UNIVERSITY OF LEEDS

This is a repository copy of *Harms Reported by Patients in Rheumatology Drug Trials: A Systematic Review of Randomized Trials in the Cochrane Library from an OMERACT Working Group*.

White Rose Research Online URL for this paper:
<https://eprints.whiterose.ac.uk/166282/>

Version: Accepted Version

Article:

Berthelsen, DB, Woodworth, TG, Goel, N et al. (15 more authors) (2021) Harms Reported by Patients in Rheumatology Drug Trials: A Systematic Review of Randomized Trials in the Cochrane Library from an OMERACT Working Group. *Seminars in Arthritis and Rheumatism*. ISSN 0049-0172

<https://doi.org/10.1016/j.semarthrit.2020.09.023>

© 2021 Elsevier Inc. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Harms Reported by Patients in Rheumatology Drug Trials: A Systematic Review of Randomized Trials in the Cochrane Library from an OMERACT Working Group

Dorthe B. Berthelsen^{1,2}, Thasia G. Woodworth³, Niti Goel⁴, John P. A. Ioannidis⁵, Peter Tugwell⁶, Dan Devoe⁷, Paula Williamson⁸, Caroline B. Terwee⁹, Maria E. Suarez-Almazor¹⁰, Vibeke Strand¹¹, Amye L. Leong¹², Philip G. Conaghan^{13,14}, Maarten Boers¹⁵, Beverley J. Shea¹⁶, Peter M. Brooks¹⁷, Lee S. Simon¹⁸, Daniel E. Furst^{3†}, Robin Christensen^{1,19†}, on behalf of the OMERACT Safety Working Group.

* Corresponding author

† Shared last author

¹ Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark.

² Department of Rehabilitation, Municipality of Guldborgsund, Nykoebing F, Denmark

³ David Geffen School of Med. Division Rheumatology. UCLA, USA.

⁴ Duke University School of Medicine, Durham, NC, USA.

⁵ Departments of Medicine, Epidemiology and Population Health, Biomedical Data Science and Statistics, and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, California, USA.

⁶ Department of Medicine, School of Epidemiology, Public Health and Community Medicine, University of Ottawa, Canada.

⁷ Department of Medicine, University of Calgary, Cumming School of Medicine, Calgary, Canada.

⁸ MRC North West Hub for Trials Methodology Research, Institute of Translational Medicine, University of Liverpool, Liverpool, UK.

⁹ Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Epidemiology and Biostatistics and the Amsterdam Public Health Research Institute, Amsterdam, NL.

¹⁰ Department of Health Services Research and Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Centre, Houston, TX, USA.

¹¹ Division of Immunology/Rheumatology, Stanford University, Palo Alto CA, USA.

¹² Healthy Motivation; Global Alliance for Musculoskeletal Health, Bone and Joint Decade, Santa Barbara, California USA.

¹³ Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK.

¹⁴ NIHR Leeds Biomedical Research Centre, Leeds, UK.

¹⁵ Department of Epidemiology and Biostatistics and the Amsterdam Rheumatology and immunology Centre, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, NL.

37 ¹⁶ Ottawa Hospital Research Institute, Clinical Epidemiology Program and School of Epidemiology and
38 Public Health, University of Ottawa, Canada.

39 ¹⁷ Centre for Health Policy Melbourne School of Population and Global Health University of Melbourne and
40 Northern Health, Australia.

41 ¹⁸ SDG LLC Cambridge, MA 02138, USA.

42 ¹⁹ Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark,
43 Odense University Hospital, Denmark.

44

45 **Correspondence to:**

46 Robin Christensen, BSc, MSc, PhD; Biostatistician & Professor.

47 Head of Musculoskeletal Statistics Unit,

48 The Parker Institute,

49 Bispebjerg and Frederiksberg Hospital,

50 Nordre Fasanvej 57

51 DK-2000 Copenhagen F

52 Denmark

53 Phone: (+45) 3816 4165, Fax: (+45) 3816 4159

54 E-mail: Robin.Christensen@regionh.dk

55

56

57 **ABSTRACT**

58 **Background**

59 Underreporting of harms in randomized controlled trials (RCTs) may lead to incomplete or
60 erroneous assessments of the perceived benefit-to-harm profile of an intervention. To compare
61 benefit with harm in clinical practice and future clinical studies, adverse event (AE) profiles
62 including severity need to be understood. Even though patients report harm symptoms earlier and
63 more frequently than clinicians, rheumatology RCTs currently do not provide a reporting framework
64 from the patient’s perspective regarding harms. Our objective for this meta-research project was to
65 identify AEs in order to determine harm clusters and whether these could be self-reported by
66 patients. Our other objective was to examine reported severity grading of the reported harms.

67
68 **Methods**

69 We considered primary publications of RCTs eligible if they were published between 2008 and
70 2018 evaluating pharmacological interventions in patients with a rheumatic or musculoskeletal
71 condition and if they were included in Cochrane reviews. We extracted data on harms such as
72 reported AE terms together with severity (if described), and categorized AE- and severity-terms
73 into overall groups. We deemed all AEs with felt components appropriate for patient self-reporting.

74
75 **Results**

76 The literature search identified 187 possible Cochrane reviews, of which 94 were eligible for
77 evaluation, comprising 1,297 articles on individual RCTs. Of these RCTs, 93 pharmacological trials
78 met our inclusion criteria (including 31,023 patients; representing 20,844 accumulated patient
79 years), which reported a total of 21,498 AEs, corresponding to 693 unique reported terms for AEs.
80 We further sub-categorized these terms into 280 harm clusters (i.e., themes). AEs appropriate for
81 patient self-reporting accounted for 58% of the AEs reported. Among the reported AEs, we

82 identified medical terms for all of the 117 harm clusters appropriate for patient reporting and lay
83 language terms for 86%. We intended to include severity grades of the reported AEs, but there
84 was no evidence for systematic reporting of clinician- or patient-reported severity in the primary
85 articles of the 93 trials. However, we identified 33 terms suggesting severity, but severity grading
86 was discernible in only 9%, precluding a breakdown by severity in this systematic review.

87

88 **Conclusions**

89 Our results support the need for a standardized framework for patients' reporting of harms in
90 rheumatology trials. Reporting of AEs with severity should be included in future reporting of harms,
91 both from the patients' and investigators' perspectives.

92

93 **Registration**

94 PROSPERO: CRD42018108393

95

96 **Keywords**

97 Harms, adverse events, Core Outcome Set, rheumatology, OMERACT

98

99 **ABBREVIATIONS**

- 100 ACR, American College of Rheumatology
- 101 AE, adverse event
- 102 EULAR, European League Against Rheumatism
- 103 CDSR, Cochrane database of systematic reviews
- 104 CMSG, Cochrane Musculoskeletal Group
- 105 COMET, Core Outcome Measures in Effectiveness Trials
- 106 CONSORT, consolidated Standards of Reporting Trials
- 107 COS, core outcome set
- 108 CRs, Cochrane reviews
- 109 DMARDs, disease-modifying antirheumatic drugs
- 110 IQR, interquartile range
- 111 MedDRA, Medical Dictionary for Regulatory Activities
- 112 NSAIDs, nonsteroidal anti-inflammatory drugs
- 113 OARSI, OsteoArthritis Research Society International
- 114 OMERACT, Outcome Measures in Rheumatology
- 115 PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- 116 PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for
- 117 Adverse Events
- 118 PROSPERO, International prospective register of systematic reviews

- 119 RCT, randomized clinical trials
- 120 RCTC, Rheumatology Common Toxicity Criteria
- 121 SD, standard deviation
- 122

123 INTRODUCTION

124 Balanced adequate reporting of harms, as well as benefits, of an intervention in randomized
125 controlled trials (RCTs) and future research is essential to allow patients and clinicians to make the
126 most appropriate treatment decisions concerning a specific intervention (1). However, the reporting
127 of harms (adverse events, AEs) in studies of health care interventions is typically less
128 comprehensive than that of benefit (efficacy) (2–4). Further, regional differences in reporting of
129 harms may reflect underreporting of AEs as well (5). Such underreporting may lead to incomplete
130 or erroneous judgments on the benefit-to-harm profile of an intervention (2,6). Even though the
131 harm extension of *Consolidated Standards of Reporting Trials* (CONSORT) statement provides
132 guidance on items to include when reporting harms in RCTs (7), the quality of reporting RCTs in
133 the literature is poor based on examination of articles published in high impact-factor journals in
134 general medicine and rheumatology (8).

135 *Outcome Measures in Rheumatology* (OMERACT) is an independent international
136 organization of health care professionals and patient research partners, which strives to improve
137 outcome measurement and instrument methodology in studies assessing rheumatology
138 treatments. Beginning in 1992, OMERACT has developed Core Outcome Sets (COS) for many
139 rheumatologic conditions (9,10) and has actively involved patients since 2002 (11). A COS is a
140 minimum consensus-based set of outcome domains that should be measured and reported in all
141 RCTs and longitudinal observational studies of a specific health condition and/or intervention (12).
142 OMERACT uses the term ‘Core Domain Set’ to distinguish it from the ‘Core Outcome
143 Measurement Set’ that specifies instruments for each of the core domains. Many initiatives other
144 than OMERACT are also establishing COS (see e.g. the *Core Outcome Measures in Effectiveness*
145 *Trials* [COMET] database) (13), and although it is recommended that COS or systematic reviews
146 covering multiple intervention types should address the potential for AEs, only one-third of COS
147 explicitly call for AEs to be recorded (14). To correct this apparent oversight, OMERACT recently

148 recommended that benefits *and* harms should be equally and explicitly considered when
149 developing COS (10).

150 Specifically, we in the OMERACT Safety Working Group aim to improve the guidance
151 on what and how to measure and report harms, explicitly including the patient perspective (15).
152 Thus, the group developed the Rheumatology Common Toxicity Criteria 2.0 (RCTC 2.0) (16),
153 which encourage standardization of assessment and reporting of AEs in RCTs and longitudinal
154 observational studies in rheumatology. However, the RCTC 2.0 does not provide guidance on how
155 to collect harm information taking into account whether clinicians or patients are in the best position
156 to assess specific AEs. Nevertheless, focusing on the patient perspective to complement the
157 clinician perspective on harms is highly relevant because patients report harm symptoms earlier
158 and more frequently than clinicians (17), and because clinicians tend to systematically downgrade
159 the severity, i.e., the intensity, of patients' symptoms (18–20).

160 A measurement instrument suitable for assessing and reporting patient perspectives
161 on harms experienced during treatment for rheumatologic conditions is lacking (21), but such
162 instruments have been developed in other conditions e.g., the Patient-Reported Outcomes version
163 of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) within oncology (22). To
164 address this need in rheumatology and to identify candidate Core Outcome Domains as part of
165 developing a reporting framework for patient-reported harms in rheumatology (23), we provide a
166 systematic review of harms reported in primary publications of RCTs published between 2008 and
167 2018 included in Cochrane reviews. The results of our systematic review will inform a Delphi
168 process. Our primary objective for this meta-research project was to identify all harm domains
169 reported in those RCTs of pharmacological interventions in rheumatic and musculoskeletal
170 conditions evaluated in systematic reviews by the Cochrane Musculoskeletal Group (CMSG), in
171 order to determine if we could identify harm clusters appropriate to be self-reported by patients.
172 Our other objective was to examine reported severity grading of the identified harms.

173 **METHODS**

174 We registered the study protocol on the international prospective register of systematic reviews
175 (PROSPERO: CRD42018108393) and report our findings according to the guidance in Preferred
176 Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement (24), with additional
177 guidance of knowledge synthesis from PRISMA Extension for Scoping Reviews (PRISMA-ScR)
178 when feasible (25).

179

180 **Data Sources and Searches**

181 We searched the Cochrane Database of Systematic Reviews (CDSR) for all harms reported in
182 RCTs of pharmacological interventions. Cochrane reviews (CRs) examine large numbers of trials
183 and are recognized to be thorough in searching for eligible studies (26). Thus, by searching CRs,
184 we obtained a broad sampling across rheumatology indications, as well as industry and non-
185 industry sponsored trials. Using the website <https://www.cochranelibrary.com>, we browsed by
186 Cochrane Review Group, selecting Musculoskeletal (across all years available), limiting Type by
187 intervention and Topics by Rheumatology. We conducted our search on 16 October 2018.

188

189 **Study Selection**

190 Two reviewers (DBB supported by RC) screened all identified CRs by reviewing titles and
191 abstracts. We excluded protocols without data and withdrawn reviews. We then used reference
192 lists of included articles in the selected CRs to identify eligible rheumatology trials. Trials were
193 eligible if they investigated any type of pharmacological intervention against any comparator(s) in
194 patients with rheumatic and musculoskeletal conditions. We identified primary publications from the
195 reference lists of the included reviews (i.e., referred to as major publications in CRs), and excluded
196 manuscripts/reports of unpublished data and publications that were not journal articles. We

197 removed articles not written in English and article duplicates; for practical reasons we included only
198 articles published between 2008 and 2018.

199

200 **Data Extraction**

201 We used a standardized data extraction form to collect information from eligible trials. At review
202 level, we extracted CR-registration number, author, year of publication, and rheumatic or
203 musculoskeletal condition. At trial level, we assigned all trials an ID and extracted data on author,
204 year of publication, condition, intervention, trial duration (i.e., duration for reported harms), funding
205 source, surveillance method for AEs, sample size (i.e., total number of patients randomized),
206 number of completers of the trial, number of withdrawals, and number of withdrawals due to AEs.
207 When not explicitly reported, we estimated total patient-years per trial of exposure by assuming a
208 linear dropout rate between baseline and end of the trial period (i.e., the area under the curve
209 (27)). Further, we extracted patient characteristics i.e., participants' age, weight, BMI, sex (number
210 of included women), and disease duration.

211 We categorized type of condition by topic categories of conditions in the CMSG
212 library. Interventions were categorized according to American College of Rheumatology (ACR),
213 European League Against Rheumatism (EULAR), and Osteoarthritis Research Society
214 International (OARSI) recommendations and guidelines (28–39). Categories included comparator
215 interventions: placebo/sham, usual care/no intervention, and active treatment (such as non-
216 pharmacological interventions). Trial duration was categorized as <27 weeks (short), 27-52 weeks
217 (intermediate), or >52 weeks (long-term). Funding source was categorized as industry-sponsored
218 (for any industry involvement in funding or any role in design, conception, analysis, and reporting of
219 the trial); non-industry sponsored; neutral (such as industry's providing the study drug with no other
220 role); or unclear. Further, we categorized surveillance of AEs as active (e.g., when the method of
221 collecting harms was based on systematic recording at each follow up), passive, or unclear.

222 For each trial, we (DBB and RC) extracted all AEs by the reported term presented in
223 the article and tabulated the number of reports for each AE. From each article, we extracted harm
224 information from tables and supplemented by description in the main text in the most specific way
225 for each AE. I.e., we only extracted domains of AEs, such as “musculoskeletal and connective
226 tissue signs and symptoms” if no specific AEs (e.g., “myalgia”) were mentioned. For each reported
227 AE, we extracted the verbatim severity of the specific AE if provided in the article. If severity was
228 not clearly described for the specific harm, we extracted overall categories possibly related to
229 severity (e.g., serious AEs, AEs of interest or AEs leading to withdrawal), if reported. When such
230 wording was not available, we implemented a reasonable, consistent, well-defined approach. First,
231 we considered the regulatory definition of a serious AE: results in death; is life threatening; requires
232 inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or
233 significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important
234 event or reaction (40). We then considered previous work in rheumatology (16) and oncology (41),
235 and categorized severity as grades 1-5, rating as follows: mild (1), moderate (2), severe (3), life
236 threatening (4), and death (5). Although it’s mandatory to report serious AEs, we modified the
237 regulatory definition and categorized serious AEs as grade 4, because we assumed AEs resulting
238 in death to be reported as so, and because “life-threatening” in the definition of “serious” refers to
239 an event/reaction in which the patient was at risk of death at the time of the event/reaction (40). We
240 did this to emphasize the patient perspective, which may be different from the regulatory approach
241 and less clear but, in our view, is just as important. To ensure the patient’s perspective in this
242 process, we included patients among the reviewers. We avoided double counting (e.g., severity
243 reported as “AEs of interest, serious infection” counted only as serious infection).

244

245 **Data Analysis**

246 DBB organized the extracted data in a customized spreadsheet enabling analysis in collaboration
247 with TGW and DEF. Two reviewers (DBB and TGW) identified overall terms covering the same

248 severity (e.g., “mild” would include “mild adverse events” and “mild in nature”) and overall AE terms
249 covering the same type of harm (e.g., “abdominal abscess” would include “abdominal wall
250 abscess” and “peridiverticular abscess”). We also categorized the severity of each of these harm
251 clusters as mild, moderate, severe, life threatening or fatal. If a group of extracted AEs fell into the
252 same harm cluster, but none of the AE terms was appropriate as the overall term for the harm
253 cluster, we added an appropriate term (e.g., the overall term “antibodies to biologics” was used to
254 cover related terms such as “antibodies to certolizumab pegol,” “antibodies to golimumab,” and
255 “antibodies to pegloticase”).

