



Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports

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Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports

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3
4 22 **Patient consent statement** No consent was necessary as no patients were involved

5
6 23 **Ethics approval statement** No ethical approval was necessary as no patients were involved
7 and all data were aggregate or anonymized and publicly available.
8

9
10 25 **Role of the sponsor statement** As the review had no extramural funding, there was no
11 sponsor.
12

13
14 27 **Author Contributions:** Doshi had full access to all of the data in the study and takes
15 responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept*
16 *and design:* Doshi and Jefferson. *Acquisition of data:* Doshi and Jefferson. *Analysis and*
17 *interpretation of data:* Doshi and Jefferson. *Critical revision of the manuscript for important*
18 *intellectual content:* Doshi and Jefferson. *Statistical analysis:* Doshi.
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ARTICLE SUMMARY

33

Research questions or hypotheses addressed

What are Clinical Study Reports (CSRs)? What do they contain and how long are they?

Might CSRs help address reporting biases associated with the published literature, and improve the quality of evidence synthesis?

Key Messages (up to 3)

CSRs represent a hitherto hidden and untapped source of detailed RCT data (mean page length: 1,854 pages), increasingly becoming publicly available, and should form the basic unit for evidence synthesis to minimize the problem of reporting bias.

CSRs show that numerous individuals make important technical contributions to the design, conduct, and reporting of each trial, but journal publications often fail to record these details, resulting in a loss in individual responsibility for what is reported.

The E3 guideline to which most CSRs conform was published in 1995, and needs updating.

Strengths and Limitations

We cannot say whether our sample is representative and whether our conclusions are generalizable to an undefined and undefineable population of CSRs.

49

Abstract

Objective: To explore the structure and content of a non-random sample of clinical study reports (CSRs) to guide clinicians and systematic reviewers.

Search strategy: We searched public sources and lodged Freedom of Information requests for previously confidential CSRs primarily written by industry for regulators.

Selection criteria: CSR reporting sufficient information for extraction (“adequate”)

Primary outcome measures: Presence and length of essential elements of trial design and reporting and compression factor (ratio of page length for CSR compared to its published counterpart in a scientific journal).

Data extraction: data were extracted on standard forms and cross-checked for accuracy

Results: We assembled a population of 84 CSRs (covering 90 RCTs; 144,610 pages total) dated 1991-2011 of 14 pharmaceuticals. 78 were adequate. Report synopses had a median length of 5 pages, efficacy evaluation 13.5 pages, safety evaluation 17 pages, attached tables 337 pages, trial protocol 62 pages, statistical analysis plan 15 pages, and individual efficacy and safety listings had a median length of 447 and 109.5 pages, respectively. While 16 (21%) of CSRs contained completed case report forms, these were accessible to us in only one case (765 pages representing 16 individuals). Compression factors ranged between 1 and 8805.

Conclusions: Clinical study reports represent a hitherto mostly hidden and untapped source of detailed and exhaustive data on each trial. They should be consulted by independent parties interested in a detailed record of a clinical trial, and should form the basic unit for evidence synthesis as their use is likely to minimize the problem of reporting bias. We cannot say whether our sample is representative and whether our conclusions are generalizable to an undefined and undefineable population of CSRs.

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86 Introduction

87 Systematic reviews are thought to provide one of the most robust ways to evaluate the effects of
88 healthcare interventions. But the robustness of findings clearly rests upon reviewers' access to
89 clinical trial information sufficient to critically evaluate and reproduce the original research.
90 Research on reporting bias over the last decades has shown that trusting the published
91 literature at face value, even peer-reviewed publications, can be fraught with difficulty—a
92 problem that spans drug classes.¹⁻¹²

93 Following the decision by the European regulator, European Medicines Agency (EMA) on 30
94 Nov 2010, to make available a broad spectrum of documents related to medicinal products for
95 human and veterinary use,^{13,14} attention is focusing on one particular type of regulatory
96 document: clinical study reports (CSRs).¹⁵⁻¹⁸ CSRs are usually written for regulators following
97 guidelines developed by the industry-regulatory collaborative effort "International Conference on
98 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use"
99 (ICH). The ICH guidelines "Structure and Content of Clinical Study Reports"¹⁹ (See Appendix 1)
100 are known by the document code "E3". They were formalized in 1995 "to assist sponsors in the
101 development of a report that is complete, free from ambiguity, well organised and easy [for
102 regulators] to review."¹⁹ E3 has not been edited or changed since 1995.

103 CSRs are but one category of information that is transmitted from study sponsors to regulators
104 (Figure 1), but are important as they contain substantially more information and detail on the
105 intervention being tested than published versions of the same trial. The wealth of information
106 may be sought with increasing frequency by researchers appraising single trials, entire trial
107 programmes, or by those synthesizing evidence.^{17,20} We are aware of two recent examples of
108 systematic reviews carried out using CSRs and other regulatory material.^{12,21} One group also
109 concluded that journal publications insufficiently report clinical trials.²²

110 Despite CSRs' potential importance very little is known about their structure and content outside
111 of those individuals with direct involvement in regulatory processes. This knowledge gap may
112 hinder development of methods for fair and reliable appraisal of CSRs and their use in evidence
113 synthesis. We are not aware of any instruments specifically designed for appraising CSRs. Lack
114 of visibility may also conceal the complexity of the organization and reporting of clinical trials.

115 We carried out an exploratory review to describe the structure and content of a non-random
116 sample of clinical study reports. Our long-term intention is to improve the credibility of research
117 synthesis by facilitating a move from the level of detail found in journal articles to the level of

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118 detail found in regulatory documents, thus guiding clinicians and other decision makers at all
119 levels.

120 **Methods**

121 We obtained CSRs from public sources, as follows:

- 122 1. Requesting from EMA, under its freedom of information (FOI) policy, CSRs for
123 manufacturer sponsored trials of the 10 best-selling prescription-bound products in the
124 United States in 2010.²³
- 125 2. Reusing CSRs from our own previous research¹²
- 126 3. Downloading CSRs openly available on the Internet.
- 127 4. Corresponding with other researchers who have obtained CSRs through FOI requests
- 128 5. Requesting manufacturers fill any gaps in the completeness of reports that we believe
129 are legally required to be publicly available.

130 To create as broad a database as possible, we did not apply restrictions in drug type or family or
131 sponsor. We did not submit requests under the Freedom of Information Act to the Food and
132 Drug Administration because such requests can take years to be fulfilled and—once fulfilled—
133 may be heavily redacted.²⁴

134 We did not draw a random sample of CSRs as there is no known sampling frame. No one
135 knows how many reports have been written by intervention category as there is no central
136 register of CSRs. Through familiarity with CSRs for oseltamivir and zanamivir, which were
137 included in one of our Cochrane reviews,¹² we developed and piloted a data extraction sheet
138 designed to capture the salient characteristics of CSRs. We created a list of around 40 potential
139 sections we expected to find, generated from elements specified in E3. For each element in the
140 list, we checked whether the obtained CSR included that section (confirmed either by direct
141 identification of the section or an indication the section existed based on the CSR's table of
142 contents), whether we had access to it, and its page length. Because of previous difficulties we
143 had accessing CSR appendices, we also recorded whether sections were listed as appendices
144 or not. Page length was calculated either by directly counting the pages or by estimating their
145 size from the table of contents of each report, and was used as a crude proxy for the level of
146 detail available. Page lengths were rounded up to the next integer, and were summarized by
147 reporting medians and ranges. We also included questions relating to trial registration and
148 authorship. Our (blank) data extraction sheet is in Appendix 2.

149 All variables from CSRs were first extracted in single. We subsequently audited each other's
150 extractions, checking the accurateness of the information. We chose to present elements

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151 analogous with those that typically appear in trials reported in scientific journals including the
152 study Synopsis (a brief summary of the study), the study Protocol (written prospectively,
153 describing the study methods), Efficacy and Safety Evaluations (a narrative summary of the
154 efficacy and safety results of the study, including tables and figures), as well as attached tables.
155 We also included elements rarely found in journal publications: sample (blank) and completed
156 case report forms (CRFs are paper or electronic forms designed to capture pre-specified
157 efficacy and safety related information for each study participant), the statistical analysis plan (a
158 prospectively written narrative and/or statistical code indicating how trial data will be analyzed),
159 and individual participant efficacy and safety listings. The corresponding E3 section numbers
160 are listed in Table 2. Disagreements were resolved by discussion.

161 Our uncorrected (original) and corrected extraction sheets as well as audit records are available
162 upon request from the corresponding author.

163 We calculated a compression factor for published trials: the ratio of CSR page length compared
164 to the page length of the same trial as published in scientific journals. Trial publications were
165 searched for in multiple sources: clinical trial registers, published systematic reviews, and
166 correspondence with sponsors. Because in most cases we could not access all parts of all
167 CSRs, we calculated both “conservative” and “realistic” compression factors. “Conservative”
168 compression factors were calculated using the total number of pages of CSRs available to us
169 divided by the length of journal reports, while “realistic” compression factors were based on the
170 true total page length of the CSR, when known, even if inaccessible.

171 **Results**

172 We identified 84 documents believed to be CSRs for 14 compounds. These covered
173 therapeutic and biological interventions including antipsychotics, antidepressants, antivirals,
174 natural antiarthritics, anti-inflammatory agents, pandemic influenza vaccines, statins,
175 erythropoietins, and anti-platelet compounds. We included English-language summaries of two
176 Japanese oseltamivir studies (JV15823, JV15824) as they had been presented to EMA in this
177 form. We excluded CSRs which were too fragmentary to evaluate (olanzapine F1D-LC-HGAV,
178 F1D-MC-HGAJ and F1D-MC-HGAO) and documents which were not in fact CSRs (reboxetine
179 14, 22 and 37). This left 78 CSRs (144,610 pages) (Figure 2). The median pages obtained per
180 CSR was 644 (range 9 to 15,440). Only 4 of 78 CSRs (reboxetine 8, 16, 17, and 91) were
181 written prior to November 30 1995 when ICH E3 was approved. Table 1 summarizes the
182 pharmaceutical, manufacturer, date and provenance of the CSRs in our review. EMA reported
183 not holding studies for esomepazole magnesium (Nexium), Advair diskus, quetiapine fumarate
184 (Seroquel), montelukast sodium (Singulair), epoetin alfa (Epogen), and simvastatin.

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185
186 All of the 78 included CSRs comprised of a synopsis (median page length 5 pages). The
187 efficacy evaluation was identifiable and directly accessible in 76 (97%, median length 13.5
188 pages) and safety in 77 (99%; median length 17 pages). Attached tables were likewise present
189 in 63 (81%) of CSRs, and were a median of 337 pages long (range: 1 to 3665). Seventy-three
190 CSRs (94%) reported including the study protocol. In the 40 we could access, the median page
191 length was 62. We found blank CRFs included in 68 (87%) of CSRs. Of the 33 we could
192 directly access, the median length was 133 pages (range 14 to 981). For completed CRFs, 16
193 (21%) reports made direct mention of a section on completed CRFs, but we had access to
194 completed CRFs in only 1 case (Arthronat; length 765 pages).

195
196 Fifty-five (71%) of 78 included CSRs included a statistical analysis plan in some form. Of those
197 for which we could directly access the content (n=37), the median page length was 15 (range 3
198 to 85). Individual efficacy and safety listings were included in 53 (69%) and 62 (81%) CSRs
199 respectively. The median page length was 447 (range 15 to 21,698) for efficacy and 109.5
200 (range 2 to 10,954) for safety.

201 A summary is presented in Table 2.

202 All trial reports in our review were sponsored by industry.

203 Median conservative compression factors ranged between 1 and 1221. The realistic
204 compression factors, calculated for the Arthronat, paroxetine, and clopidogrel CAPRIE trials,
205 were 379, 1021, and 8805, respectively. (Table 3)

206 Discussion

207 We collected and described a sizeable number of CSRs written in the last two decades. All
208 CSRs contained a table of contents (as specified in E3 section 3); this, together with optical
209 character recognition (to enable searching the full text of the scanned documents) and the
210 occasional need to combine multiple files to create a single document, substantially improved
211 the ease of navigating CSRs.

212 The future basic currency of research synthesis?

213 The median length of 644 pages for reports in this study confirms that CSRs are the most
214 detailed and complete, integrated form of reporting of the design, conduct, and results of clinical
215 trials. They far surpass the level of detail available in journal publications, and as such they are
216 prime candidates for the next basic currency of evidence synthesis and appraisal of a trial.
217 Given the EMA's new policy making such documents publicly available, access to these

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218 documents is now relatively straightforward. However including CSRs in reviews is labor-
219 intensive, given their size and complexity.¹²

220 **Accessing complete CSRs**

221 While CSRs may trump other forms of trial reporting in the public domain (such as conference
222 abstracts or journal publications), serious limitations remain. Despite obtaining 144,610 pages
223 for 78 CSRs, in almost all instances, we lacked full access to the CSRs' numerous appendices.
224 Even for the sole complete CSR we obtained (Arthronat MA-CT-10-002) case report forms were
225 provided for only 20% of participants. The text does not provide a reason for this omission, but
226 it reflects the vagueness of the relevant section of the E3 guidance (16.3.2) which does not
227 define "Other CRF's submitted." Also, we could only access the original trial protocol in 40
228 (51%) of 78 CSRs obtained. This is important because trial protocols, written prior to patient
229 enrollment in a trial, are an important way to guard against reporting biases.^{25,26}

230 We could obtain individual patient listings in only a minority of cases despite confirming their
231 inclusion in the majority of CSRs (Table 2). This may be a significant limitation, as the E3
232 specifies that "the report with its appendices should also provide enough individual patient data,
233 including the demographic and baseline data, and details of analytical methods, to allow
234 replication of the critical analyses..."¹⁹ Unavailability was possibly due to the fact that EMA
235 allows manufacturers to submit CSRs omitting a number of appendices including individual
236 patient data and case report forms (which EMA states should be available within 48 hours if
237 requested).²⁷ In the case of oseltamivir, the subject of a Cochrane review we conducted,¹² the
238 manufacturer refused to share with us report appendices not submitted to EMA,²⁸ and EMA
239 declined requesting them on our behalf.⁸ Although FDA likely possesses more complete CSRs
240 and patient level data, it historically has treated such data as trade secret and/or confidential.²⁹⁻
241 ³¹ EMA is therefore at present the only reliable source of obtaining CSRs. As such, despite
242 European regulators' progressive stance—announcing that "clinical trial data should not be
243 considered commercial confidential information"³²—the completeness gap is unlikely to be filled
244 any time soon.

245 **Individual participant listings**

246 Individual participant listings—which identify participants by a unique ID—were accessible in 29
247 of the 78 CSRs we reviewed. But these data are difficult to analyze because they are presented
248 as database printouts rather than in electronic form. This is understandable considering that
249 CSRs are a written/archival format, but because EMA does not accept SAS datasets,^{33,34} the
250 industry standard, third-party access to databases of patient-level data remains elusive. We
251 see no compelling reason why all regulators should not request these from sponsors and make

252 them publicly available. Whether availability of individual listings and CRFs, with its attendant
253 laborious analysis, would increase our understanding of the trial and its results is unclear. But
254 there is at least one case where the re-analysis of CRFs added invaluable knowledge to that
255 already available in CSRs.³⁵

256 Despite the apparent size of our non-random sample, we are not sure our conclusions are
257 broadly generalisable to all other CSRs because we have extremely limited knowledge about
258 the total population of CSRs in regulators' and sponsors' possession. Nevertheless, we found
259 that the structure of CSRs was, within different house styles of presentation, strikingly similar
260 across medical products and sponsors, probably thanks to ICH's E3.³⁶ This suggests that the
261 structure and content of other CSRs is likely to be similar.

262 **The public-private debate**

263 One manufacturer has claimed that the non-release of case report forms is motivated by
264 concerns over protecting participant confidentiality.³⁷ Nothing we have seen so far corroborates
265 this claim. The EMA has deemed case report forms and individual patient listings to be, in
266 principle, releasable in their entirety (after a preliminary review).³⁸ Furthermore, individual
267 patient listings are intended to duplicate information contained in filled case report forms. The
268 release of case report forms would ensure the accuracy of individual patient listings with little
269 additional risk to patient confidentiality. Moreover, extra checks such as registration of protocols
270 by bona fide research groups could deter any inappropriate use. We also believe that the sheer
271 bulk of the forms acts as a deterrent against malice.

272 **Size matters**

273 Our range of compression factors show the scale of selection and synthesis which must
274 (consciously or unconsciously) occur in the process of transforming CSRs into journal-length
275 articles. We found a strong resemblance in detail, page length, structure, and purpose between
276 the short Synopsis section of CSRs and reports of trials as published in scientific journals. . In
277 some cases essential items of information such as the trial protocol and its subsequent
278 amendments are simply not included in journal articles or are replaced by methods written post
279 facto. In other cases of items essential for the interpretations of the trial results (such as the
280 statistical analysis plan), tens of pages are reduced to a paragraph on sample size calculation in
281 the journal report, underscoring the lack of detail (and its attendant problems) common to public
282 forms of trial reporting. This is true even in databases not restricted by length, such as
283 ClinicalTrials.gov.³⁹

284 Our study raises the question of why the medical community has accepted the low (summary,
285 aggregate) level of detail found in most peer-reviewed journal publications compared to the
286 depth of detail available in CSRs. European regulators recently noted: “Documents that provide
287 critical information on a study, such as the protocol (16.1.1), statistical methods (16.1.9), list of
288 investigators and study sites and sample case report forms, would always be needed by
289 reviewers assessing a study”⁴⁰ Why have those outside of the regulatory world tolerated journal
290 publications lacking such details?

291 One possibility may be that while the clinical trial enterprise has changed dramatically in the last
292 half century, the scientific journal publication model has not. Since the 1950s, there have been
293 considerable transformations in the political economy of clinical trials driven by the increasingly
294 commercialized and global nature of the pharmaceutical industry, the rise in academic-industry
295 “partnerships” in medicine, and increased communication among regulators. It is now common
296 to find trials with study centers scattered around the globe. This increasing complexity and the
297 need to provide an audit record is reflected in the comprehensive tomes documenting the
298 trials—CSRs—but trial reporting in scientific journals remains limited to summary and aggregate
299 details.

300 **Authorship or Contributorship?**

301 Examination of CSRs revealed scores of important technical contributions to the design,
302 conduct, and reporting of each trial. These included contributions from database programmers,
303 records officers, and CSR writers, often invisible in the published journal article. In some cases,
304 we found no mention in CSRs of individuals who figured as authors of subsequent published
305 trial reports while individuals named as CSR authors went unacknowledged in journal
306 publications. Current ICMJE guidelines on authorship and contributorship are largely focused on
307 ensuring those placed on by-lines deserve to be authors. But the guidelines also suggest that
308 “all contributors who do not meet the criteria for authorship should be listed in an
309 acknowledgments section.”⁴¹ Given the complexity of clinical trials, the ICMJE should call for
310 itemized contributorship: the names of all contributors to be specified along with their role in the
311 design, conduct, analysis, or reporting of the trial. If the contribution of most people goes
312 unrecorded, so does their individual responsibility for what is produced. Itemized contributorship
313 records, to all phases of a trial, could be piloted in trial registers.

314 **E3 guidance**

315 The E3 guideline set an excellent standard, but it needs formal updating and further
316 development. For example, there should be a self-standing set of definitions for terms such as
317 “case report forms” and “Other CRF’s submitted,” (section 16.3.2) and a description of how a

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318 particular trial fits within a sponsor's trial programme of pharmaceutical development.
319 Apparently forgotten items such as certificates of analysis (describing the appearance and
320 content of the interventions being tested) and post-1995 details such as trial registration
321 numbers should be mentioned.

322 We hope our review has given CSRs what they have lacked so far: visibility. CSRs represent a
323 largely untapped source of detailed data that we believe can serve as a means of addressing
324 the ravages of reporting bias in all its forms, leading to a more accurate understanding of the
325 effects of medicines.

327 **Conflicts of interest statement**

328 All authors have completed the Unified Competing Interest form at
329 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
330 declare that:

331 Both authors are co-recipients of a UK National Institute for Health Research grant to carry out a
332 Cochrane review of neuraminidase inhibitors (<http://www.hta.ac.uk/2352>).

