of regulatory documents

Annotated Case Report Form (Source: Zanamivir trial NAI30031, ACRF Contact, PDF p. 6)

GlaxoWellcome CONFIDENTIAL FINAL - 26 APR 00

Protocol code	Session number	Subject number
NAI30031	1	

Demography / Concurrent Medications
Screening

Date of assessment (day / month / year) VSDT R (D7)

Date of birth (day / month / year) BTHDT R (D6)

Sex

Male M SEX R (A1)

Female F [NSEX]

Race, ✔ *one:*

ETHCR1 R (A1) [NETHCR1]

White W *Origins in the original peoples of Europe, the Middle East, Western Russia, Afghanistan, or the white racial groups of Africa.*

Black B *Origins in any of the black racial groups of Africa.*

Asian A *Origins in the original peoples of the Indian subcontinent, the Far East, Southeast Asia, or the Pacific islands.*

American Hispanic H *Hispanics of North, Central, or South American origin.*

Other X *People whose racial group is not represented above, or whose predominant origin cannot be determined.*

[DEMOG]

Current smoker Yes Y No N SBSMK R (A1) [VYNALL]

Concurrent Medications

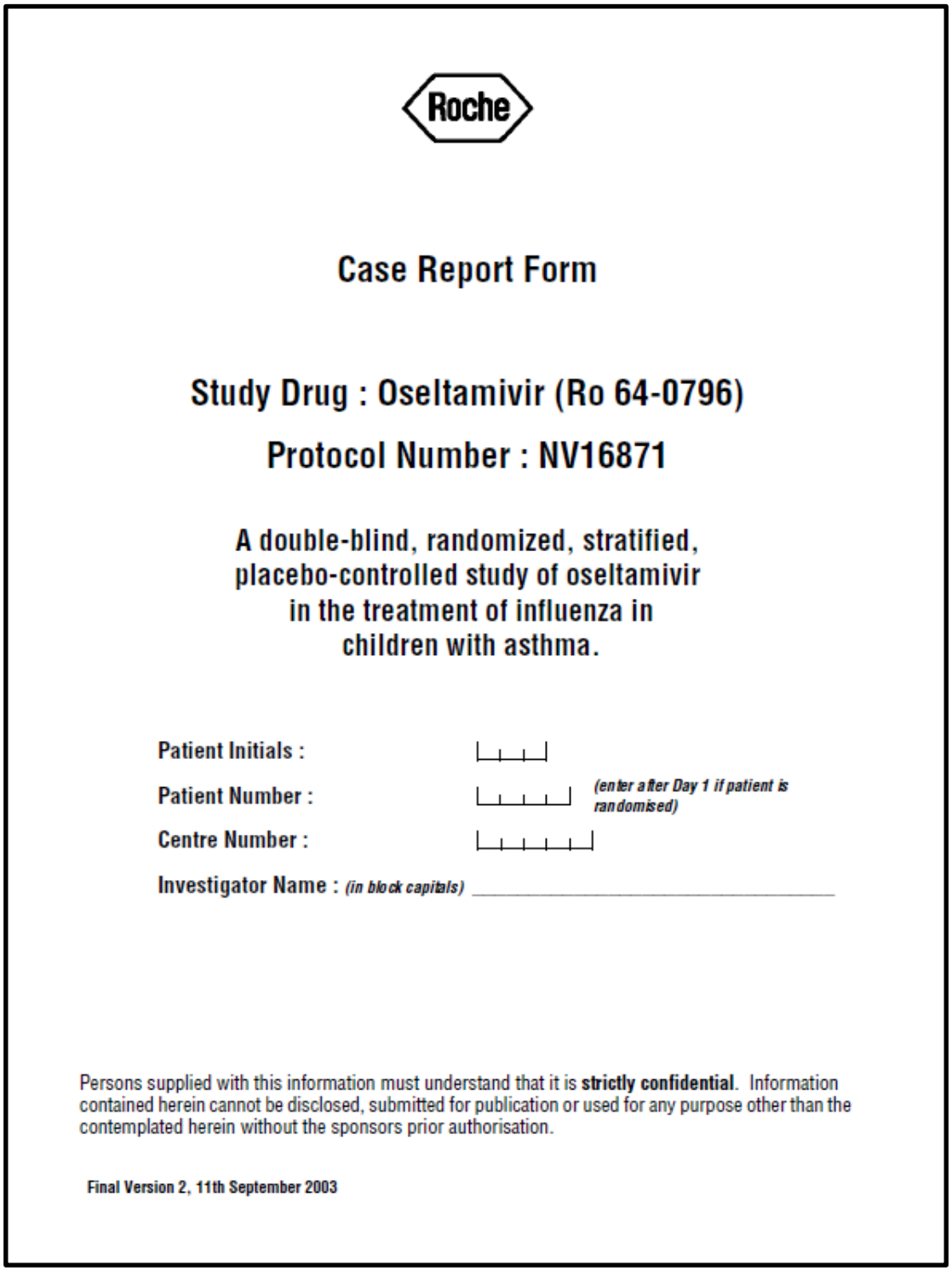
Enter any concurrent medications the subject is currently taking on the CONCURRENT MEDICATIONS page if appropriate. ☐ DNE ✔ *if done*

