

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

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40 **Background and scope of the document**

41 Systematic reviews of randomised controlled trials play an important role in decision-making. If properly
42 designed and conducted, they identify, evaluate and summarise complex trial-derived information and
43 provide more reliable and precise estimates of intervention effects than individual studies. Up to now most
44 systematic reviews have used data extracted from journal publications. In a survey of 348 systematic
45 reviews published in 2014, around three-quarters relied solely on data provided in peer reviewed
46 journals.¹ Of those that accessed other sources, data from trials registries (such as ClinicalTrials.gov),
47 conference proceedings or contacting authors were the most used and no reviews reported using or
48 attempting to obtain CSRs even though the majority of the reviews evaluated drug interventions.¹ A
49 survey of 2184 Cochrane authors also found that contacting ‘trialists/investigators,’ was one of the most
50 common methods for accessing unpublished data and that data from manufacturers or from regulatory
51 agencies were rarely obtained.²

52
53 In late 2010, the European Medicines Agency (EMA) began releasing CSRs (on request), from
54 manufacturers of drugs and biologics in support of their request for marketing authorisation under their
55 Policy 0043.^{3,4} In October 2016, they began to release CSRs under their [Policy 0070](#).^{3,5} The policy
56 applies only to documents received since 1 January 2015. These regulatory documents provide more
57 detailed information and more complete data than are usually available in journal articles. Documents
58 available from the EMA normally include the clinical overview, clinical summary, and clinical study reports
59 (CSRs) of individual trials (which describe the trial design, conduct and results of analyses including three
60 selected appendices of each CSR--study protocol, statistical analysis plan, and sample case report
61 forms).³ See glossary of terms for definitions.

62
63 Availability of information from regulatory submissions has the potential to profoundly alter the way that
64 systematic reviews are conducted in future. Recognising the need to widen the scope of data sources
65 beyond electronic databases of journal publications, conference abstracts or trial registry reports, the
66 Cochrane Methods Innovation Fund (MIF) has funded the crafting and production of guidance on the
67 circumstances under which clinical study reports and other regulatory documents should be considered
68 for inclusion in Cochrane reviews, either in addition to or instead of data from more traditional sources.

69
70 At the outset of this project in 2014, we decided to focus on clinical study reports and other regulatory
71 documents relating to pharmaceuticals and biologics because clinical study reports and other regulatory
72 documents generally exist for such interventions. We acknowledge, however, that non-pharmaceutical
73 interventions (such as implantable devices, surgery, rehabilitation, behavioural interventions and
74 diagnostics) are responsible for a large part of healthcare expenditure and regulatory activity and
75 transparency have been recently increasing in this area, at a slower pace in the field of devices. It is also
76 important to note that publicly funded trials, even of drugs and biologics, do not usually produce
77 internationally standardised documentation similar to a CSR.

78
79 We refer to ‘interim’ guidance on how to decide whether to incorporate clinical study reports and other
80 regulatory documents into Cochrane reviews, as we have been unable to identify any research evidence
81 in this area. We also recognize that the scope of this project is limited to ‘whether’ to incorporate
82 regulatory data, as opposed to ‘how’ to incorporate such data.

83
84 **Rationale for the consideration of regulatory documents (including clinical study reports) as**
85 **sources of data for inclusion in Cochrane reviews**

86 There has been an accumulation of evidence on the unreliability of information on trials of
87 pharmaceuticals, biologics and medical devices; and a gradual realisation that sources of evidence
88 historically considered to be reliable (such as peer-reviewed literature) were affected by reporting bias
89 (see Table 1). Reporting bias generally refers to selective reporting of research depending on the nature
90 and direction of research results. Reporting bias includes publication bias⁶⁻¹⁰ and outcome reporting

91 bias,⁶⁻¹² among many others.¹³

92
93 A number of studies published in the last decade have shed light on the insidious reporting biases
94 present in publicly available reports of trials of pharmaceuticals and lack of transparency, both major
95 obstacles in assessing bias in studies included in Cochrane reviews (Table 1). The biases can only be
96 detected when two or more reports of the same trial are compared: for example, peer-reviewed
97 publications compared with relevant regulatory documents (see Glossary of terms for definitions of
98 regulatory documents). In addition to reporting bias, lack of transparency and lack of detail in journal
99 publications may prevent or hinder detailed analyses of data which could be relevant to specific
100 subpopulations potentially benefiting from or being harmed by the intervention.¹⁴ This situation is likely to
101 be the consequence of compressing thousands of pages of text and tables into the historically restricted
102 confines of a printed journal article.¹⁵ However, aggregate data on subpopulations are often found in
103 CSRs.