333 Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998-1999. He
334 receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore,
335 none of which are on clinical study reports. He is occasionally interviewed by market research
336 companies for anonymous interviews about Phase 1 or 2 products unrelated to products in this
337 review. In 2011-12 he has acted as an expert witness in a litigation case related to one of the
338 compounds in the review (oseltamivir). He is on a legal retainer for expert advice on litigation
339 for influenza vaccines in health care workers.

340 Peter Doshi received €1500 from the European Respiratory Society in support of his travel to
341 the society's September 2012 annual congress where he gave an invited talk on oseltamivir.

342 Both authors' spouses and children have no financial relationships that may be relevant to the
343 submitted work.

344 **Data sharing statement**

345 The original extraction forms and audit record are available on request from the corresponding
346 author.

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Figure Legends:

Figure 1. Types of clinical trial data typically held within and transferred between three realms: trial sponsor, regulatory, and public.

Figure 2. Study flow

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For peer review only

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481 **Table 1. Pharmaceutical, trials, producers, dates and sources of CSRs in the**
482 **review.**

Pharmaceutical and number (n) of assessed trial documents	Trial IDs	Manufacturer	Date of CSRs	Provenance in our study
Aripiprazole (Abilify) n=1	CN1368135	Bristol-Myers Squibb	2007	Freedom of Information request to EMA
Arthronat n=1	MA-CT-10-002	Rowtasha	2011	Manufacturer website http://arthronat.com/clinical-study.php
Atorvastatin (Lipitor) n=1	981-080	Pfizer	1999	Freedom of Information request to EMA
Clopidogrel (Plavix) n=5	CURE, CLARITY, COMMIT-CCS2, CAPRIE, PICOLO	Bristol-Myers Squibb	1997-2007	Freedom of Information request to EMA
Epoetin alfa (Epogen) n=1	930107	Amgen	1996	Freedom of Information request to FDA
H5N1 influenza vaccine n=1	H5N1-008, H5N1-011 EXT 008	GSK	2006	Freedom of Information request to EMA
H5N1 influenza vaccines n=2	V87P1, V87P6	Novartis	2008-2009	Freedom of Information request to EMA
Olanzapine (Zyprexa) n=3	F1D-LC-HGAV*, F1D-MC-HGAO*, F1D-MC-HGAJ*	Eli Lilly	1995 [†]	Litigation http://zyprexalitigationdocuments.com/unsealed.php http://www.furiouseasons.com/zyprexadocs.html
Oseltamivir (Tamiflu) n=19	JV15823, JV15824, M76001, NP15757, NV16871, WP16263, WV15670, WV15671, WV15673 WV15697, WV15707, WV15708, WV15730, WV15758, WV15759 WV15871, WV15799, WV15812 WV15872, WV15819 WV15876 WV15978, WV15825, WV16193	Roche	1999-2004	Documents obtained as part of previous Cochrane review ¹²
Paroxetine (Paxil, Aropax, Pexeva, Seroxat, Sereupin) n=9	329, 377, 453, 511, 676, 701, 704, 715, 716	GSK	1998-2002	Litigation (2004 legal settlement mandated release of clinical study reports on manufacturer's website of 9 studies on

				pediatric and adolescent patients) http://www.gsk.com/media/paroxetine.htm
Quetiapine (Seroquel) n=7	015, 041, 049, 125, 126, 127, 135	AstraZeneca	1996-2007	Litigation http://psychrights.org/research/Digest/NLPs/Seroquel/UnsealedSeroquelStudies/
Reboxetine (Edronax, Norebox, Prolift, Solvex, Davedax, Vestra) n=24	8, 9, 13, 14*, 15, 16, 17, 22*, 32, 32a, 34, 35, 37*, 43, 45, 46, 47, 49, 50, 52, 71, 83, 91, 96	Pfizer	1991-2009	Health Technology Assesment website (The German IQWiG obtained CSRs as part of its health technology assessment work) https://www.iqwig.de/information-on-studies-of-reboxetine.980.en.html
Rofecoxib (Vioxx) n=1	78	Merck	2003	Litigation http://dida.library.ucsf.edu/
Zanamivir (Relenza) n=9	NAI30009, NAI300010, NAIA2005, NAIA3002, NAIA3005, NAIB2005, NAIB2007, NAIB3001, NAIB3002	GSK	1998-1999	Documents obtained as part of previous Cochrane review ¹²

483 * Subsequently excluded because of insufficient documentation

484 † H1D-MC-HGAO clinical study report date unknown

485 EMA = European Medicines Agency

486 FDA = Food and Drug Administration

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488 **Table 2. Key characteristics of the CSRs in the review**

489

Section of CSR (corresponding section of E3)	Presence	Length	
	CSRs including section, n	CSRs with section length available, n	Median length (range), pages
Synopsis (E3 section 2)	78 (100%)	78	5 (1 - 15)
Efficacy evaluation (E3 sec. 11)	76 (97%)	77	13.5 (2 - 132)
Safety evaluation (E3 sec. 12)	77 (99%)	58	17 (2 - 188)
Attached tables not in report text (E3 sec. 14)	63 (81%)	76	337 (1 - 3665)
Protocol (E3 sec 16.1.1)	73 (94%)	41	62 (21 - 139)
Blank Case Report Form (CRF) (E3 sec. 16.1.2)	68 (87%)	33	133 (14 - 981)
Statistical Analysis Plan (E3 sec. 16.1.9)	55 (71%)	37	15 (3 - 85)
Individual participant efficacy listings (E3 sec. 16.2.6)	53 (69%)	19	447 (15 - 21698)
Individual participant safety listings (E3 sec. 16.2.7)	62 (81%)	26	109.5 (2 - 10954)
Completed CRFs (E3 sec. 16.3.2)	16 (21%)	1	765

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492 **Table 3. Conservative and realistic compression factors. A ratio of CSR page**
 493 **length to corresponding journal publication page length.**

494

Pharmaceutical	Studies published in journals, n	Mean compression factor (range)
Conservative compression factors		
Aripiprazole	1	672
Clopidogrel	5	11 (4 - 19)
Epoetin Alfa	1	41
Fluad	2	488 (367 - 609)
GSK H5N1 vaccine	1	19
Oseltamivir	12	195 (1 - 1221)
Quetiapine	2	578 (352 - 803)
Reboxetine	5	88 (9 - 245)
Zanamivir	8	54 (28 - 92)
Realistic compression factors		
Arthronat*	1	379
Clopidogrel	1	8805
Paroxetine	9	1021 (50 - 5473)

495 * The Arthronat trial has not yet been published. Compression factor calculation is based on
 496 the page length of a draft manuscript "to be published soon," according to Arthronat.com.

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4 498 **Appendix 1. Elements specified ICH E3 “Structure and Content of Clinical Study**
5 499 **Reports” (1995)¹⁹**

- 6
7 500 1. TITLE PAGE
8 501 2. SYNOPSIS
9
10 502 3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT
11 503 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
12
13 504 5. Ethics
14 505 5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
15 506 5.2. Ethical conduct of the study
16 507 5.3. Patient information and consent
17
18 508 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE
19 509 7. INTRODUCTION
20
21 510 8. STUDY OBJECTIVES
22
23 511 9. INVESTIGATIONAL PLAN
24 512 9.1. Overall study design and plan – description
25 513 9.2. Discussion of study design, including the choice of control groups
26 514 9.3. Selection of study population
27 515 9.3.1. Inclusion criteria
28 516 9.3.2. Exclusion criteria
29 517 9.3.3. Removal of Patients from Therapy or Assessment
30 518 9.4. Treatments
31 519 9.4.1. Treatments Administered
32 520 9.4.2. Identity of Investigational Product(s)
33 521 9.4.3. Method of Assigning Patients to Treatment Groups
34 522 9.4.4. Selection of Doses in the Study
35 523 9.4.5. Blinding
36 524 9.4.6. Prior and Concomitant Therapy
37 525 9.4.7. Treatment Compliance
38 526 9.5. Efficacy and safety variables
39 527 9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart
40 528 9.5.2. Appropriateness of Measurements
41 529 9.5.3. Primary Efficacy Variable(s)
42 530 9.5.4. Drug Concentration Measurements
43 531 9.6. Data quality assurance
44 532 9.7. Statistical methods planned in the protocol and determination of sample size
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4 533 9.7.1. Statistical and Analytical Plans
5 534 9.7.2. Determination of Sample Size
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7 535 9.8. Changes in the conduct of the study or planned analyses
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9 536 10. STUDY PATIENTS
10 537 10.1. Disposition of patients
11 538 10.2. Protocol deviations
12
13 539 11. EFFICACY EVALUATION
14
15 540 11.1. Data sets analyzed
16 541 11.2. Demographic and other baseline characteristics
17 542 11.3. Measurements of treatment compliance
18
19 543 11.4. Efficacy results and tabulations of individual patient data
20
21 544 11.4.1. Analysis of efficacy
22 545 11.4.2. Statistical/analytical issues
23
24 546 11.4.2.1. Adjustments for covariates
25 547 11.4.2.2. Handling of Dropouts or Missing Data
26
27 548 11.4.2.3. Interim Analyses and Data Monitoring
28
29 549 11.4.2.4. Multicentre Studies
30 550 11.4.2.5. Multiple Comparison/Multiplicity
31 551 11.4.2.6. Use of an "Efficacy Subset" of Patients
32
33 552 11.4.2.7. Active-Control Studies Intended to Show Equivalence
34
35 553 11.4.2.8. Examination of Subgroups
36 554 11.4.3. Tabulation of Individual Response Data
37
38 555 11.4.4. Drug Dose, Drug Concentration, and Relationships to Response
39 556 11.4.5. Drug-Drug and Drug-Disease Interactions
40
41 557 11.4.6. Drug Dose, Drug Concentration, and Relationships to Response
42 558 11.4.7. By-Patient Displays
43
44 559 12. SAFETY EVALUATION
45 560 12.1. Extent of exposure
46
47 561 12.2. Adverse events (AES)
48 562 12.2.1. Brief Summary of Adverse Events
49
50 563 12.2.2. Display of Adverse Events
51 564 12.2.3. Analysis of Adverse Events
52
53 565 12.2.4. Listing of Adverse Events by Patient
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55 566 12.3. Deaths, other Serious Adverse Events and Other Significant Adverse Events
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4 567 12.3.1. Listing of Deaths, other Serious Adverse Events and Other Significant Adverse
5 568 Events
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7 569 12.3.1.1. Deaths
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9 570 12.3.1.2. Other Serious Adverse Events
10 571 12.3.1.3. Other Significant Adverse Events
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12 572 12.3.2. Narratives of Deaths, Other Serious Adverse Events and Certain Other
13 573 Significant Adverse Events
14 574 12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other
15 575 Significant Adverse Events
16
17 576 12.4. Clinical laboratory evaluation
18
19 577 12.4.1. Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each
20 578 Abnormal Laboratory Value (14.3.4)
21
22 579 12.4.2. Evaluation of Each Laboratory Parameter
23
24 580 12.4.2.1. Laboratory Values Over Time
25 581 12.4.2.2. Individual Patient Changes
26
27 582 12.4.2.3. Individual Clinically Significant Abnormalities
28
29 583 12.5. Vital signs, physical findings and other observations related to safety
30 584 12.6. Safety conclusions
31
32 585 13. DISCUSSION AND OVERALL CONCLUSIONS
33 586 14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT
34
35 587 14.1. Demographic data
36 588 14.2. Efficacy data
37
38 589 14.3. Safety data
39 590 14.3.1. Displays of Adverse Events
40
41 591 14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events
42 592 14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse
43 593 Events
44
45 594 14.3.4. Abnormal Laboratory Value Listing (Each Patient)
46
47 595 15. REFERENCE LIST
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49 596 16. APPENDICES
50 597 16.1. Study Information
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52 598 16.1.1. Protocol and protocol amendments
53 599 16.1.2. Sample case report form (unique pages only)
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4 600 16.1.3. List of IECs or IRBs (plus the name of the committee Chair if required by the
5 601 regulatory authority) - Representative written information for patient and sample
6 602 consent forms
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8 603 16.1.4. List and description of investigators and other important participants in the study,
9 604 including brief (1 page) CVs or equivalent summaries of training and experience
10 605 relevant to the performance of the clinical study
11
12 606 16.1.5. Signatures of principal or coordinating investigator(s) or sponsor's responsible
13 607 medical officer, depending on the regulatory authority's requirement
14
15 608 16.1.6. Listing of patients receiving test drug(s)/investigational product(s) from specific
16 609 batches, where more than one batch was used
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18 610 16.1.7. Randomisation scheme and codes (patient identification and treatment assigned)
19 611 16.1.8. Audit certificates (if available)
20
21 612 16.1.9. Documentation of statistical methods
22
23 613 16.1.10. Documentation of inter-laboratory standardisation methods and quality
24 614 assurance procedures if used
25
26 615 16.1.11. Publications based on the study
27
28 616 16.1.12. Important publications referenced in the report
29
30 617 16.2. Patient Data Listings
31
32 618 16.2.1. Discontinued patients
33 619 16.2.2. Protocol deviations
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35 620 16.2.3. Patients excluded from the efficacy analysis
36 621 16.2.4. Demographic data
37
38 622 16.2.5. Compliance and/or drug concentration data (if available)
39 623 16.2.6. Individual efficacy response data
40
41 624 16.2.7. Adverse event listings (each patient)
42 625 16.2.8. Listing of individual laboratory measurements by patient, when required by
43 626 regulatory authorities
44
45 627 16.3. Case Report Forms
46
47 628 16.3.1. CRFs for deaths, other serious adverse events and withdrawals for AE
48 629 16.3.2. Other CRFs submitted
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50 630 16.4. Individual Patient Data Listings (US Archival Listings)
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Basic Extraction Information

Questions	Answer	Notes
1. Drug common name:		
2. Trial ID:		
→ Now, fill in the drug and trial ID in the bottom-right corner the page.	E.g. "Tamiflu, WV15670"	
→ Now, save this file under a new filename	Use the naming convention "Drugname Trial ID - Extractor's initials - YYYYMMDD.docx", e.g. "Seroquel 015 - TJ - 20120311.docx"	
3. Report/CSR ID (if different from Trial ID):		
4. Extractor's name (Initials)		
5. Date of extraction		

Notes to extractor:

- Page numbers should be referred to by the format p.(page # as printed)/PDFp.(PDF page number, possibly indicating volume), e.g.
 - p.V-235/PDFp.945 = page "V-235", on PDF page 945
 - p.234/PDF(3)p.18 = page "234", on the 3rd PDF for this CSR, PDF page 18
- Most questions can be answered with a Y or N (indicating Yes or No) or a number (e.g. the number of PDF pages).
- Where specified as "Free form answer", the extractor may answer in his/her own words based on the extractor's reading of the CSR.

Item	Content	Notes
Overview questions		
6. Does the CSR list a ISRCTN/NCT or equivalent registration number for this trial?		
7. List CSR number of authors		
8. List CSR authors & trialists (Copy names if available; "redacted" if redacted; "not listed" if not listed)		
9. Total length of CSR obtained, in PDF pages		
10. List CSR completion date		
11. Is the trial published?		
12. If Y give publication citation		
13. If Y give publication size (in pages)		
14. Who appears to be responsible for CSR? (Free form answer)		
Trial programme questions		
15. How many trials appear to be in the trial programme?		
16. Does CSR indicate where this trial fits in the trial programme? (Free form answer)		
17. Does CSR say how much of the trial programme is published?		
18. How many trials are in possession of a ISRCTN/NCT or equivalent registration number?		
Basic elements of the Clinical Study Report		

19.	Does the CSR contain a table of contents ?		
20.	If Y, is the table of contents listed as an Appendix?		
21.	If Y, is the table of contents accessible to us?		
22.	If Y, how long is the table of contents (in pages)?		
23.	Does the table of contents list a title page ?		
24.	If Y, is the title page listed as an Appendix?		
25.	If Y, is the title page accessible to us?		
26.	If Y, how long is the title page (in pages)?		
27.	Does the table of contents list a synopsis ?		
28.	If Y, is the synopsis listed as an Appendix?		
29.	If Y, is the synopsis accessible to us?		
30.	If Y, how long is the synopsis (in pages)?		
31.	Does the CSR contain a list of abbreviations and definitions ?		
32.	If Y, is the list of abbreviations and definitions listed as an Appendix?		
33.	If Y, is the list of abbreviations and definitions accessible to us?		
34.	If Y, how long is the list of abbreviations and definitions (in pages)?		
35.	Does the CSR contain an ethics section ?		
36.	If Y, is the ethics section listed as an Appendix?		
37.	If Y, is the ethics section accessible to us?		
38.	If Y, how long is the ethics section (in pages)?		
39.	Does the CSR contain a investigators and study administrative structure ?		
40.	If Y, is the investigators and study administrative structure listed as an Appendix?		
41.	If Y, is the investigators and study administrative structure accessible to us?		
42.	If Y, how long is the investigators and study administrative structure (in pages)?		
43.	Does the CSR contain an introduction ?		
44.	If Y, is the introduction listed as an Appendix?		
45.	If Y, is the introduction accessible to us?		
46.	If Y, how long is the introduction (in pages)?		
47.	Does the CSR contain a section on study objectives?		
48.	If Y, is the section on study objectives listed as an Appendix?		
49.	If Y, is the section on study objectives accessible to us?		
50.	If Y, how long is the section on study objectives (in pages)?		
51.	Does the CSR contain an investigational plan (from IHR 1995 E3, PDF p.13)?		
52.	If Y, is the investigational plan listed as an Appendix?		
53.	If Y, is the investigational plan accessible to us?		
54.	If Y, how long is the investigational plan (in pages)?		
55.	Does the CSR contain a section on study patients ?		
56.	If Y, is the study patients listed as an Appendix?		
57.	If Y, is the study patients accessible to us?		
58.	If Y, how long is the study patients (in pages)?		