256 Referring to the OMERACT filter 2.1 ([Supplementary Fig A.1](#) and [A.2](#)), the two
257 reviewers (DBB and TGW) independently also categorized each cluster of harms under one of the
258 three areas (that is *life impact* [e.g., patient perception of health or quality of life]; *pathophysiologic*
259 *manifestations* [e.g., body function and structure or biomarkers and surrogate measures that
260 accompany a condition]; and *death*) (9,10). Area of life impact included harm clusters most likely to
261 be felt and reported by the patients (such as nausea and diarrhea), whereas the area of
262 pathophysiologic manifestations included harm clusters most likely to be observed/measured and
263 reported by clinicians (such as neutropenia or peripheral vascular disease). Further, each harm
264 cluster’s appropriateness for patient self-reporting was categorized according to being best
265 assessed from an internal (patient) view when the AE is mostly felt (previous referred to as
266 “subjective” [such as headache or nausea]); best assessed from a mixed (patient/clinician) view
267 when the AE is mostly felt with observed components (such as vomiting or constipation) and
268 mostly observed with felt components (such as rash or fever); and best assessed form an external
269 (clinician) view when the AE is mostly observed ([Fig. 1](#)). For the last category, we distinguished
270 clinically/measurable observable (such as pneumonia or abdominal abscess) and
271 laboratory/biomarker-based (such as hyperlipidemia or increases in liver transaminase levels) (22);
272 we deemed the external category as harms inappropriate for patient self-reporting. Our
273 categorization allowed that a patient would report AEs with a degree of observable components, as
274 the patient might still be in the best position to report these as a patient reported outcome.

275 Harm clusters were then mapped into categories of system organ classes according
276 to the OMERACT Rheumatology Common Toxicity Criteria v. 2.0 (RCTC) (16). When the RCTC
277 2.0 did not list clusters in any category, we mapped the clusters into an RCTC-category considered
278 relevant for the specific cluster. Finally, we added a lay language term and a medical term to each
279 harm cluster. We used the overall term for the harm cluster as either the lay language or the
280 medical term; if none of the extracted AE terms were appropriate for the lay language term, we
281 added a synonym if it was evident (e.g., joint pain was added as a lay language term for
282 arthralgia). We resolved discrepancies between the two reviewers through discussion. In case of
283 uncertainty, we consulted a third reviewer (NG, DEF or RC). To ensure that the study objectives
284 were assessed from patient's point of view, we included patients among the reviewers.

View to assess harms:

Preferred assessor:

Fig 1. Perspective on outcome assessment to cover harms.

*Harm-paradoxes occur when harms appear unequally important/severe when observed from two different points of view.

289 **Statistical Analysis**

290 We present descriptive statistics for categorical variables of trial characteristics using counts and
291 proportions. For continuous variables, we reported mean ($\pm$ SD) or medians (with interquartile
292 ranges [IQRs]) as appropriate.

293 Agreement between the two reviewers assessing harms appropriateness for patient
294 reporting was estimated (by unweighted Cohen's *k*-statistic) in terms of dichotomous assessment
295 (i.e., harms appropriate for patient self-reporting or harms not appropriate for patient self-reporting)
296 and interpreted according to Landis and Koch (42): *k* values of <0 were considered poor, 0-0.20
297 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, and 0.81-1 almost perfect
298 agreement.

299

300 **RESULTS**

301 **Eligible Reviews and Trials**

302 As presented in [Fig. 2](#), our search retrieved 187 Cochrane reviews. We excluded protocols, and
303 after screening titles and abstracts, we excluded reviews not including RCTs. This process
304 narrowed the field to 94 eligible Cochrane reviews, encompassing 1,297 potentially eligible articles,
305 from which we identified 98 eligible articles with 96 distinct RCTs. We excluded three trials that did
306 not examine rheumatologic conditions, yielding a total of 93 trials included in the final analysis
307 ([Supplementary Table A](#)).

308

Fig 2. Flow diagram for the study selection.
R = review.

314 **Characteristics of Included Trials**

315 The reviewed trials included 31,023 participants, representing 20,844 patient years. Patients' mean
316 (SD) age was 54 (7), disease duration 7 (4) years, weight 84 (17) kilos with a BMI of 31 (4) and
317 59% of patients were female. [Table 1](#) shows that most participants suffered from rheumatoid
318 arthritis (45%), osteoarthritis (26%) and gout (22%). The most commonly studied active
319 interventions were biologic DMARDs (bDMARDs), as monotherapy or in combination with
320 conventional synthetic DMARDs (csDMARDs) (23%); and urate-lowering therapy (16%). Placebo
321 or sham interventions (13%) were the most commonly used comparators. Overall, 7,280 (24%)
322 participants withdrew from the trials with 1,777 (6%) withdrawing due to AEs.

323 On an individual trial level, the median sample size in the included trials was 164
324 (IQR 26-499) participants; the median trial duration was 24 weeks (IQR 12-52) with 60 (65%) trials
325 of less than 27 weeks', 19 (20%) of 27-52 weeks', and 14 (15%) of more than 52 weeks' duration.
326 In 52 trials (56%), investigators used active surveillance of harms, whereas surveillance was
327 passive in one trial (1%). In 40 trials (43%), the method of surveillance was unclear. Most trials (61
328 [66%]) were industry-sponsored; 14 (15%) were non-industry-funded; and funding sources were
329 unclear or neutral in 14 (15%) and 4 trials (4%), respectively.

330

Table 1.
Characteristics of included trials (*k*=93)

	Trials, <i>k</i>	%	Patients, <i>n</i>	%
Total	93	100	31,023	100.0
Condition*				
Rheumatoid arthritis	29	31	13,897	44.8
Osteoarthritis	32	34	8,147	26.3
Gout	16	17	6,823	22.0
Spondyloarthropathy (incl. PsA and AS)	6	6	1,252	4.0
Soft tissue disorders	4	4	252	0.8
Mixed	2	2	240	0.8
Osteoporosis	1	1	173	0.6
Lupus erythematosus	2	2	138	0.4
Fibromyalgia	1	1	101	0.3
Intervention†				
bDMARDs + csDMARDs			7,228	23.3
Urate-lowering therapy			5,097	16.4
Placebo/sham			3,941	12.7
csDMARDs + placebo			3,198	10.3
bDMARDs			2,868	9.2
Nutraceuticals			2,530	8.2
Opioids			1,840	5.9
NSAIDs			1,233	4.0
Glucocorticoid and intraarticular hyaluronate			795	2.6
csDMARDs			521	1.7
Other pharmacological interventions‡			107	0.3
Colchicine			385	1.2
bDMARDs + placebo			367	1.2
Antiresorptive and osteoanabolic drugs			234	0.8
Active treatment§			115	0.4
Other combination of interventions¶			107	0.3
NSAIDs + placebo			76	0.2
bDMARDs + NSAIDs			74	0.2
Usual care/no intervention			22	0.1
Sample size, median (IQR)			164 (26-499)	
Funding source				
Industry sponsored	61	66		
Non-industry funded	14	15		
Unclear	14	15		
Neutral	4	4		
Surveillance of harms				
Active	52	56		
Passive	1	1		
Unclear	40	43		
Trial duration				
<27 weeks	60	65		
27-52 weeks	19	20		
>52 weeks	14	15		
Trial duration (weeks), median (IQR)			24 (12-52)	

* Index according to Rheumatology topics in the Cochrane Library.

†Categorized according to American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and Osteoarthritis Research Society International (OARSI) recommendations and guidelines.

‡ E.g., doxycycline or botulinum toxin.

§ E.g., acupuncture or exercise therapy.

¶ E.g., aspiration plus corticosteroid injection plus horizontal therapy or hyaluronate plus exercise.

AS = ankylosing spondylitis; bDMARDs = biologic disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; IQR = interquartile range; NSAIDs = nonsteroidal anti-inflammatory drugs; PsA = psoriatic arthritis.

332 **Harms Reported in Rheumatology Drug Trials**

333 In the 93 included trials, we identified 21,498 reported AEs, covering 693 unique reported terms for
334 AEs ([Supplementary Table B](#)). By categorizing these 693 terms into overall groups covering the
335 same harms, we narrowed the field to 280 harm clusters. Most of the harm clusters were within the
336 core area of pathophysiological manifestations: 194 (69%); fewer were in the areas of life impact:
337 85 (30%) or death: 1 (<1%).

338 Among the 280 harm clusters, we judged 117 (42%) to be appropriate for patient self-
339 reporting: 29% mostly felt, 16% mostly felt with observed components, and 13% mostly observed
340 with felt components. A total of 58% of the harm clusters were considered mostly observed; i.e.,
341 not appropriate for patient self-reporting: 51% clinically/measurable and 7% laboratory-/biomarker-
342 based. Our judgement of whether they were appropriate for patient self-report is presented in
343 [Supplementary Fig B](#) Reviewers agreed on 80% of the assessments (kappa=0.61).

344 [Table 2](#) shows the 117 harm clusters appropriate for patient self-reporting. However,
345 as it was difficult to achieve consensus, [Supplementary Table C](#) explains the reasons for the
346 specific categorization of the harms appropriate for patient self-reporting where ambiguity might
347 exist. From the unique reported terms, we identified or added medical terms describing all of the
348 harm clusters appropriate for patient reporting, although we were only able to identify or add lay
349 language terms for 86% of these clusters. We judged 73% of the harm clusters appropriate for
350 patient self-reporting to be within the core area of life impact, while 27% were within the area of
351 pathophysiological manifestations.

352 The 117 harm clusters appropriate for patient self-reporting accounted for 58% of the
353 AEs reported in the included trials. As harms not appropriate for patient self-reporting accounted
354 for 42% of the total number of AEs reported, the (rate) ratio of reporting a harm appropriate for
355 patient self-reporting compared with a harm not appropriate for patient self-reporting was 1.41
356 (95% CI, 1.37-1.44).

357

Table 2.
Harms appropriate for patient self-reporting*

Mostly felt AEs		Mostly felt AEs with observed components		Mostly observed AEs with felt components	
No of reported harms	Harm cluster [†]	No of reported harms	Harm cluster [†]	No of reported harms	Harm cluster [†]
1138	Headache	713	Diarrhea	1685	Upper respiratory tract infection
1038	Nausea	649	Musculoskeletal and connective tissue signs and symptoms (none)	507	Injection-site reactions
401	Dizziness	597	Constipation	327	Joint-related signs and symptoms (none)
268	Fatigue	565	Nasopharyngitis (<i>common cold</i>)	303	RA flare
204	Arthralgia (<i>joint pain</i>)	520	Vomiting	266	Gout flare
184	Pruritus (<i>itching</i>)	288	Injury, poisoning, and procedural complications	243	Rash
180	Abdominal pain	255	Somnolence (<i>sleepiness</i>)	241	Lower respiratory tract infection (<i>bronchitis</i>)
172	Gastrointestinal symptoms (none)	162	Back pain	62	Erythema (<i>redness</i>)
130	Dyspepsia (<i>indigestion</i>)	134	Influenza (<i>flu syndrome</i>)	62	Infusion reaction
56	Pain	94	Sinusitis	62	Mouth ulcers
27	Injection site pain	89	Dry mouth	41	Psychiatric disorders (none)
24	Asthenia (<i>feeling weak</i>)	87	Pharyngitis (<i>sore throat</i>)	35	Pyrexia (<i>fever</i>)
19	Depression	70	Cough	32	Muscle-related signs and symptoms: muscle cramps, muscle twitching, night cramps (none)
10	Pain in the study joint	65	Skin injuries	29	Allergic reactions
8	Itch or dizziness	41	Vertigo (<i>spinning sensation</i>)	24	Osteoarthritis (none)
8	Myalgia (<i>muscle pain</i>)	39	Dyspnea (<i>shortness of breath</i>)	16	Joint effusion (<i>joint swelling</i>)
7	Pain in extremity	38	Sun sensitivity	13	Eczema
5	Joint stiffness	34	Peripheral oedema (<i>swelling</i>)	8	Allergic conjunctivitis (none)
4	Dysphagia (<i>difficulty in swallowing</i>)	33	Paresthesia (<i>'pins and needles'</i>)	8	Contusion (<i>bruise</i>)
3	Burning	24	Rhinitis (<i>runny nose</i>)	6	Colitis (none)
3	Malaise (<i>feeling badly</i>)	21	Chest pain	6	Effusion (none)
2	Change of bowel habit	21	Flare	4	Recurrent falls
2	Flatulence (<i>passing gas</i>)	16	Nephrolithiasis (<i>renal colic</i>)	3	Hospitalized
2	Increased appetite	16	Urticarial (<i>hives</i>)	3	Induration (none)
2	Stinging	15	Insomnia (<i>difficulty sleeping</i>)	3	Optic neuritis (none)
2	Tendon pain	13	Pleurisy (none)	1	Abdominal hernia, obstructive (none)
1	Ear pain	11	Gastroenteritis (<i>stomach flu</i>)	1	Abdominal wall abscess
1	Feeling of warmth	10	Flushing	1	Alopecia (<i>hair loss</i>)
1	Hallucination (<i>sensing things that are not real</i>)	6	Angina pectoris (<i>angina</i>)	1	Anal fistula (none)
1	Hyperesthesia (<i>increased sensitivity of any sense</i>)	6	Palpitations	1	Blepharitis (<i>eyelid inflammation</i>)
1	Hypoesthesia (<i>reduced sensitivity of any sense</i>)	4	Dental pain	1	Increased body weight
1	Lack of appetite	3	Gastritis	1	Infected tophus (none)
1	Pain in rectum	2	Abdominal distension (<i>bloating</i>)	1	Inguinal hernia (none)
1	Restless legs syndrome (<i>restless legs</i>)	2	Anxiety attack	1	Mastitis (<i>inflamed breast</i>)
1	Straining	2	Muscular weakness (<i>muscular weakness in the area around the study joint</i>)	1	Menometrorrhagia (<i>abnormally heavy, prolonged, and irregular uterine bleeding</i>)
		1	Asthma	1	Ptosis (<i>droopy eyelid</i>)
		1	Ataxia (<i>impaired coordination</i>)	1	Yellow discoloration of urine
		1	Constipation-related bloating		
		1	Cystitis (<i>bladder inflammation</i>)		
		1	Irritable bowel syndrome		
		1	Neuralgia (<i>nerve pain</i>)		
		1	Skin peeling		
		1	Syncope (<i>fainting, losing consciousness</i>)		
		1	Tooth abscess		
		1	Tremor		

*Sample is based on harms reported in primary articles of both industry and non-industry trials.

[†]When difference between medical and lay language terms exists, terms are described in medical term (*lay language term*). Underscore indicates terms added by authors. "None" indicates that no lay language term was identified. Harms in blue highlight indicate disagreements that were resolved by discussion until consensus was reached among authors as whether appropriate for patient self-reports.

AE = adverse event; RA = rheumatoid arthritis.