104
105 The examples from Table 1, covering more than 50 different interventions, offer glimpses of the
106 contribution of the different data sources across an array of interventions. There are indications that
107 CSRs may be incomplete and in some cases may be internally inconsistent between different
108 components of the same CSR. However, a consistent picture emerges when comparing different data
109 sources for the same trial: CSRs provide the greatest wealth, breadth and depth of information compared
110 to journal articles, register data and grey literature. Such a wealth of information allows access to a fuller
111 and more reliable picture of the strengths and weaknesses of each trial as well as a more reliable
112 assessment of the benefits and harms of the studied interventions. In addition to CSRs, other regulatory
113 documents such as medical officers' reports within the FDA's Drug Approval Packages (see below) may
114 provide important information. The Cochrane review of neuraminidase inhibitors for influenza (which used
115 both sources) found FDA reports an important source of data and detail.

116
117 There are limitations to the studies that compare different sources of evidence to inform a review (Table
118 1). First, the studies compare information from documents which have very different objectives. CSRs
119 inform regulators and, by law, provide a comprehensive record of a study. Trials registers are primarily a
120 visible collection of trials and their reporting format is heterogeneous. For example ClinicalTrials.gov does
121 not have a methods section and results can be either absent or incomplete. Under some circumstances
122 (such as for specific funding sources), reporting of trials within trials registers, including the submission of
123 results, is compulsory (but not always adhered to nor adequately policed¹⁶). Within the US requirements
124 exist for the National Institutes of Health (NIH)¹⁷ but in many cases worldwide trial registration is
125 voluntary. EMA's European Public Assessment Reports (EPARs) and the FDA's Drug Approval Packages
126 are records of regulators' work in assessing a medicine for potential registration and are not primarily
127 meant to provide summaries of trials for reviewing purposes (see Glossary of terms and definitions for
128 taxonomy of regulatory documents). Journal articles are the main means of communicating clinical trial
129 results providing short, accessible summaries of trial findings; but there is increasing evidence that
130 articles may be incomplete or biased. Journal trial articles are readily available and provide relatively
131 short, usually readable, summaries. These qualities are offset by the bias they may introduce and the
132 considerable time and effort expended (sometimes in vain) to clear up discrepancies, contradictions and
133 missing information.

134
135 A further limitation is linked to the debatable generalisability of each finding of the studies in Table 1 to the
136 reference population of trials or topic area. Some journals have taken steps to limit the bias introduced by
137 the current format of trial reporting, by requiring adherence to CONSORT, by publishing the trial protocol
138 or supplementary online data as an appendix or by requiring data sharing as a condition of publication.¹⁸⁻
139 ²⁰ As it is physically impossible to squeeze thousands of pages' worth of information into a 10-page
140 publication and the resulting information selection is based on unknown criteria, we should also expect
141 more complete reporting in journal articles, perhaps with links to the relevant CSR and other summary

142 data (e.g. FDA Drug Approval Packages).

143

144 We identified three examples of four systematic reviews, (a Cochrane review, twin reviews of the same
145 intervention and the review of reboxetine), allowing assessment of contributions of regulatory data
146 compared to the same trial data from articles.²¹⁻²⁴

147

148 In the case of recombinant human bone morphogenetic protein 2 (rhBMP-2), both aggregate and
149 individual participant data were included in the twin reviews,^{22,23} while the Cochrane review of
150 neuraminidase inhibitors for influenza was based solely on aggregate regulatory data.²¹ The outcomes of
151 the comparisons, however, were similar. In both cases the conclusions of important aspects of the
152 reviews were changed with access to the more complete data available in the CSRs. Access to the CSRs
153 also provided a deeper understanding of the strengths and limitations of the trial evidence. This may also
154 be true of FDA drug approval package data. In the case of the review of reboxetine, the inclusion of CSR
155 data changed the conclusions of the review. and allowed quantification of the exaggeration in favour of
156 the effects of reboxetine compared to placebo (99-115%) and other SSRIs (19-23%)²⁴.

157

158 It is reasonable to assume that, given what we now know about the potential multiple biases expressed
159 through trial publications, similar findings may be expected in a number of topic areas. As Cochrane
160 reviews are considered to be a gold standard of reliable research synthesis, we need to address the issue
161 of how to decide whether regulatory data, including CSRs, should be included in a systematic review. The
162 approach, however, is new and unfamiliar to most Cochrane reviewers and at the time of writing,
163 regulatory data are not always immediately available. When available, using such documents involves
164 reviewing very large quantities of information, which is time-consuming and resource intensive. Thus, a
165 framework to help identify where using data from regulatory documents is likely to matter most, and
166 prioritising those reviews which should adopt such an approach, will be helpful for Cochrane groups
167 grappling with how to respond to the increasing availability of these new sources of information.