SESSION Ø

TMTSGPL R (N3) = 1
TMTSGSL R (A13) = 1
TMTSTDT R (D7) = VSDT
p.101

[TMTLOG]

Blank Case Report Form (Source: Oseltamivir trial NV16871 PDF pp. 336-527)



Roche

Case Report Form

Study Drug : Oseltamivir (Ro 64-0796)

Protocol Number : NV16871

A double-blind, randomized, stratified, placebo-controlled study of oseltamivir in the treatment of influenza in children with asthma.

Patient Initials : ⌊_ _ _⌋

Patient Number : ⌊_ _ _ _⌋ *(enter after Day 1 if patient is randomised)*

Centre Number : ⌊_ _ _ _ _⌋

Investigator Name : *(in block capitals)* _____

Persons supplied with this information must understand that it is **strictly confidential**. Information contained herein cannot be disclosed, submitted for publication or used for any purpose other than the contemplated herein without the sponsors prior authorisation.

Final Version 2, 11th September 2003

Roche	NV16871	Centre Number	Patient Number	Patient Initials	Baseline (Day 1)	CRF Page Number 3

Date of Baseline Visit : Day Month 2 0 Year

Demographic Data

Date of Birth : Day Month Year

Sex : ☐ Male ☐ Female

Race : Tick (✓) one box only

☐ Caucasian / White
☐ Black
☐ Oriental
☐ Asian
☐ Other _____
(please specify)

Asthma History/diagnosis

Date of first diagnosis of asthma : Day Month Year

Current Asthma severity : Tick (✓) current asthma severity

☐ Mild
☐ Moderate
☐ Severe

(refer to appendix 2 of the protocol to ascertain asthma severity)

Recurrent Asthma Symptoms :

	Tick (✓) if symptom present	Frequency (in last 4 weeks) **refer to code below*
Cough during the night	☐	☐
Cough during the day	☐	☐
Wheeze during the night	☐	☐
Wheeze during the day	☐	☐
Difficulty breathing or shortness of breath	☐	☐
Not fit to go to school because of chest problems	☐	☐

***Frequency :**
1 = less than one a week
2 = once a week
3 = twice a week
4 = 3 times a week
5 = 4-6 times a week
6 = every night

Case Report Form (Source: Arthronat trial MA-CT-10-002 PDF pp. 3988-3989)

PROTOCOL NO. MA-CT-10-002	SITE ID	SUBJECT INITIAL	SUBJECT ID
	001	N-V	001

SCREENING (V1 / -14 to -1 days)

SMOKING HISTORY

☒ 1 Non smoker		
☐ 2 Smoker, Date started :	___ ___ ___/___ ___ ___ ___ (mmm / yyyy)	Duration : ☐☐.☐☐ years
☐ 3 Ex-smoker, Date stopped :	___ ___ ___/___ ___ ___ ___ (mmm / yyyy)	Duration : ☐☐.☐☐ years

OSTEOARTHRITIC HISTORY

Date of onset of symptoms:	02/FEB/2010 (dd / mmm / yyyy)
Date of Diagnosis :	06/APR/2010 (dd / mmm / yyyy)
Joints affected *(check all that apply) :*	☐ 1 Hip ☐ 2 Knee ☒ 3 Shoulder ☐ 4 Wrist ☐ 5 Neck ☐ 6 Other, specify : _____