59.	If Y, does it include a list of protocol deviations?		
60.	Does the CSR contain a section on efficacy evaluation ?		
61.	If Y, is the efficacy evaluation listed as an Appendix?		
62.	If Y, is the efficacy evaluation accessible to us?		
63.	If Y, how long is the efficacy evaluation (in pages)?		
64.	Does the CSR contain a section on safety evaluation ?		
65.	If Y, is the safety evaluation listed as an Appendix?		
66.	If Y, is the safety evaluation accessible to us?		
67.	If Y, how long is the safety evaluation (in pages)?		
68.	Does the CSR contain a discussion and overall conclusions section?		
69.	If Y, is the discussion and overall conclusions listed as an Appendix?		
70.	If Y, is the discussion and overall conclusions accessible to us?		
71.	If Y, how long is the discussion and overall conclusions (in pages)?		
72.	Does the CSR contain a section on tables, figures and graphs referred to but not included in the text ?		
73.	If Y, is the tables, figures and graphs referred to but not included in the text listed as an Appendix?		
74.	If Y, is the tables, figures and graphs referred to but not included in the text accessible to us?		
75.	If Y, how long is the tables, figures and graphs referred to but not included in the text (in pages)?		
76.	Does the CSR contain a references section?		
77.	If Y, is the references listed as an Appendix?		
78.	If Y, is the references accessible to us?		
79.	If Y, how long is the references (in pages)?		
Appendices related questions			
80.	Does the table of contents indicate that the CSR contains appendices ?		
81.	If Y, does the table of contents list the titles of the appendices ?		
82.	Does the CSR include the study Protocol ?		
83.	If Y, is the study Protocol accessible to us?		
84.	If Y, how long is the study Protocol (in pages)?		
85.	Does the CSR contain a section on Protocol amendments ?		
86.	If Y, is the section on Protocol amendments accessible to us?		
87.	If Y, how long is the section on Protocol amendments (in pages)?		
88.	Does the CSR contain a section on Sample case report form (unique pages only) ?		
89.	If Y, is the section on Sample case report form (unique pages only) accessible to us?		
90.	If Y, how long is the section on Sample case report form (unique pages only) (in pages)?		
91.	Does the CSR contain a section on List of IECs or IRBs (plus the name of the committee Chair if required by the		

	regulatory authority) - Representative written information for patient and sample consent forms?		
92.	If Y, is the section on List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms accessible to us?		
93.	If Y, how long is the section on List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms (in pages)?		
94.	Does the CSR contain a section on List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study?		
95.	If Y, is the section on List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study accessible to us?		
96.	If Y, how long is the section on List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study (in pages)?		
97.	Does the CSR contain a section on Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement?		
98.	If Y, is the section on Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement accessible to us?		
99.	If Y, how long is the section on Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement (in pages)?		
100.	Does the CSR contain a section on Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used?		
101.	If Y, is the section on Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used accessible to us?		
102.	If Y, how long is the section on Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used (in pages)?		
103.	Does the CSR contain a section on Randomisation scheme and codes (patient identification and treatment assigned)?		
104.	If Y, is the section on Randomisation scheme and codes		

	(patient identification and treatment assigned) accessible to us?		
105.	If Y, how long is the section on Randomisation scheme and codes (patient identification and treatment assigned) (in pages)?		
106.	Does the CSR contain a section on Audit certificates (if available) (see Annex IVa and IVb of the guideline)?		
107.	If Y, is the section on Audit certificates (if available) (see Annex IVa and IVb of the guideline) accessible to us?		
108.	If Y, how long is the section on Audit certificates (if available) (see Annex IVa and IVb of the guideline) (in pages)?		
109.	Does the CSR contain a section on Documentation of statistical methods ?		
110.	If Y, is the section on Documentation of statistical methods accessible to us?		
111.	If Y, how long is the section on Documentation of statistical methods (in pages)?		
112.	If Y, is the Documentation of statistical methods dated?		
113.	If Y, what is the date of the Documentation of statistical methods ?		
114.	Does the CSR contain a section on Documentation of inter-laboratory standardisation methods and quality assurance procedures if used ?		
115.	If Y, is the section on Documentation of inter-laboratory standardisation methods and quality assurance procedures if used accessible to us?		
116.	If Y, how long is the section on Documentation of inter-laboratory standardisation methods and quality assurance procedures if used (in pages)?		
117.	Does the CSR contain a section on Publications based on the study ?		
118.	If Y, is the section on Publications based on the study accessible to us?		
119.	If Y, how long is the section on Publications based on the study (in pages)?		
120.	Does the CSR contain a section on Important publications referenced in the report ?		
121.	If Y, is the section on Important publications referenced in the report accessible to us?		
122.	If Y, how long is the section on Important publications referenced in the report (in pages)? Edfgyh+		
123.	Does the CSR contain a section on Discontinued patients ?		
124.	If Y, is the section on Discontinued patients accessible to us?		
125.	If Y, how long is the section on Discontinued patients (in pages)?		
126.	Does the CSR contain a section on Protocol deviations ?		
127.	If Y, is the section on Protocol deviations accessible to us?		
128.	If Y, how long is the section on Protocol deviations (in		

1	pages)?		
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4	129. Does the CSR contain a section on Patients excluded from the efficacy analysis ?		
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6	130. If Y, is the section on Patients excluded from the efficacy analysis accessible to us?		
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8	131. If Y, how long is the section on Patients excluded from the efficacy analysis (in pages)?		
9			
10	132. Does the CSR contain a section on Demographic data ?		
11			
12	133. If Y, is the section on Demographic data accessible to us?		
13			
14	134. If Y, how long is the section on Demographic data (in pages)?		
15			
16	135. Does the CSR contain a section on Compliance and/or drug concentration data (if available) ?		
17			
18	136. If Y, is the section on Compliance and/or drug concentration data (if available) accessible to us?		
19			
20	137. If Y, how long is the section on Compliance and/or drug concentration data (if available) (in pages)?		
21			
22	138. Does the CSR contain a section on Individual efficacy response data ?		
23			
24	139. If Y, is the section on Individual efficacy response data accessible to us?		
25			
26	140. If Y, how long is the section on Individual efficacy response data (in pages)?		
27			
28	141. Does the CSR contain a section on Adverse event listings (each patient) ?		
29			
30	142. If Y, is the section on Adverse event listings (each patient) accessible to us?		
31			
32	143. If Y, how long is the section on Adverse event listings (each patient) (in pages)?		
33			
34	144. Does the CSR contain a section on Listing of individual laboratory measurements by patient, when required by regulatory authorities ?		
35			
36	145. If Y, is the section on Listing of individual laboratory measurements by patient, when required by regulatory authorities accessible to us?		
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38	146. If Y, how long is the section on Listing of individual laboratory measurements by patient, when required by regulatory authorities (in pages)?		
39			
40	147. Does the CSR contain a section on Case Report Forms for deaths, other serious adverse events and withdrawals for AE ?		
41			
42	148. If Y, is the section on Case Report Forms for deaths, other serious adverse events and withdrawals for AE accessible to us?		
43			
44	149. If Y, how long is the section on Case Report Forms for deaths, other serious adverse events and withdrawals for AE (in pages)?		
45			
46	150. Does the CSR contain a section on Other Case Report Forms submitted?		
47			
48	151. If Y, is the section on Other Case Report Forms submitted accessible to us?		
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50	152. If Y, how long is the section on Other Case Report Forms		
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<p>submitted (in pages)?</p>		
<p>153. Does the CSR contain a section on Individual patient data listings?</p>		
<p>154. If Y, is the section on Individual patient data listings accessible to us?</p>		
<p>155. If Y, how long is the section on Individual patient data listings (in pages)?</p>		

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3 **Millner, Marcus**

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5 General comments

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8 Is this new? “Yes but, no but, yes but...” (Vicky Pollard in most likely every show of Little Britain).

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11 Everybody who ever saw a clinical study report (CRS) – several meters of printed paper or many mega-
12 bites of data, usually too large to be sent via regular email – just knows what this review shows. And
13 regulators frequently work with clinicians and academics, provided they have no conflicts of interest.
14 Likewise, everybody who works with an ethics committee reviews industry sponsored study protocols
15 covering up to hundreds of pages. And it seems that nobody ever was greatly surprised that these pages
16 are then compressed to a half-page maximum (which the majority doesn’t even want to read). To a
17 certain extent this was hidden in plain sight. This paper makes a blind spot visible – well done!
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21 I particularly like the discussion and my feeling is that very important points are not reflected in the
22 “what this study adds” section. In particular I am referring to the point on authors and contributors (and
23 their ghosts) but also to a necessary overhaul of E3 – maybe this is an opportunity where the academic
24 community can realign with regulators? At the level of ICH the European Commission is very active to
25 reduce the role and influence of industry.
26
27

28
29 Finally I propose to modify the last sentence of the abstract’s conclusion. From a scientifically purist
30 perspective this is certainly correct but you can safely assume that there is always much, much, much
31 more information submitted to a regulatory authority than to a journal for publishing (take also my
32 example above concerning protocol submitted to ethics committees – this is just the front end of the
33 same stick). If so, this should be addressed in slightly more detail in the discussion.
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37
38 In case the BMJ will publish that paper, which I would greatly support, I assume that some of the
39 contents will go on the BMJ’s website, such as the appendix, table 1 and figure 1? Actually I think figure
40 one could be generally improved or even omitted – it is very well described in the text.
41
42

43
44 In case the BMJ will not publish this paper I dare to recommend editorialising these findings in some
45 form. I really think that this paper touches a few related important things which went largely
46 unquestioned for a long time.
47

48 Minor comments (in chronological order)

49
50 Page 4, line 72 (abstract): “78 were adequate”. Later in the text you say that four in fact were not CSRs.
51 In this case isn’t it rather that four were just incorrectly classified? This is also an issue with figure 2
52 (page 23) where instead of 6 only 2 had inadequate data and 4 were no CRS (but maybe I
53 misunderstand).
54
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56
57 Page 5, line 112: I am sure there are more systematic reviews using regulatory data, actually I happen to
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3 be an author of one (<http://www.ncbi.nlm.nih.gov/pubmed/17907590?dopt=Citation>) and there are
4 FDA reviews as well. I believe, however, that there are no systematic reviews using such data on the
5 efficacy and safety of medicinal products. The authors might narrow down their statement to such
6 systematic reviews.
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3 **Ross, Joseph**
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8 In this manuscript, Doshi and Jefferson search public data sources and file Freedom of Information Act
9 requests to obtain clinical study reports (CSRs) which they then descriptively explore in an effort to
10 guide clinicians and systematic reviewers and inform evidence based medicine. While I am strongly
11 supportive of better understanding the use of additional data sources such as CSRs to ensure better
12 systematic reviews and summary analysis of clinical trial research, I do not think this research project
13 achieved its maximum potential impact.
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15

16
17 **Originality and Importance**
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19
20 The investigators descriptively analyze 78 CSRs of 14 pharmaceuticals, providing information on page
21 length and presence of key sections of information. While such a description has not been done
22 previously to my knowledge, it does not provide sufficient insights to advance the field. This past
23 January, Wieseler and colleagues published their findings in BMJ (2012;344:d8141) that demonstrated
24 that CSRs reported higher quality information for clinical trials when compared with publications or
25 results reporting systems. Their study was limited by the inaccessibility of CSRs for many of the
26 comparisons they conducted. I had hoped that this study would advance the field further by making a
27 comparison of this sort for a complete sample of study article-CSR pairs.
28
29

30
31 Instead, the investigators predominantly focus their analysis on descriptive information and imply the
32 significance of missing information for systematic reviewers and summary analysis, without proving the
33 impact of the absence. I strongly agree that the information missing is likely to be consequential, but as
34 a research project, the purpose is to generate evidence that proves or disproves the hypothesis.
35
36

37
38 Moreover, some of the investigators conclusions are focused on what is missing from CSRs. But it is
39 unclear what the implication of missing that information is for the field.
40
41

42 **Scientific Reliability**
43

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45 The investigators explain that they did an exploratory review with a long-term intention of improving
46 the credibility of research synthesis. I think the research question could be more clearly defined. It is not
47 clear what the purpose of exploring the structure and content of CSRs, how new insights would be
48 gained from this research, and so forth.
49

50
51 I am also not clear how this research is “exploratory”. That term is usually reserved for qualitative
52 research that seeks to generate hypotheses, rather than test hypotheses. Although the investigators do
53 not state an explicit hypothesis, neither are they using qualitative methods to develop one.
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57 **Overall Design of Study**
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5 I am concerned about the sample of trials used for analysis. By using a non-random sample, the findings
6 are not generalizable. Moreover, more than a third were obtained from the investigators Tamiflu work,
7 which they have already discussed in great detail in previous articles (PLoS Med 9(4): e1001201).
8
9

10 A stronger study would include a larger number of CSRs, ideally all from more recent time periods after
11 ICH E3 approval (why include the 4 written prior?). 78 CSRs is a very small number. Moreover, given the
12 number of products for which documents have been produced as part of litigation, it is likely that more
13 CSRs are available in the UCSF DIDA web-base or in other places.
14

15 16 17 Methods

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19 More methodological information would be useful. For instance, in the 5 steps for obtaining CSRs, I had
20 a number of questions. How were CSRs identified for downloading on the internet? How were additional
21 investigators identified for correspondence about CSRs obtained via Freedom of Information Act
22 requests? What CSRs were manufacturers approached about?
23
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26 I am not sure that I agree with the investigators contention that there is no known sampling frame to
27 obtain CSRs. I would expect that a CSR would have been generated for every trial conducted as part of
28 an application to a pharmaceutical regulator like the FDA or EMA. From regulator documents, all phase
29 III trials could be identified and CSRs could have been requested.
30
31

32 Why did the investigators not simply abstract the information requested by ICH E3? Or maybe they did,
33 but the text suggests to me that they developed their own abstraction form.
34
35

36 The compression factor objective was not established in the Introduction and the Methods are unclear,
37 particularly the generation of "conservative" versus "realistic" compression factors. How many were
38 inaccessible?
39
40

41 42 Results

43
44 The results are predominantly focused on page length and presence of content; a deeper analysis is
45 necessary to provide new insight for the field. The new knowledge that is generated by the study is not
46 convincing that key information is being lost when reporting clinical trial results in a CSR format as
47 opposed to a journal article.
48
49

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51 Given the narrow focus of the results, perhaps this article would be better structured as a research
52 letter.
53
54

55 Interpretation and Conclusions

56
57 I thought the interpretation and conclusions, of the manuscript text and the abstract, went well beyond
58
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3 the data presented. The investigators engaged in a substantial amount of editorializing, which detracts
4 from the objectivity of their research. I would suggest a full re-write of these sections that were focused
5 on summarizing their findings and clarifying the implications for the field.
6
7

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9 For instance, the 2nd paragraph of the results states “[CSRs] far surpass the level of detail available in
10 journal publications ...” Any reader would assume this to be true based on a general understanding of
11 the field, so this statement could be appropriately made in a commentary. However, the purpose of this
12 article was to examine this question – and no measurable comparison to journal article content was
13 made (to assess the level of detail), just journal article length. So this statement, in the context of this
14 article, is unproven.
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17 Abstract

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20 The abstract should only make reference to the 78 CSRs that were the sample for the analysis.
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Scherer, Roberta

Review for Doshi and Jefferson “Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports”

The authors of this report were able to obtain 84 Clinical Study Reports (CSR) from a variety of sources, and have reviewed the contents of 78, assessing whether specific sections as recommended by International Committee on Harmonisation were included in the report and noting the length of the various sections when included in the report.

Given that the decision by the European Medicines Agency to allow public access to these reports was made late in 2010, there is little current work in the literature on describing the contents. Other than sporadic articles on individual reports obtained through litigation, I am aware of only one report in the literature (Weiseler et al BMJ 2012 which the authors cite). It is likely that a great deal of effort was required to obtain the number of reports presented in this paper. This work is original and so adds to the current state of understanding in this field.

The authors argue that access to CSR will allow systematic reviewers to obtain trial information in more detail than can presently be obtained through journal articles. They state that little is known about the structure and content and aimed to describe what was included in a report. In this sense this information is of general use and of special interest to those persons performing and using systematic reviews of drug interventions. By its nature, however, this study cannot address the inadequacies of reporting other types of trials nor will it likely be of specific interest to practitioners.

It would be helpful if the author explicitly describe their definition of “adequate” for purposes of inclusion of a CSR in this report. They do say “too fragmentary” but that is somewhat vague. Using a detailed extraction form, the authors scored the presence of each of the sections recommended by the ICH, either by direct observation or by noting the table of contents, and then recorded the page length of each section. The study is straightforward and the authors have appropriately audited each others’ extraction as a check for bias. I found that the authors make a fairly large assumption, however, in that they equate the length of a section (in number of pages) with the amount of detail that is provided by the report. While this assumption may be true, there is no data to support it. For example, although the number of pages in a typical journal trial report may be equivalent from article to article, the trial elements reported may vary widely. While page length might well be a reasonable surrogate for “amount of detail” I would have liked to have seen at least one or two direct comparisons to support this claim. Possibly, the information from Weiseler would support this assumption, but the authors do not describe it.

Because of this, I did not find the “compression factor” (a measure of the ratio of number of pages in a journal report to that in the CSR) to be a particularly useful measure and I wasn’t sure how to interpret

1
2
3 it, especially the “conservative” vs the “realistic” factors. Further, the authors are over-interpreting the
4 data when they say “The median length of 644 pages for reports in this study confirms that CSRs are the
5 most detailed and complete, integrated form of reporting of the design, conduct and results of clinical
6 trials” [line 218-220] when all they have shown is the number of pages in the report. This conclusion is
7 based completely on the equation that page length is proportional to amount of detail and the authors
8 provide no evidence in the paper or in the cited literature to support this assumption.
9
10

11
12 The authors also note the presence of individual case report forms available in one of the CSRs.
13 Although the authors perceive the presence of individual patient data to be a good thing, it would be
14 important to consider safeguards in place to protect patient confidentiality. For example, is there any
15 assurance that the data have been correctly de-identified beyond simply changing the study ID.
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19 In the discussion, lines 302-304, the authors should note that the presence of open access journals
20 increase the possibility of more detailed reporting in journal articles so that trial reports may no longer
21 be “limited to summary and aggregate details”
22
23

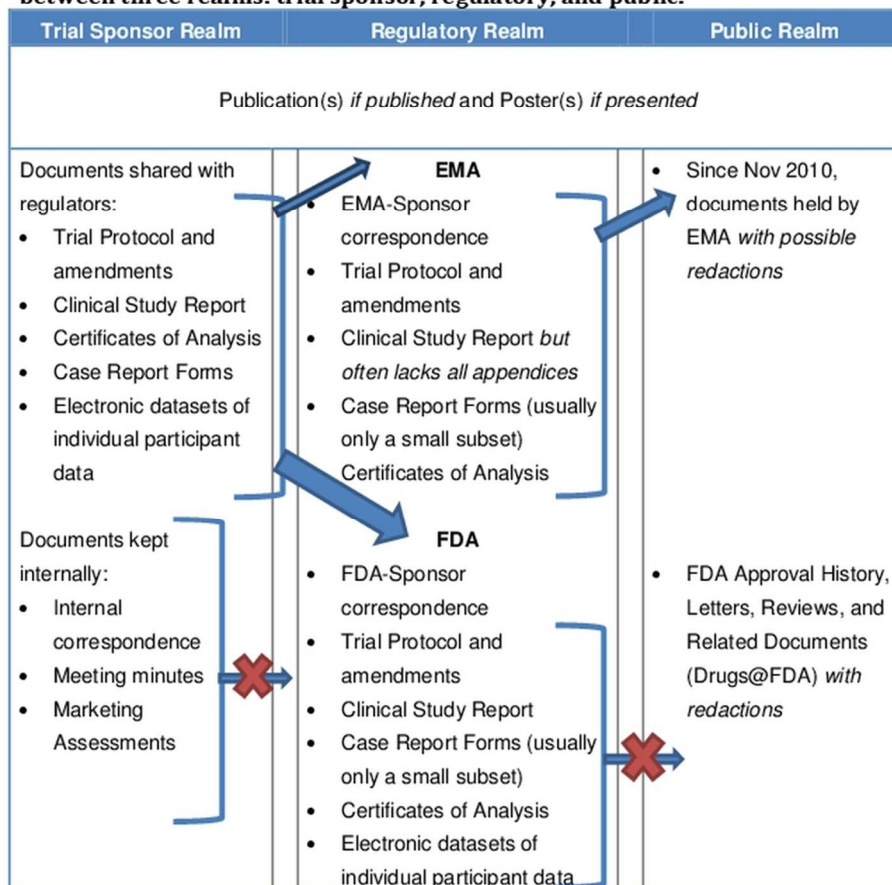
24 Some minor issues:

25 Line 119: Not quite a mixed metaphor says that “lack of visibility may also conceal”

26 Line 191: sentence is unclear (are there words missing?). Also in that paragraph, there are some “of”s”
27 that should not be present (e.g. line 194)
28

29 Line 281 – too many periods
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Figure 1. Types of clinical trial data typically held within and transferred between three realms: trial sponsor, regulatory, and public.