358

359

360 **Severity of Harms**

361 We intended to include severity grades of the reported AEs, but there was no evidence for
362 systematic reporting of clinician or patient-reported severity in the primary articles of the 93 trials.
363 As shown in [Table 3](#), we identified 33 overall terms suggesting severity in the primary articles.
364 Only 2% of the events described severity in terms of “mild” 326 (2%), “moderate” 1 (<1%) or
365 “severe” 11 (<1%). We further considered 5 (<1%) AEs described as “slight” to be in the same
366 grade as “mild”. Furthermore, 1280 (7%) of the reported AEs were “life threatening”, while 8 (<1%)
367 fatal events were reported in terms of “adverse events leading to death”. Thus, of 21,498 reported
368 AEs in the included trials, only 9% were broken down by severity in the articles.
369

Table 3. Terms for reported severity of harms in the primary articles.		
Unique terms (frequency)	Overall terms (%)	Severity (%)
Mild (317); Mild adverse effects (8); Mild in nature (1)	Mild (2)	Mild (2)
Slight (5)	Slight (<1)	
Moderate (1)	Moderate (<1)	Moderate (<1)
Severe (8); Severe intensity adverse events (2); Severe AE (1)	Severe (<1)	Severe (<1)
Serious AEs (620); Serious adverse events (482); SAE (66); SAEs (47); Serious AE (47); Serious adverse event (9); SAEs not assigned pegloticase causality (7); Serious event (2)	Serious adverse events (6)	
Serious infections (108); Serious infectious events (43); Serious infections and infestations (24); AEs of interest, serious infection (13); Serious infectious AEs (4)	Serious infections (<1)	Life threatening (7)
Serious TEAEs (9); Treatment-emergent serious adverse events (6)	Treatment-emergent serious adverse events (<1)	
Serious noninfectious adverse events (12)	Serious noninfectious adverse events (<1)	
Adjudicated CV events (9)	Adjudicated cv events (0<1)	
SAEs were assigned causality (5)	SAEs were assigned causality (<1)	
Adverse events leading to death (8)	Adverse events leading to death (<1)	Death (<1)
Adverse events (5020); AEs (2455); AE (1490); Adverse event (418); Side effects (70); Adverse effects (55); Adverse effect (4)	Adverse events (44)	
Treatment-emergent adverse events (1,914); TEAEs (740); TEAE (664); Treatment-emergent gastrointestinal adverse events (293)	Treatment-emergent adverse events (17)	
Common adverse events (488); Common AEs (397); Most commonly reported (361)	Common adverse events (6)	
AEs of interest (493); Adverse events of interest (32)	Adverse events of interest (2)	
Infectious adverse events (173); Infectious AEs (25)	Infectious adverse events (<1)	
Noninfectious adverse events (149)	Noninfectious adverse events (<1)	
Other events (119); Other adverse events (6)	Other adverse events (<1)	
Non-serious adverse events (112)	Non-serious adverse events (<1)	
Events that occurred in 10% (99)	Events that occurred in 10% (<1)	
Adverse drug reactions (81); Adverse reactions (7); Adverse reaction (5)	Adverse reactions (<1)	
Gastrointestinal adverse events (89)	Gastrointestinal adverse events (<1)	
Acute infusional events (60)	Acute infusional events (<1)	
Adverse events of special interest (45)	Adverse events of special interest (<1)	
Reasons for withdrawals (17); Reasons for withdrawal (10); AEs leading to withdrawal (3)	AEs leading to withdrawal (<1)	
Injection-site reactions (24)	Injection-site reactions (<1)	
Non-APTC events (19)	Non-APTC events (<1)	
Mild or moderate (15); Mild to moderate (2)	Mild to moderate (<1)	
Laboratory abnormalities (7)	Laboratory abnormalities (<1)	
Bowel movement (6)	Bowel movement (<1)	
APTC events (4)	APTC events (<1)	
Laboratory evaluations (3)	Laboratory evaluations (<1)	
Transient non-specific symptoms (2)	Transient non-specific symptoms (<1)	
NA (3,658)	NA (17)	

AE=adverse event; APTC = Antiplatelet Trialists' Collaboration; CV = cardiovascular; NA = not available; SAE=serious adverse event; TEAE = treatment emergent adverse events.

372 Harm Domains

373 When we categorized the 280 harm clusters into system organ classes according to the RCTC 2.0,
374 general 56 (20%), gastrointestinal 41 (15%) and musculoskeletal 36 (13%) were the most used
375 categories ([Supplementary Table D](#)). The least used categories were laboratory data: hematology
376 9 (3%), chemistry 7 (3%), and urinalysis 1 (<1%). However, we lacked categories for mapping 15
377 (5%) harm clusters (e.g., somnolence, lymphoma, and abdominal wall abscess) into the RCTC 2.0.
378 We found, for example, the following gaps: non-specific terms (e.g., fracture), hyperlipidemia
379 (secondary to AEs associated with interleukin [IL]-6 and Janus kinase [JAK] inhibitors), specific
380 infections (e.g., viral, opportunistic, mycobacterial associated with biologics and JAK inhibitors),
381 and cancer-related terms (e.g., basal cell carcinoma). Further, there were no clear groupings for
382 harms related to the renal system and to reproductive organs.

383

384 DISCUSSION

385 In our critical review of 93 RCTs in rheumatology, we (DBB, TGW with support from NG, DEF and
386 RC) identified 117 out of a total of 280 harm clusters that could be appropriate for patient self-
387 reporting. These 117 accounted for more than half of AEs reported in the primary publications.
388 Medical terms could describe all harm clusters appropriate for patient reporting whereas lay
389 language terms described 86% of the clusters. The observer- or patient-reported severity was
390 poorly reported for more than 90% of the identified harms. Further, we identified important and
391 frequently reported harms that we could not map as the RCTC 2.0 presently lacks domains such
392 as infections, malignancies, fractures, and neurological terms such as somnolence.

393 Building on the premise that patients' and clinicians' different perspectives on a
394 disease might influence the assessment of effects in RCTs (43), we feel patients should assess
395 harms and their severity when the harm involves "felt" components. Likewise, clinicians should
396 assess harms when "observed" components are involved. However, if the patient can also observe

397 the AE, then the patient may still be the best person to report it as a patient reported outcome.
398 Each perspective provides clinically meaningful information although a patient-clinician or clinician-
399 patient harm-paradox might occur if harms appear unequally important or severe when observed
400 from two different points of view (Fig. 1).

401 Our study showed that most harm terms reported in the selected articles were in
402 medical (e.g., pyrexia) rather than lay language (e.g., fever). Though most trials used active
403 surveillance to collect AE information, it is unclear whether the collection method was based on
404 e.g., interview or patients' own input. Regardless, "felt" AEs were likely to have been collected from
405 patients in lay language terms and to be spontaneously reported or reported in answer to a
406 question, either general or specific. Then, they were subsequently analyzed and described
407 ("coded") in medical terms e.g., industry typically uses the Medical Dictionary for Regulatory
408 Activities (MedDRA) to harmonize data reporting. As the OMERACT safety working group intends
409 to develop a framework for patient self-reported harms, it is necessary to identify lay language
410 descriptor terms to represent analogous medical terms – initially, to inform a Delphi process
411 including all stakeholders (e.g., patients, clinicians, researchers, ancillary personnel) with the
412 purpose to reach consensus on harm-domains to measure.

413 Our study revealed a major deficiency in the reporting of harm severity in the
414 published literature, though less so for SAEs. We had planned to categorize the severity level of
415 the reported AEs but, even though severity might be systematically reported to trial databases, in
416 clinical study reports, or to regulators, we found no evidence for systematic reporting of the level of
417 severity in the primary articles. It was also difficult to determine how severity was categorized and
418 whether severity of the AEs was assessed by clinicians or patients, though in industry trials, it is
419 typically assessed by the investigator. From the given (lack of) reporting, it was not possible to
420 formally address harm severity in our study, as a meaningful severity assessment would require
421 more consistent reporting than was found in the included trial literature.

422 Although it is mandatory to report SAEs in trials relevant to regulatory oversight,
423 seriousness of an AE may not always correlate with severity of the AE though we categorically

424 assessed SAEs as life-threatening for our analysis. Severity is a measure of intensity, whereas
425 seriousness is defined by the criteria presented previously. An AE of severe intensity need not
426 necessarily to be considered serious, e.g., nausea that persists for several hours may be
427 considered severe nausea, but not a serious AE. Alternatively, a stroke that results in
428 hospitalization but minimal to no permanent disability may be considered mild by an investigator
429 but would be a serious AE. From the patient's perspective, one could consider that a patient would
430 also deem the latter scenario severe – thus there is a risk of a patient-clinician harm paradox. The
431 lack of information on harm severity in primary articles makes it difficult to assess the true benefit-
432 harm profile of an intervention, thereby complicating decision making for patients and clinicians
433 alike when considering medical treatment. Because clinicians tend to systematically downgrade
434 the severity of patients' symptoms (18–20) (our study revealed that most AEs reported in trials
435 within rheumatology involved harms with felt components), a fair assessment of severity should
436 include the patients' perspective (44).

437 To stimulate a balanced and transparent reporting of harms, with emphasis on the
438 rheumatic diseases, we suggest reporting the severity level of harms based on uniform criteria,
439 such as that in the RCTC 2.0 (16). To achieve complete understanding, harms and their severity
440 should be assessed by both the investigator and the patient, and the reporting of harms should
441 reflect both perspectives. The predominating clinician perspective on harms in the selected articles
442 might explain why less than one-third (85/280, 30%) of the harm clusters concerned domains in the
443 core area of life impact (a patient domain). Possibly such patient-reported harms may also have
444 been reflected to a certain degree in the score of a health-related quality of life instrument, but
445 these instruments may not cover all harms relevant to patients. A comprehensive collection of
446 patient-reported harms and their impact is essential because patient self-reports reflect impact on
447 daily health (17). Since other patient-reported harm-instruments, e.g., the PRO-CTCAE, allow
448 severity for some AEs to be based on interference with activities of daily living (22), some might
449 argue that we need a measure that reports life impact of AEs instead. Ultimately, a standardized

450 reporting structure for patient-reported harms within rheumatology RCTs and longitudinal
451 observational studies needs to be developed with patient input.

452 Our results show a diversity of reporting for harms. Some trials reported harms based
453 on system organ class (e.g., gastrointestinal disorders), whereas other trials reported harms using
454 more specific terms (e.g., preferred terms such as vomiting, dizziness or headache). More non-
455 specific terms (e.g., hospitalized or infections) were also reported. Differences in grouping and
456 reporting of harms between trials might lead to more biased, less reliable and less reproducible
457 results (45). We did not systematically analyze reporting levels of all reported AEs according to
458 MedDRA, as we were aiming to optimize reporting according to RCTC 2.0. Industry-sponsored
459 trials will report preferred terms due to use of MedDRA (46) which is less likely to occur with non-
460 industry sponsored trials or investigator-initiated studies - this may also explain the observed
461 difference in reporting levels. MedDRA is a licensed tool and thus not often available to the
462 academic investigator. Also, MedDRA is not always easy to use: observers must be trained to
463 code of AE terms accurately. The RCTC 2.0 might be more accessible, and easier for
464 rheumatologists to use to classify harms for standardized reporting.

465 Our categorization of harm clusters identified some missing categories in RCTC 2.0
466 (16). E.g., there were no clear groupings for harms related to specific infections, cancer-related
467 terms, the renal system, and reproductive organs. We incorporated some of these in the General
468 category, thus making it the most used category (20% of the harm clusters), which may or may not
469 be ideal. While RCTC 2.0 is quite usable, these gaps clearly indicate a need for a revision, and
470 periodic updating, of the RCTC 2.0, as has been suggested previously (47). A revision of the
471 RCTC should also address appropriate use of preferred terms, and match classification to
472 MedDRA for easy cross-referencing.

473 Our study has some strengths. It included a large amount of data from trials during a
474 10-year period. It comprised an exhaustive compilation of harms and a collaborative, consensus-
475 driven consolidation of terms into groupings that can be used to further develop standardized harm
476 instruments. It utilized an international team of experts in the field. It brought to the forefront the

477 need for a separate patient-oriented instrument to report and assess harms from the patient's point
478 of view. It also highlighted the way forward for an update of a specific rheumatology-oriented,
479 relatively easy-to-use harms instrument.

480 A limitation of our study, there is likely underreporting of harms. In published trial
481 literature of health care interventions, harms are underreported in general (2,3), and some of the
482 selected publications from the included trials only described events that were "reported by $\geq 5\%$ of
483 patients" or "most frequent AEs". Limiting reporting of AEs based on frequency may be important to
484 identify true signals for harm from a single clinical trial based on the rule of three (48). However,
485 reporting all events that occur can assist in subsequent meta-analyses of data to detect true
486 signals for rare AEs. The use of nonspecific terms to describe AEs might also explain why half of
487 the AEs we found to be appropriate for patient self-reporting were reported fewer than 10 times in
488 the publications of the included trials. Our extraction of data from the included trials most likely
489 worsened underreporting in our study (2). We excluded secondary publications; we did not
490 examine appendices; we did not seek unpublished data such as clinical study reports, Summary
491 Basis of Approvals, or European Public Assessment Reports; and we extracted the most specific
492 AE terms, not including data such as "total number of AEs" as we could not classify them. Despite
493 these limitations, we established 693 specific unique reported terms for AEs.

494 We cannot be confident that we identified all harms important to rheumatology
495 patients in this study. We chose specifically to explore rheumatology in this review - such as
496 previously done within cancer (22). To expand the list of reported harms with felt AEs, additional
497 relevant harms might be identified via review of publications from trials in fields other than
498 rheumatology (7), review of unpublished data (2), and input from patients.

499 Our study also has other limitations. We selected trials included in systematic reviews
500 conducted by the CMSG over a 10-year period. We cannot exclude the possibility that other
501 rheumatologic trials would describe relevant harm-information not identified from the included trials
502 (e.g., a significant increase in the number of published articles within psoriatic arthritis occurred
503 from 2016 to 2018 and these recent trials were not yet included in selected Cochrane reviews;

504 many large trials of systemic lupus erythematosus were also not available in Cochrane reviews).
505 We also did not request Freedom of Information data, as it is a very lengthy process which might
506 have delayed this project indefinitely. Further, some Cochrane reviews might deal only with
507 efficacy but not safety. As we selected only primary publications from RCTs included in Cochrane
508 reviews, we might have missed secondary papers on safety. Finally, two authors (supported by a
509 third author when in doubt) did the clustering and classification of AEs, and some classification of
510 harms might have been done differently if more authors had been involved.

511 We believe our results suggest that the development of a framework for patient self-
512 reported harms can potentially provide a more balanced account of treatment experiences as well
513 as a more balanced assessment of treatment strategies when deciding on new treatments. To
514 inform a Delphi process, we need patients and experts globally both to identify lay language terms
515 to cover medical terms for the harm clusters and to identify relevant additional harms. When
516 deciding on which outcomes to measure in the framework, we need a standardized reporting
517 structure for patient-reported harms including severity – a structure that we should develop in
518 collaboration with patients. Further, we also need a revision and expansion of domains included in
519 the RCTC 2.0, and the relative weights to give to the patient perspective and the harms related to
520 pathophysiology etc. will need to be addressed in future research.

521 In conclusion, we found that 42% of the AEs described in the rheumatology trial
522 literature are appropriate for patient self-reporting, and these represent the majority (58%) of the
523 total number of AEs reported in primary articles of rheumatology clinical trials. For more than 90%
524 of the identified harms, the AE severity was poorly reported. Our results support the development
525 of a standardized reporting framework for patient-reported harms in rheumatology RCTs and
526 longitudinal observational studies to ensure reliable reporting of AEs with severity grading
527 according to both patients and investigators.

528

529 **ACKNOWLEDGMENTS**

530 The Parker Institute is supported by grants from the Oak Foundation. The Oak Foundation is a
531 group of philanthropic organizations and, since its establishment in 1983; it has given grants to not-
532 for-profit organizations around the world.

533

534 **FUNDING**

535 This research did not receive any specific grant from funding agencies in the public, commercial, or
536 not-for-profit sectors. The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a
537 core grant from the Oak Foundation (OCAY-18-774-OFIL); the Oak Foundation had no role in the
538 study design, data collection and analyses, interpretation or reporting of this work, or the decision
539 to submit the work for publication. P.G. Conaghan is supported in part by the UK National Institute
540 for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of
541 the authors and not necessarily those of the UK National Health Service, the NIHR, or the
542 Department of Health.

543

544 **AUTHOR CONTRIBUTIONS**

545 Berthelsen and Christensen had full access to all data in the study and take responsibility for the
546 integrity of the data and the accuracy of the data analysis.