Index Joint *(check only one) :*	AREA	SIDE	
	☐ 1 Hip	☐ 1 Left	☒ 2 Right
	☐ 2 Knee		
	☒ 3 Shoulder		
	☐ 4 Wrist		
	☐ 5 Neck		

Treatment for OA *(check all that apply) :*	
	☐ 0 NA ☐ 1 Corticosteroids ☐ 2 Hyaluronic Acid ☒ 3 NSAIDs ☐ 4 Other

If Corticosteroid or Hyaluronic Acid is checked, please provide all details in the Prior Concomitant Medication page and exclude the subject from the study.
If NSAIDs or Other is checked, please provide the details in Prior Concomitant Medication page.

PROTOCOL NO. MA-CT-10-002	SITE ID	SUBJECT INITIALS	SUBJECT ID
	001	N-V	001

SCREENING (V1 / -14 to -1 days)

MEDICAL AND SURGICAL HISTORY

Does the subject have any past or ongoing medical / surgical history? ☒ 1 Yes ☐ 2 No If 'Yes', please provide details below :

Description	Start Date (dd / mmm / yyyy)	Stop Date (dd / mmm / yyyy)	Ongoing	Any Past/Ongoing medications recorded?
Type II Diabetes Mellitus	UK/UK/1990	__/__/____	☒	☐
Hypertension	UK/UK/1995	__/__/____	☒	☐
Underwent Surgery for Kidney Stones	UK/UK/2007	UK/UK/2007	☐	☐
	__/__/____	__/__/____	☐	☐
	__/__/____	__/__/____	☐	☐
	__/__/____	__/__/____	☐	☐

**If past / ongoing medication is recorded, then please provide details in Prior Concomitant Medication page.*

☐ 1 *Check this box if supplementary page is used.*

Certificate of analysis (Source: Tamiflu (Oseltamivir) trial WP16263 PDF pp. 422-3)

Placebo Capsules
Ro 64-0796/V16

Prepared by: [redacted]
Approved by:
Date: 21.09.9

CERTIFICATE OF ANALYSIS

No. 07039556 Batch: G MZ 0163

Date of manufacture: August 1999
Batch size: 104'827 capsules
Place of manufacture: Hoffmann-la Roche Ltd, Basle, Switzerland
Date of analysis: September 1999
Retest date: 08.2002

Capsule size	No. 2
Colour of the capsules	
Body	grey, opaque
Cap	ivory, opaque
Capsule contents	
Appearance	powder
Colour	white
Identity of	
Ro 64-0796	negative
Dehydrocholic acid	corresponds

Clinical Study Report (source: Tamiflu (Oseltamivir) trial M76001 PDF p.13)

FINAL STUDY REPORT MODULES

This report consists of 5 modules

Those not supplied in this submission are obtainable from the sponsor on request

MODULE I: CORE REPORT AND STUDY PUBLICATIONS
- Introduction
- Rationale
- Objectives
- Methodology
- Efficacy Results
- Safety Results
- Discussion / Conclusions
- Appendices