168

169 **Current Cochrane practice**

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

178

179 There were 160 respondents who completed the Cochrane and non-Cochrane surveys combined, and we
180 identified a total of 7181 Cochrane authors over the last 2 years that have logged in to work on their
181 review. Therefore the rate of response from Cochrane authors was approximately 2.1% (Appendix Table
182 1). Twenty (13%) of the respondents had previously requested or used regulatory data, 7 (4%) had only
183 considered using (but had not used) regulatory data, and 133 (83%) had never considered using
184 regulatory data. The primary sources of regulatory data were the EMA and FDA, where 40% of the
185 requests were made. Amongst the 20 respondents that requested regulatory data, 12 involved CSRs,
186 five obtained medical and statistical reviews from the FDA, two European public assessment reports
187 (EPAR). Of the authors who acquired CSRs, 9 had used data from them to enable inclusion of
188 unpublished trials in their meta-analysis and to supplement published data.

189

190 When authors were asked which criteria were considered most important when considering access to
191 regulatory data (Table 2), omission and underreporting of trial outcomes and results were the most
192 frequently cited because of likelihood of reporting bias (criteria 10-14). However, the other criteria listed in

193 Table 3 were also considered important by most authors. 14 (70%) of the authors that had used or
 194 requested, and 6 (86%) authors who only considered regulatory data had faced certain barriers. These
 195 were identified mainly as the restricted and limited sharing of trials data, and the time constraints involved
 196 in searching and requesting the data.

197
 198 The survey results in brief show a lack of familiarity with regulatory sources of data, barriers to access
 199 and lack of resources to do so. The main rationale with authors seeking regulatory data, however, was
 200 driven by the minimisation of bias.

201
 202 **The circumstances under which clinical study reports and / or other regulatory documents should**
 203 **be considered for inclusion in Cochrane reviews**

204 We have been unable to identify any research on the topic of how to decide whether to incorporate
 205 clinical study reports and other regulatory documents into systematic reviews. What follows is the product
 206 of our opinion and experience supplemented by our peer reviewers' comments to date. The reviewers are
 207 listed in the acknowledgment section.

208
 209 Because of the large investment in resources required to search for additional data we do not consider
 210 that the preparation and/or updating of Cochrane reviews can be converted immediately to the routine
 211 search for, or inclusion of, regulatory data without a period of preparation and consideration of some of
 212 the consequences of such an action. It may not be necessary for all reviews to adopt such an in-depth
 213 approach. It is also important to take stock of current practice.

214
 215 Selection of likely candidate reviews is therefore required. Table 4 outlines a proposed instrument for
 216 selection, listing variables that should be taken into consideration during the process.

217
 218 **Table 4. Criteria for judging priority for including regulatory data of a drug or biologic (not in order**
 219 **of priority)**

Consideration i.e. potential impact on health outcomes and/or resources	Lower priority for regulatory data	Higher priority for regulatory data
1. Expenditure (current and potential) by the health service	Lower expenditure	Higher expenditure
2. Disease burden	Lower	Higher
3. Number of people with condition using drug/biologic?	Less	More
4. Regulator-approved indication?	Yes	No
5. Off-label use?	No	Yes
6. Established therapy?	Yes	No
7. New drug class or pharmacological target?	No	Yes
8. Claims of safety and/or efficacy advantage over current treatment	No	Yes
9. Potential interactions with other drugs?	No	Yes
10. Corrections/retractions to published RCTs?	No	Yes
11. Evidence of publication or other reporting biases?	No	Yes
12. Important outcomes not published?	No	Yes
13. Majority of RCTs industry funded?	No	Yes
14. Concerns about under-reporting or lack of data on harms	No	Yes

220
 221 Expenditure includes the cost of the drug/biologic multiplied by courses prescribed. Consideration of
 222 expenditure is important as it reflects the opportunity cost of using the drug/biologic, i.e. the amount of
 223 resources that could be used to fund an alternative intervention shown to be effective on the basis of
 224 more reliable evidence.

225

226 There may be exceptions to or different cost bands, as in the case of use of generics, but the underlying
227 principle is that expenditure is one of the key variables for identifying priority topics.

228

229 Other variables are self-explanatory, reflecting either known or suspected bias in published results or the
230 potential for greatest impact in terms of public health - what are the human costs of reaching and acting
231 on biased estimates of effectiveness or harm? There is no proposed scoring or algorithm for combining
232 domains to identify priority topics or topic area. The relative importance of domains included in Table 4
233 will depend very much on context and prioritisation is inevitably a somewhat subjective process.

234 The Working Group, who have authored this document, would be interested in receiving suggestions or
235 reports of experience regarding accessing regulatory data and including such data in systematic reviews.
236 It should be noted, however, as mentioned elsewhere, that that is beyond the scope of this project.

237

238

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240

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248

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251 and summarise the survey results.

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253 Cochrane reviews over the last 2 years to complement our survey results.