547 Study concept and design: Berthelsen and Christensen.

548 Acquisition: Berthelsen with support from Christensen.

549 Extraction: Berthelsen and Woodworth.

550 Analysis and interpretation: Berthelsen and Woodworth with support from Furst, Goel and

551 Christensen.

552 Drafting of the manuscript: Berthelsen and Christensen.
553 Critical revision of the manuscript for important intellectual content: All authors.
554 Statistical analysis: Berthelsen and Christensen.
555

556 **DECLARATION OF INTEREST**

557 Berthelsen: none
558 Woodworth: none
559 Ioannidis: none
560 Tugwell: none relevant
561 Devoe: none relevant
562 Williamson: none
563 Terwee: none
564 Suarez-Almazor: none
565 Strand: none relevant
566 Leong: none
567 Goel: none relevant
568 Conaghan: none relevant
569 Boers: none relevant
570 Shea: none relevant
571 Brooks: none relevant
572 Simon: none relevant
573 Furst: none relevant
574 Christensen: none relevant
575

576 REFERENCES

- 577 1. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured
578 approach. *BMC Med Res Methodol*. 2007 Jul;7:32.
- 579 2. Golder S, Loke YK, Wright K, Norman G. Reporting of adverse events in published and unpublished
580 studies of health care interventions: A Systematic Review. *PLoS Med*. 2016 Sep;13(9):e1002127.
- 581 3. Tang E, Ravaud P, Riveros C, Perrodeau E, Dechartres A. Comparison of serious adverse events posted
582 at ClinicalTrials.gov and published in corresponding journal articles. *BMC Med*. 2015 Aug 14;13:189.
- 583 4. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm
584 outcomes within studies: findings from a cohort of systematic reviews. *BMJ (Clinical research ed)*.
585 2014 Nov 21;349:g6501.
- 586 5. Keebler D, Teng E, Chia J, Galanter J, Peake J, Tuckwell K. Regional variations in adverse event
587 reporting rates and ACR responses in placebo/standard-of-care arms of rheumatoid arthritis trials.
588 *Rheumatology (Oxford)* [Internet]. Available from: [http://academic.oup.com/rheumatology/advance-](http://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keaa043/5809194)
589 [article/doi/10.1093/rheumatology/keaa043/5809194](http://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keaa043/5809194)
- 590 6. Hodkinson A, Kirkham JJ, Tudur-Smith C, Gamble C. Reporting of harms data in RCTs: a systematic
591 review of empirical assessments against the CONSORT harms extension. *BMJ Open*. 2013 Sep
592 27;3(9):e003436.
- 593 7. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in
594 randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004 Nov
595 16;141(10):781–8.
- 596 8. Hadi MA, McHugh GA, Conaghan PG. Quality of reporting of harms in randomised controlled trials of
597 pharmacological interventions for rheumatoid arthritis: a systematic review. *Evid Based Med*. 2017
598 Oct;22(5):170–7.
- 599 9. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome
600 measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol*. 2014 Jul;67(7):745–53.
- 601 10. Boers M, Beaton DE, Shea BJ, Maxwell LJ, Bartlett SJ, Bingham CO, et al. OMERACT filter 2.1:
602 elaboration of the conceptual framework for outcome measurement in health intervention studies. *J*
603 *Rheumatol*. 2019 Aug 1;46(8):1021–7.
- 604 11. Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to
605 improve outcome measurement in rheumatology. *Trials*. 2007 Nov 26;8:38.
- 606 12. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core
607 outcome sets for clinical trials: issues to consider. *Trials*. 2012 Aug 6;13:132.
- 608 13. COMET Initiative [Internet]. [cited 2020 May 30]. Available from: <http://www.comet-initiative.org/>

- 609 14. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed
610 for outcomes in medical research to help improve knowledge discovery. *J Clin Epidemiol*. 2018
611 Apr;96:84–92.
- 612 15. Klokke L, Tugwell P, Furst DE, Devoe D, Williamson P, Terwee CB, et al. Developing an OMERACT core
613 outcome set for assessing safety components in rheumatology trials: the OMERACT Safety Working
614 Group. *J Rheumatol*. 2017 Dec 1;44(12):1916.
- 615 16. Woodworth T, Furst DE, Alten R, Bingham CO 3rd, Yocum D, Sloan V, et al. Standardizing assessment
616 and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity
617 Criteria v.2.0. *J Rheumatol*. 2007 Jun;34(6):1401–14.
- 618 17. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients
619 vs clinicians: relationships with clinical outcomes. *J Natl Cancer Inst*. 2009 Dec;101(23):1624–32.
- 620 18. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and
621 their documentation in the medical record. *Am J Manag Care*. 2008 Aug;14(8):530–9.
- 622 19. Efficace F, Rosti G, Aaronson N, Cottone F, Angelucci E, Molica S, et al. Patient- versus physician-
623 reporting of symptoms and health status in chronic myeloid leukemia. *Haematologica*. 2014
624 Apr;99(4):788–93.
- 625 20. Yen JC, Abrahamowicz M, Dobkin PL, Clarke AE, Battista RN, Fortin PR. Determinants of discordance
626 between patients and physicians in their assessment of lupus disease activity. *J Rheumatol*. 2003
627 Sep;30(9):1967–76.
- 628 21. Klokke L, Berthelsen DB, Woodworth T, Andersen KM, Furst DE, Devoe D, et al. Identifying possible
629 outcome domains from existing outcome measures to inform an OMERACT core domain set for safety
630 in rheumatology trials. *J Rheumatol*. 2019 May;46(9):1173–8.
- 631 22. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the
632 National Cancer Institute’s patient-reported outcomes version of the common terminology criteria for
633 adverse events (PRO-CTCAE). *J Natl Cancer Inst*. 2014 Sep;106(9).
- 634 23. OMERACT Handbook [Internet]. OMERACT Handbook. [cited 2020 Apr 6]. Available from:
635 <https://omeracthandbook.org/>
- 636 24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for
637 reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions:
638 explanation and elaboration. *BMJ (Clinical research ed)*. 2009 Jul 21;339:b2700.
- 639 25. Tricco AC, Lillie E, Zarin W, O’Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping
640 reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018 Oct 2;169(7):467.
- 641 26. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of
642 systematic reviews. *PLoS Med*. 2007 Mar 27;4(3):e78.
- 643 27. Tarp S, Eric Furst D, Boers M, Luta G, Bliddal H, Tarp U, et al. Risk of serious adverse effects of
644 biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis.
645 *Rheumatology (Oxford)*. 2017 Mar 1;56(3):417–25.

- 646 28. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of
647 Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies
648 in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012 Apr;64(4):465–74.
- 649 29. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR
650 recommendations for the management of rheumatoid arthritis with synthetic and biological disease-
651 modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017 Jun;76(6):960–77.
- 652 30. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of
653 Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol (Hoboken,
654 NJ)*. 2016 Jan;68(1):1–26.
- 655 31. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Hauser W, Fluss E, et al. EULAR revised
656 recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017 Feb;76(2):318–28.
- 657 32. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of
658 Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and
659 pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012
660 Oct;64(10):1431–46.
- 661 33. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of
662 Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis
663 of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012 Oct;64(10):1447–61.
- 664 34. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated
665 EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017
666 Jan;76(1):29–42.
- 667 35. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of
668 Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care
669 Res (Hoboken)*. 2012 Jun;64(6):797–808.
- 670 36. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, et al. Joint European League
671 Against Rheumatism and European Renal Association-European Dialysis and Transplant Association
672 (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis.
673 *Ann Rheum Dis*. 2012 Nov;71(11):1771–82.
- 674 37. Lems WF, Dreinhofer KE, Bischoff-Ferrari H, Blauth M, Czerwinski E, da Silva J, et al. EULAR/EFORT
675 recommendations for management of patients older than 50 years with a fragility fracture and
676 prevention of subsequent fractures. *Ann Rheum Dis*. 2017 May;76(5):802–10.
- 677 38. van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update
678 of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017
679 Jun;76(6):978–91.
- 680 39. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR
681 recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017 Aug;76(8):1327–39.
- 682 40. Post Approval Safety Data Management. Note for guidance on definitions and standards for
683 expedited reporting E2D; 2006: Available at <https://www.ema.europa.eu/en/documents/scientific->

684 guideline/international-conference-harmonisation-technical-requirements-registration-
685 pharmaceuticals-human-use_en-12.pdf. Accessed April 8, 2020.

686 41. U.S. Department of Health and Human Services: Common Terminology Criteria for Adverse Events
687 (CTCAE) Version 4.0 (v4.03: June 14, 2010): Available at
688 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed
689 October 28, 2017.

690 42. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977
691 Mar;33(1):159–74.

692 43. Berthelsen DB, Ginnerup-Nielsen E, Juhl C, Lund H, Henriksen M, Hróbjartsson A, et al. Treatment
693 effect sizes vary in randomized trials depending on type of outcome measure. *J Clin Epidemiol*. 2020
694 Mar;(123):27–38.

695 44. Basch E. The missing patient voice in drug-safety reporting. *N Engl J Med*. 2010 Mar 11;362(10):865–
696 9.

697 45. Schroll JB, Maund E, Gøtzsche PC. Challenges in coding adverse events in clinical trials: a systematic
698 review. *PLoS ONE*. 2012;7(7):e41174.

699 46. Introductory Guide MedDRA version 22.1.pdf. [Internet]. [cited 2019 Nov 18]. Available from:
700 https://www.meddra.org/sites/default/files/guidance/file/000354_intguide_22.1.pdf

701 47. Stach CM, Sloan VS, Woodworth TG, Kilgallen B, Furst DE. Rheumatology Common Toxicity Criteria
702 (RCTC): An Update Reflecting Real-World Use. *Drug Saf*. 2019;42(12):1499–506.

703 48. Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a
704 statistical reminder. *BMJ*. 1995 Sep 2;311(7005):619–20.

APPENDIX A

SUPPLEMENTARY MATERIAL

Supplementary Fig A.1. Conceptual framework of Core Areas for outcome measurement in the setting of health intervention studies	36
Supplementary Fig A.2. Development of a Core Domain Set from the Core Areas of measurement.....	37
Supplementary Fig B. Agreements of harms appropriate/not appropriate for patient self-reporting	38
Supplementary Table A. List of included trials.....	39
Supplementary Table B. List of harms reported in drug rheumatology trials.....	45
Supplementary Table C. Reasons for categorization when ambiguity might exist in AEs appropriate for patient self-reporting	67
Supplementary Table D. Number of harms within RCTC-categories.....	70

Supplementary Fig A.1. Conceptual framework of Core Areas for outcome measurement in the setting of health intervention studies

Fig A.1. Conceptual framework of Core Areas for outcome measurement in the setting of health intervention studies.

Resource Use has a lighter shade to indicate it is currently strongly recommended, but not mandatory for inclusion. The choice of specific Domains within an Area depends on the context for which the core set is being developed in all areas, domains can be generic or made more specific, for example disease-specific, time-specific (e.g., short or long-term), specific for patient preference, and so forth. ICF, International Classification of Functioning, Disability and Health.

Supplementary Fig A.2. Development of a Core Domain Set from the Core Areas of measurement

Journal of Clinical Epidemiology 2014 67, 745-753 DOI: (10.1016/j.jclinepi.2013.11.013)
Copyright © 2014 The Authors. [Terms and Conditions](#)

Fig A.2. Development of a Core Domain Set from the Core Areas of measurement.

A Core Domain Set is defined as the minimum set of Domains and Subdomains necessary to adequately cover all Core Areas, that is, fully measure all relevant concepts of a specific health condition within a specified setting.

Supplementary Fig B. Agreements of harms appropriate/not appropriate for patient self-reporting

Fig B. Agreements of harms appropriate/not appropriate for patient self-reporting.

Harm-clusters are reported in medical terms. Harms in blue highlight illustrate the 117 harm-clusters appropriate for patient reporting. Harms in black highlight illustrate the 163 harm-clusters non-appropriate for patient reporting. Harms included in both blue and black circle illustrate disagreements that were resolved by discussion until consensus was reached among authors as whether appropriate for patient self-reports (illustrated by the different colors).

Supplementary Table A. List of included trials

- Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clinical Drug Investigation* 2010;30(8): 489–505.
- Alten R, Gomez-Reino J, Durez P, Beaulieu A, Sebba A, Krammer G, et al. Efficacy and safety of the human anti- IL-1_α monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study. *BMC Musculoskeletal Disorder* 2011;12:153–63.
- Asmus MJ, Essex MN, Brown PB, Mallen SR. Efficacy and tolerability of celecoxib in osteoarthritis patients who previously failed naproxen and ibuprofen: results from two trials. *International Journal of Clinical Rheumatology* 2014;9(6):551–8.
- Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. *Annals of the Rheumatic Diseases* 2016;75(1):75–83.
- Barkham N, Coates LC, Keen H, Hensor E, Fraser A, Redmond A, et al. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. *Annals of the Rheumatic Diseases* 2010;69(11): 1926–8.
- Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Research Therapy* 2010;12(2):R63.
- Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful long-term urate lowering with febuxostat or allopurinol in subjects with gout. *Journal of Rheumatology* 2009;36(6): 1273–82.
- Beyaz S G. Comparison of efficacy of intra-articular morphine and steroid in patients with knee osteoarthritis. *Journal of Anaesthesiology Clinical Pharmacology* 2012;28(4): 496–500.
- Brahmachari B, Chatterjee S, Ghosh A. Efficacy and safety of diacerein in early knee osteoarthritis: a randomized placebo-controlled trial. *Clinical Rheumatology* 2009;28: 1193–1198.
- Braun J, van der Horst-Bruinsma IE, Huang F, Burgos- Vargas R, Vlahos B, Koenig AS, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: A randomized, double-blind trial. *Arthritis and Rheumatism* 2011;63(6):1543–51.
- Campos G C, Rezende M U, Pailo A F, Frucchi R, Camargo O P. Adding triamcinolone improves viscosupplementation: A randomized clinical trial. *Clinical Orthopaedics and Related Research* 2013;471(2):613–20.
- Chao J, Wu C, Sun B, Hose M K, Quan A, Hughes T H, et al. Inflammatory characteristics on ultrasound predict poorer long-term response to intraarticular corticosteroid injections in knee osteoarthritis. *Journal of Rheumatology* 2010;37(3):650–5.
- Chatzidionysiou K, Turesson C, Teleman A, Knight A, Lindqvist E, Larsson P, et al. Multicenter, randomised, controlled, open-label pilot study of the feasibility of discontinuation of adalimumab in rheumatoid arthritis patients is stable clinical remission. *Arthritis and Rheumatism* 2012;64(Suppl 10):776.
- Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology (Oxford)* 2012;51(7):1226–34.
- Cohen MM, Altman RD, Hollstrom R, Hollstrom C, Sun C, Gipson B. Safety and efficacy of intra-articular sodium hyaluronate (Hyalgan) in a randomized, double-blind study for osteoarthritis of the ankle. *Foot and Ankle International* 2008;29(7):657–63. [PUBMED: 18785414]
- Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulphasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. *Annals of the Rheumatic Diseases* 2009;68(7):1146–52. [PUBMED: 18794178]

Supplementary Table A

- DeGroot H, Uzunishvili S, Weir R, Al-omari A, Gomes B. Intra-articular injection of hyaluronic acid is not superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo-controlled study. *The Journal of Bone and Joint Surgery, American Volume* 2012;94(1):2–8. [PUBMED: 22218376]
- Di Sante L, Paoloni M, Dimaggio M, Colella L, Cerino A, Bernetti A, et al. Ultrasound-guided aspiration and corticosteroid injection compared to horizontal therapy for treatment of knee osteoarthritis complicated with Baker's cyst: a randomized controlled trial. *European Journal of Physical & Rehabilitation Medicine* 2012;48(4):561–7.
- Ekeberg OM, Bautz-Holter E, Tveita EK, Juel NG, Kvalheim S, Brox JI, et al. Subacromial ultrasound guided or systemic steroid injection for rotator cuff disease: randomised double blind study. *BMJ* 2009;338:a3112.
- Emery P, Bingham III CO, Burmester GR et al. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. *Ann Rheum Dis* 2017;76:96–104
- Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *The Lancet* 2008;372(9636):375–82.
- Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human antitumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naïve patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;60(8):2272–83.
- Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, Alecock E, Lee J, Kremer J. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Annals of the Rheumatic Disease* 2008;67:1516–23.
- Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. *Advances in Therapy* 2011;28(5):401–17.
- Fardellone P, Zaim M, Saurel AS, Maheu E. Comparative efficacy and safety study of two chondroitin sulfate preparations from different origin (avian and bovine) in symptomatic osteoarthritis of the knee. *The open rheumatology journal* 2013;7(1):1–12.
- Fautrel B, Pham T, Alfaïate et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid Arthritis Study). *Ann Rheum Dis* 2016;75:59–67
- Fleischmann R, Vencovsky J, Van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease modifying antirheumatic therapy: the FAST4WARD study. *Annals of the Rheumatic Diseases* 2009;68(6):805–11.
- Gabay C, Medinger-Sadowski C, Gascon D, Kolo F, Finckh A. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis. *Arthritis and Rheumatism* 2011;63(11):3383–91.
- Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs. The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis & Rheumatism* 2008;58(10):2968–80.
- Giardina AR, Ferrante A, Ciccia F, Impastato R, Miceli M, Principato A, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. *Rheumatology International* 2009 October 23 [Epub ahead of print]. [DOI: 10.1007/s00296-009-1157-3]
- Goldfarb, D. S. MacDonald, P. Hunt, B. Gunawardhana, L. Febuxostat in Gout: Serum Urate Responses in Uric Acid Overproducers vs. Underexcretors. *American Journal of Kidney Diseases*. 2010; Vol. 55:B59.
- Hakala M, Kröger H, Valleala H, Hienonen-Kempas T, Lehtonen-Veromaa M, Heikkinen J, et al. Once-monthly oral ibandronate provides significant improvement in bone mineral density in postmenopausal women treated with glucocorticoids for inflammatory rheumatic diseases: a 12-month, randomized, double-blind, placebo-controlled trial. *Scandinavian Journal of Rheumatology* 2012;41(4):260–6.

Supplementary Table A

Harigai M, Takeuchi T, Tanaka Y, Matsubara T, Yamanaka H, Miyasaka N. Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. *Modern Rheumatology* 2012;22:814–22.

Hartrick C, Van Hove I, Stegmann JU, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clinical Therapeutics* 2009;31(2):260–71.