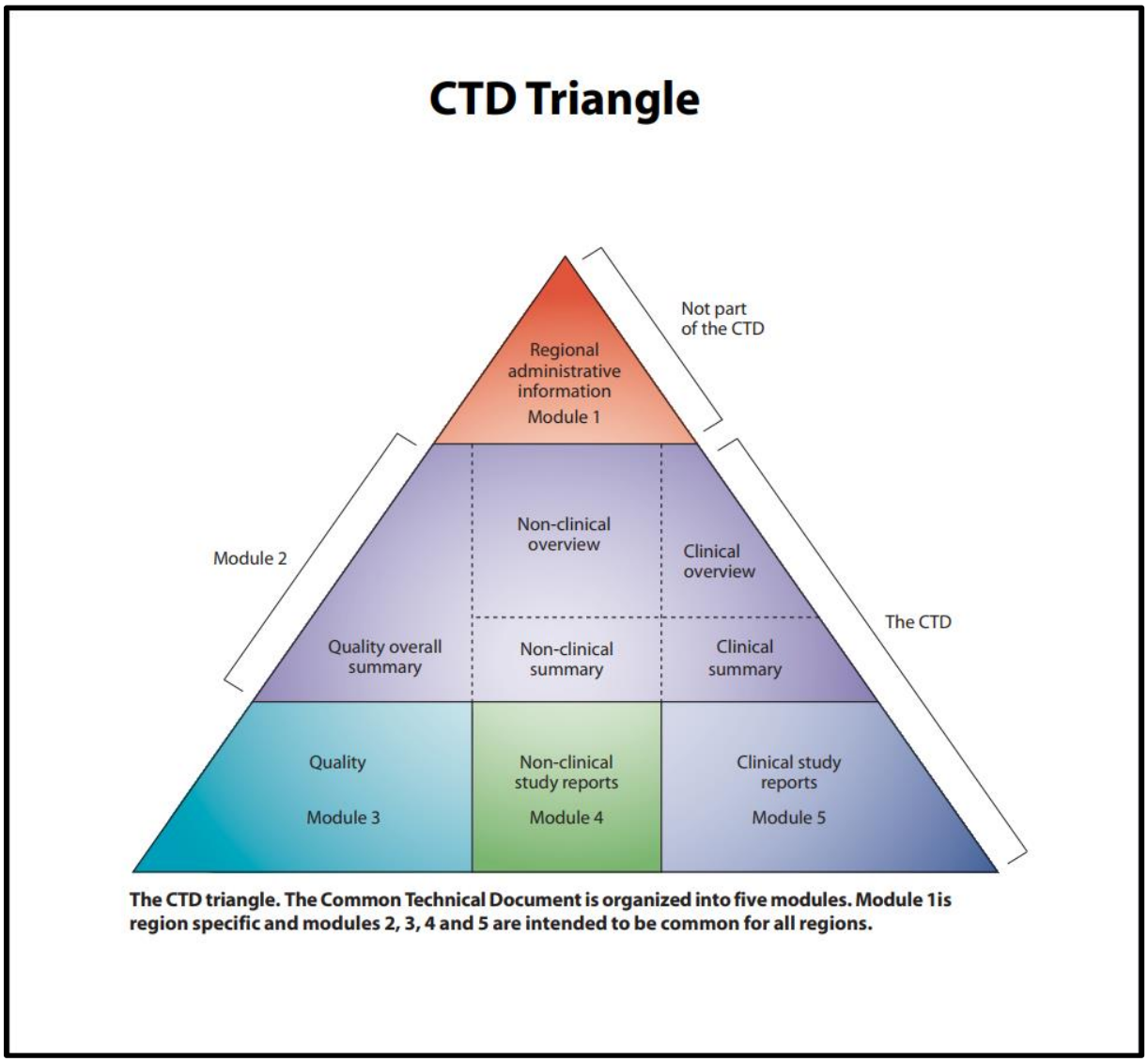
MODULE II: PRESTUDY DOCUMENTS AND STUDY METHODOLOGY
- Protocol and Amendment History
- Blank CRF
- Patient Information Sheet
- Glossary of Original and Preferred Terms
- Randomization List
- Reporting Analysis Plan (RAP)
- Certificates of Analysis
- List of Investigators
- List of Responsible Ethics Committees

MODULE III: INDIVIDUAL PATIENT LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA
- Demographic Data Listings
- Previous and Concomitant Diseases
- Previous and Concomitant Medications
- Efficacy Listings

MODULE IV: INDIVIDUAL PATIENT LISTINGS OF SAFETY DATA
- Laboratory Parameters
- Vital Signs Data