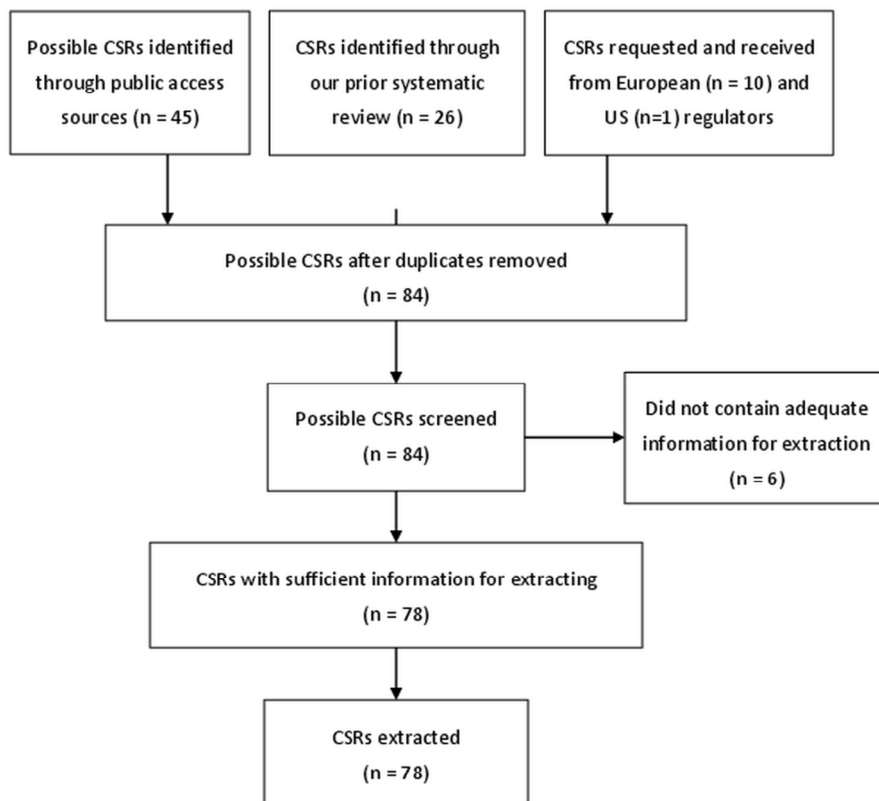
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Figure 2. Study flow



92x90mm (300 x 300 DPI)

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Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002496.R1
Article Type:	Research
Date Submitted by the Author:	23-Jan-2013
Complete List of Authors:	Doshi, Peter; Johns Hopkins University, Jefferson, Tom; Cochrane Vaccines Field
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Medical publishing and peer review, Ethics, Research methods, Pharmacology and therapeutics
Keywords:	MEDICAL ETHICS, MEDICAL JOURNALISM, INTERNAL MEDICINE

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Manuscripts

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Clinical Study Reports of randomized controlled trials manuscript

Peter Doshi and Tom Jefferson
January 23, 2013, Page 1 of 28

Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports

Authors:

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Word count: 3464

Tables: 3
Figures: 2
Appendices: 2
References: 42

For peer review only

1 Clinical Study Reports of randomized controlled trials
2 manuscript

Peter Doshi and Tom Jefferson
January 23, 2013, Page 2 of 28

3
4 22 **Patient consent statement** No consent was necessary as no patients were involved

5
6 23 **Ethics approval statement** No ethical approval was necessary as no patients were involved
7 and all data were aggregate or anonymized and publicly available.
8

9
10 25 **Role of the sponsor statement** As the review had no extramural funding, there was no
11 sponsor.
12

13
14 27 **Author Contributions:** Doshi had full access to all of the data in the study and takes
15 responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept*
16 *and design:* Doshi and Jefferson. *Acquisition of data:* Doshi and Jefferson. *Analysis and*
17 *interpretation of data:* Doshi and Jefferson. *Critical revision of the manuscript for important*
18 *intellectual content:* Doshi and Jefferson. *Statistical analysis:* Doshi.
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32 Research questions or hypotheses addressed

33 What are Clinical Study Reports (CSRs)? What do they contain and how long are they?

34 Might CSRs help address reporting biases associated with the published literature, and improve
35 the quality of evidence synthesis?

36 Key Messages (up to 3)

37 CSRs represent a hitherto hidden and untapped source of detailed RCT data (mean page
38 length: 1,854 pages), increasingly becoming publicly available, and should form the basic unit
39 for evidence synthesis to minimize the problem of reporting bias.

40 CSRs show that numerous individuals make important technical contributions to the design,
41 conduct, and reporting of each trial, but journal publications often fail to record these details,
42 resulting in a loss in individual responsibility for what is reported.

43 The E3 guideline to which most CSRs conform was published in 1995, and needs updating.

44 Strengths and Limitations

45 We cannot say whether our sample is representative and whether our conclusions are
46 generalizable to an undefined and undefineable population of CSRs.

47

Abstract

Objective: To explore the structure and content of a non-random sample of clinical study reports (CSRs) to guide clinicians and systematic reviewers.

Search strategy: We searched public sources and lodged Freedom of Information requests for previously confidential CSRs primarily written by industry for regulators.

Selection criteria: CSR reporting sufficient information for extraction (“adequate”)

Primary outcome measures: Presence and length of essential elements of trial design and reporting and compression factor (ratio of page length for CSR compared to its published counterpart in a scientific journal).

Data extraction: data were extracted on standard forms and cross-checked for accuracy

Results: We assembled a population of 78 CSRs (covering 90 RCTs; 144,610 pages total) dated 1991-2011 of 14 pharmaceuticals. Report synopses had a median length of 5 pages, efficacy evaluation 13.5 pages, safety evaluation 17 pages, attached tables 337 pages, trial protocol 62 pages, statistical analysis plan 15 pages, and individual efficacy and safety listings had a median length of 447 and 109.5 pages, respectively. While 16 (21%) of CSRs contained completed case report forms, these were accessible to us in only one case (765 pages representing 16 individuals). Compression factors ranged between 1 and 8805.

Conclusions: Clinical study reports represent a hitherto mostly hidden and untapped source of detailed and exhaustive data on each trial. They should be consulted by independent parties interested in a detailed record of a clinical trial, and should form the basic unit for evidence synthesis as their use is likely to minimize the problem of reporting bias. We cannot say whether our sample is representative and whether our conclusions are generalizable to an undefined and undefineable population of CSRs.

Word count: 272

Primary Funding Source: The review had no extramural funding.

84 Introduction

85 Systematic reviews are thought to provide one of the most robust ways to evaluate the effects of
86 healthcare interventions. But the robustness of findings clearly rests upon reviewers' access to
87 clinical trial information sufficient to critically evaluate and reproduce the original research.
88 Research on reporting bias over the last decades has shown that trusting the published
89 literature at face value, even peer-reviewed publications, can be fraught with difficulty—a
90 problem that spans drug classes.¹⁻¹²

91 Following the decision by the European regulator, European Medicines Agency (EMA) on 30
92 Nov 2010, to make available a broad spectrum of documents related to medicinal products for
93 human and veterinary use,^{13,14} attention is focusing on one particular type of regulatory
94 document: clinical study reports (CSRs).¹⁵⁻¹⁸ CSRs are usually written for regulators following
95 guidelines developed by the industry-regulatory collaborative effort "International Conference on
96 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use"
97 (ICH). The ICH guidelines "Structure and Content of Clinical Study Reports"¹⁹ (See Appendix 1)
98 are known by the document code "E3". They were formalized in 1995 "to assist sponsors in the
99 development of a report that is complete, free from ambiguity, well organised and easy [for
100 regulators] to review."¹⁹ E3 has not been edited or changed since 1995.

101 CSRs are but one category of information that is transmitted from study sponsors to regulators
102 (Figure 1), but are important as they contain substantially more information and detail on the
103 intervention being tested than published versions of the same trial. The wealth of information
104 may be sought with increasing frequency by researchers appraising single trials, entire trial
105 programmes, or by those synthesizing evidence.^{17,20} We are aware of two recent examples of
106 systematic reviews of the effects of pharmaceuticals carried out using CSRs and other
107 regulatory material.^{12,21} One group also concluded that journal publications insufficiently report
108 clinical trials.²²

109 Despite CSRs' potential importance very little is known about their structure and content outside
110 of those individuals with direct involvement in regulatory processes. This knowledge gap may
111 hinder development of methods for fair and reliable appraisal of CSRs and their use in evidence
112 synthesis. We are not aware of any instruments specifically designed for appraising CSRs. Lack
113 of visibility may also hinder understanding of the complexity of the organization and reporting of
114 clinical trials.

115 We carried out an exploratory review to describe the structure and content of a non-random
116 sample of clinical study reports. By describing the contents of CSRs, this research seeks to

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117 transform CSRs from an obscure document only known to regulators and industry into a more
118 widely known and accessible document. Our long-term intention is to improve the credibility of
119 research synthesis by facilitating a move from the level of detail found in journal articles to the
120 level of detail found in regulatory documents, thus guiding clinicians and other decision makers
121 at all levels.

122 **Methods**

123 We obtained CSRs from public sources, as follows:

- 124 1. Requesting from EMA, under its freedom of information (FOI) policy, CSRs for
125 manufacturer sponsored trials of the 10 best-selling prescription-bound products in the
126 United States in 2010.²³
- 127 2. Reusing CSRs from our own previous research (oseltamivir, zanamivir)¹²
- 128 3. Downloading CSRs openly available on the Internet. Search terms were not predefined,
129 but sites searched included Google (<http://www.google.com>), the Drug Industry
130 Document Archive (<http://dida.library.ucsf.edu/>), and IQWiG's library of reboxetine
131 studies (<https://www.iqwig.de/information-on-studies-of-reboxetine.980.en.html>)
- 132 4. Corresponding with one researcher who obtained CSRs through a FOI request to FDA
133 (epoetin alfa)
- 134 5. Requesting manufacturers fill any gaps in the completeness of reports that we believe
135 are legally required to be publicly available (paroxetine).

136 To create as broad a database as possible, we did not apply restrictions in drug type or family or
137 sponsor. We did not submit requests under the Freedom of Information Act to the Food and
138 Drug Administration because such requests can take years to be fulfilled and—if fulfilled—may
139 be heavily redacted.²⁴

140 We did not draw a random sample of CSRs as there is no known sampling frame. No one
141 knows how many reports have been written by intervention category as there is no central
142 register of CSRs. Through familiarity with CSRs for oseltamivir and zanamivir, which were
143 included in one of our Cochrane reviews,¹² we developed and piloted a data extraction sheet
144 designed to capture the salient characteristics of CSRs. We created a list of around 40 potential
145 sections we expected to find, generated directly from elements specified in E3. For each
146 element in the list, we checked whether the obtained CSR included that section (confirmed
147 either by direct identification of the section or an indication the section existed based on the
148 CSR's table of contents), whether we had access to it, and its page length. Because of
149 previous difficulties we had accessing CSR appendices, we also recorded whether sections

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4 150 were listed as appendices or not. Page length was calculated either by directly counting the
5 151 pages or by estimating their size from the table of contents of each report, and was used as a
6 152 crude proxy for the level of detail available. Page lengths were rounded up to the next integer,
7 153 and were summarized by reporting medians and ranges. We also included questions relating to
8 154 trial registration and authorship. Our (blank) data extraction sheet is in Appendix 2.

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12 155 All variables from CSRs were first extracted in single. We subsequently audited each other's
13 156 extractions, checking the accurateness of the information. We chose to present elements
14 157 analogous with those that typically appear in trials reported in scientific journals including the
15 158 study Synopsis (a brief summary of the study), the study Protocol (written prospectively,
16 159 describing the study methods), Efficacy and Safety Evaluations (a narrative summary of the
17 160 efficacy and safety results of the study, including tables and figures), as well as attached tables.
18 161 We also included elements rarely found in journal publications: sample (blank) and completed
19 162 case report forms (CRFs are paper or electronic forms designed to capture pre-specified
20 163 efficacy and safety related information for each study participant), the statistical analysis plan (a
21 164 prospectively written narrative and/or statistical code indicating how trial data will be analyzed),
22 165 and individual participant efficacy and safety listings. The corresponding E3 section numbers
23 166 are listed in Table 2. Disagreements were resolved by discussion.

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32 167 Our uncorrected (original) and corrected extraction sheets as well as audit records are available
33 168 upon request from the corresponding author.

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36 169 We calculated a compression factor for published trials which we defined as the ratio of CSR
37 170 page length compared to the page length of the same trial as published in scientific journals.
38 171 The objective of this metric was to convey a rough sense of how much information present in
39 172 CSRs may be being condensed ("compressed") in short journal publications, in consideration of
40 173 CSRs' far greater length and level of detail. Size (page length) reflects the level of detail as well
41 174 as the presence of many elements such as protocols and their amendments, randomization
42 175 lists, statistical analysis plans, certificates of analysis and extra data on subpopulations. We
43 176 have demonstrated¹² that these elements are essential for understanding and appraising a trial.
44 177 The compression factor is a crude measure of how much is compressed or simply left out of
45 178 each publication which will affect the reliability of the appraisal and interpretation of trials. Trial
46 179 publications were searched for in multiple sources: clinical trial registers, published systematic
47 180 reviews, and correspondence with sponsors. Because in most cases we could not access all
48 181 parts of all CSRs (and therefore do not know their complete page length), we calculated
49 182 "conservative" compression factors as well as "realistic" compression factors. "Conservative"
50 183 compression factors were calculated on a trial by trial basis using the total number of pages in

184 CSRs available to us divided by the length of journal reports for that same trial, while “realistic”
185 compression factors were based on the true total page length of the CSR.

186 Results

187 We identified 84 documents believed to be CSRs for 14 compounds. These covered
188 therapeutic and biological interventions including antipsychotics, antidepressants, antivirals,
189 natural antiarthritics, anti-inflammatory agents, pandemic influenza vaccines, statins,
190 erythropoietins, and anti-platelet compounds. We included English-language summaries of two
191 Japanese oseltamivir studies (JV15823, JV15824) as they had been presented to EMA in this
192 form. We excluded documents which were sections of CSRs but nonetheless contained
193 insufficient information to understand the overall content of the CSR (olanzapine F1D-LC-
194 HGAV, F1D-MC-HGAJ and F1D-MC-HGAO) and 3 documents which we had originally
195 classified as CSRs but were not (reboxetine 14, 22 and 37). This left 78 CSRs (144,610 pages)
196 (Figure 2). The median pages obtained per CSR was 644 (range 9 to 15,440). Only 4 of 78
197 CSRs (reboxetine 8, 16, 17, and 91) were written prior to November 30 1995 when ICH E3 was
198 approved. Table 1 summarizes the pharmaceutical, manufacturer, date and provenance of the
199 CSRs in our review. EMA reported not holding studies for esomeprazole magnesium (Nexium),
200 Advair diskus, quetiapine fumarate (Seroquel), montelukast sodium (Singulair), epoetin alfa
201 (Epogen), and simvastatin.

202
203 All of the 78 included CSRs contained a synopsis (median page length 5 pages). The efficacy
204 evaluation was identifiable and directly accessible in 76 (97%, median length 13.5 pages) and
205 safety in 77 (99%; median length 17 pages). Attached tables were likewise present in 63 (81%)
206 CSRs, and were a median of 337 pages long (range: 1 to 3665). Seventy-three CSRs (94%)
207 reported including the study protocol. In the 40 we could access, the median page length was
208 62. We found blank CRFs included in 68 (87%) CSRs. Of the 33 we could directly access, the
209 median length was 133 pages (range 14 to 981). For completed CRFs, 16 (21%) reports made
210 direct mention of a section on completed CRFs, but we had access to completed CRFs in only 1
211 case (Arthronat; length 765 pages).

212
213 Fifty-five (71%) of 78 included CSRs included a statistical analysis plan in some form. Of those
214 for which we could directly access the content (n=37), the median page length was 15 (range 3
215 to 85). Individual efficacy and safety listings were included in 53 (69%) and 62 (81%) CSRs
216 respectively. The median page length was 447 (range 15 to 21,698) for efficacy and 109.5
217 (range 2 to 10,954) for safety.

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218 A summary is presented in Table 2.

219 All trial reports in our review were sponsored by industry.

220 Median conservative compression factors ranged between 1 and 1221. The realistic
221 compression factors, calculated for the Arthronat, paroxetine, and clopidogrel CAPRIE trials,
222 were 379, 1021, and 8805, respectively. (Table 3)

223 Discussion

224 We collected and described a sizeable number of CSRs written in the last two decades. All
225 CSRs contained a table of contents (as specified in E3 section 3); this, together with optical
226 character recognition (to enable searching the full text of the scanned documents) and the
227 occasional need to combine multiple files to create a single document, substantially improved
228 the ease of navigating CSRs.

229 Despite the size of our non-random sample, it is unclear whether our conclusions are
230 generalisable to all other CSRs. This is because we have extremely limited knowledge about
231 the total population of CSRs in regulators' and sponsors' possession. Nevertheless, within our
232 sample spanning different manufacturers, therapeutic classes, and times, we found that the
233 structure of CSRs was, within different house styles of presentation, strikingly similar, probably
234 due to the guidance by ICH E3.³⁷ This suggests that the structure and content of other CSRs is
235 likely to be similar.

236 The future basic currency of research synthesis?

237 The median length of 644 pages for reports in this study, as well as CSRs' routine inclusion of
238 trials' protocol, statistical analysis plans, and blank case report forms, strongly suggests that
239 CSRs are the most detailed and complete, integrated form of reporting of the design, conduct,
240 and results of clinical trials. In a study that directly compared the adequacy of reporting
241 between journal articles and CSRs, the authors found that complete information regarding
242 greater than 40% of methods items were only available in CSRs.²² The level of detail found in
243 CSRs thus far surpass the level of detail available in journal publications, and as such they are
244 prime candidates for the next basic currency of evidence synthesis and appraisal of a trial.
245 Given the EMA's new policy making such documents publicly available, access to these
246 documents is now relatively straightforward.²⁵ However including CSRs in systematic reviews is
247 labor-intensive, given their size and complexity.¹²

248 **Accessing complete CSRs**

249 While CSRs may trump other forms of trial reporting in the public domain (such as conference
250 abstracts or journal publications), serious limitations remain. Despite obtaining 144,610 pages
251 for 78 CSRs, in almost all instances, we lacked full access to the CSRs' numerous appendices.
252 Even for the sole complete CSR we obtained (Arthronat MA-CT-10-002), case report forms
253 were provided for only 20% of participants. The Arthronat text does not provide a reason for
254 this omission, but it reflects the vagueness of the relevant section of the E3 guidance (16.3.2)
255 which does not define "Other CRFs submitted." Also, we could only access the original trial
256 protocol in 40 (51%) of 78 CSRs obtained. This is important because trial protocols, written
257 prior to patient enrollment in a trial, are an important way to guard against reporting biases.^{26,27}

258 We could obtain individual patient listings in only a minority of cases despite confirming their
259 inclusion in the majority of CSRs (Table 2). This may be a significant limitation, as the E3
260 specifies that "the report with its appendices should also provide enough individual patient data,
261 including the demographic and baseline data, and details of analytical methods, to allow
262 replication of the critical analyses..."¹⁹ Unavailability was possibly due to the fact that EMA
263 allows manufacturers to submit CSRs omitting a number of appendices including individual
264 patient data and case report forms (which EMA states should be available within 48 hours if
265 requested).²⁸ In the case of oseltamivir, the subject of a Cochrane review we conducted,¹² the
266 manufacturer refused to share with us report appendices not submitted to EMA,²⁹ and EMA
267 declined requesting them on our behalf.⁸ Although FDA likely possesses more complete CSRs
268 and patient level data, it historically has treated such data as trade secret and/or confidential.³⁰⁻
269 ³² EMA is therefore at present the only reliable source of obtaining CSRs. As such, despite
270 European regulators' progressive stance—announcing that "clinical trial data should not be
271 considered commercial confidential information"³³—the completeness gap is unlikely to be filled
272 any time soon.

273 Another significant limitation is that CSRs are only written for therapeutic, prophylactic, or
274 diagnostic agents, and therefore inadequacies remain in evidence synthesis of other types of
275 interventions such as surgical or behavioral interventions.

276 **Individual participant listings**

277 Individual participant listings—which identify participants by a unique ID—were accessible in 29
278 of the 78 CSRs we reviewed. But these data are difficult to analyze because they are presented
279 as database printouts rather than in electronic form. This is understandable considering that
280 CSRs are a written/archival format, but because EMA does not accept SAS datasets,^{34,35} the
281 industry standard, third-party access to databases of patient-level data remains elusive. We

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282 see no compelling reason why all regulators should not request these from sponsors and make
283 them publicly available. Whether availability of individual listings and CRFs, with its attendant
284 laborious analysis, would increase our understanding of the trial and its results is unclear. But
285 there is at least one case where the re-analysis of CRFs added invaluable knowledge to that
286 already available in CSRs.³⁶

287 **The public-private debate**

288 One manufacturer has claimed that the non-release of case report forms is motivated by
289 concerns over protecting participant confidentiality.³⁸ Nothing we have seen so far corroborates
290 this claim, however an ongoing EMA working group is specifically discussing issues related to
291 protecting participant confidentiality. Based on current document releases and position
292 statements, however, it appears that EMA has deemed case report forms and individual patient
293 listings to be, in principle, releasable in their entirety (after a preliminary review).³⁹ Furthermore,
294 individual patient listings are intended to duplicate information contained in filled case report
295 forms. The release of case report forms would ensure the accuracy of individual patient listings
296 with little additional risk to patient confidentiality. Moreover, extra checks such as registration of
297 protocols by bona fide research groups could deter any inappropriate use. We also believe that
298 the sheer bulk of the forms acts as a deterrent against malice.