Henriksen M, Christensen R, Klokke L, Bartholdy C, Bandak E, Ellegaard K, et al. Evaluation of the benefit of corticosteroid injection before exercise therapy in patients with osteoarthritis of the knee. A randomized clinical trial. *JAMA Internal Medicine* 2015;175(6):923–30. DOI: 10.1001/jamainternmed.2015.0461

Hussain SA, Al-Khalifa II, Jasim NA, Gorial F. Adjuvant use of melatonin for treatment of fibromyalgia. *Journal of Pineal Research* 2011;50(3):267–71.

Inman R, Maksymowych W, CANDLE group. A doubleblind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. *Journal of Rheumatology* 2010;37 (6):1–8. [DOI: doi:10.3899/jrheum.091042]

Inman RD, Davis JC Jr, Heijde Dv, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis and Rheumatism* 2008;58(11):3402–12.

Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* 2008;371:1854–60.

Kahan A, Uebelhart D, De Vathaire F, Delmas PD, Reginster JY. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, doubleblind, placebo-controlled trial. *Arthritis and Rheumatism* 2009;60(2):524–33.

Kanzaki N, Saito K, Maeda A, Kitagawa Y, Kiso Y, Watanabe K, et al. Effect of a dietary supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides on symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled study. *Journal of Science and Food Agriculture* 2012;92:862–9.

Karatosun V, Unver B, Ozden A, Ozay Z, Gunal I. Intraarticular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up. *Clinical and Experimental Rheumatology* 2008;26(2):288–294. [PUBMED: 18565251]

Katz N, Hale M, Morris D, Stauffer J. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. *Postgraduate Medicine* 2010;122(4):112–28.

Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, doubleblind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008;58:964–75.

Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis and Rheumatism* 2008;58(11):3319–29.

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;68:789–96.

Lee H-J, Lim K-B, Kim D-Y, Lee K-T. Randomized-controlled trial for efficacy of intra-articular injection for-adhesive capsulitis: ultrasonography-guided versus blind-technique. *Archives of Physical Medicine & Rehabilitation* 2009;90(12):1997–2002.

Li EK, Zhu TY, Hung VY, Kwok AW, Lee VW, Lee KK, et al. Ibandronate increases cortical bone density in patients with systemic lupus erythematosus on long-term glucocorticoid. *Arthritis Research & Therapy* 2010;12(5): R198.

Magrans-Courtney T, Wilborn C, Rasmussen C, Ferreira M, Greenwood L, Campbell B, et al. Effects of diet type and supplementation of glucosamine, chondroitin, and MSM on body composition, functional status, and markers of health in women with knee osteoarthritis initiating a resistance-based exercise and weight loss program. *Journal of International Society of Sports Medicine* 2011;8:8.

Supplementary Table A

- Möller I, Pérez M, Monfort J, Benito P, Cuevas J, Perna C, et al. Effectiveness of chondroitin sulphate in patients with concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study. *Osteoarthritis and Cartilage* 2010;18:S32–40.
- Nakasone Y, Watabe K, Watanabe K, Tomonaga A, Nagaoka I, Yamamoto T, et al. Effect of a glucosaminebased combination supplement containing chondroitin sulfate and antioxidant micronutrients in subjects with symptomatic knee osteoarthritis: a pilot study. *Experimental and Therapeutic Medicine* 2011;2(5):893.
- Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Modern Rheumatology* 2009;19:12–19.
- Pavelka K, Coste P, Géher P. Efficacy and safety of piascledine 300 versus chondroitin sulfate in a 6 months treatment plus 2 months observation in patients with osteoarthritis of the knee. *Clinical Rheumatology* 2010;29: 659–70.
- Petrella R J, Emans P J, Alleyne J, Dellaert F, Gill D P, Maroney M. Safety and performance of Hydros and Hydros-TA for knee osteoarthritis. A prospective, multicenter, randomized, double-blind feasibility trial. *BMC Musculoskeletal Disorders* 2015;16:57:1–9.
- Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker- Hermann E, Zeidler H, et al. Effect of non-steroidal antiinflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Annals of the Rheumatic Diseases* 2012;71(10):1616–22.
- Railhac JJ, Zaim M, Saurel AS, Vial J, Fournie B. Effect of 12 months treatment with chondroitin sulfate on cartilage volume in knee osteoarthritis patients: A randomized, double-blind, placebo-controlled pilot study using MRI. *Clinical Rheumatology* 2012;31(9):1347–57.
- Reinders MK, Haagsma C, Jansen TL, van Roon EN, Delsing J, van de Laar MA, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100- 200 mg/day in patients with gout. *Annals of the Rheumatic Diseases* 2009;68(6):892–7.
- Reinders MK, van Roon EN, Jansen TL, Delsing J, Griep EN, Hoekstra M, et al. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Annals of the Rheumatic Diseases* 2009;68(1): 51–6.
- Rozendaal RM, Koes BW, m van Osch G, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis. *Annals of Internal Medicine* 2008;148:268–77.
- Sawitzke AD, Shi H, Finco MF, Dunlop DD, Harris CL, Singer NG, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Annals of the Rheumatic Diseases* 2010; 69:1459-64.
- Schiff M, Keiserman M, Coddling C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Annals of the Rheumatic Diseases* 2008;67(8):1096–103.
- Schumacher HR, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5- yr findings of the FOCUS efficacy and safety study. *Rheumatology* 2009;48:188–94.
- Schumacher HR, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis and Rheumatism* 2008;59(11):1540–8.
- Schumacher HR, Berger MF, Li-Yu J, Perez-Ruiz F, Burgos- Vargas R, Li C. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. *Journal of Rheumatology* 2012;39:1859–66.
- Shu-Fen Sun, Chien-Wei Hsu, Huey-Shyan Lin, Yi- Jiun Chou, Jun-Yang Chen, Jue-Long Wang. Efficacy of intraarticular botulinum toxin A and intraarticular hyaluronate plus rehabilitation exercise in patients with unilateral ankle osteoarthritis: a randomized controlled trial. *Journal of Foot and Ankle Research* 2014;7(9):1–9.
- Singal KK, Goyal S, Gupta P, Aggawal BK. Comparison between allopurinol and febuxostat in management of gout patients - a prospective study. *Bangladesh Journal of Medical Science* 2011;10:257–9.

Supplementary Table A

- Singh JA, Mahowald ML, Noorbaloochi S. Intra-articular botulinum toxin A for refractory shoulder pain: a randomized, double-blinded, placebo-controlled trial. *Translational Research: The Journal Of Laboratory and Clinical Medicine* 2009;153(5):205–16.
- Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. for the OPTION Investigators*. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;371:987–97.
- Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. *Annals of the Rheumatic Diseases* 2015; Vol. 74, issue 5:843–50. [DOI: 10.1136/annrheumdis-2013-204632]
- Smolen JS, Emery P, Fleischmann R et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone; the randomised controlled OPTIMAL trial. *Lancet* 2014;383:321–32
- Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;374(9685):210–21.
- Smolen JS, Landewe RB, Mease PJ, Brzezicki J, Mason D, Lijntens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Annals of the Rheumatic Diseases* 2009;68:797–804.
- Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque- Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013; 381:918–29.
- Snijders GF, van den Ende CH, van Riel PL, van den Hoogen FH, den Broeder AA. The effects of doxycycline on reducing symptoms in knee osteoarthritis: results from a triple-blinded randomised controlled trial. *Annals of the Rheumatic Diseases* 2011;70(7):1191–6. [PUBMED: 21551510]
- Stoch SA, Saag KG, Greenwald M, Sebba AI, Cohen S, Verbruggen N, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone loss: a 12-month randomized, placebo-controlled clinical trial. *Journal of Rheumatology* 2009;36:1705–14.
- Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology (Oxford)* 2012;51(10):1860–9.
- Strand V, Mease P, Burmester GR, Nikai E, Coteur G, Van Vollenhoven R, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Research and Therapy* 2009;11(6):R170.
- Sundy JS, Baraf HSB, Yood RA, Edwards NL, Gutierrez- Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment; two randomized controlled trials. *JAMA* 2011;306:711–20. [ClinicalTrials.gov Identifier NCT00325195]
- Sundy JS, Becker MA, Baraf HSB, Barkhuizen A, Moreland LW, Huang W, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: Results of a phase II randomized study. *Arthritis & Rheumatism* 2008;58(9):2882–91.
- Saadati N, Rajabian R. The effect of bisphosphonate on prevention of glucocorticoid-induced osteoporosis. *Iranian Red Crescent Medical Journal* 2008;10(1):8–11.
- Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *American Journal of Medicine* 2012;125(11):1126–34.
- Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomised, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis and Rheumatism* 2010;62:1060–8.

Supplementary Table A

Terkeltaub RA, Schumacher HR, Carter JD, Baraf HSB, Evans RR, Wang J, et al. Rilonacept in the treatment of acute gouty arthritis: a randomised, controlled clinical trial using indomethacin as the active comparator. *Arthritis Research & Therapy* 2013;15:R25.

Ucuncu F, Capkin E, Karkucak M, Ozden G, Cakirbay-H, Tosun M, et al. A comparison of the effectiveness of-landmark-guided injections and ultrasonography guided-injections for shoulder pain. *Clinical Journal of Pain* 2009;25(9):786–9.-

Weinblatt ME, Fleischmann R, Huizinga TW, Emery P, Pope J, Massarotti EM, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology (Oxford)* 2012;51:2204–14.

Wildi LM, Raynauld J-P, Martel-Pelletier J, Beaulieu A, Bessette L, Morin F, et al. Chondroitin sulfate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomized, double-blind, placebo- controlled pilot study using MRI. *Annals of the Rheumatic Diseases* 2011;70:982-9.

Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. *Foot and Ankle Surgery* 2010;16(4):159–63.

Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebocontrolled trial. *Modern Rheumatology* 2014;24(5):715–24. [DOI: 10.3109/14397595.2013.864224]

Yavuz U, Sokucu S, Albayrak A, Ozturk K. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. *Rheumatology International* 2012;32(11):3391–6.

Yeap SS, Fauzi AR, Kong NC, Halim AG, Soehardy Z, Rahimah I, et al. A comparison of calcium, calcitriol, and alendronate in corticosteroid-treated premenopausal patients with systemic lupus erythematosus. *Journal of Rheumatology* 2008;35:2344–7.

Zegels B, Crozes P, Uebelhart D, Bruyere O, Reginster JY. Equivalence of a single dose (1200 mg) compared to a threetime a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. *Osteoarthritis & Cartilage* 2013;21(1):22–7.

Zhou L, Xu QF, Zhang WS. Comparative observation of therapeutic effects of acupuncture combined with infrared irradiation and western medicine on acute gouty arthritis. *World Journal of Acupuncture* 2012;22(1):30–4.

Østergaard M, Jacobsson LTH, Schaufelberger C, Hansen MS, Bijlsma JWJ, Dudek A, et al. MRI assessment of early response to certolizumab pegol in rheumatoid arthritis: a randomised, double-blind, placebo-controlled phase IIIb study applying MRI at weeks 0, 1, 2, 4, 8 and 16. *Annals of the Rheumatic Diseases* 2015;74(6):1156–63.

Supplementary Table B. List of harms reported in drug rheumatology trials**Table B**

List of harms reported in drug rheumatology trials.

No of reported harms	Reported AEs	Harm-cluster*	Sum of harms	Core Area	Category of appropriateness for patient reporting	RCTC category
390	Increase in the ALT level ≤ 3 -fold the upper limit of normal	Increases in liver transaminase levels (<i>liver function tests abnormal</i>)	1833	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
335	Increase in the AST level ≤ 3 -fold the upper limit of normal					
216	ALT ≥ 1.5 times the ULN					
165	Liver function analysis					
149	AST ≥ 1.5 times the ULN					
138	Hepatic disorders					
64	ALT increased					
48	AST increased					
41	Increases in alanine aminotransferase concentrations of more than three times the upper limit of normal					
36	Increase in the ALT level > 3 -fold the upper limit of normal					
26	Raised alanine aminotransferase					
21	ALT level increased					
20	Abnormal hepatic function					
19	Elevated ALT					
18	AST level increased					
15	Liver function analyses					
15	Liver function analyses abnormalities					
15	Increase in the AST level > 3 -fold the upper limit of normal					
14	Hepatobiliary disorders					
12	Abnormal alanine aminotransferase levels (75 iu/liter and increased by 100%)					
11	Increases in alanine aminotransferase concentrations of more than five times the upper limit of normal					
10	Increases in ALT					
10	Hepatic enzyme increased					
9	Increases in ALT from normal at baseline to more than three times ULN to five times ULN					
7	Increases in AST					
5	Liver function tests abnormal					
4	Elevated AST					
4	Raised aspartate aminotransferase					
3	Increases in liver transaminase levels					
2	Hepatotoxicity					
2	Elevations in both ALT and AST ≥ 3 times the ULN					
2	> 10 times the upper limit of normal ALT/AST with concurrent bilirubin > 2 times the upper limit of normal					
2	Liver function abnormalities					
1	Increased levels of alanine aminotransferase					
1	ALT ≥ 5 times the ULN and AST ≥ 3 times the ULN					

Supplementary Table B

1	ALT ≥ 5 times ULN					
1	ALT elevation ≥ 3 times the ULN					
1	Changes in liver function					
1167	Upper respiratory tract infections	Upper respiratory tract infection	1685	PM	Mostly observed AEs with felt components	Ear/nose/throat
4	Upper respiratory symptoms					
499	Upper respiratory tract infection					
8	Upper respiratory tract infection NOS					
7	Upper respiratory tract inflammation					
881	Headache	Headache	1138	Life impact	Mostly felt AEs	General (constitutional)
198	Headaches					
58	Headaches NEC					
1	Migraine					
1023	Nausea	Nausea	1038	Life impact	Mostly felt AEs	Gastrointestinal
15	Nausea (all occurrences)					
960	Infections and infestations	Infections and infestations (none)	964	PM	Clinically/measurable observable AEs	General (constitutional)
4	Infections and infestations (diverticulitis; pneumonia; urosepsis)					
463	Diarrhea	Diarrhea	713	Life impact	Mostly felt AEs with observed components	Gastrointestinal
184	Diarrhoea					
65	Diarrhea (all occurrences)					
1	Soft stool					
536	Musculoskeletal and connective tissue signs and symptoms	Musculoskeletal and connective tissue signs and symptoms (none)	649	Life impact	Mostly felt AEs with observed components	Musculoskeletal
113	Musculoskeletal and connective tissue signs and symptoms NEC					
596	Constipation	Constipation	597	Life impact	Mostly felt AEs with observed components	Gastrointestinal
1	Stool hardness					
207	Increase in the total cholesterol level from <240 mg/dl at baseline to ≥240 mg/dl at week 24	Hyperlipidemia (<i>increase in total cholesterol level</i>)	587	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
141	Increases in the LDL level from <160 mg/dl at baseline to ≥160 mg/dl at week 24					
105	Increase in total cholesterol to more than 6.2 mmol/l					
60	Increases in the ratio of total to HDL cholesterol of more than 30% above baseline					
52	Low-density lipoprotein elevation to >160 mg/dl					
15	Changes in the triglyceride level from <500 mg/dl at baseline to ≥ 500 mg/dl					
5	Hyperlipidemia					
2	Clinically relevant triglyceride increases					
572	Infections	Infections	583	PM	Clinically/measurable observable AEs	General (constitutional)
6	Infection					
3	Severe infections					
1	Non-specific bacterial infections					
1	Infective bursitis					
551	Nasopharyngitis	Nasopharyngitis (<i>common cold</i>)	565	PM	Mostly felt AEs with observed components	Ear/nose/throat
13	Common cold					
1	Cold symptoms					
169	Grade 1 neutropenia	Neutropenia (none)	520	PM	Laboratory/biomarker based AEs	Laboratory data: hematology
108	Transient decreases in neutrophil counts below the lower limit of normal					
95	Grade 2 neutropenia					
83	Neutropenia					
30	Grade 3 neutropenia					