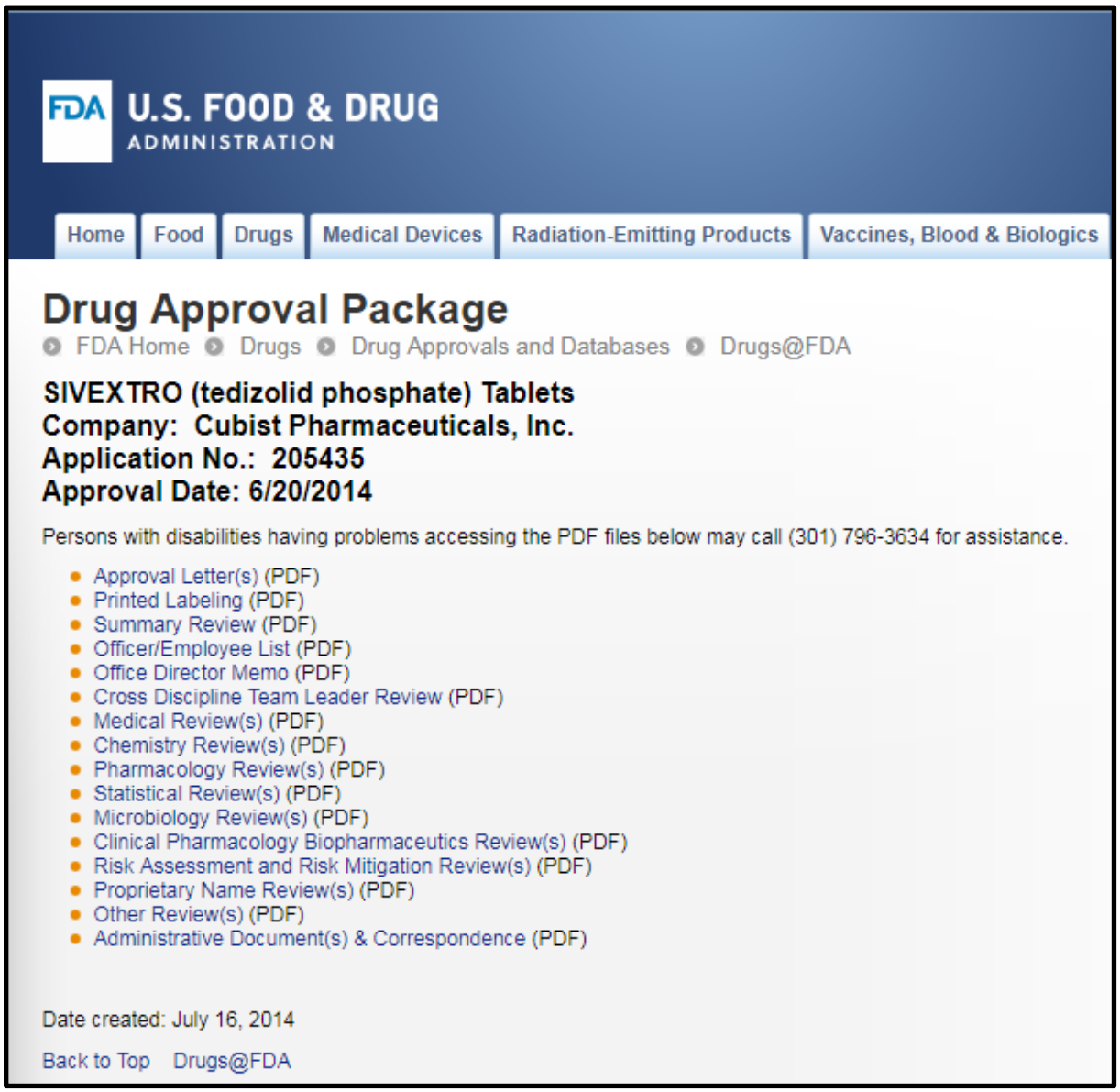
MODULE V: STATISTICAL REPORT

Common Technical Document (Source: ICH website)



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Drug Approval Package (Source: FDA website)



U.S. FOOD & DRUG ADMINISTRATION

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics

Drug Approval Package

FDA Home › Drugs › Drug Approvals and Databases › Drugs@FDA

SIVEXTRO (tedizolid phosphate) Tablets
Company: Cubist Pharmaceuticals, Inc.
Application No.: 205435
Approval Date: 6/20/2014

Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance.

- Approval Letter(s) (PDF)
- Printed Labeling (PDF)
- Summary Review (PDF)
- Officer/Employee List (PDF)
- Office Director Memo (PDF)
- Cross Discipline Team Leader Review (PDF)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
- Statistical Review(s) (PDF)
- Microbiology Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)

Date created: July 16, 2014

Back to Top Drugs@FDA

Drug Label (Source)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DALVANCE® safely and effectively. See full prescribing information for DALVANCE.