299 **Size matters**

300 Our range of compression factors show the scale of selection and synthesis which must
301 (consciously or unconsciously) occur in the process of transforming CSRs into journal-length
302 articles. We found a strong resemblance in detail, page length, structure, and purpose between
303 the short Synopsis section of CSRs and reports of trials as published in scientific journals. In
304 some cases essential items of information such as the trial protocol and its subsequent
305 amendments are simply not included in journal articles or are replaced by methods written *post*
306 *facto*. In other cases of items essential for the interpretations of the trial results (such as the
307 statistical analysis plan), tens of pages are reduced to a paragraph on sample size calculation in
308 the journal report, underscoring the lack of detail (and its attendant problems) common to public
309 forms of trial reporting. For example, the ratio of words in Protocol of the CSR for Aripiprazole
310 CN138135 to the Methods section for published journal article of the same trial is 30.5 (53,713
311 words in the CSR Protocol versus 1,763 words in the journal article). For the oseltamivir
312 WP16263 trial, the ratio was 22.7 (26,761 words in the CSR Protocol and amendments versus
313 1,177 words in the journal article).

314 This compression of information also occurs in databases not restricted by length, such as
315 ClinicalTrials.gov.⁴⁰

316 Our study raises the question of why the medical community has accepted the low (summary,
317 aggregate) level of detail found in most peer-reviewed journal publications compared to the
318 depth of detail available in CSRs. European regulators recently noted: “Documents that provide
319 critical information on a study, such as the protocol (16.1.1), statistical methods (16.1.9), list of
320 investigators and study sites and sample case report forms, would always be needed by
321 reviewers assessing a study”⁴¹ Why have those outside of the regulatory world tolerated journal
322 publications lacking such details?

323 One possibility may be that while the clinical trial enterprise has changed dramatically in the last
324 half century, the scientific journal publication model has not. Since the 1950s, there have been
325 considerable transformations in the political economy of clinical trials driven by the increasingly
326 commercialized and global nature of the pharmaceutical industry, the rise in academic-industry
327 “partnerships” in medicine, and increased communication among regulators. It is now common
328 to find trials with study centers scattered around the globe. This increasing complexity and the
329 need to provide an audit record is reflected in the comprehensive tomes documenting the
330 trials—CSRs—but trial reporting in scientific journals remains limited to summary and aggregate
331 details. It should be noted, however, that many journals now have websites which enables
332 them to make available extended content beyond what traditionally appears in the printed
333 journal.

334 **Authorship or Contributorship?**

335 Examination of CSRs revealed scores of important technical contributions to the design,
336 conduct, and reporting of each trial. These included contributions from database programmers,
337 records officers, and CSR writers, often invisible in the published journal article. In some cases,
338 we found no mention in CSRs of individuals who figured as authors of subsequent published
339 trial reports while individuals named as CSR authors went unacknowledged in journal
340 publications. Current ICMJE guidelines on authorship and contributorship are largely focused on
341 ensuring those placed on by-lines deserve to be authors. But the guidelines also suggest that
342 “all contributors who do not meet the criteria for authorship should be listed in an
343 acknowledgments section.”⁴² Given the complexity of clinical trials, the ICMJE should call for
344 itemized contributorship: the names of all contributors to be specified along with their role in the
345 design, conduct, analysis, or reporting of the trial. If the contribution of most people goes
346 unrecorded, so does their individual responsibility for what is produced. Itemized contributorship
347 records, to all phases of a trial, could be piloted in trial registers.

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348 **E3 guidance**

349 The E3 guideline set an excellent standard, but it needs formal updating and further
350 development. For example, there should be a self-standing set of definitions for terms such as
351 “case report forms” and “Other CRF’s submitted,” (section 16.3.2) and a description of how a
352 particular trial fits within a sponsor’s trial programme of pharmaceutical development.
353 Apparently forgotten items such as certificates of analysis (describing the appearance and
354 content of the interventions being tested) and post-1995 details such as trial registration
355 numbers should be mentioned.

356 We hope our review has given CSRs what they have lacked so far: visibility. CSRs represent a
357 largely untapped source of detailed data that we believe can serve as a means of addressing
358 the ravages of reporting bias in all its forms, leading to a more accurate understanding of the
359 effects of medicines.

361 **Conflicts of interest statement**

362 All authors have completed the Unified Competing Interest form at
363 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
364 declare that:

365 Both authors are co-recipients of a UK National Institute for Health Research grant to carry out a
366 Cochrane review of neuraminidase inhibitors (<http://www.hta.ac.uk/2352>).

367 Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998-1999. He
368 receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore,
369 none of which are on clinical study reports. He is occasionally interviewed by market research
370 companies for anonymous interviews about Phase 1 or 2 products unrelated to products in this
371 review. In 2011-12 he has acted as an expert witness in a litigation case related to one of the
372 compounds in the review (oseltamivir). He is on a legal retainer for expert advice on litigation
373 for influenza vaccines in health care workers.

374 Peter Doshi received €1500 from the European Respiratory Society in support of his travel to
375 the society’s September 2012 annual congress where he gave an invited talk on oseltamivir.

376

377 Both authors’ spouses and children have no financial relationships that may be relevant to the
378 submitted work.

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4 379 **Data sharing statement**

5 380 The original extraction forms and audit record are available on request from the corresponding
6
7 381 author.

8
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11
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15 514 from: http://www.icmje.org/ethical_1author.html

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517 **Table 1. Pharmaceutical, trials, producers, dates and sources of CSRs in the**
518 **review.**

Pharmaceutical and number (n) of assessed trial documents	Trial IDs	Manufacturer	Date of CSRs	Provenance in our study
Aripiprazole (Abilify) n=1	CN1368135	Bristol-Myers Squibb	2007	Freedom of Information request to EMA
Arthronat n=1	MA-CT-10-002	Rowtasha	2011	Manufacturer website http://arthronat.com/clinical-study.php
Atorvastatin (Lipitor) n=1	981-080	Pfizer	1999	Freedom of Information request to EMA
Clopidogrel (Plavix) n=5	CURE, CLARITY, COMMIT-CCS2, CAPRIE, PICOLO	Bristol-Myers Squibb	1997-2007	Freedom of Information request to EMA
Epoetin alfa (Epogen) n=1	930107	Amgen	1996	Freedom of Information request to FDA
H5N1 influenza vaccine n=1	H5N1-008, H5N1-011 EXT 008	GSK	2006	Freedom of Information request to EMA
H5N1 influenza vaccines n=2	V87P1, V87P6	Novartis	2008-2009	Freedom of Information request to EMA
Olanzapine (Zyprexa) n=3	F1D-LC-HGAV*, F1D-MC-HGAO*, F1D-MC-HGAJ*	Eli Lilly	1995 [†]	Litigation http://zyprexalitigationdocuments.com/unsealed.php http://www.furiouseasons.com/zyprexadocs.html
Oseltamivir (Tamiflu) n=19	JV15823, JV15824, M76001, NP15757, NV16871, WP16263, WV15670, WV15671, WV15673 WV15697, WV15707, WV15708, WV15730, WV15758, WV15759 WV15871, WV15799, WV15812 WV15872, WV15819 WV15876 WV15978, WV15825, WV16193	Roche	1999-2004	Documents obtained as part of previous Cochrane review ¹²
Paroxetine (Paxil, Aropax, Pexeva, Seroxat, Sereupin) n=9	329, 377, 453, 511, 676, 701, 704, 715, 716	GSK	1998-2002	Litigation (2004 legal settlement mandated release of clinical study reports on manufacturer's website of 9 studies on

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				pediatric and adolescent patients) http://www.gsk.com/media/paroxetine.htm
Quetiapine (Seroquel) n=7	015, 041, 049, 125, 126, 127, 135	AstraZeneca	1996-2007	Litigation http://psychrights.org/research/Digest/NLPs/Seroquel/UnsealedSeroquelStudies/
Reboxetine (Edronax, Norebox, Prolift, Solvex, Davedax, Vestra) n=24	8, 9, 13, 14*, 15, 16, 17, 22*, 32, 32a, 34, 35, 37*, 43, 45, 46, 47, 49, 50, 52, 71, 83, 91, 96	Pfizer	1991-2009	Health Technology Assessment website (The German IQWiG obtained CSRs as part of its health technology assessment work) https://www.iqwig.de/information-on-studies-of-reboxetine.980.en.html
Rofecoxib (Vioxx) n=1	78	Merck	2003	Litigation http://dida.library.ucsf.edu/
Zanamivir (Relenza) n=9	NAI30009, NAI300010, NAIA2005, NAIA3002, NAIA3005, NAIB2005, NAIB2007, NAIB3001, NAIB3002	GSK	1998-1999	Documents obtained as part of previous Cochrane review ¹²

519 * Subsequently excluded because of insufficient documentation

520 † H1D-MC-HGAO clinical study report date unknown

521 EMA = European Medicines Agency

522 FDA = Food and Drug Administration

523

524 **Table 2. Key characteristics of the CSRs in the review**

525

Section of CSR (corresponding section of E3)	Presence	Length	
		CSRs with section length available, n	Median length (range), pages
Synopsis (E3 section 2)	78 (100%)	78	5 (1 - 15)
Efficacy evaluation (E3 sec. 11)	76 (97%)	77	13.5 (2 - 132)
Safety evaluation (E3 sec. 12)	77 (99%)	58	17 (2 - 188)
Attached tables not in report text (E3 sec. 14)	63 (81%)	76	337 (1 - 3665)
Protocol (E3 sec 16.1.1)	73 (94%)	41	62 (21 - 139)
Blank Case Report Form (CRF) (E3 sec. 16.1.2)	68 (87%)	33	133 (14 - 981)
Statistical Analysis Plan (E3 sec. 16.1.9)	55 (71%)	37	15 (3 - 85)
Individual participant efficacy listings (E3 sec. 16.2.6)	53 (69%)	19	447 (15 - 21698)
Individual participant safety listings (E3 sec. 16.2.7)	62 (81%)	26	109.5 (2 - 10954)
Completed CRFs (E3 sec. 16.3.2)	16 (21%)	1	765

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527

528 **Table 3. Conservative and realistic compression factors. A ratio of CSR page**
 529 **length to corresponding journal publication page length.**

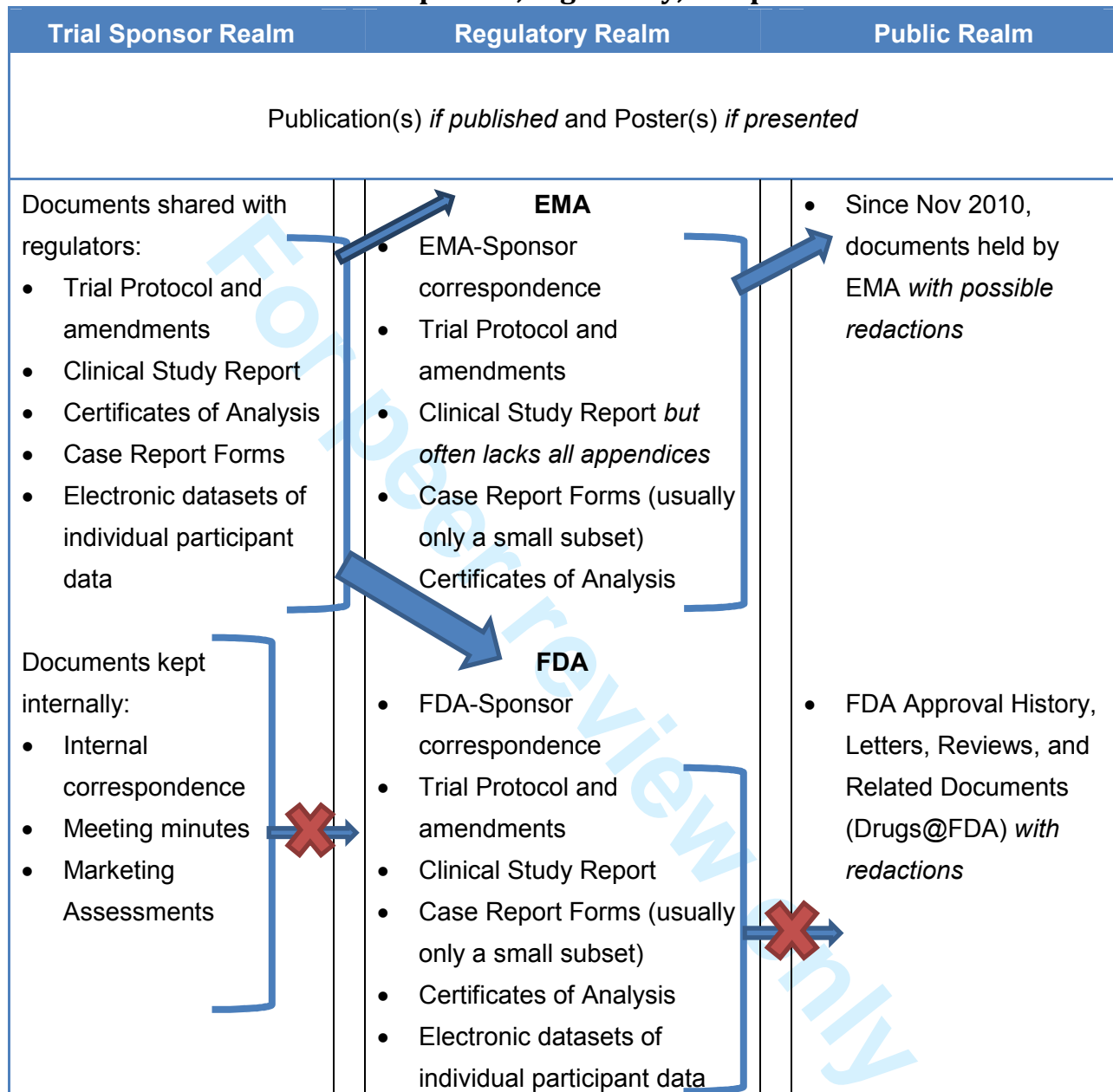
530

Pharmaceutical	Studies published in journals, n	Mean compression factor (range)
Conservative compression factors		
Aripiprazole	1	672
Clopidogrel	5	11 (4 - 19)
Epoetin Alfa	1	41
Fluad	2	488 (367 - 609)
GSK H5N1 vaccine	1	19
Oseltamivir	12	195 (1 - 1221)
Quetiapine	2	578 (352 - 803)
Reboxetine	5	88 (9 - 245)
Zanamivir	8	54 (28 - 92)
Realistic compression factors		
Arthronat*	1	379
Clopidogrel	1	8805
Paroxetine	9	1021 (50 - 5473)

531 * The Arthronat trial has not yet been published. Compression factor calculation is based on the
 532 page length of a draft manuscript "to be published soon," according to Arthronat.com.

533

534 **Figure 1. Types of clinical trial data typically held within and transferred**
535 **between three realms: trial sponsor, regulatory, and public.**



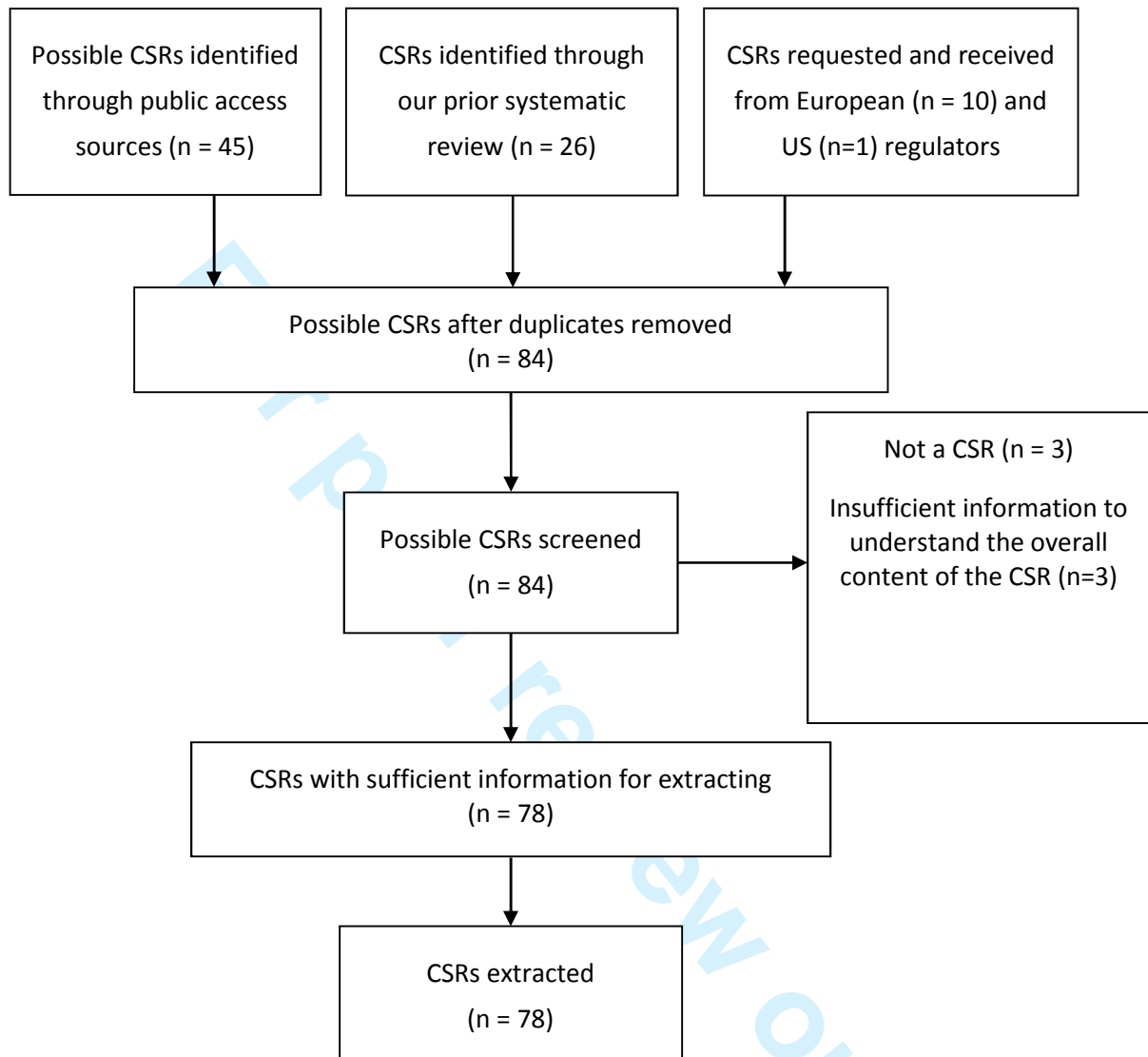
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538 **Figure 2. Study flow**

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4 541 **Appendix 1. Elements specified ICH E3 “Structure and Content of Clinical Study**
5 542 **Reports” (1995)¹⁹**