Supplementary Table B

25	Hematopoietic cytopenias					
10	Leucopenia					
1	Agranulocytosis					
344	Vomiting	Vomiting	520	Life impact	Mostly felt AEs with observed components	Gastrointestinal
96	Nausea and vomiting symptoms					
71	Nausea/vomiting/decreased appetite					
9	Vomiting (all occurrences)					
188	Injection-site reactions					
78	Injection site reaction	Injection-site reactions	507	Life impact	Mostly observed AEs with felt components	Dermatologic
68	Injection-site erythema					
51	Injection and infusion site reactions					
39	Injection site-related events					
26	Injection site reactions					
26	Injection site haemorrhage					
15	Mild or moderate injection-site reactions					
6	Administration site reaction					
2	Infusion site urticaria					
2	Injection site erythema					
1	Injection site movement impairment					
1	Injection site warmth					
1	Application site warmth					
1	Injection site mass					
1	Injection site hematoma					
1	Injection site hemorrhage					
285	Gastrointestinal disorders	Gastrointestinal disorders (none)	501	PM	Clinically/measurable observable AEs	Gastrointestinal
172	Gastrointestinal					
33	Various gastrointestinal aes					
10	Gastro-intestinal disorders					
1	Gastrointestinal inflammation					
208	Hypertension	Hypertension (<i>increased blood pressure</i>)	419	PM	Clinically/measurable observable AEs	Cardiac
134	Vascular hypertensive disorders					
36	Vascular hypertensive disorders (hypertension)					
31	Increased blood pressure					
6	Blood pressure increased					
4	Increases in sitting systolic blood pressure > 30 mm hg					
372	Dizziness	Dizziness	401	Life impact	Mostly felt AEs	Neuropsychiatric
27	Neurologic signs and symptoms (dizziness)					
1	Dizziness and flushing					
1	Postural dizziness					
213	Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue disorders (none)	352	PM	Clinically/measurable observable AEs	Musculoskeletal
103	Musculoskeletal and connective tissue					
26	Musculoskeletal					
5	Musculoskeletal and connective tissue disorders (intervertebral disc degeneration; rotator cuff syndrome; oa; osteoporotic fracture; lumbar spinal stenosis)					
5	Musculoskeletal disorders					
327	Joint-related signs and symptoms	Joint-related signs and symptoms (none)	327	Life impact	Mostly observed AEs with felt components	Musculoskeletal
134	Antibodies to pegloticase	Antibodies to biologics	319	PM	Laboratory/biomarker based AEs	Allergic/immunologic
75	Anti-certolizumab pegol antibodies					
48	Antibodies to golimumab					
31	Antibody to pegloticase					

Supplementary Table B

17	Anti-czp antibodies					
9	Antibodies to certolizumab pegol					
5	Anti-tocilizumab antibodies					
114	Ra					
54	Rheumatoid arthropathies					
50	Rheumatoid arthritis					
27	Aggravation of rheumatoid arthritis					
23	Worsening of RA					
19	Rheumatoid arthritis exacerbation					
7	Worsening of rheumatoid arthritis					
5	Worsening of RA disease activity					
2	RA flare					
2	Aggravated RA					
106	Injury, poisoning, and procedural complications					
46	Injuries and procedural					
44	Accidental injury					
40	Non-site-specific injuries					
20	Limb injuries					
12	Non-site-specific injuries					
8	Injury/poisoning					
7	Injuries, poisoning					
3	Injury, poisoning and procedural complications (concussion; traumatic fracture; excoriation; radiation injury)					
1	Poisoning					
1	Acute intermediate syndrome					
164	Skin and subcutaneous tissue disorders					
111	Skin and subcutaneous tissue					
7	Skin disorders					
268	Fatigue					
207	Gout flare					
33	Gouty arthritis					
17	Gout flares					
8	Worsening of gout/gouty arthritis					
1	Gout (only severe intensity)					
157	Nervous system disorders					
98	Nervous system					
2	Nervous system disorders (alzheimer;cerebrovascular accident)					
255	Somnolence					
224	Rash					
14	Rashes, eruptions and exanthems					
2	Skin rash					
2	Rash/skin reactions					
1	Lupus erythematosus rash					
142	Lower respiratory tract and lung infections					
81	Bronchitis					
7	Lower respiratory tract/lung infection					
6	Lower respiratory tract infection NOS					

Supplementary Table B

1	Lower respiratory tract infection	Lower respiratory tract infection (<i>bronchitis</i>)				
1	Exacerbated chronic obstructive airway disease					
1	Low respiratory tract infection NOS					
1	Lower respiratory tract infections					
1	Lower rti					
189	Arthralgia	Arthralgia (<i>joint pain</i>)	204	Life impact	Mostly felt AEs	Musculoskeletal
8	Arthralgia/myalgia					
4	Polyarthrititis					
3	Arthritis					
182	Pruritus	Pruritus (<i>itching</i>)	184	Life impact	Mostly felt AEs	Dermatologic
2	Pruritu					
80	Abdominal pain	Abdominal pain	180	Life impact	Mostly felt AEs	Gastrointestinal
31	Upper abdominal pain					
30	Gastrointestinal and abdominal pains (excluding oral and throat)					
18	Gastric or abdominal pain					
14	Gastrointestinal and abdominal pains					
4	Abdominal pain upper					
1	Incisional hernia abdominal pain					
1	Pain in abdomen					
1	GI pain	Gastrointestinal symptoms (none)	172	Life impact	Mostly felt AEs	Gastrointestinal
44	Stomach symptoms					
37	Gastrointestinal side effects					
36	Intestinal symptoms					
20	Gastrointestinal symptoms					
16	Abdominal discomfort					
15	Gastrointestinal reaction					
1	Abdominal cramp					
1	Stomach discomfort					
1	Gastric distress					
1	GI discomfort	General disorders and administration-site conditions	171	PM	Clinically/measurable observable AEs	General (constitutional)
96	General disorders and administration-site conditions					
70	General and administrative					
4	General disorders and administration site conditions					
1	General disorders and administration site conditions (non-cardiac chest pain)					
103	Respiratory, thoracic, and mediastinal disorders	Respiratory, thoracic, and mediastinal disorders (none)	169	PM	Clinically/measurable observable AEs	Pulmonary
66	Respiratory					
160	Back pain	Back pain	162	Life impact	Mostly felt AEs with observed components	Musculoskeletal
1	Back pain associated with aprestudy operation					
1	Lumbalgia					
119	Urinary tract infection	Urinary tract infections	155	PM	Clinically/measurable observable AEs	General (constitutional)
18	Bacteriuria					
7	Urinary tract infections					
7	URT infection					
3	Uti					
1	Urological tract infection	Laboratory investigations (none)	149	PM	Laboratory/biomarker based AEs	Missing
148	Laboratory investigations					
1	Investigations					
93	Vascular disorders					

Supplementary Table B

40	Vascular					
1	Peripheral vascular disease					
1	Arteriosclerosis					
1	Arterial occlusion	Peripheral vascular disease (none)	140	PM	Clinically/measurable observable AEs	Cardiac
1	Atherosclerosis					
1	Peripheral arterial occlusive disease					
1	Superficial femoral artery occlusion					
1	Ischemia/ulcer on his left fifth toe					
34	Antinuclear antibodies	Antinuclear autoantibodies (ana)	134	PM	Laboratory/biomarker based AEs	Allergic/immunologic
34	Antinuclear autoantibodies	titres increased (none)				
32	Newly positive for anas					
31	Antinuclear autoantibodies (ana) titres increased					
2	Newly positive for antidsdna					
1	Anti-doublestranded dna antibodies					
47	Influenza viral infections	Influenza (<i>flu syndrome</i>)	134	PM	Mostly felt AEs with observed components	General (constitutional)
46	Influenza					
36	Flu syndrome					
4	Flu-like symptoms					
1	Influenza-like illness					
81	Dyspepsia	Dyspepsia (<i>indigestion</i>)	130	Life impact	Mostly felt AEs	Gastrointestinal
48	Dyspepsia and abdominal pain					
1	Reflux oesophagitis					
72	Cardiac disorders	Cardiovascular disorders (coronary artery disease, acute coronary syndrome, myocardial infarction)(none)	109	PM	Clinically/measurable observable AEs	Cardiac
15	Cardiac problems					
13	Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)					
6	Cardiac disorders (atrioventricular block; atrial fibrillation)					
3	Cardiovascular disorders (coronary artery disease, acute coronary syndrome, myocardial infarction)					
89	Sinusitis	Sinusitis	94	PM	Mostly felt AEs with observed components	Ear/nose/throat
5	Sinusitis NOS					
89	Dry mouth	Dry mouth	89	Life impact	Mostly felt AEs with observed components	Ear/nose/throat
37	Pharyngitis/laryngitis	Pharyngitis (<i>sore throat</i>)	87	PM	Mostly felt AEs with observed components	Ear/nose/throat
21	Pharyngolaryngeal pain					
18	Pharyngitis					
9	Pharyngeal pain					
1	Sore throat					
1	Tonsillitis					
43	Serious infections	Serious infections	87	PM	Clinically/measurable observable AEs	General (constitutional)
24	Serious infectious adverse event					
20	Treatment-emergent serious infections					
74	Elevations in the bilirubin level ≤ 3 -fold the upper limit of normal	Elevated total bilirubin (none)	85	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
6	Elevated total bilirubin					
2	Increases in total bilirubin concentration					
2	Elevations in the bilirubin level >3 -fold the upper limit of normal					
1	Increases in total bilirubin					
62	Pneumonia	Pneumonia	80	PM		Pulmonary
9	Pneumonia bacterial					

Adverse Event		Number of cases	Severity	Frequency	Clinical significance	System	
2	Pneumonia mycoplasmal	1	1	1	Clinically/measurable observable AEs		
1	Bronchopneumonia						
1	Broncho-pneumonia						
1	Lobar pneumonia						
1	Lung infection pseudomonal						
1	Necrotising pneumonia						
1	Organized pneumonia						
1	Pneumonitis						
31	Death	16	Deaths	12	Death	Clinically/measurable observable AEs	General (constitutional)
4	Deaths occurring outside the treatment period						
3	Fatal adverse event						
3	Died from infective complications of sle						
2	Died of cardiac arrest						
1	Died because of acute respiratory failure						
47	Cough						
64	Skin injuries	1	Skin laceration	65	Life impact	Mostly felt AEs with observed components	Dermatologic
61	Erythema						
59	Infusion reaction	2	Infusion site reaction	62	PM	Mostly observed AEs with felt components	Allergic/immunologic
1	Infusion-related reaction						
52	Stomatitis						
57	Gastrointestinal atonic and hypomotility disorders	57	PM	Clinically/measurable observable AEs	Gastrointestinal		
37	Pain					12	Pain and discomfort
5	Increase in pain						
1	Pain (hip, tooth or head)						
1	Severe pain and diffuse swelling						
16	Neoplasms benign, malignant, and unspecified	12	Malignancy	47	PM		
6	Other malignancies						
5	Malignancies						
4	Neoplasms benign, malignant and unspecified (malignant tongue neoplasm; prostate cancer; benign lung neoplasm; basal cell carcinoma)						
2	Cancer						
2	Cancer (malignant parathyroid tumor, Hodgkin's disease)	4	Psychiatric disorders	41	Life impact	Mostly observed AEs with felt components	Neuropsychiatric
35	Psychiatric						
1	Psychosis						

Supplementary Table B

1	Suicide attempt					
41	Vertigo	Vertigo (<i><u>spinning sensation</u></i>)	41	PM	Mostly felt AEs with observed components	Neuropsychiatric
27	Dyspnea	Dyspnea (<i><u>shortness of breath</u></i>)	39	Life impact	Mostly felt AEs with observed components	Pulmonary
6	Dyspnoea					
6	Dyspnoea or palpitations					
38	Sun sensitivity	Sun sensitivity	38	Life impact	Mostly felt AEs with observed components	Dermatologic
34	Pyrexia	Pyrexia (<i>fever</i>)	35	PM	Mostly observed AEs with felt components	General (constitutional)
1	Fever					
31	Miscellaneous skin infections	Miscellaneous skin infections	35	PM	Clinically/measurable observable AEs	Dermatologic
1	Infection skin ulcer					
1	Soft tissue abscess					
1	Subcutaneous tissue abscess					
1	Sc abscess					
23	Tachycardia	Arrhythmia (none)	34	PM	Clinically/measurable observable AEs	Cardiac
8	Arrhythmia, no evidence of ischemia					
2	Arrhythmia					
1	Supraventricular tachycardia					
18	Oedema	Peripheral oedema (swelling)	34	Life impact	Mostly felt AEs with observed components	Cardiac
11	Peripheral oedema					
2	General (peripheral oedema)					
2	Swellings					
1	Swelling					
16	Parasthesia	Paresthesia (<i><u>'pins and needles'</u></i>)	33	Life impact	Mostly felt AEs with observed components	Neuropsychiatric
16	Paresthesias and dysesthesias					
1	Paresthesia					
15	Muscle-related signs and symptoms (muscle cramps, muscle twitching, night cramps)	Muscle-related signs and symptoms (muscle cramps, muscle twitching, night cramps) (none)	32	Life impact	Mostly observed AEs with felt components	Musculoskeletal
14	Muscle spasms					
3	Muscle pain/cramps					
12	Allergic episode	Allergic reactions	29	Life impact	Mostly observed AEs with felt components	Allergic/immunologic
8	Hypersensitivity					
4	Allergic reactions					
1	Anaphylactic reaction					
1	Non-life threatening anaphylactic reaction					
1	Hypersensitivity reaction with rash, fever, and mild transaminitis					
1	Nonserious hypersensitivity					
1	Hypersensitivity reactions					
22	Basal cell carcinoma	Basal cell carcinoma (none)	28	PM	Clinically/measurable observable AEs	Dermatologic
3	Basal cell carcinomas					
3	Basal-cell carcinoma					
16	Injection site pain	Injection site pain	27	Life impact	Mostly felt AEs	Dermatologic
5	Post-injection pain					
4	Transient injectionsite reactions with mild to moderate pain or local swelling					
1	Injection-site pain					

Supplementary Table B

1	Postinjection pain				
23	Metabolism and nutrition	Metabolism and nutrition disorders	27	PM	Clinically/measurable observable AEs
4	Metabolism and nutrition disorders	(none)			General (constitutional)
25	Eye	Vision disorder	27	PM	Clinically/measurable observable AEs
1	Vision disorder	(none)			Eye/ophthalmologic
1	Eye disorders				
26	Prolonged activated partial thromboplastin time (APTT)	Prolonged activated partial thromboplastin time (APTT) (none)	26	PM	Laboratory/biomarker based AEs
23	Asthenia	Asthenia (<i>feeling weak</i>)	24	Life impact	Mostly felt AEs
1	Paresis				General (constitutional)
13	Osteoarthropathies	Osteoarthritis (none)	24	PM	Mostly observed AEs with felt components
11	Osteoarthritis				Musculoskeletal
19	Rhinorrhea	Rhinitis (<i>runny nose</i>)	24	PM	Mostly felt AEs with observed components
5	Rhinitis				Ear/nose/throat
23	Breast cancer	Breast cancer	23	PM	Clinically/measurable observable AEs
					General (constitutional)
17	Cellulitis	Cellulitis	23	PM	Clinically/measurable observable AEs
4	Erysipelas				Dermatologic
1	Cellulitis, abscess limb				
1	Soft tissue infection				
21	Herpes zoster	Herpes zoster (none)	23	PM	Clinically/measurable observable AEs
1	Herpes zoster virus infection				Dermatologic
1	Opportunistic herpes zoster infection				
20	Uveitis or iritis	Uveitis (none)	23	PM	Clinically/measurable observable AEs
3	Uveitis				Eye/ophthalmologic
12	Anemia	Anemia (none)	22	PM	Clinically/measurable observable AEs
5	Decreased hemoglobin				Laboratory data: hematology
1	Anaemia				
1	Anaemia due to gastrointestinal bleeding				
1	Decreases in hemoglobin				
1	Decreases in hematocrit				
1	Decreases in rbc				
19	Chest pain	Chest pain	21	Life impact	Mostly felt AEs with observed components
1	Atypical chest pain				Cardiac
1	Non-cardiac chest pain				
21	Flare	Flare	21	Life impact	Mostly felt AEs with observed components
					Musculoskeletal
21	Gingival/dental infection	Gingival/dental infection	21	PM	Clinically/measurable observable AEs
					Ear/nose/throat
6	Tuberculosis	Tuberculosis	20	PM	Clinically/measurable observable AEs
5	Tuberculosis infection				Pulmonary
3	Pulmonary tuberculosis				