254

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Reference	Type of study	Intervention comparisons	Source comparison	Take home message
Turner 2008¹	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 2010²	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 2012³	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 2012⁴	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 2012⁵	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 2013⁶	Systematic review of 101 trials with full CSR available included in 16 HTA reports prepared by IQWiG. The study population is the same as Wiesler 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 2013⁷ & Fu 2013⁸	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

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				the effectiveness and harms through selective reporting, duplicate publication, and underreporting.”
Doshi 2013 ⁹	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 ¹⁰	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 ¹¹	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 ¹²	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 ¹³	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	“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)”

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			publications vs register entries available at market entry date point	
Beaumier 2015 ¹⁴	Cochrane review update of 4 CSR (3 journal-published in 4 publications)	Olanzapine 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 DAP 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 ¹⁵	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 DAP (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 ¹⁶	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 ¹⁷	Litigation documents vs publication	Citalopram 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 ¹⁸	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 ¹⁹	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.”

Table 1. Examples of studies comparing different sources of data for the same trials. Key: CSR = clinical study reports; DAP = FDA drug approval package; IQWiG = Institute for Quality and Efficiency in Health Care, Germany; AMNOG = Arzneimittelmarktneuordnungsgesetz (Germany’s Act on reform of the market for medicinal products); R1 (Registration 1) = in public register; R2 (Registration 2) = in manufacturer register); SAE = serious adverse events; S = statistically significantly different; NS = statistically not significantly different; NR = Not reported (by the authors); NK = Not known; NA = Not applicable; CV = cardiovascular; QoL = quality of life.

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Appendix – 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) ^{***}

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No	N/A	N/A	20 (15)
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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) over uncertainty in quality assessment domains and (1) basis on national Australian guidelines

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 Reason not familiar: (2) Respondents conduct non-pharmacological reviews that do not require familiarity with regulatory data

*** (2) respondents mentioned the AllTrials initiative,¹ (2) mentioned the Tamiflu review,² (1) respondent was involved in the EMA's policy 70 regarding access to clinical trial data in 2014³ and (1) Ben Goldacre's Bad Pharma⁴.

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Appendix - Table 3: Possible sources for respondents who had not considered regulatory data

Question	Not considered regulatory data
Do you know where to access trial regulatory data?	n=133
Yes	16 (12)
No	77 (58)
Unsure	40 (30)
Where do you think regulatory data/information are available?	n=47
FDA	19
EMA	18
Other regulators	4 ^β
Trial registries	10 [€]
Pharmaceutical company	10
NICE	3
MHRA	5
Clinical Study Data Requests website	1
Ethics committee	3
Research council (MRC)	1
Governmental body	2
Are authors familiar with the type's documents produced?	n=91
Yes very familiar	3 (3) ^π
Yes have some knowledge	51 (56) ^α
No	26 (29) ^γ
Unsure	11 (12)

N/A: question was not applicable to the questionnaire; EMA: European medicines agency; FDA: food and drug administration; NICE: national institute for health and care excellence; MHRA: the Medicines and Healthcare products Regulatory Agency

^β The Health Products Regulatory Authority (HPRA) of Ireland, Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, Therapeutic Good Administration (TGA) Department of Health Australia (listed twice)

^γ Reason no familiarity: (3) respondents conduct non-pharmacological reviews that do not require familiarity with document types for regulatory data

[€] (9) ClinicalTrials.gov website and (2) international standard randomised controlled trial number (ISRCTN) registry.

^π One respondent had previous experience using open data sources from EMA

^α One respondent was a member of a regional ethical committee, and therefore is aware of the type of documents produced at that level, another respondent had worked for the Italian drug agency and has some expertise on the content of dossiers submitted for regulatory purposes, and one author has previous experience writing periodic safety update reports.

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Glossary of terms and definitions for taxonomy of regulatory documents

(Also see supplemental file: [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 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](#)
- Lookup 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 are 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 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. In addition, CSRs generally contain, as appendices, important study documents including the study protocol and amendments, statistical analysis plan and amendments, case report forms (CRF), 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**) This 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 for, 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.
 - Online here: <http://www.fda.gov/drugsatfda>
- **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 medicine 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 EU languages while other documents are in English only, and some 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 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 titled “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 **CSRs**, 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.¹ IPD generally comes 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 efficacy data (ISE) and of safety (harms) data (ISS) 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).** Same as the **Integrated Summary of Effectiveness**, but instead of a 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)**.

¹ <http://www.bmj.com/content/346/bmj.f2865>

- **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 similar 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.²
 - Example: [Rituximab Investigator's Brochure](#)
- **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 of 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 of a given medicine in a given jurisdiction. The EMA uses the term MAH whereas 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 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 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).

² <http://www.bmj.com/content/346/bmj.f2865>

- **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 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.
- **Pharmacovigilance.** (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 a 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.³
 - 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 GCP 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.

³ <http://www.bmj.com/content/346/bmj.f2865>

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