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

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ABSTRACT

Background

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

Methods

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

Results

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

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

Conclusions

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

Registration

PROSPERO: CRD42018108393

Keywords

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

ABBREVIATIONS

ACR, American College of Rheumatology

AE, adverse event

EULAR, European League Against Rheumatism

CDSR, Cochrane database of systematic reviews

CMSG, Cochrane Musculoskeletal Group

COMET, Core Outcome Measures in Effectiveness Trials

CONSORT, consolidated Standards of Reporting Trials

COS, core outcome set

CRs, Cochrane reviews

DMARDs, disease-modifying antirheumatic drugs

IQR, interquartile range

MedDRA, Medical Dictionary for Regulatory Activities

NSAIDs, nonsteroidal anti-inflammatory drugs

OARSI, OsteoArthritis Research Society International

OMERACT, Outcome Measures in Rheumatology

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

PROSPERO, International prospective register of systematic reviews

RCT, randomized clinical trials

RCTC, Rheumatology Common Toxicity Criteria

SD, standard deviation

INTRODUCTION

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

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

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

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

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

METHODS

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

Data Sources and Searches

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

Study Selection

Two reviewers (DBB supported by RC) screened all identified CRs by reviewing titles and abstracts. We excluded protocols without data and withdrawn reviews. We then used reference lists of included articles in the selected CRs to identify eligible rheumatology trials. Trials were eligible if they investigated any type of pharmacological intervention against any comparator(s) in patients with rheumatic and musculoskeletal conditions. We identified primary publications from the reference lists of the included reviews (i.e., referred to as major publications in CRs), and excluded 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.