- 6 543 1. TITLE PAGE
7
8 544 2. SYNOPSIS
9
10 545 3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT
11 546 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
12
13 547 5. Ethics
14 548 5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
15 549 5.2. Ethical conduct of the study
16 550 5.3. Patient information and consent
17
18 551 6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE
19
20 552 7. INTRODUCTION
21
22 553 8. STUDY OBJECTIVES
23
24 554 9. INVESTIGATIONAL PLAN
25 555 9.1. Overall study design and plan – description
26 556 9.2. Discussion of study design, including the choice of control groups
27 557 9.3. Selection of study population
28 558 9.3.1. Inclusion criteria
29 559 9.3.2. Exclusion criteria
30 560 9.3.3. Removal of Patients from Therapy or Assessment
31 561 9.4. Treatments
32 562 9.4.1. Treatments Administered
33 563 9.4.2. Identity of Investigational Product(s)
34 564 9.4.3. Method of Assigning Patients to Treatment Groups
35 565 9.4.4. Selection of Doses in the Study
36 566 9.4.5. Blinding
37 567 9.4.6. Prior and Concomitant Therapy
38 568 9.4.7. Treatment Compliance
39 569 9.5. Efficacy and safety variables
40 570 9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart
41 571 9.5.2. Appropriateness of Measurements
42 572 9.5.3. Primary Efficacy Variable(s)
43 573 9.5.4. Drug Concentration Measurements
44 574 9.6. Data quality assurance
45 575 9.7. Statistical methods planned in the protocol and determination of sample size
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3
4 576 9.7.1. Statistical and Analytical Plans
5 577 9.7.2. Determination of Sample Size
6
7 578 9.8. Changes in the conduct of the study or planned analyses
8
9 579 10. STUDY PATIENTS
10 580 10.1. Disposition of patients
11 581 10.2. Protocol deviations
12
13 582 11. EFFICACY EVALUATION
14
15 583 11.1. Data sets analyzed
16 584 11.2. Demographic and other baseline characteristics
17 585 11.3. Measurements of treatment compliance
18
19 586 11.4. Efficacy results and tabulations of individual patient data
20
21 587 11.4.1. Analysis of efficacy
22 588 11.4.2. Statistical/analytical issues
23
24 589 11.4.2.1. Adjustments for covariates
25 590 11.4.2.2. Handling of Dropouts or Missing Data
26 591 11.4.2.3. Interim Analyses and Data Monitoring
27 592 11.4.2.4. Multicentre Studies
28 593 11.4.2.5. Multiple Comparison/Multiplicity
29 594 11.4.2.6. Use of an "Efficacy Subset" of Patients
30 595 11.4.2.7. Active-Control Studies Intended to Show Equivalence
31 596 11.4.2.8. Examination of Subgroups
32
33 597 11.4.3. Tabulation of Individual Response Data
34 598 11.4.4. Drug Dose, Drug Concentration, and Relationships to Response
35 599 11.4.5. Drug-Drug and Drug-Disease Interactions
36 600 11.4.6. Drug Dose, Drug Concentration, and Relationships to Response
37 601 11.4.7. By-Patient Displays
38
39 602 12. SAFETY EVALUATION
40 603 12.1. Extent of exposure
41 604 12.2. Adverse events (AES)
42 605 12.2.1. Brief Summary of Adverse Events
43 606 12.2.2. Display of Adverse Events
44 607 12.2.3. Analysis of Adverse Events
45 608 12.2.4. Listing of Adverse Events by Patient
46
47 609 12.3. Deaths, other Serious Adverse Events and Other Significant Adverse Events
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4 610 12.3.1. Listing of Deaths, other Serious Adverse Events and Other Significant Adverse
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7 612 12.3.1.1. Deaths
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9 613 12.3.1.2. Other Serious Adverse Events
10 614 12.3.1.3. Other Significant Adverse Events
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12 615 12.3.2. Narratives of Deaths, Other Serious Adverse Events and Certain Other
13 616 Significant Adverse Events
14
15 617 12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other
16 618 Significant Adverse Events
17
18 619 12.4. Clinical laboratory evaluation
19
20 620 12.4.1. Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each
21 621 Abnormal Laboratory Value (14.3.4)
22
23 622 12.4.2. Evaluation of Each Laboratory Parameter
24 623 12.4.2.1. Laboratory Values Over Time
25 624 12.4.2.2. Individual Patient Changes
26
27 625 12.4.2.3. Individual Clinically Significant Abnormalities
28
29 626 12.5. Vital signs, physical findings and other observations related to safety
30 627 12.6. Safety conclusions
31
32 628 13. DISCUSSION AND OVERALL CONCLUSIONS
33
34 629 14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT
35 630 14.1. Demographic data
36 631 14.2. Efficacy data
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38 632 14.3. Safety data
39 633 14.3.1. Displays of Adverse Events
40 634 14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events
41
42 635 14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse
43 636 Events
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45 637 14.3.4. Abnormal Laboratory Value Listing (Each Patient)
46
47 638 15. REFERENCE LIST
48
49 639 16. APPENDICES
50 640 16.1. Study Information
51
52 641 16.1.1. Protocol and protocol amendments
53 642 16.1.2. Sample case report form (unique pages only)
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4 643 16.1.3. List of IECs or IRBs (plus the name of the committee Chair if required by the
5 644 regulatory authority) - Representative written information for patient and sample
6 645 consent forms
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8 646 16.1.4. List and description of investigators and other important participants in the study,
9 647 including brief (1 page) CVs or equivalent summaries of training and experience
10 648 relevant to the performance of the clinical study
11
12 649 16.1.5. Signatures of principal or coordinating investigator(s) or sponsor's responsible
13 650 medical officer, depending on the regulatory authority's requirement
14
15 651 16.1.6. Listing of patients receiving test drug(s)/investigational product(s) from specific
16 652 batches, where more than one batch was used
17
18 653 16.1.7. Randomisation scheme and codes (patient identification and treatment assigned)
19
20 654 16.1.8. Audit certificates (if available)
21
22 655 16.1.9. Documentation of statistical methods
23
24 656 16.1.10. Documentation of inter-laboratory standardisation methods and quality
25 657 assurance procedures if used
26
27 658 16.1.11. Publications based on the study
28
29 659 16.1.12. Important publications referenced in the report
30 660 16.2. Patient Data Listings
31
32 661 16.2.1. Discontinued patients
33 662 16.2.2. Protocol deviations
34 663 16.2.3. Patients excluded from the efficacy analysis
35 664 16.2.4. Demographic data
36 665 16.2.5. Compliance and/or drug concentration data (if available)
37 666 16.2.6. Individual efficacy response data
38 667 16.2.7. Adverse event listings (each patient)
39 668 16.2.8. Listing of individual laboratory measurements by patient, when required by
40 669 regulatory authorities
41 670 16.3. Case Report Forms
42 671 16.3.1. CRFs for deaths, other serious adverse events and withdrawals for AE
43 672 16.3.2. Other CRFs submitted
44 673 16.4. Individual Patient Data Listings (US Archival Listings)
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Clinical Study Reports of randomized controlled trials – an exploratory review of previously confidential industry reports

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Tables: 3

Figures: 2

Appendices: 2

References: 4442

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6 Clinical Study Reports of randomized controlled trials
7 manuscript

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8
9 22 **Patient consent statement** No consent was necessary as no patients were involved

10
11 23 **Ethics approval statement** No ethical approval was necessary as no patients were involved
12 and all data were aggregate or anonymized and publicly available.
13

14 25 **Role of the sponsor statement** As the review had no extramural funding, there was no
15 sponsor.
16

17 27 **Author Contributions:** Doshi had full access to all of the data in the study and takes
18 responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept*
19 *and design:* Doshi and Jefferson. *Acquisition of data:* Doshi and Jefferson. *Analysis and*
20 *interpretation of data:* Doshi and Jefferson. *Critical revision of the manuscript for important*
21 *intellectual content:* Doshi and Jefferson. *Statistical analysis:* Doshi.
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32 **Research questions or hypotheses addressed**

33 What are Clinical Study Reports (CSRs)? What do they contain and how long are they?

34 Might CSRs help address reporting biases associated with the published literature, and improve
35 the quality of evidence synthesis?

36 **Key Messages (up to 3)**

37 CSRs represent a hitherto hidden and untapped source of detailed RCT data (mean page
38 length: 1,854 pages), increasingly becoming publicly available, and should form the basic unit
39 for evidence synthesis to minimize the problem of reporting bias.

40 CSRs show that numerous individuals make important technical contributions to the design,
41 conduct, and reporting of each trial, but journal publications often fail to record these details,
42 resulting in a loss in individual responsibility for what is reported.

43 The E3 guideline to which most CSRs conform was published in 1995, and needs updating.

44 **Strengths and Limitations**

45 We cannot say whether our sample is representative and whether our conclusions are
46 generalizable to an undefined and undefineable population of CSRs.

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Abstract

Objective: To explore the structure and content of a non-random sample of clinical study reports (CSRs) to guide clinicians and systematic reviewers.

Search strategy: We searched public sources and lodged Freedom of Information requests for previously confidential CSRs primarily written by industry for regulators.

Selection criteria: CSR reporting sufficient information for extraction (“adequate”)

Primary outcome measures: Presence and length of essential elements of trial design and reporting and compression factor (ratio of page length for CSR compared to its published counterpart in a scientific journal).

Data extraction: data were extracted on standard forms and cross-checked for accuracy

Results: We assembled a population of 7884 CSRs (covering 90 RCTs; 144,610 pages total) dated 1991-2011 of 14 pharmaceuticals. 78 were adequate. Report synopses had a median length of 5 pages, efficacy evaluation 13.5 pages, safety evaluation 17 pages, attached tables 337 pages, trial protocol 62 pages, statistical analysis plan 15 pages, and individual efficacy and safety listings had a median length of 447 and 109.5 pages, respectively. While 16 (21%) of CSRs contained completed case report forms, these were accessible to us in only one case (765 pages representing 16 individuals). Compression factors ranged between 1 and 8805.

Conclusions: Clinical study reports represent a hitherto mostly hidden and untapped source of detailed and exhaustive data on each trial. They should be consulted by independent parties interested in a detailed record of a clinical trial, and should form the basic unit for evidence synthesis as their use is likely to minimize the problem of reporting bias. We cannot say whether our sample is representative and whether our conclusions are generalizable to an undefined and undefineable population of CSRs.

Word count: 2725

Primary Funding Source: The review had no extramural funding.

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84 Introduction

85 Systematic reviews are thought to provide one of the most robust ways to evaluate the effects of
86 healthcare interventions. But the robustness of findings clearly rests upon reviewers' access to
87 clinical trial information sufficient to critically evaluate and reproduce the original research.
88 Research on reporting bias over the last decades has shown that trusting the published
89 literature at face value, even peer-reviewed publications, can be fraught with difficulty—a
90 problem that spans drug classes.^{1–12}

91 Following the decision by the European regulator, European Medicines Agency (EMA) on 30
92 Nov 2010, to make available a broad spectrum of documents related to medicinal products for
93 human and veterinary use,^{13,14} attention is focusing on one particular type of regulatory
94 document: clinical study reports (CSRs).^{15–18} CSRs are usually written for regulators following
95 guidelines developed by the industry-regulatory collaborative effort “International Conference on
96 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use”
97 (ICH). The ICH guidelines “Structure and Content of Clinical Study Reports”¹⁹ (See Appendix 1)
98 are known by the document code “E3”. They were formalized in 1995 “to assist sponsors in the
99 development of a report that is complete, free from ambiguity, well organised and easy [for
100 regulators] to review.”¹⁹ E3 has not been edited or changed since 1995.

101 CSRs are but one category of information that is transmitted from study sponsors to regulators
102 (Figure 1), but are important as they contain substantially more information and detail on the
103 intervention being tested than published versions of the same trial. The wealth of information
104 may be sought with increasing frequency by researchers appraising single trials, entire trial
105 programmes, or by those synthesizing evidence.^{17,20} We are aware of two recent examples of
106 systematic reviews [of the effects of pharmaceuticals](#) carried out using CSRs and other
107 regulatory material.^{12,21} One group also concluded that journal publications insufficiently report
108 clinical trials.²²

109 Despite CSRs' potential importance very little is known about their structure and content outside
110 of those individuals with direct involvement in regulatory processes. This knowledge gap may
111 hinder development of methods for fair and reliable appraisal of CSRs and their use in evidence
112 synthesis. We are not aware of any instruments specifically designed for appraising CSRs. Lack
113 of visibility may also [hinder understanding of](#) ~~conceal~~ the complexity of the organization and
114 reporting of clinical trials.

115 We carried out an exploratory review to describe the structure and content of a non-random
116 sample of clinical study reports. [By describing the contents of CSRs, this research seeks to](#)

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transform CSRs from an obscure document only known to regulators and industry into a more widely known and accessible document. Our long-term intention is to improve the credibility of research synthesis by facilitating a move from the level of detail found in journal articles to the level of detail found in regulatory documents, thus guiding clinicians and other decision makers at all levels.

Methods

We obtained CSRs from public sources, as follows:

1. Requesting from EMA, under its freedom of information (FOI) policy, CSRs for manufacturer sponsored trials of the 10 best-selling prescription-bound products in the United States in 2010.²³
2. Reusing CSRs from our own previous research ([oseltamivir, zanamivir](#))¹²
3. Downloading CSRs openly available on the Internet. Search terms were not predefined, but sites searched included Google (<http://www.google.com>), the Drug Industry Document Archive (<http://dida.library.ucsf.edu/>), and IQWIG's library of reboxetine studies (<https://www.iqwig.de/information-on-studies-of-reboxetine.980.en.html>)
4. Corresponding with ~~other one~~ researchers who ~~have~~ obtained CSRs through a FOI requests to FDA (epoetin alfa)
5. Requesting manufacturers fill any gaps in the completeness of reports that we believe are legally required to be publicly available ([paroxetine](#)).

To create as broad a database as possible, we did not apply restrictions in drug type or family or sponsor. We did not submit requests under the Freedom of Information Act to the Food and Drug Administration because such requests can take years to be fulfilled and—~~once if~~ fulfilled—may be heavily redacted.²⁴

We did not draw a random sample of CSRs as there is no known sampling frame. No one knows how many reports have been written by intervention category as there is no central register of CSRs. Through familiarity with CSRs for oseltamivir and zanamivir, which were included in one of our Cochrane reviews,¹² we developed and piloted a data extraction sheet designed to capture the salient characteristics of CSRs. We created a list of around 40 potential sections we expected to find, generated directly from elements specified in E3. For each element in the list, we checked whether the obtained CSR included that section (confirmed either by direct identification of the section or an indication the section existed based on the CSR's table of contents), whether we had access to it, and its page length. Because of previous difficulties we had accessing CSR appendices, we also recorded whether sections

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150 were listed as appendices or not. Page length was calculated either by directly counting the
151 pages or by estimating their size from the table of contents of each report, and was used as a
152 crude proxy for the level of detail available. Page lengths were rounded up to the next integer,
153 and were summarized by reporting medians and ranges. We also included questions relating to
154 trial registration and authorship. Our (blank) data extraction sheet is in Appendix 2.

155 All variables from CSRs were first extracted in single. We subsequently audited each other's
156 extractions, checking the accurateness of the information. We chose to present elements
157 analogous with those that typically appear in trials reported in scientific journals including the
158 study Synopsis (a brief summary of the study), the study Protocol (written prospectively,
159 describing the study methods), Efficacy and Safety Evaluations (a narrative summary of the
160 efficacy and safety results of the study, including tables and figures), as well as attached tables.
161 We also included elements rarely found in journal publications: sample (blank) and completed
162 case report forms (CRFs are paper or electronic forms designed to capture pre-specified
163 efficacy and safety related information for each study participant), the statistical analysis plan (a
164 prospectively written narrative and/or statistical code indicating how trial data will be analyzed),
165 and individual participant efficacy and safety listings. The corresponding E3 section numbers
166 are listed in Table 2. Disagreements were resolved by discussion.

167 Our uncorrected (original) and corrected extraction sheets as well as audit records are available
168 upon request from the corresponding author.

169 We calculated a compression factor for published trials: which we defined as the ratio of CSR
170 page length compared to the page length of the same trial as published in scientific journals.
171 The objective of this metric was to convey a rough sense of how much information present in
172 CSRs may be being condensed ("compressed") in short journal publications, in consideration of
173 CSRs' far greater length and level of detail. Size (page length) reflects the level of detail as well
174 as the presence of many elements such as protocols and their amendments, randomization
175 lists, statistical analysis plans, certificates of analysis and extra data on subpopulations. We
176 have demonstrated¹² that these elements are essential for understanding and appraising a trial.
177 The compression factor is a crude measure of how much is compressed or simply left out of
178 each publication which will affect the reliability of the appraisal and interpretation of trials. Trial
179 publications were searched for in multiple sources: clinical trial registers, published systematic
180 reviews, and correspondence with sponsors. Because in most cases we could not access all
181 parts of all CSRs (and therefore do not know their complete page length), we calculated ~~both~~
182 "conservative" compression factors as well as ~~and~~ "realistic" compression factors.
183 "Conservative" compression factors were calculated on a trial by trial basis using the total

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184 number of pages ~~of in~~ CSRs available to us divided by the length of journal reports ~~for that~~
185 ~~same trial~~, while “realistic” compression factors were based on the true total page length of the
186 ~~CSR, when known, even if inaccessible.~~

187 Results

188 We identified 84 documents believed to be CSRs for 14 compounds. These covered
189 therapeutic and biological interventions including antipsychotics, antidepressants, antivirals,
190 natural antiarthritics, anti-inflammatory agents, pandemic influenza vaccines, statins,
191 erythropoietins, and anti-platelet compounds. We included English-language summaries of two
192 Japanese oseltamivir studies (JV15823, JV15824) as they had been presented to EMA in this
193 form. We excluded ~~CSRs documents~~ which ~~were sections of CSRs but nonetheless contained~~
194 ~~insufficient information to understand the overall content of the CSR were too fragmentary to~~
195 ~~evaluate~~ (olanzapine F1D-LC-HGAV, F1D-MC-HGAJ and F1D-MC-HGAO) and 3 documents
196 which we ~~had originally classified as CSRs re not~~ but were not in fact CSRs (reboxetine 14, 22
197 and 37). This left 78 CSRs (144,610 pages) (Figure 2). The median pages obtained per CSR
198 was 644 (range 9 to 15,440). Only 4 of 78 CSRs (reboxetine 8, 16, 17, and 91) were written
199 prior to November 30 1995 when ICH E3 was approved. Table 1 summarizes the
200 pharmaceutical, manufacturer, date and provenance of the CSRs in our review. EMA reported
201 not holding studies for esomeprazole magnesium (Nexium), Advair diskus, quetiapine fumarate
202 (Seroquel), montelukast sodium (Singulair), epoetin alfa (Epogen), and simvastatin.

204 All of the 78 included CSRs ~~comprised of~~ contained a synopsis (median page length 5 pages).
205 The efficacy evaluation was identifiable and directly accessible in 76 (97%, median length 13.5
206 pages) and safety in 77 (99%; median length 17 pages). Attached tables were likewise present
207 in 63 (81%) ~~of~~ CSRs, and were a median of 337 pages long (range: 1 to 3665). Seventy-three
208 CSRs (94%) reported including the study protocol. In the 40 we could access, the median page
209 length was 62. We found blank CRFs included in 68 (87%) ~~of~~ CSRs. Of the 33 we could
210 directly access, the median length was 133 pages (range 14 to 981). For completed CRFs, 16
211 (21%) reports made direct mention of a section on completed CRFs, but we had access to
212 completed CRFs in only 1 case (Arthronat; length 765 pages).

214 Fifty-five (71%) of 78 included CSRs included a statistical analysis plan in some form. Of those
215 for which we could directly access the content (n=37), the median page length was 15 (range 3
216 to 85). Individual efficacy and safety listings were included in 53 (69%) and 62 (81%) CSRs
217 respectively. The median page length was 447 (range 15 to 21,698) for efficacy and 109.5
218 (range 2 to 10,954) for safety.

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219 A summary is presented in Table 2.

220 All trial reports in our review were sponsored by industry.

221 Median conservative compression factors ranged between 1 and 1221. The realistic
222 compression factors, calculated for the Arthronat, paroxetine, and clopidogrel CAPRIE trials,
223 were 379, 1021, and 8805, respectively. (Table 3)

224 Discussion

225 We collected and described a sizeable number of CSRs written in the last two decades. All
226 CSRs contained a table of contents (as specified in E3 section 3); this, together with optical
227 character recognition (to enable searching the full text of the scanned documents) and the
228 occasional need to combine multiple files to create a single document, substantially improved
229 the ease of navigating CSRs.

230 Despite the ~~apparent~~ size of our non-random sample, ~~we are not sure it is unclear whether~~ our
231 conclusions are ~~broadly~~ generalisable to all other CSRs. ~~This is~~ because we have extremely
232 limited knowledge about the total population of CSRs in regulators' and sponsors' possession.
233 Nevertheless, ~~within our sample spanning different manufacturers, therapeutic classes, and~~
234 ~~times~~, we found that the structure of CSRs was, within different house styles of presentation,
235 strikingly similar ~~across medical products and sponsors~~, probably ~~thanks due to the guidance by~~
236 ICH's E3.³⁷ This suggests that the structure and content of other CSRs is likely to be similar.