Supplementary Table B

2	Peritoneal tuberculosis					
1	Active tuberculosis					
1	Disseminated tuberculosis					
1	Tb of the spine					
1	Tuberculous lymphadenitis					
13	Stage 3 chronic kidney disease	Chronic renal failure	19	PM	Clinically/measurable observable AEs	General (constitutional)
4	Renal impairment					
1	Chronic renal failure					
1	Renal insufficiency					
16	Depressive mood	Depression	19	Life impact	Mostly felt AEs	Neuropsychiatric
2	Depression					
1	Psychiatric disorders (depression)					
12	Sepsis	Sepsis (none)	18	PM	Clinically/measurable observable AEs	General (constitutional)
3	Haemophilus sepsis					
2	Septic shock					
1	Listeria sepsis					
7	Fracture					
2	Hip fracture					
1	Facial bone fracture					
1	Femur fracture					
1	Femoral neck fracture	Fracture	17	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Fractured coccyx					
1	Radius fracture					
1	Thoracic vertebral fracture					
1	Traumatic patella fracture					
1	Ulnar fracture					
17	Haematological	Haematological (none)	17	PM	Laboratory/biomarker based AEs	Laboratory data: hematology
10	Herpes simplex	Herpes simplex	17	PM	Clinically/measurable observable AEs	Ear/nose/throat
5	Herpes viral infections	(none)				
2	Herpes viral infection					
16	Bone loss	Bone loss (none)	16	PM	Clinically/measurable observable AEs	Musculoskeletal
9	Hypotension					
7	Decreased blood pressure	Hypotension (none)	16	PM	Clinically/measurable observable AEs	Cardiac
9	Joint effusion	Joint effusion (<i>joint swelling</i>)	16	Life impact	Mostly observed AEs with felt components	Musculoskeletal
7	Joint swelling					
15	Nephrolithiasis	Nephrolithiasis (<i>renal colic</i>)	16	Life impact	Mostly felt AEs with observed components	General (constitutional)
1	Renal colic					
16	Urticaria	Urticarial (<i>hives</i>)	16	PM	Mostly felt AEs with observed components	Dermatologic
15	Cerebrovascular accident	Cerebrovascular accident (none)	15	PM	Clinically/measurable observable AEs	Neuropsychiatric
15	Insomnia	Insomnia (<i>difficulty sleeping</i>)	15	Life impact	Mostly felt AEs with observed components	General (constitutional)

Supplementary Table B

8 Myocardial infarction 2 Myocardial infarctions 2 Nonfatal myocardial infarction 1 Acute myocardial infarction 1 Lateral heart ischaemia 1 Myocardial infraction	Myocardial infarctions (none)	15 PM	Clinically/measurable observable AEs	Cardiac
13 Haematuria 1 Hematuria	Hematuria (none)	14 PM	Clinically/measurable observable AEs	Laboratory data: urinalysis
13 Eczema	Eczema	13 PM	Mostly observed AEs with felt components	Dermatologic
12 Pleurisy 1 Pleuritis	Pleurisy (none)	13 PM	Mostly felt AEs with observed components	Pulmonary
12 Pneumocystis jiroveci pneumonia 1 Pneumocystis jirovecii pneumonia	Pneumocystis jiroveci pneumonia (none)	13 PM	Clinically/measurable observable AEs	Pulmonary
4 Congestive heart failure 4 Congestive heart failure-related 3 Chf 1 Congestive cardiac failure	Congestive heart failure	12 PM	Clinically/measurable observable AEs	Cardiac
12 Tendon disorders	Tendon disorders (none)	12 PM	Clinically/measurable observable AEs	Musculoskeletal
10 Gastroenteritis 1 Viral gastroenteritis	Gastroenteritis (<i>stomach flu</i>)	11 Life impact	Mostly felt AEs with observed components	Gastrointestinal
11 Granulomatosis with polyangiitis (Wegener's)	Granulomatosis with polyangiitis (Wegener's) (none)	11 PM	Clinically/measurable observable AEs	Allergic/immunologic
11 Interstitial lung disease	Interstitial lung disease (none)	11 PM	Clinically/measurable observable AEs	Pulmonary
4 Diverticulitis 3 Gastrointestinal disorders (small intestinal obstruction; diverticular perforation; appendicitis perforated) 2 Abdominal abscess 1 Peridiverticular abscess	Abdominal abscess	10 PM	Clinically/measurable observable AEs	Gastrointestinal
10 Flushing	Flushing	10 Life impact	Mostly felt AEs with observed components	Dermatologic
6 Nonmelanoma skin cancers 3 Non-melanoma skin cancer 1 Non-melanomatous skin cancer	Non-melanoma skin cancer (none)	10 PM	Clinically/measurable observable AEs	Dermatologic
7 Swelling and increased pain in the injected ankle joint, sometimes associated with increased local temperature 3 Pain in the study joint	Pain in the study joint	10 Life impact	Mostly felt AEs	Musculoskeletal
9 Renal and urinary disorders 1 Renal and urinary disorders (urinary retention)	Renal and urinary disorders (none)	10 PM	Clinically/measurable observable AEs	General (constitutional)

Supplementary Table B

9	Opportunistic infections	Opportunistic infections (none)	9	PM	Clinically/measurable observable AEs	General (constitutional)
9	Pregnant	Pregnant	9	PM	Clinically/measurable observable AEs	General (constitutional)
9	Neutralising antibodies	Neutralising antibodies	9	PM	Laboratory/biomarker based AEs	Allergic/immunologic
8	Allergic conjunctivitis	Allergic conjunctivitis (none)	8	PM	Mostly observed AEs with felt components	Allergic/immunologic
8	Contusion	Contusion (<i>bruise</i>)	8	Life impact	Mostly observed AEs with felt components	Dermatologic
8	Itch or dizziness	Itch or dizziness	8	Life impact	Mostly felt AEs	General (constitutional)
7	Myalgia	Myalgia (<i>muscle pain</i>)	8	Life impact	Mostly felt AEs	Musculoskeletal
1	Myalgia/muscle stiffness					
4	Acute pyelonephritis					
2	Pyelonephritis	Pyelonephritis (none)	8	PM	Clinically/measurable observable AEs	General (constitutional)
1	Kidney infection					
1	Pyelonephritis acute					
4	Stroke					
2	Nonfatal stroke	Stroke	8	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Ischaemic stroke					
1	Lacunar infarction					
8	Tendon rupture	Tendon rupture	8	PM	Clinically/measurable observable AEs	Musculoskeletal
4	Transient ischemic attack					
2	Transient ischaemic attack	Transient ischemic attack (<i>TIA</i>)	8	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Tia					
1	Transit ischaemic attack					
2	Bacterial arthritis					
1	Infective arthritis	Bacterial arthritis (none)	7	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Infectious arthritis					
1	Salmonella arthritis					
1	Streptococcal infections					
1	Staphylococcal polyarthritis					
7	Intervertebral disc protrusion	Intervertebral disc protrusion (none)	7	PM	Clinically/measurable observable AEs	Musculoskeletal
7	Low-normal vitamin b12 levels	Low-normal vitamin b12 levels	7	PM	Laboratory/biomarker based AEs	Missing
4	Lymphoma					
1	Hodgkin's lymphoma	Lymphoma (none)	7	PM	Clinically/measurable observable AEs	Missing
1	Follicle centre lymphoma					
1	Extranodal marginal-zone b cell lymphoma					
6	Pain in extremity					

Supplementary Table B

1 Pain in the extremities	Pain in extremity	7 Life impact	Mostly felt AEs	Musculoskeletal
2 Angina	Angina pectoris (<i>angina</i>)	6 PM	Mostly felt AEs with observed components	Cardiac
2 Chest pain/pressure/palpitation				
1 Angina pectoris				
1 Unstable angina	Colitis (none)	6 PM	Mostly observed AEs with felt components	Gastrointestinal
3 Colitis				
1 Enterocolitis				
1 Viral enterocolitis				
1 Ulcerative colitis	Deep vein thrombosis (none)	6 PM	Clinically/measurable observable AEs	Missing
3 Deep vein thrombosis				
2 Venous and peripheral arterial vascular thrombotic event				
1 Dvt	Effusion (none)	6 PM	Mostly observed AEs with felt components	Musculoskeletal
5 Effusion				
1 Effusion and erythema	Hemorrhaging	6 PM	Clinically/measurable observable AEs	Gastrointestinal
4 Hemorrhaging				
1 Gastrointestinal hemorrhage				
1 Gastric ulcer hemorrhage	Palpitations	6 Life impact	Mostly felt AEs with observed components	Cardiac
4 Irregular heartbeat				
2 Palpitations				
6 Urosepsis	Urosepsis (none)	6 PM	Clinically/measurable observable AEs	General (constitutional)
5 Atrial fibrillation	Atrial fibrillation	5 PM	Clinically/measurable observable AEs	Cardiac
5 Hypercalcemia	Hypercalcemia (none)	5 PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
5 Joint stiffness	Joint stiffness	5 Life impact	Mostly felt AEs	Musculoskeletal
2 Lung neoplasm	Lung cancer	5 PM	Clinically/measurable observable AEs	Pulmonary
1 Lung cancer				
1 Lung adenocarcinoma				
1 Malignant lung neoplasm				
3 Malignant melanoma	Malignant melanoma	5 PM	Clinically/measurable observable AEs	Dermatologic
2 Skin melanoma				
3 Meniscus lesion	Meniscal lesion (none)	5 PM	Clinically/measurable observable AEs	Musculoskeletal
2 Meniscal lesion				
5 Mycosis	Mycosis (none)	5 PM	Clinically/measurable observable AEs	Missing
1 Squamous cell carcinoma	Squamous cell carcinoma (none)	5 PM	Clinically/measurable observable AEs	Missing
1 Actinic squamous cell carcinoma				
1 Lip squamous cell skin cancer				
1 Squamous cell carcinoma of the skin				
1 Bowen's disease				

Supplementary Table B

4	Autoimmune symptoms and disorders	Autoimmune symptoms and disorders (none)	4	PM	Clinically/measurable observable AEs	Allergic/immunologic
4	Cholelithiasis	Cholelithiasis (none)	4	PM	Clinically/measurable observable AEs	Gastrointestinal
4	Dental pain	Dental pain	4	Life impact	Mostly felt AEs with observed components	Ear/nose/throat
4	Difficulty in swallowing	<i>Dysphagia (difficulty in swallowing)</i>	4	Life impact	Mostly felt AEs	Ear/nose/throat
4	Ear and labyrinth disorders	Ear and labyrinth disorders (none)	4	PM	Clinically/measurable observable AEs	Ear/nose/throat
2	Elevation of serum creatinine	Elevation of serum creatinine (none)	4	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
1	Increased blood creatinine/increased blood urea					
1	Investigations (creatinine increased)					
2	Tongue neoplasms	Malignant tongue neoplasm (none)	4	PM	Clinically/measurable observable AEs	Ear/nose/throat
1	Malignant tongue neoplasm					
1	Epidermoid cancer of the tongue					
4	Recurrent falls	Recurrent falls	4	Life impact	Mostly observed AEs with felt components	Missing
3	Abnormal clinically relevant 12-lead ecg results	Abnormal clinically relevant 12-lead ecg results (none)	3	PM	Clinically/measurable observable AEs	Cardiac
2	Hepatobiliary disorders (cholecystitis)					
1	Acute cholecystitis	Acute cholecystitis	3	PM	Clinically/measurable observable AEs	Gastrointestinal
3	Burning	Burning	3	Life impact	Mostly felt AEs	General (constitutional)
1	Coronary artery disease	Coronary artery disease (none)	3	PM	Clinically/measurable observable AEs	Cardiac
1	Coronary artery arteriosclerosis					
1	Ischemic coronary artery disorders					
3	Coronary revascularization	Coronary revascularization (none)	3	PM	Clinically/measurable observable AEs	Cardiac
3	Gastritis	Gastritis	3	Life impact	Mostly felt AEs with observed components	Gastrointestinal
3	Hip arthroplasty	Hip arthroplasty (none)	3	PM	Clinically/measurable observable AEs	Musculoskeletal
3	Hospitalized	Hospitalized	3	Life impact	Mostly observed AEs with felt components	General (constitutional)
3	Increased platelet count	Increased platelet count	3	PM	Laboratory/biomarker based AEs	Laboratory data: hematology

Supplementary Table B

3 Induration	Induration (none)	3 PM	Mostly observed AEs with felt components	Dermatologic
1 Malaise	Malaise (<i>feeling</i>	3 Life	Mostly felt AEs	General
1 Abnormal feeling	<i>badly</i>)	impact		(constitutional)
1 Malaise and/or fever				
2 Optic neuritis	Optic neuritis (none)	3 PM	Mostly observed AEs with felt components	Eye/ophthalmologic
1 Optical neuritis				
2 Otitis media	Otitis media	3 PM	Clinically/measurable observable AEs	Ear/nose/throat
1 Chronic otitis media				
3 Peptic ulcers	Peptic ulcers (none)	3 PM	Clinically/measurable observable AEs	Gastrointestinal
3 Postoperative wound infection	Postoperative wound infection (none)	3 PM	Clinically/measurable observable AEs	General (constitutional)
2 Knee arthroplasty	Total knee replacement	3 PM	Clinically/measurable observable AEs	Musculoskeletal
1 Total knee replacement				
2 Abdominal distension	Abdominal distension (<i>bloating</i>)	2 Life	Mostly felt AEs with observed components	Gastrointestinal
		impact		
2 Acute renal failure	Acute renal failure (none)	2 PM	Clinically/measurable observable AEs	General (constitutional)
1 Anxiety attack	Anxiety attack	2 Life	Mostly felt AEs with observed components	Neuropsychiatric
1 Worsening of anxiety		impact		
2 Bladder cancer	Bladder cancer	2 PM	Clinically/measurable observable AEs	General (constitutional)
2 Blood and lymphatic system disorders	Blood and lymphatic system disorders (none)	2 PM	Clinically/measurable observable AEs	General (constitutional)
2 Cardiac tamponade	Cardiac tamponade (none)	2 PM	Clinically/measurable observable AEs	Cardiac
1 Change of bowel habit	Change of bowel habit	2 Life	Mostly felt AEs	Gastrointestinal
1 Bowel movements		impact		
2 Colon cancer	Colon cancer	2 PM	Clinically/measurable observable AEs	Gastrointestinal
2 Corneal perforation	Corneal perforation (none)	2 PM	Clinically/measurable observable AEs	Eye/ophthalmologic
1 Elective surgery	Elective surgery	2 PM	Clinically/measurable observable AEs	General (constitutional)
1 Scheduled cataract surgery				
1 Esophageal carcinoma				

Supplementary Table B

1 Oesophageal squamous cell carcinoma	Esophageal carcinoma (none)	2 PM	Clinically/measurable observable AEs	Missing
2 Flatulence	Flatulence (<i>passing gas</i>)	2 Life impact	Mostly felt AEs	Gastrointestinal
2 Hepatic steatosis	Hepatic steatosis (none)	2 PM	Clinically/measurable observable AEs	Gastrointestinal
2 Increased appetite	Increased appetite	2 Life impact	Mostly felt AEs	General (constitutional)
1 Meningitis	Meningitis	2 PM	Clinically/measurable observable AEs	Neuropsychiatric
1 Meningitis fungal				
2 Muscular weakness in the area around the study joint	<u>Muscular weakness</u> (<i>muscular weakness in the area around the study joint</i>)	2 Life impact	Mostly felt AEs with observed components	Musculoskeletal
1 Pancreatitis	Pancreatitis	2 PM	Clinically/measurable observable AEs	Gastrointestinal
1 Acute pancreatitis				
2 Prostate cancer	Prostate cancer	2 PM	Clinically/measurable observable AEs	General (constitutional)
2 Pulmonary embolism	Pulmonary embolism	2 PM	Clinically/measurable observable AEs	Pulmonary
1 Small-bowel obstruction	Small-bowel obstruction (none)	2 PM	Clinically/measurable observable AEs	Gastrointestinal
1 Intestinal blockage				
2 Spinal compression fracture	Spinal compression fracture (none)	2 PM	Clinically/measurable observable AEs	Musculoskeletal
2 Stinging	Stinging	2 Life impact	Mostly felt AEs	Neuropsychiatric
2 Tendon pain	Tendon pain	2 Life impact	Mostly felt AEs	Musculoskeletal
1 Uterine cancer	Uterine cancer	2 PM	Clinically/measurable observable AEs	General (constitutional)
1 Uterine sarcoma				
1 Abdominal hernia, obstructive	Abdominal hernia, obstructive (none)	1 PM	Mostly observed AEs with felt components	Gastrointestinal
1 Abdominal wall abscess	Abdominal wall abscess	1 Life impact	Mostly observed AEs with felt components	Missing
1 Adenocarcinoma of the pancreas	Adenocarcinoma of the pancreas (none)	1 PM	Clinically/measurable observable AEs	Gastrointestinal

Supplementary Table B

1	Adrenal adenoma	Adrenal adenoma (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Alcohol withdrawal syndrome	Alcohol withdrawal syndrome (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Alopecia	Alopecia (<i>hair loss</i>)	1	Life impact	Mostly observed AEs with felt components	Dermatologic
1	Alzheimer's-related dementia	Alzheimer's-related dementia	1	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Anal fistula	Anal fistula (none)	1	PM	Mostly observed AEs with felt components	Gastrointestinal
1	Aortic aneurysm	Aortic aneurysm (none)	1	PM	Clinically/measurable observable AEs	Cardiac
1	Appendicitis	Appendicitis	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Arthroscopic meniscectomy	Arthroscopic meniscectomy (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Asthma	Asthma	1	Life impact	Mostly felt AEs with observed components	Pulmonary
1	Asymptomatic mycobacterium aviumintracellulare	Asymptomatic mycobacterium aviumintracellulare (none)	1	PM	Clinically/measurable observable AEs	Pulmonary
1	Ataxia	Ataxia (<i>impaired coordination</i>)	1	Life impact	Mostly felt AEs with observed components	Neuropsychiatric
1	Avascular necrosis of the hip	Avascular necrosis of the hip (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Bacterial peritonitis	Bacterial peritonitis (none)	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Benign parathyroid tumour	Benign parathyroid tumour (none)	1	PM	Clinically/measurable observable AEs	Missing
1	Bile duct cancer	Bile duct cancer	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Blepharitis	Blepharitis (<i>eyelid inflammation</i>)	1	PM	Mostly observed AEs with felt components	Eye/ophthalmologic
1	Bone marrow failure	Bone marrow failure (none)	1	PM	Clinically/measurable observable AEs	Laboratory data: hematology