DALVANCE (dalbavancin) for injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

- Dosage and Administration (2) 01/2016

----------INDICATIONS AND USAGE----------

DALVANCE is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DALVANCE and other antibacterial drugs, DALVANCE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Dosage in patients with normal or impaired renal function (2.1, 2.2):

Estimated CrCl	Single Dose Regimen	Two-Dose Regimen
≥ 30 mL/min or on regular hemodialysis	1500 mg	1000 mg followed one week later by 500 mg
< 30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed one week later by 375 mg

- Administer by intravenous infusion over 30 minutes (2.1, 2.3)
- See Full Prescribing Information for instructions on reconstitution of lyophilized powder and preparation of injection (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 500 mg of lyophilized powder in a vial for reconstitution (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to dalbavancin (4)

----------WARNINGS AND PRECAUTIONS----------

- Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents, including DALVANCE; exercise caution in patients with known hypersensitivity to glycopeptides. (5.1)
- Rapid intravenous infusion of glycopeptide antibacterial agents can cause reactions. (5.2)
- ALT elevations with DALVANCE treatment were reported in clinical trials. (5.3)
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including DALVANCE. Evaluate if diarrhea occurs. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions in patients treated with DALVANCE were nausea (4.7%), headache (3.8%), and diarrhea (3.4%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Durata Therapeutics, Inc. at 1-855-387-2825 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

Dosage adjustment is required in patients whose creatinine clearance is less than 30 mL/min and who are not receiving regularly scheduled hemodialysis. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised 01/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

European Public Assessment Report (Source: website and document)

Olazax

olanzapine

About | **Authorisation details** | **Product information** | **Assessment history**

Next tab »

This is a summary of the European public assessment report (EPAR). It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the studies performed, to reach its recommendations on how to use the medicine.

If you need more information about your medical condition or your treatment, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist. If you want more information on the basis for the CHMP recommendations, read the scientific discussion (also part of the EPAR).

Expand all items in this list

- **What is Olazax?**
- **What is Olazax used for?**
- **How is Olazax used?**
- **How does Olazax work?**
- **How has Olazax been studied?**
- **What are the benefit and risk of Olazax?**
- **Why has Olazax been approved?**
- **Other information about Olazax**

Name	Language	First published	Last updated
Olazax : EPAR - Summary for the public	EN = English GO	29/01/2010	15/09/2014

This EPAR was last updated on 19/04/2017 .

More detail is available in the summary of product characteristics

European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/774081/2009

ASSESSMENT REPORT
FOR

OLAZAX

International Nonproprietary Name: **olanzapine**

Procedure No. EMEA/H/C/1087

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Medical Officer Review (Source)

Clinical Review
Sarah M. Connelly, MD
NDA 205834
Ledipasvir/Sofosbuvir Fixed-Dose Combination

Table of Contents

Table 3 Overview of Phase 2 and Pivotal Phase 3 LDV/SOF Trials

Trial Number	Trial Design	Population	Regimen and Duration	Number Enrolled	Primary Efficacy Endpoint
Pivotal Phase 3 LDV/SOF Trials					
GS-US-337-0102 (ION-1)	Randomized, open-label, international, multicenter trial	GT 1 Treatment-naïve ≤20% may have had cirrhosis at screening	**LDV/SOF:** 12 or 24 weeks **LDV/SOF+RBV**: 12 or 24 weeks	865	SVR12
GS-US-337-0109 (ION-2)	Randomized, open-label, multicenter trial	GT 1 Treatment-experienced, including prior PI-failures ≤ 20% may have had cirrhosis at screening	**LDV/SOF:** 12 or 24 weeks **LDV/SOF+RBV**: 12 or 24 weeks	440	SVR12
GS-US-337-0108 (ION-3)	Randomized, open-label, multicenter trial	GT 1 Treatment-naïve, non-cirrhotic	**LDV/SOF:** 8 or 12 weeks **LDV/SOF+RBV**: 8 weeks	647	SVR12
Phase 2 LDV/SOF Trials					
GS-US-337-0118 (LONESTAR)	Open-label Single center trial	GT 1 Treatment-naïve and Treatment-experienced, including prior PI-failures; ≤50% of treatment-experienced subjects may have had cirrhosis at screening	**LDV/SOF:** 8 or 12 weeks **LDV/SOF+RBV:** 8 or 12 weeks	100	SVR12
GS-US-337-0122 (ELECTRON-2; Cohort 2, Groups 3 and 4)	Open-label Two center trial (New Zealand)	GT 3 Treatment-naïve Subjects may have had cirrhosis	**LDV/SOF:** 12 weeks **LDV/SOF+RBV**: 12 weeks	51	SVR12
P7977-0523 (ELECTRON; Part 4, Groups 12 and 13; Part 6, Groups 16-18, 20, and 21)	Open-label Two center trial (New Zealand)	GT 1, 2 or 3 Treatment-naïve and Treatment-experienced Subjects may have had cirrhosis at screening	**LDV+SOF:** 12 weeks **LDV/SOF:** 12 weeks **LDV/SOF+RBV**: 6 or 12 weeks	102	SVR12