237 The future basic currency of research synthesis?

238 The median length of 644 pages for reports in this study, ~~as well as CSRs' routine inclusion of~~
239 ~~trials' protocol, statistical analysis plans, and blank case report forms, confirms strongly~~
240 ~~suggests~~ that CSRs are the most detailed and complete, integrated form of reporting of the
241 design, conduct, and results of clinical trials. ~~In a study that directly compared the adequacy of~~
242 ~~reporting between journal articles and CSRs, the authors found that complete information~~
243 ~~regarding greater than 40% of methods items were only available in CSRs.~~²² ~~They~~ The level of
244 ~~detail found in CSRs thus~~ far surpass the level of detail available in journal publications, and as
245 such they are prime candidates for the next basic currency of evidence synthesis and appraisal
246 of a trial. Given the EMA's new policy making such documents publicly available, access to
247 these documents is now relatively straightforward.²⁵ However including CSRs in ~~systematic~~
248 reviews is labor-intensive, given their size and complexity.¹²

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249 **Accessing complete CSRs**

250 While CSRs may trump other forms of trial reporting in the public domain (such as conference
251 abstracts or journal publications), serious limitations remain. Despite obtaining 144,610 pages
252 for 78 CSRs, in almost all instances, we lacked full access to the CSRs' numerous appendices.
253 Even for the sole complete CSR we obtained (Arthronat MA-CT-10-002), case report forms
254 were provided for only 20% of participants. The [Arthronat](#) text does not provide a reason for
255 this omission, but it reflects the vagueness of the relevant section of the E3 guidance (16.3.2)
256 which does not define "Other CRF's submitted." Also, we could only access the original trial
257 protocol in 40 (51%) of 78 CSRs obtained. This is important because trial protocols, written
258 prior to patient enrollment in a trial, are an important way to guard against reporting biases.^{26,27}

259 We could obtain individual patient listings in only a minority of cases despite confirming their
260 inclusion in the majority of CSRs (Table 2). This may be a significant limitation, as the E3
261 specifies that "the report with its appendices should also provide enough individual patient data,
262 including the demographic and baseline data, and details of analytical methods, to allow
263 replication of the critical analyses..."¹⁹ Unavailability was possibly due to the fact that EMA
264 allows manufacturers to submit CSRs omitting a number of appendices including individual
265 patient data and case report forms (which EMA states should be available within 48 hours if
266 requested).²⁸ In the case of oseltamivir, the subject of a Cochrane review we conducted,¹² the
267 manufacturer refused to share with us report appendices not submitted to EMA,²⁹ and EMA
268 declined requesting them on our behalf.⁸ Although FDA likely possesses more complete CSRs
269 and patient level data, it historically has treated such data as trade secret and/or confidential.³⁰⁻
270 ³² EMA is therefore at present the only reliable source of obtaining CSRs. As such, despite
271 European regulators' progressive stance—announcing that "clinical trial data should not be
272 considered commercial confidential information"³³—the completeness gap is unlikely to be filled
273 any time soon.

274 Another significant limitation is that CSRs are only written for therapeutic, prophylactic, or
275 diagnostic agents, and therefore inadequacies remain in evidence synthesis of other types of
276 interventions such as surgical or behavioral interventions.

277 **Individual participant listings**

278 Individual participant listings—which identify participants by a unique ID—were accessible in 29
279 of the 78 CSRs we reviewed. But these data are difficult to analyze because they are presented
280 as database printouts rather than in electronic form. This is understandable considering that
281 CSRs are a written/archival format, but because EMA does not accept SAS datasets,^{34,35} the
282 industry standard, third-party access to databases of patient-level data remains elusive. We

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283 see no compelling reason why all regulators should not request these from sponsors and make
284 them publicly available. Whether availability of individual listings and CRFs, with its attendant
285 laborious analysis, would increase our understanding of the trial and its results is unclear. But
286 there is at least one case where the re-analysis of CRFs added invaluable knowledge to that
287 already available in CSRs.³⁶

288 **The public-private debate**

289 One manufacturer has claimed that the non-release of case report forms is motivated by
290 concerns over protecting participant confidentiality.³⁸ Nothing we have seen so far corroborates
291 this claim, [however an ongoing EMA working group is specifically discussing issues related to](#)
292 [protecting participant confidentiality. The Based on current document releases and position](#)
293 [statements, however, it appears that](#) EMA has deemed case report forms and individual patient
294 listings to be, in principle, releasable in their entirety (after a preliminary review).³⁹ Furthermore,
295 individual patient listings are intended to duplicate information contained in filled case report
296 forms. The release of case report forms would ensure the accuracy of individual patient listings
297 with little additional risk to patient confidentiality. Moreover, extra checks such as registration of
298 protocols by bona fide research groups could deter any inappropriate use. We also believe that
299 the sheer bulk of the forms acts as a deterrent against malice.

300 **Size matters**

301 Our range of compression factors show the scale of selection and synthesis which must
302 (consciously or unconsciously) occur in the process of transforming CSRs into journal-length
303 articles. We found a strong resemblance in detail, page length, structure, and purpose between
304 the short Synopsis section of CSRs and reports of trials as published in scientific journals. —In
305 some cases essential items of information such as the trial protocol and its subsequent
306 amendments are simply not included in journal articles or are replaced by methods written *post*
307 *facto*. In other cases of items essential for the interpretations of the trial results (such as the
308 statistical analysis plan), tens of pages are reduced to a paragraph on sample size calculation in
309 the journal report, underscoring the lack of detail (and its attendant problems) common to public
310 forms of trial reporting. [For example, the ratio of words in Protocol of the CSR for Aripiprazole](#)
311 [CN138135 to the Methods section for published journal article of the same trial is 30.5 \(53,713](#)
312 [words in the CSR Protocol versus 1,763 words in the journal article\). For the oseltamivir](#)
313 [WP16263 trial, the ratio was 22.7 \(26,761 words in the CSR Protocol and amendments versus](#)
314 [1,177 words in the journal article\).](#)

315 This [compression of information is true even also occurs](#) in databases not restricted by length,
316 such as ClinicalTrials.gov.⁴⁰

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Our study raises the question of why the medical community has accepted the low (summary, aggregate) level of detail found in most peer-reviewed journal publications compared to the depth of detail available in CSRs. European regulators recently noted: “Documents that provide critical information on a study, such as the protocol (16.1.1), statistical methods (16.1.9), list of investigators and study sites and sample case report forms, would always be needed by reviewers assessing a study”⁴¹ Why have those outside of the regulatory world tolerated journal publications lacking such details?

One possibility may be that while the clinical trial enterprise has changed dramatically in the last half century, the scientific journal publication model has not. Since the 1950s, there have been considerable transformations in the political economy of clinical trials driven by the increasingly commercialized and global nature of the pharmaceutical industry, the rise in academic-industry “partnerships” in medicine, and increased communication among regulators. It is now common to find trials with study centers scattered around the globe. This increasing complexity and the need to provide an audit record is reflected in the comprehensive tomes documenting the trials—CSRs—but trial reporting in scientific journals remains limited to summary and aggregate details. It should be noted, however, that many journals now have websites which enables them to make available extended content beyond what traditionally appears in the printed journal.

Authorship or Contributorship?

Examination of CSRs revealed scores of important technical contributions to the design, conduct, and reporting of each trial. These included contributions from database programmers, records officers, and CSR writers, often invisible in the published journal article. In some cases, we found no mention in CSRs of individuals who figured as authors of subsequent published trial reports while individuals named as CSR authors went unacknowledged in journal publications. Current ICMJE guidelines on authorship and contributorship are largely focused on ensuring those placed on by-lines deserve to be authors. But the guidelines also suggest that “all contributors who do not meet the criteria for authorship should be listed in an acknowledgments section.”⁴² Given the complexity of clinical trials, the ICMJE should call for itemized contributorship: the names of all contributors to be specified along with their role in the design, conduct, analysis, or reporting of the trial. If the contribution of most people goes unrecorded, so does their individual responsibility for what is produced. Itemized contributorship records, to all phases of a trial, could be piloted in trial registers.

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349 **E3 guidance**

350 The E3 guideline set an excellent standard, but it needs formal updating and further
351 development. For example, there should be a self-standing set of definitions for terms such as
352 “case report forms” and “Other CRF’s submitted,” (section 16.3.2) and a description of how a
353 particular trial fits within a sponsor’s trial programme of pharmaceutical development.
354 Apparently forgotten items such as certificates of analysis (describing the appearance and
355 content of the interventions being tested) and post-1995 details such as trial registration
356 numbers should be mentioned.

357 We hope our review has given CSRs what they have lacked so far: visibility. CSRs represent a
358 largely untapped source of detailed data that we believe can serve as a means of addressing
359 the ravages of reporting bias in all its forms, leading to a more accurate understanding of the
360 effects of medicines.

361

362 **Conflicts of interest statement**

363 All authors have completed the Unified Competing Interest form at
364 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
365 declare that:

366 Both authors are co-recipients of a UK National Institute for Health Research grant to carry out a
367 Cochrane review of neuraminidase inhibitors (<http://www.hta.ac.uk/2352>).

368 Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998-1999. He
369 receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore,
370 none of which are on clinical study reports. He is occasionally interviewed by market research
371 companies for anonymous interviews about Phase 1 or 2 products unrelated to products in this
372 review. In 2011-12 he has acted as an expert witness in a litigation case related to one of the
373 compounds in the review (oseltamivir). He is on a legal retainer for expert advice on litigation
374 for influenza vaccines in health care workers.

375 Peter Doshi received €1500 from the European Respiratory Society in support of his travel to
376 the society’s September 2012 annual congress where he gave an invited talk on oseltamivir.

377

378 Both authors’ spouses and children have no financial relationships that may be relevant to the
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380 **Data sharing statement**

381 The original extraction forms and audit record are available on request from the corresponding
382 author.

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518 **Table 1. Pharmaceutical, trials, producers, dates and sources of CSRs in the**
519 **review.**

Pharmaceutical and number (n) of assessed trial documents	Trial IDs	Manufacturer	Date of CSRs	Provenance in our study
Aripiprazole (Abilify) n=1	CN1368135	Bristol-Myers Squibb	2007	Freedom of Information request to EMA
Arthronat n=1	MA-CT-10-002	Rowtasha	2011	Manufacturer website http://arthronat.com/clinical-study.php
Atorvastatin (Lipitor) n=1	981-080	Pfizer	1999	Freedom of Information request to EMA
Clopidogrel (Plavix) n=5	CURE, CLARITY, COMMIT-CCS2, CAPRIE, PICOLO	Bristol-Myers Squibb	1997-2007	Freedom of Information request to EMA
Epoetin alfa (Epogen) n=1	930107	Amgen	1996	Freedom of Information request to FDA
H5N1 influenza vaccine n=1	H5N1-008, H5N1-011 EXT 008	GSK	2006	Freedom of Information request to EMA
H5N1 influenza vaccines n=2	V87P1, V87P6	Novartis	2008-2009	Freedom of Information request to EMA
Olanzapine (Zyprexa) n=3	F1D-LC-HGAV*, F1D-MC-HGAO*, F1D-MC-HGAJ*	Eli Lilly	1995 [†]	Litigation http://zyprexalitigationdocuments.com/unsealed.php http://www.furiousseasons.com/zyprexadocs.html
Oseltamivir (Tamiflu) n=19	JV15823, JV15824, M76001, NP15757, NV16871, WP16263, WV15670, WV15671, WV15673, WV15697, WV15707, WV15708, WV15730, WV15758, WV15759, WV15871, WV15799, WV15812, WV15872, WV15819, WV15876, WV15978, WV15825, WV16193	Roche	1999-2004	Documents obtained as part of previous Cochrane review ¹²
Paroxetine (Paxil, Aropax, Peveva, Seroxat, Sereupin) n=9	329, 377, 453, 511, 676, 701, 704, 715, 716	GSK	1998-2002	Litigation (2004 legal settlement mandated release of clinical study reports on manufacturer's website of 9 studies on

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				pediatric and adolescent patients) http://www.gsk.com/media/paroxetine.htm
Quetiapine (Seroquel) n=7	015, 041, 049, 125, 126, 127, 135	AstraZeneca	1996-2007	Litigaton http://psychrights.org/research/Digest/NLPs/Seroquel/UnsealedSeroquelStudies/
Reboxetine (Edronax, Norebox, Prolift, Solvex, Davedax, Vestra) n=24	8, 9, 13, 14*, 15, 16, 17, 22*, 32, 32a, 34, 35, 37*, 43, 45, 46, 47, 49, 50, 52, 71, 83, 91, 96	Pfizer	1991-2009	Health Technology Assessment website (The German IQWiG obtained CSRs as part of its health technology assessment work) https://www.iqwig.de/information-on-studies-of-reboxetine.980.en.html
Rofecoxib (Vioxx) n=1	78	Merck	2003	Litigation http://dida.library.ucsf.edu/
Zanamivir (Relenza) n=9	NAI30009, NAI300010, NAIA2005, NAIA3002, NAIA3005, NAIB2005, NAIB2007, NAIB3001, NAIB3002	GSK	1998-1999	Documents obtained as part of previous Cochrane review ¹²

Field Code Changed

520 * Subsequently excluded because of insufficient documentation

521 † H1D-MC-HGAO clinical study report date unknown

522 EMA = European Medicines Agency

523 FDA = Food and Drug Administration

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525 **Table 2. Key characteristics of the CSRs in the review**
526

Section of CSR (corresponding section of E3)	Presence	Length	
	CSRs including section, n	CSRs with section length available, n	Median length (range), pages
Synopsis (E3 section 2)	78 (100%)	78	5 (1 - 15)
Efficacy evaluation (E3 sec. 11)	76 (97%)	77	13.5 (2 - 132)
Safety evaluation (E3 sec. 12)	77 (99%)	58	17 (2 - 188)
Attached tables not in report text (E3 sec. 14)	63 (81%)	76	337 (1 - 3665)
Protocol (E3 sec 16.1.1)	73 (94%)	41	62 (21 - 139)
Blank Case Report Form (CRF) (E3 sec. 16.1.2)	68 (87%)	33	133 (14 - 981)
Statistical Analysis Plan (E3 sec. 16.1.9)	55 (71%)	37	15 (3 - 85)
Individual participant efficacy listings (E3 sec. 16.2.6)	53 (69%)	19	447 (15 - 21698)
Individual participant safety listings (E3 sec. 16.2.7)	62 (81%)	26	109.5 (2 - 10954)
Completed CRFs (E3 sec. 16.3.2)	16 (21%)	1	765

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529 **Table 3. Conservative and realistic compression factors. A ratio of CSR page**
530 **length to corresponding journal publication page length.**

531

Pharmaceutical	Studies published in journals, n	Mean compression factor (range)
Conservative compression factors		
Aripiprazole	1	672
Clopidogrel	5	11 (4 - 19)
Epoetin Alfa	1	41
Fluad	2	488 (367 - 609)
GSK H5N1 vaccine	1	19
Oseltamivir	12	195 (1 - 1221)
Quetiapine	2	578 (352 - 803)
Reboxetine	5	88 (9 - 245)
Zanamivir	8	54 (28 - 92)
Realistic compression factors		
Arthronat*	1	379
Clopidogrel	1	8805
Paroxetine	9	1021 (50 - 5473)

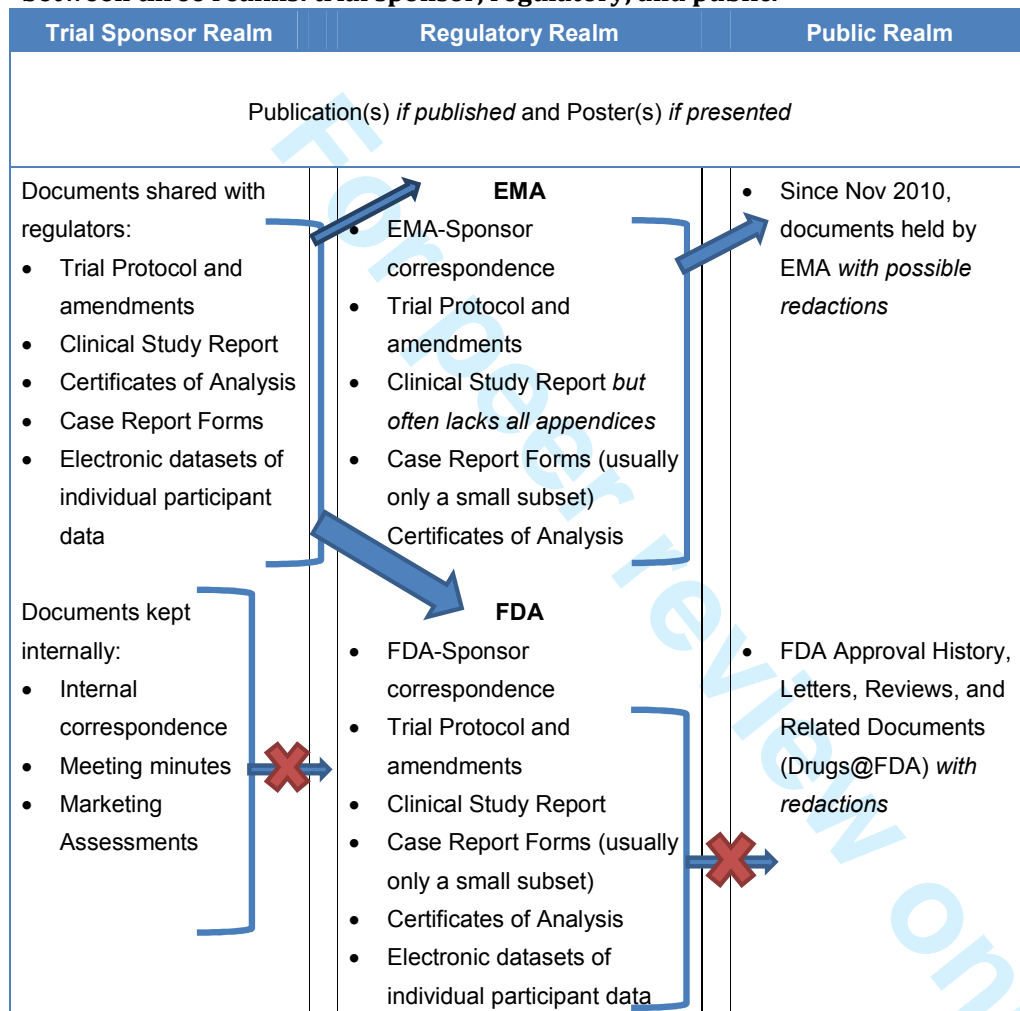
532 * The Arthronat trial has not yet been published. Compression factor- calculation is based on
533 the page length of a draft manuscript "to be published soon," according to Arthronat.com.