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

Data Analysis

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

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

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

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

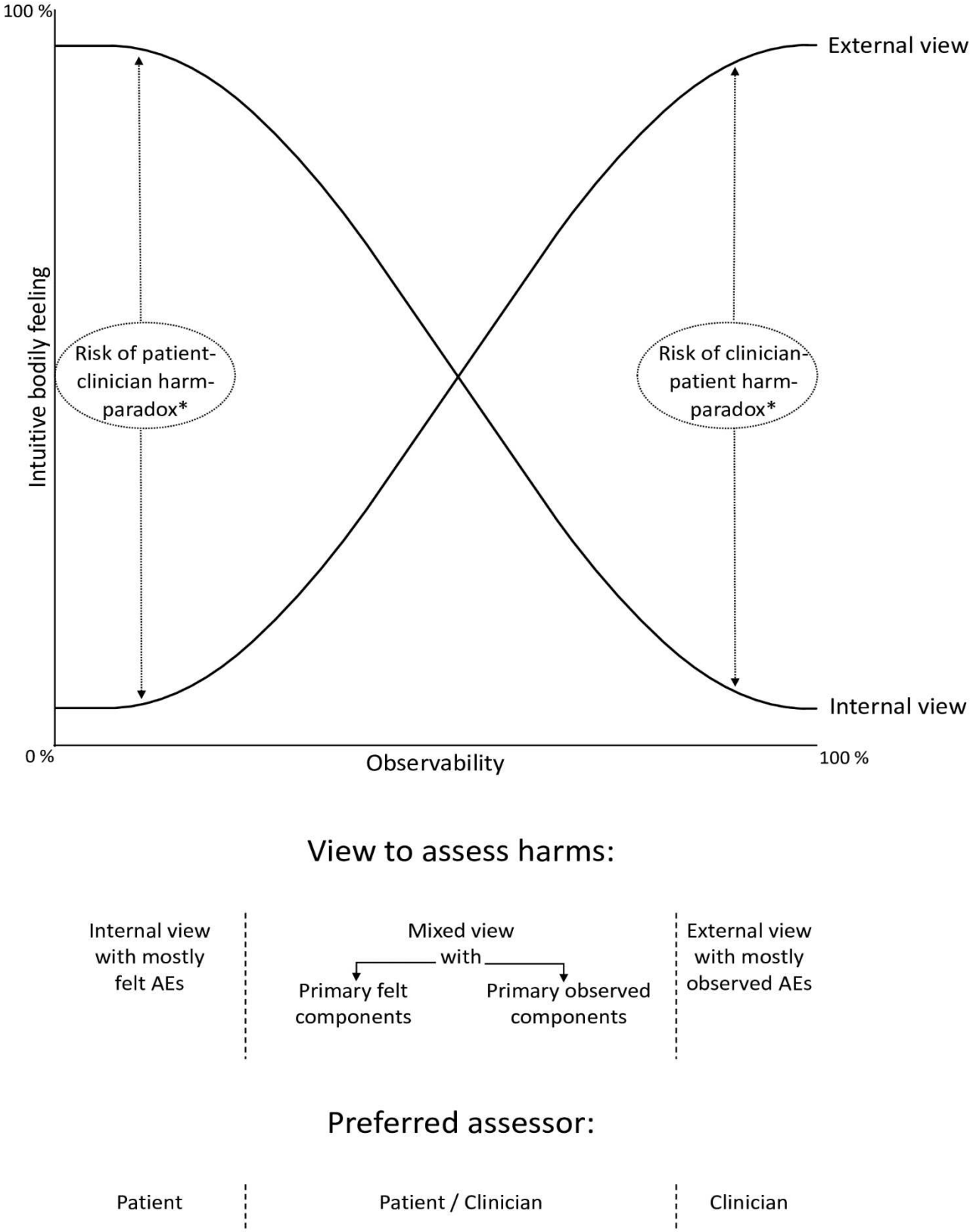

Fig 1. Perspective on outcome assessment to cover harms.
*Harm-paradoxes occur when harms appear unequally important/severe when observed from two different points of view.