Supplementary Table B

1	Carcinoid tumour	Carcinoid tumour (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Chronic lymphocytic leukaemia	Chronic lymphocytic leukaemia (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Colonic polyp	Colonic polyp (none)	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Concussion	Concussion	1	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Congenital, familial, and genetic disorders	Congenital, familial, and genetic disorders (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Constipation-related bloating	Constipation-related bloating	1	Life impact	Mostly felt AEs with observed components	Gastrointestinal
1	Coronary angioplasty	Coronary angioplasty (none)	1	PM	Clinically/measurable observable AEs	Cardiac
1	Cyst aspiration	Cyst aspiration (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Cystitis	Cystitis (<i>bladder inflammation</i>)	1	PM	Mostly felt AEs with observed components	Missing
1	Dysphasia	Dysphasia (none)	1	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Ear pain	Ear pain	1	Life impact	Mostly felt AEs	Ear/nose/throat
1	Empyema	Empyema (none)	1	PM	Clinically/measurable observable AEs	Pulmonary
1	Encephalitis herpetic	Encephalitis herpetic (none)	1	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Endourethral prostate resection	Endourethral prostate resection (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Enlarged lymph node in the ipsilateral groin	Enlarged lymph node in the ipsilateral groin (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Feeling of warmth	Feeling of warmth	1	Life impact	Mostly felt AEs	General (constitutional)
1	Fibrosarcoma	Fibrosarcoma (none)	1	PM	Clinically/measurable observable AEs	Missing

Supplementary Table B

1	Hallucination	Hallucination (<i>sensing things that are not real</i>)	1	Life impact	Mostly felt AEs	Neuropsychiatric
1	Hepatic neoplasm	Hepatic neoplasm (none)	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Hepatitis	Hepatitis	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Histoplasmosis	Histoplasmosis (none)	1	PM	Clinically/measurable observable AEs	Pulmonary
1	Hyperchlorhydria	Hyperchlorhydria (none)	1	PM	Laboratory/biomarker based AEs	Gastrointestinal
1	Hyperglycemia	Hyperglycemia (none)	1	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
1	Hyperesthesia	Hyperesthesia (<i>increased sensitivity of any sense</i>)	1	Life impact	Mostly felt AEs	Neuropsychiatric
1	Hypoesthesia	Hypoesthesia (<i>reduced sensitivity of any sense</i>)	1	Life impact	Mostly felt AEs	Neuropsychiatric
1	Hypoglycemia	Hypoglycemia (none)	1	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
1	Idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis (none)	1	PM	Clinically/measurable observable AEs	Pulmonary
1	Increased body weight	Increased body weight	1	Life impact	Mostly observed AEs with felt components	General (constitutional)
1	Infected tophus	Infected tophus (none)	1	PM	Mostly observed AEs with felt components	Musculoskeletal
1	Infectious mononucleosis	Infectious mononucleosis (none)	1	PM	Clinically/measurable observable AEs	Missing
1	Inguinal hernia	Inguinal hernia (none)	1	PM	Mostly observed AEs with felt components	Gastrointestinal
1	Inr increase	Inr increase (none)	1	PM	Laboratory/biomarker based AEs	Laboratory data: hematology
1	Irritable bowel syndrome	Irritable bowel syndrome	1	PM	Mostly felt AEs with observed components	Gastrointestinal

Supplementary Table B

1	Lack of appetite	Lack of appetite	1	Life impact	Mostly felt AEs	Gastrointestinal
1	Leukaemoid reaction	Leukaemoid reaction (none)	1	PM	Clinically/measurable observable AEs	Laboratory data: hematology
1	Malignant anorectal neoplasm	Malignant anorectal neoplasm (none)	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Mastitis	Mastitis (<i>inflamed breast</i>)	1	PM	Mostly observed AEs with felt components	General (constitutional)
1	Melena (only severe intensity)	Melena (only severe intensity) (none)	1	PM	Clinically/measurable observable AEs	Gastrointestinal
1	Meningitis noninfective	Meningitis noninfective (none)	1	PM	Clinically/measurable observable AEs	Neuropsychiatric
1	Menometrorrhagia	Menometrorrhagia (<i>abnormally heavy, prolonged, and irregular uterine bleeding</i>)	1	Life impact	Mostly observed AEs with felt components	General (constitutional)
1	Neuralgia	Neuralgia (<i>nerve pain</i>)	1	Life impact	Mostly felt AEs with observed components	Neuropsychiatric
1	Osteomyelitis	Osteomyelitis (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Osteoporotic fracture of her right tibia and fibula	Osteoporotic fracture of her right tibia and fibula (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Ovarian abscess	Ovarian abscess (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Pain in rectum	Pain in rectum	1	Life impact	Mostly felt AEs	Gastrointestinal
1	Papilloma	Papilloma (none)	1	PM	Clinically/measurable observable AEs	Dermatologic
1	Ptosis	Ptosis (<i>droopy eyelid</i>)	1	PM	Mostly observed AEs with felt components	Eye/ophthalmologic
1	Purulent myositis	Purulent myositis (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Pyoderma gangrenosum	Pyoderma gangrenosum (none)	1	PM	Clinically/measurable observable AEs	Dermatologic

Supplementary Table B

1	Radical prostatectomy	Radical prostatectomy (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Renal cell carcinoma	Renal cell carcinoma (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Restless legs syndrome	Restless legs syndrome (<u>restless legs</u>)	1	Life impact	Mostly felt AEs	Missing
1	Severe thrombocytopenia	Severe thrombocytopenia (none)	1	PM	Laboratory/biomarker based AEs	Laboratory data: hematology
1	Skin peeling	Skin peeling	1	Life impact	Mostly felt AEs with observed components	Dermatologic
1	Spondylitic myelopathy	Spondylitic myelopathy (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Straining	Straining	1	Life impact	Mostly felt AEs	Missing
1	Superficial thrombophlebitis	Superficial thrombophlebitis (none)	1	PM	Clinically/measurable observable AEs	Missing
1	Surgery on lumbar spinal stenosis	Surgery on lumbar spinal stenosis (none)	1	PM	Clinically/measurable observable AEs	Musculoskeletal
1	Surgery related to frequent angina and snoring	Surgery related to frequent angina and snoring (none)	1	PM	Clinically/measurable observable AEs	Cardiac
1	Syncope	Syncope (<u>fainting, losing consciousness</u>)	1	PM	Mostly felt AEs with observed components	Neuropsychiatric
1	Testicular cancer	Testicular cancer	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Thyroid neoplasm	Thyroid neoplasm (none)	1	PM	Clinically/measurable observable AEs	Ear/nose/throat
1	Tooth abscess	Tooth abscess	1	PM	Mostly felt AEs with observed components	Ear/nose/throat
1	Tremor	Tremor	1	Life impact	Mostly felt AEs with observed components	Neuropsychiatric

Supplementary Table B

1	Tubulointerstitial nephritis	Tubulointerstitial nephritis (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Uterine fibroids	Uterine fibroids (none)	1	PM	Clinically/measurable observable AEs	General (constitutional)
1	Yellow discoloration of urine	Yellow discoloration of urine	1	Life impact	Mostly observed AEs with felt components	General (constitutional)

*When difference between medical and lay language terms exists, terms are described in medical term (*lay language term*). "None" indicates that no medical term or no lay language term was identified.

(S)AE = serious adverse event; RCTC = Rheumatology Common Toxicity Criteria v. 2.0; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = the upper limit of normal; NOS = not Otherwise Specified; NEC = not elsewhere classified; GI = gastrointestinal; URT = urological tract; Uti = urological tract infection; Sc = subcutaneous; APTT = activated partial thromboplastin time; Tb = tuberculous; Chf = congestive heart failure; Dvt = deep vein thrombosis; Inr = international normalised ratio.

Supplementary Table C. Reasons for categorization when ambiguity might exist in AEs appropriate for patient self-reporting

Table C Reasons for categorization when ambiguity might exist in AEs appropriate for patient self-reporting.		
Harm-cluster*	Categorization	Reason for categorization
Pruritus (<i>itching</i>)	Mostly felt AEs	With or without observable components? Pruritus is a sensation - we cannot assume it is observable
Abdominal pain	Mostly felt AEs	With or without observable components? (Abdominal) pain is usually not observable although it can be measured using a pain scale
Gastrointestinal symptoms (none)	Mostly felt AEs	With or without observable components? We consider “symptoms” mostly felt (subjective) rather than observable – and symptoms might not include observable components
Pain	Mostly felt AEs	With or without observable components? Pain is usually not observable although it can be measured using a pain scale
Depression	Mostly felt AEs	With or without observable components? Depression can occur without observable components (however, in order to grade depression, it should be measured)
Pain in the study joint	Mostly felt AEs	With or without observable components? Pain (in the study joint) is usually not observable although it can be measured using a pain scale
Myalgia (muscle pain)	Mostly felt AEs	With or without observable components? Muscle pain and cramp is usually not observable although it can be measured using e.g. a VAS
Pain in extremity	Mostly felt AEs	With or without observable components? Pain (in extremity) is usually not observable although it can be measured using a pain scale
Joint stiffness	Mostly felt AEs	With or without observable components? Joint stiffness is not always observable although it can be measured using e.g. a VAS
<i>Dysphagia (difficulty in swallowing)</i>	Mostly felt AEs	With or without observable components? We consider difficulty in swallowing to be a subjective feeling (and examination will far from always explain reasons for difficulty in swallowing)
Ear pain	Mostly felt AEs	With or without observable components? (Ear) pain is usually not observable although it can be measured using a pain scale
Pain in rectum	Mostly felt AEs	With or without observable components? Pain (in rectum) is usually not observable although it can be measured using a pain scale
Diarrhea	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Diarrhea will usually be felt (and next observed) and reported by patients but the clinician will usually not observe the event
Musculoskeletal and connective tissue signs and symptoms (none)	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Can be both subjective and observable. We consider “symptoms” mostly subjective, whereas we consider “signs” more observable than subjective
Vomiting	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Vomiting will usually be felt (and next observed) and reported by patients. Although it is also observable, clinicians will usually not observe the event
Injury, poisoning, and procedural complications	Mostly felt AEs with observed components	Felt (subjective), observable or clinically/measurable observable AEs? Could be reported by both patient and clinician and could be both observable/measurable, observable, and felt (subjective). Patients might feel injury or poisoning before it is observed

Supplementary Table C

Back pain	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? (Back) pain is usually not observable, however there might be an objective component as we can observe e.g. positive neurological tests
Sinusitis	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? The felt uncomfortable symptoms of facial pain/pressure and stuffed up/running nose was judged to exceed the observable inflammation
Dry mouth	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Patients would have a feeling of dry mouth, although dry mouth can also be measurable by objective test
Sun sensitivity	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Mostly felt uncomfortable symptoms over objective components
Paresthesia (<u>pins and needles</u>)	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Mostly a subjective sensation although we might observe e.g. positive neurological tests
Pleurisy (none)	Mostly felt AEs with observed components	Felt (subjective), observable or clinically observable AEs? Symptoms of cough and pain were judged to exceed the observable inflammation of the pleura
Flushing	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Can be both felt (feelings of warmth) and observable (reddening) – the subjective feeling was judged to have a bigger impact on the patient than the observable component
Dental pain	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? (Dental) pain is usually not observable but dental examination will usually lead to an explanation for pain
Abdominal distension (<u>bloating</u>)	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Mostly felt symptoms rather than observable expansion of abdomen
Anxiety attack	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Mostly subjective feeling although physical symptoms and signs, such as changes in heart rate, can occur
Asthma	Mostly felt AEs with observed components	Felt (subjective) or clinically/measurable observable AEs? Felt (subjective) symptoms such as coughing, and shortness of breath was judged to exceed the observable inflammation of the lungs
Ataxia (<u>impaired coordination</u>)	Mostly felt AEs with observed components	Felt (subjective) or observable (/measurable) AEs? Can be both a subjective (feeling of involuntary movement) and an observable (affected co-ordination, balance, and speech) symptom of an underlying neurological disease. We judged the felt component to exceed the observable component.
Cystitis (<u>bladder inflammation</u>)	Mostly felt AEs with observed components	Felt (subjective) or lab/biomarker-based AEs? Can be both felt (subjective) and observable (lab). We considered it mostly felt because of the symptoms (patients' main problem will usually be pain symptoms) rather than a cultured test.
Tooth abscess	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Can be both felt (subjective) and observable, but the subjective components such as pain was judged to exceed observable component of pocket of pus
Tremor	Mostly felt AEs with observed components	Felt (subjective) or observable AEs? Can be both subjective (feeling of involuntary trembling) and observable (affected co-ordination). We considered the felt (subjective) component to have a bigger impact on patient than the observable component.
RA flare	Mostly observed AEs with felt components	Felt (subjective) or observable AEs? Can be both felt and objective. Observable because flare can be measured in RA
Gout flare	Mostly observed AEs with felt components	Felt (subjective) or observable AEs? Can be both felt and objective. Observable because flare can be measured in gout
Rash	Mostly observed AEs with felt components	Felt (subjective) or observable (/measurable) AEs? Observed usually by patients, but might need a clinician with technical expertise to grade magnitude

Supplementary Table C

Muscle-related signs and symptoms (muscle cramps, muscle twitching, night cramps) (none)	Mostly observed AEs with felt components	Felt (subjective) or observable AEs? Can be both observable and felt (subjective). Signs are considered observable, while symptoms are considered more felt (subjective)
Colitis (none)	Mostly observed AEs with felt components	Felt (subjective) or clinically observable AEs? Mostly observable as it is a diagnosis, but symptoms can be both observable (e.g. bloody floating) and felt (e.g. abd. pain)
Effusion (none)	Mostly observed AEs with felt components	Felt (subjective) or clinically/measurable observable AEs? Mostly observable as it is a diagnosis, but symptoms can be both observable/measurable (e.g. x-ray) and felt (e.g. shortness of breath)
Optic neuritis (none)	Mostly observed AEs with felt components	Felt (subjective) or clinically observable AEs? Mostly observable as it is a diagnosis, but symptoms can be both observable (inflammation) and felt/subjective (loos of vision/affected vision and pain)
Anal fistula (none)	Mostly observed AEs with felt components	Felt (subjective) or clinically/measurable observable AEs? Mostly observable as it is a diagnosis, but symptoms can be both observable (e.g. opening onto the skin may be observed) and felt (e.g. itching and pain)
Ptosis (<u>droopy eyelid</u>)	Mostly observed AEs with felt components	Felt (subjective) or observable (/measurable) AEs? Falling of the upper eyelid is observable and ptosis is a diagnosis. Could need a clinician with technical expertise to grade magnitude
Yellow discoloration of urine	Mostly observed AEs with felt components	Felt (subjective) or observable AEs? Usually observed (not felt) by patients

* When difference between medical and lay language terms exists, terms are described in medical term (*lay language term*). Underscore indicates terms added by authors. "None" indicates that no lay language term was identified.

Supplementary Table D. Number of harms within RCTC-categories

Table D		
Number of harms within RCTC-categories.		
RCTC-category	No of harm clusters (n = 280)*	No of reported AEs (n = 21,498)*
Allergic/immunologic	8 (2.9)	576 (2.7)
Cardiac	21 (7.5)	838 (3.9)
General (constitutional)	56 (20.0)	4.235 (19.7)
Dermatologic	23 (8.2)	1.585 (7.4)
Ear/nose/throat	17 (6.1)	2.666 (12.4)
Eye/ophthalmologic	6 (2.1)	57 (0.3)
Gastrointestinal	41 (14.6)	3.985 (18.5)
Musculoskeletal	36 (12.9)	2.484 (11.6)
Neuropsychiatric	24 (8.6)	841 (3.9)
Pulmonary	16 (5.7)	668 (3.1)
Laboratory data: hematology	9 (3.2)	592 (2.8)
Laboratory data: chemistry	7 (2.5)	2.516 (11.7)
Laboratory data: urinalysis	1 (0.4)	14 (0.1)
Missing	15 (5.4)	441 (2.1)

* Data are expressed as number (%).

RCTC = Rheumatology Common Toxicity Criteria v. 2.0.