Patient Information Leaflet (Source)

Package leaflet: Information for the patient

Xydalba 500 mg powder for concentrate for solution for infusion
dalbavancin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effect(s) you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xydalba is and what it is used for

Xydalba contains the active substance dalbavancin, which is an **antibiotic** of the glycopeptide group.

Xydalba is used to treat **adults with infections of the skin or in the layers of flesh below the skin.**

Xydalba works by killing certain bacteria, which can cause serious infections. It kills these bacteria by interfering with the formation of bacterial cell walls.

If you also have other bacteria that cause your infection, your doctor may decide to treat you with other antibiotics in addition to Xydalba.

2. What you need to know before you are given Xydalba

Do not use Xydalba if you are **allergic** to dalbavancin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before being given Xydalba:
- If you have or have had **kidney problems**. Depending on the condition of your kidney, your doctor may have to reduce your dose.
- If you are suffering from **diarrhoea**, or you have previously suffered from diarrhoea when being treated with antibiotics.
- If you are **allergic** to other antibiotics such as vancomycin or teicoplanin.

Diarrhoea during or after treatment

If you develop **diarrhoea during** or **after** your treatment, tell your doctor **at once**. Do not take any medicine to treat your diarrhoea without first checking with your doctor.

Statistical Officer Review (Source)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	022526 / N0062
Drug Name:	Addyi™ (Flibanserin 100 mg q.h.s.)
Indication(s):	Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women
Applicant:	Sprout Pharmaceuticals, Inc.
Date(s):	Submission: 02/18/2015 PDUFA: 08/18/2015
Review Priority:	Resubmission class2
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Kate Dwyer, Ph.D.
Concurring Reviewers:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive and Urologic Products, HFD-580
Clinical Team:	Catherine Sewell, MD, Clinical Reviewer Olivia Easley, MD, Clinical Reviewer Christina Chang, MD, Clinical Team leader
Project Manager:	Jennifer Mercier

Keywords: NDA review, ROC analysis

Table of Contents

Study Protocol (Source)

SmithKline Beecham Pharmaceuticals
Clinical Research & Development
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

STUDY DRUG : BRL 29060/PAROXETINE (PAXIL)

A MULTI-CENTER, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY OF PAROXETINE AND IMIPRAMINE IN ADOLESCENTS WITH UNIPOLAR MAJOR DEPRESSION

PROTOCOL NUMBER 29060/329

PROTOCOL	August 20, 1993	Date of approval:	August 26, 1993
Amendment #1:	March 24, 1994	Date Amendment Approved:	April 17, 1994
Amendment #2:	October 2, 1996	Date Amendment Approved:	October 29, 1996

Protocol Table of Contents

Summary of Product Characteristics (Source)

1. NAME OF THE MEDICINAL PRODUCT

Olazax 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg olanzapine.

Excipient with known effect: Each tablet contains 0.23 mg aspartame

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Tablet
Yellow coloured circular flat bevelled edge tablets with 'B' debossed on one side.

4. Clinical particulars

4.1 Therapeutic indications

Adults
Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration

Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.

Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy (see section 5.1).

Preventing recurrence in bipolar disorder**:**
The recommended starting dose is 10 mg/day.

For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.