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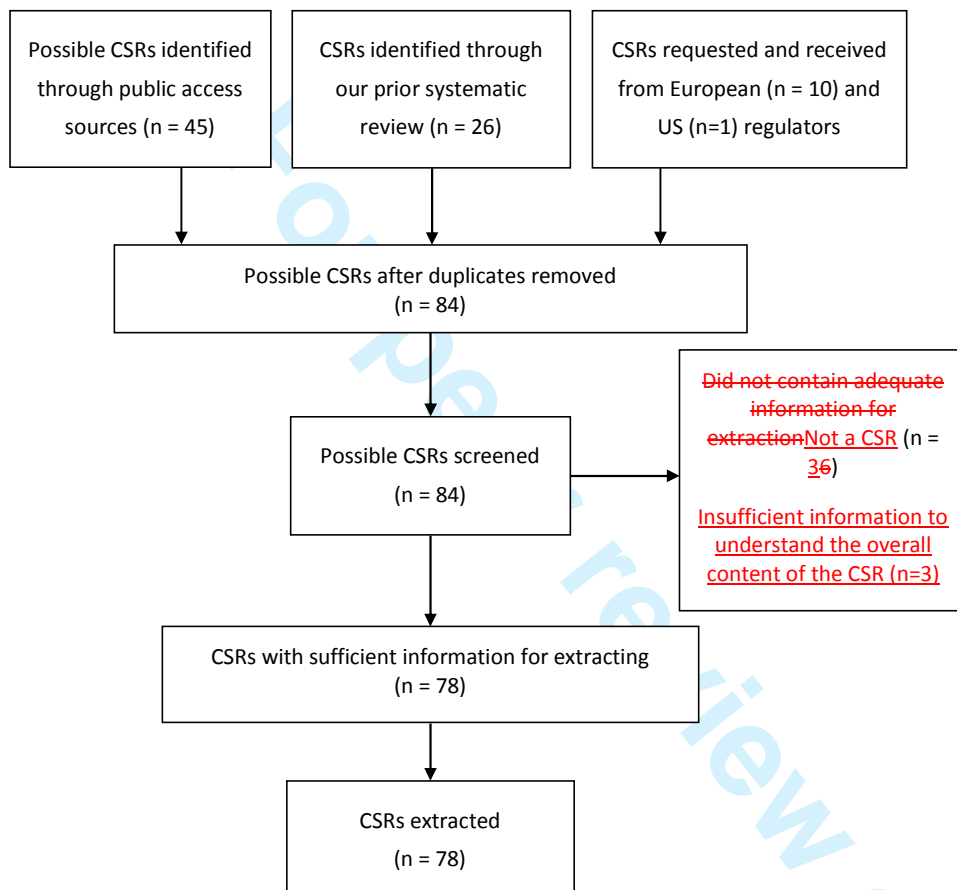
535 **Figure 1. Types of clinical trial data typically held within and transferred**
536 **between three realms: trial sponsor, regulatory, and public.**



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Figure 2. Study flow



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Appendix 1. Elements specified ICH E3 “Structure and Content of Clinical Study Reports” (1995)¹⁹

1. TITLE PAGE
2. SYNOPSIS
3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
5. Ethics
 - 5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
 - 5.2. Ethical conduct of the study
 - 5.3. Patient information and consent
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE
7. INTRODUCTION
8. STUDY OBJECTIVES
9. INVESTIGATIONAL PLAN
 - 9.1. Overall study design and plan – description
 - 9.2. Discussion of study design, including the choice of control groups
 - 9.3. Selection of study population
 - 9.3.1. Inclusion criteria
 - 9.3.2. Exclusion criteria
 - 9.3.3. Removal of Patients from Therapy or Assessment
 - 9.4. Treatments
 - 9.4.1. Treatments Administered
 - 9.4.2. Identity of Investigational Product(s)
 - 9.4.3. Method of Assigning Patients to Treatment Groups
 - 9.4.4. Selection of Doses in the Study
 - 9.4.5. Blinding
 - 9.4.6. Prior and Concomitant Therapy
 - 9.4.7. Treatment Compliance
 - 9.5. Efficacy and safety variables
 - 9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart
 - 9.5.2. Appropriateness of Measurements
 - 9.5.3. Primary Efficacy Variable(s)
 - 9.5.4. Drug Concentration Measurements
 - 9.6. Data quality assurance
 - 9.7. Statistical methods planned in the protocol and determination of sample size

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9 577 9.7.1. Statistical and Analytical Plans
10 578 9.7.2. Determination of Sample Size
11 579 9.8. Changes in the conduct of the study or planned analyses
12
13 580 10. STUDY PATIENTS
14 581 10.1. Disposition of patients
15 582 10.2. Protocol deviations
16
17 583 11. EFFICACY EVALUATION
18 584 11.1. Data sets analyzed
19 585 11.2. Demographic and other baseline characteristics
20 586 11.3. Measurements of treatment compliance
21 587 11.4. Efficacy results and tabulations of individual patient data
22
23 588 11.4.1. Analysis of efficacy
24 589 11.4.2. Statistical/analytical issues
25 590 11.4.2.1. Adjustments for covariates
26 591 11.4.2.2. Handling of Dropouts or Missing Data
27 592 11.4.2.3. Interim Analyses and Data Monitoring
28 593 11.4.2.4. Multicentre Studies
29 594 11.4.2.5. Multiple Comparison/Multiplicity
30 595 11.4.2.6. Use of an "Efficacy Subset" of Patients
31 596 11.4.2.7. Active-Control Studies Intended to Show Equivalence
32 597 11.4.2.8. Examination of Subgroups
33
34 598 11.4.3. Tabulation of Individual Response Data
35 599 11.4.4. Drug Dose, Drug Concentration, and Relationships to Response
36 600 11.4.5. Drug-Drug and Drug-Disease Interactions
37 601 11.4.6. Drug Dose, Drug Concentration, and Relationships to Response
38 602 11.4.7. By-Patient Displays
39
40 603 12. SAFETY EVALUATION
41 604 12.1. Extent of exposure
42 605 12.2. Adverse events (AES)
43 606 12.2.1. Brief Summary of Adverse Events
44 607 12.2.2. Display of Adverse Events
45 608 12.2.3. Analysis of Adverse Events
46 609 12.2.4. Listing of Adverse Events by Patient
47
48 610 12.3. Deaths, other Serious Adverse Events and Other Significant Adverse Events
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- 611 12.3.1. Listing of Deaths, other Serious Adverse Events and Other Significant Adverse
- 612 Events
- 613 12.3.1.1. Deaths
- 614 12.3.1.2. Other Serious Adverse Events
- 615 12.3.1.3. Other Significant Adverse Events
- 616 12.3.2. Narratives of Deaths, Other Serious Adverse Events and Certain Other
- 617 Significant Adverse Events
- 618 12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events and Other
- 619 Significant Adverse Events
- 620 12.4. Clinical laboratory evaluation
- 621 12.4.1. Listing of Individual Laboratory Measurements by Patient (16.2.8) and Each
- 622 Abnormal Laboratory Value (14.3.4)
- 623 12.4.2. Evaluation of Each Laboratory Parameter
- 624 12.4.2.1. Laboratory Values Over Time
- 625 12.4.2.2. Individual Patient Changes
- 626 12.4.2.3. Individual Clinically Significant Abnormalities
- 627 12.5. Vital signs, physical findings and other observations related to safety
- 628 12.6. Safety conclusions
- 629 13. DISCUSSION AND OVERALL CONCLUSIONS
- 630 14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT
- 631 14.1. Demographic data
- 632 14.2. Efficacy data
- 633 14.3. Safety data
- 634 14.3.1. Displays of Adverse Events
- 635 14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events
- 636 14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse
- 637 Events
- 638 14.3.4. Abnormal Laboratory Value Listing (Each Patient)
- 639 15. REFERENCE LIST
- 640 16. APPENDICES
- 641 16.1. Study Information
- 642 16.1.1. Protocol and protocol amendments
- 643 16.1.2. Sample case report form (unique pages only)

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- 644 16.1.3. List of IECs or IRBs (plus the name of the committee Chair if required by the
645 regulatory authority) - Representative written information for patient and sample
646 consent forms
- 647 16.1.4. List and description of investigators and other important participants in the study,
648 including brief (1 page) CVs or equivalent summaries of training and experience
649 relevant to the performance of the clinical study
- 650 16.1.5. Signatures of principal or coordinating investigator(s) or sponsor's responsible
651 medical officer, depending on the regulatory authority's requirement
- 652 16.1.6. Listing of patients receiving test drug(s)/investigational product(s) from specific
653 batches, where more than one batch was used
- 654 16.1.7. Randomisation scheme and codes (patient identification and treatment assigned)
- 655 16.1.8. Audit certificates (if available)
- 656 16.1.9. Documentation of statistical methods
- 657 16.1.10. Documentation of inter-laboratory standardisation methods and quality
658 assurance procedures if used
- 659 16.1.11. Publications based on the study
- 660 16.1.12. Important publications referenced in the report
- 661 16.2. Patient Data Listings
- 662 16.2.1. Discontinued patients
- 663 16.2.2. Protocol deviations
- 664 16.2.3. Patients excluded from the efficacy analysis
- 665 16.2.4. Demographic data
- 666 16.2.5. Compliance and/or drug concentration data (if available)
- 667 16.2.6. Individual efficacy response data
- 668 16.2.7. Adverse event listings (each patient)
- 669 16.2.8. Listing of individual laboratory measurements by patient, when required by
670 regulatory authorities
- 671 16.3. Case Report Forms
- 672 16.3.1. CRFs for deaths, other serious adverse events and withdrawals for AE
- 673 16.3.2. Other CRFs submitted
- 674 16.4. Individual Patient Data Listings (US Archival Listings)

Basic Extraction Information

Questions	Answer	Notes
1. Drug common name:		
2. Trial ID:		
→ Now, fill in the drug and trial ID in the bottom-right corner the page.	E.g. "Tamiflu, WV15670"	
→ Now, save this file under a new filename	Use the naming convention "Drugname Trial ID - Extractor's initials - YYYYMMDD.docx", e.g. "Seroquel 015 - TJ - 20120311.docx"	
3. Report/CSR ID (if different from Trial ID):		
4. Extractor's name (Initials)		
5. Date of extraction		

Notes to extractor:

- Page numbers should be referred to by the format p.(page # as printed)/PDFp.(PDF page number, possibly indicating volume), e.g.
 - p.V-235/PDFp.945 = page "V-235", on PDF page 945
 - p.234/PDF(3)p.18 = page "234", on the 3rd PDF for this CSR, PDF page 18
- Most questions can be answered with a Y or N (indicating Yes or No) or a number (e.g. the number of PDF pages).
- Where specified as "Free form answer", the extractor may answer in his/her own words based on the extractor's reading of the CSR.

Item	Content	Notes
Overview questions		
6. Does the CSR list a ISRCTN/NCT or equivalent registration number for this trial?		
7. List CSR number of authors		
8. List CSR authors & trialists (Copy names if available; "redacted" if redacted; "not listed" if not listed)		
9. Total length of CSR obtained, in PDF pages		
10. List CSR completion date		
11. Is the trial published?		
12. If Y give publication citation		
13. If Y give publication size (in pages)		
14. Who appears to be responsible for CSR? (Free form answer)		
Trial programme questions		
15. How many trials appear to be in the trial programme?		
16. Does CSR indicate where this trial fits in the trial programme? (Free form answer)		
17. Does CSR say how much of the trial programme is published?		
18. How many trials are in possession of a ISRCTN/NCT or equivalent registration number?		
Basic elements of the Clinical Study Report		

19.	Does the CSR contain a table of contents ?		
20.	If Y, is the table of contents listed as an Appendix?		
21.	If Y, is the table of contents accessible to us?		
22.	If Y, how long is the table of contents (in pages)?		
23.	Does the table of contents list a title page ?		
24.	If Y, is the title page listed as an Appendix?		
25.	If Y, is the title page accessible to us?		
26.	If Y, how long is the title page (in pages)?		
27.	Does the table of contents list a synopsis ?		
28.	If Y, is the synopsis listed as an Appendix?		
29.	If Y, is the synopsis accessible to us?		
30.	If Y, how long is the synopsis (in pages)?		
31.	Does the CSR contain a list of abbreviations and definitions ?		
32.	If Y, is the list of abbreviations and definitions listed as an Appendix?		
33.	If Y, is the list of abbreviations and definitions accessible to us?		
34.	If Y, how long is the list of abbreviations and definitions (in pages)?		
35.	Does the CSR contain an ethics section ?		
36.	If Y, is the ethics section listed as an Appendix?		
37.	If Y, is the ethics section accessible to us?		
38.	If Y, how long is the ethics section (in pages)?		
39.	Does the CSR contain a investigators and study administrative structure ?		
40.	If Y, is the investigators and study administrative structure listed as an Appendix?		
41.	If Y, is the investigators and study administrative structure accessible to us?		
42.	If Y, how long is the investigators and study administrative structure (in pages)?		
43.	Does the CSR contain an introduction ?		
44.	If Y, is the introduction listed as an Appendix?		
45.	If Y, is the introduction accessible to us?		
46.	If Y, how long is the introduction (in pages)?		
47.	Does the CSR contain a section on study objectives?		
48.	If Y, is the section on study objectives listed as an Appendix?		
49.	If Y, is the section on study objectives accessible to us?		
50.	If Y, how long is the section on study objectives (in pages)?		
51.	Does the CSR contain an investigational plan (from IHR 1995 E3, PDF p.13)?		
52.	If Y, is the investigational plan listed as an Appendix?		
53.	If Y, is the investigational plan accessible to us?		
54.	If Y, how long is the investigational plan (in pages)?		
55.	Does the CSR contain a section on study patients ?		
56.	If Y, is the study patients listed as an Appendix?		
57.	If Y, is the study patients accessible to us?		
58.	If Y, how long is the study patients (in pages)?		

59.	If Y, does it include a list of protocol deviations?		
60.	Does the CSR contain a section on efficacy evaluation ?		
61.	If Y, is the efficacy evaluation listed as an Appendix?		
62.	If Y, is the efficacy evaluation accessible to us?		
63.	If Y, how long is the efficacy evaluation (in pages)?		
64.	Does the CSR contain a section on safety evaluation ?		
65.	If Y, is the safety evaluation listed as an Appendix?		
66.	If Y, is the safety evaluation accessible to us?		
67.	If Y, how long is the safety evaluation (in pages)?		
68.	Does the CSR contain a discussion and overall conclusions section?		
69.	If Y, is the discussion and overall conclusions listed as an Appendix?		
70.	If Y, is the discussion and overall conclusions accessible to us?		
71.	If Y, how long is the discussion and overall conclusions (in pages)?		
72.	Does the CSR contain a section on tables, figures and graphs referred to but not included in the text ?		
73.	If Y, is the tables, figures and graphs referred to but not included in the text listed as an Appendix?		
74.	If Y, is the tables, figures and graphs referred to but not included in the text accessible to us?		
75.	If Y, how long is the tables, figures and graphs referred to but not included in the text (in pages)?		
76.	Does the CSR contain a references section?		
77.	If Y, is the references listed as an Appendix?		
78.	If Y, is the references accessible to us?		
79.	If Y, how long is the references (in pages)?		
Appendices related questions			
80.	Does the table of contents indicate that the CSR contains appendices ?		
81.	If Y, does the table of contents list the titles of the appendices ?		
82.	Does the CSR include the study Protocol ?		
83.	If Y, is the study Protocol accessible to us?		
84.	If Y, how long is the study Protocol (in pages)?		
85.	Does the CSR contain a section on Protocol amendments ?		
86.	If Y, is the section on Protocol amendments accessible to us?		
87.	If Y, how long is the section on Protocol amendments (in pages)?		
88.	Does the CSR contain a section on Sample case report form (unique pages only) ?		
89.	If Y, is the section on Sample case report form (unique pages only) accessible to us?		
90.	If Y, how long is the section on Sample case report form (unique pages only) (in pages)?		
91.	Does the CSR contain a section on List of IECs or IRBs (plus the name of the committee Chair if required by the		

	regulatory authority) - Representative written information for patient and sample consent forms?		
92.	If Y, is the section on List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms accessible to us?		
93.	If Y, how long is the section on List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for patient and sample consent forms (in pages)?		
94.	Does the CSR contain a section on List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study?		
95.	If Y, is the section on List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study accessible to us?		
96.	If Y, how long is the section on List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study (in pages)?		
97.	Does the CSR contain a section on Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement?		
98.	If Y, is the section on Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement accessible to us?		
99.	If Y, how long is the section on Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement (in pages)?		
100.	Does the CSR contain a section on Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used?		
101.	If Y, is the section on Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used accessible to us?		
102.	If Y, how long is the section on Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used (in pages)?		
103.	Does the CSR contain a section on Randomisation scheme and codes (patient identification and treatment assigned)?		
104.	If Y, is the section on Randomisation scheme and codes		

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6	105.	If Y, how long is the section on Randomisation scheme and codes (patient identification and treatment assigned) (in pages)?	
7			
8	106.	Does the CSR contain a section on Audit certificates (if available) (see Annex IVa and IVb of the guideline)?	
9			
10	107.	If Y, is the section on Audit certificates (if available) (see Annex IVa and IVb of the guideline) accessible to us?	
11			
12	108.	If Y, how long is the section on Audit certificates (if available) (see Annex IVa and IVb of the guideline) (in pages)?	
13			
14	109.	Does the CSR contain a section on Documentation of statistical methods?	
15			
16	110.	If Y, is the section on Documentation of statistical methods accessible to us?	
17			
18	111.	If Y, how long is the section on Documentation of statistical methods (in pages)?	
19			
20	112.	If Y, is the Documentation of statistical methods dated?	
21			
22	113.	If Y, what is the date of the Documentation of statistical methods?	
23			
24	114.	Does the CSR contain a section on Documentation of inter-laboratory standardisation methods and quality assurance procedures if used?	
25			
26	115.	If Y, is the section on Documentation of inter-laboratory standardisation methods and quality assurance procedures if used accessible to us?	
27			
28	116.	If Y, how long is the section on Documentation of inter-laboratory standardisation methods and quality assurance procedures if used (in pages)?	
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30	117.	Does the CSR contain a section on Publications based on the study?	
31			
32	118.	If Y, is the section on Publications based on the study accessible to us?	
33			
34	119.	If Y, how long is the section on Publications based on the study (in pages)?	
35			
36	120.	Does the CSR contain a section on Important publications referenced in the report?	
37			
38	121.	If Y, is the section on Important publications referenced in the report accessible to us?	
39			
40	122.	If Y, how long is the section on Important publications referenced in the report (in pages)?	
41		Edfgyh+	
42	123.	Does the CSR contain a section on Discontinued patients?	
43			
44	124.	If Y, is the section on Discontinued patients accessible to us?	
45			
46	125.	If Y, how long is the section on Discontinued patients (in pages)?	
47			
48	126.	Does the CSR contain a section on Protocol deviations?	
49			
50	127.	If Y, is the section on Protocol deviations accessible to us?	
51			
52	128.	If Y, how long is the section on Protocol deviations (in	
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1	pages)?		
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4	129. Does the CSR contain a section on Patients excluded from the efficacy analysis ?		
5			
6	130. If Y, is the section on Patients excluded from the efficacy analysis accessible to us?		
7			
8	131. If Y, how long is the section on Patients excluded from the efficacy analysis (in pages)?		
9			
10	132. Does the CSR contain a section on Demographic data ?		
11			
12	133. If Y, is the section on Demographic data accessible to us?		
13			
14	134. If Y, how long is the section on Demographic data (in pages)?		
15			
16	135. Does the CSR contain a section on Compliance and/or drug concentration data (if available) ?		
17			
18	136. If Y, is the section on Compliance and/or drug concentration data (if available) accessible to us?		
19			
20	137. If Y, how long is the section on Compliance and/or drug concentration data (if available) (in pages)?		
21			
22	138. Does the CSR contain a section on Individual efficacy response data ?		
23			
24	139. If Y, is the section on Individual efficacy response data accessible to us?		
25			
26	140. If Y, how long is the section on Individual efficacy response data (in pages)?		
27			
28	141. Does the CSR contain a section on Adverse event listings (each patient) ?		
29			
30	142. If Y, is the section on Adverse event listings (each patient) accessible to us?		
31			
32	143. If Y, how long is the section on Adverse event listings (each patient) (in pages)?		
33			
34	144. Does the CSR contain a section on Listing of individual laboratory measurements by patient, when required by regulatory authorities ?		
35			
36	145. If Y, is the section on Listing of individual laboratory measurements by patient, when required by regulatory authorities accessible to us?		
37			
38	146. If Y, how long is the section on Listing of individual laboratory measurements by patient, when required by regulatory authorities (in pages)?		
39			
40	147. Does the CSR contain a section on Case Report Forms for deaths, other serious adverse events and withdrawals for AE ?		
41			
42	148. If Y, is the section on Case Report Forms for deaths, other serious adverse events and withdrawals for AE accessible to us?		
43			
44	149. If Y, how long is the section on Case Report Forms for deaths, other serious adverse events and withdrawals for AE (in pages)?		
45			
46	150. Does the CSR contain a section on Other Case Report Forms submitted?		
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48	151. If Y, is the section on Other Case Report Forms submitted accessible to us?		
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50	152. If Y, how long is the section on Other Case Report Forms		
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	submitted (in pages)?		
153.	Does the CSR contain a section on Individual patient data listings ?		
154.	If Y, is the section on Individual patient data listings accessible to us?		
155.	If Y, how long is the section on Individual patient data listings (in pages)?		

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