Statistical Analysis

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

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

RESULTS

Eligible Reviews and Trials

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

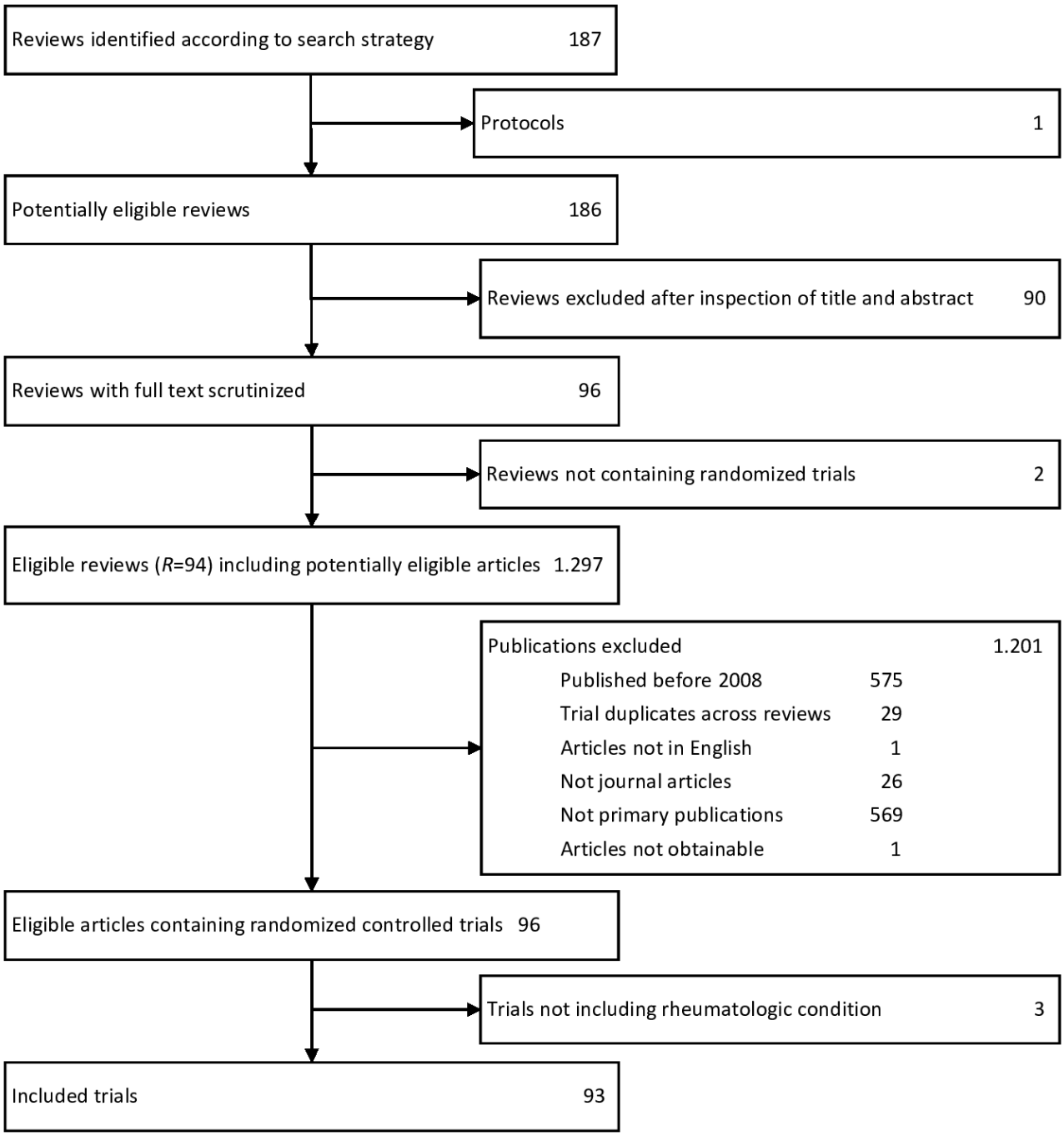

Fig 2. Flow diagram for the study selection.
R = review.

Characteristics of Included Trials

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

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

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

	Trials, *k*	%	Patients, *n*	%
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.

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Harms Reported in Rheumatology Drug Trials

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

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

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

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

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			327	Joint-related signs and symptoms (none)
268	Fatigue	597	Constipation	303	RA flare
204	Arthralgia (*joint pain*)	565	Nasopharyngitis (*common cold*)	266	Gout flare
184	Pruritus (*itching*)	520	Vomiting	243	Rash
180	Abdominal pain	288	Injury, poisoning, and procedural complications	241	Lower respiratory tract infection (*bronchitis*)
172	Gastrointestinal symptoms (none)	255	Somnolence (*sleepiness*)	62	Erythema (*redness*)
130	Dyspepsia (*indigestion*)	162	Back pain	62	Infusion reaction
56	Pain	134	Influenza (*flu syndrome*)	62	Mouth ulcers
27	Injection site pain	94	Sinusitis	41	Psychiatric disorders (none)
24	Asthenia (*feeling weak*)	89	Dry mouth	35	Pyrexia (*fever*)
19	Depression	87	Pharyngitis (*sore throat*)	32	Muscle-related signs and symptoms: muscle cramps, muscle twitching, night cramps (none)
10	Pain in the study joint	70	Cough		
8	Itch or dizziness	65	Skin injuries	29	Allergic reactions
8	Myalgia (*muscle pain*)	41	Vertigo (*spinning sensation*)	24	Osteoarthritis (none)
7	Pain in extremity	39	Dyspnea (*shortness of breath*)	16	Joint effusion (*joint swelling*)
5	Joint stiffness	38	Sun sensitivity	13	Eczema
4	Dysphagia (*difficulty in swallowing*)	34	Peripheral oedema (*swelling*)	8	Allergic conjunctivitis (none)
3	Burning	33	Paresthesia (*'pins and needles'*)	8	Contusion (*bruise*)
3	Malaise (*feeling badly*)	24	Rhinitis (*runny nose*)	6	Colitis (none)
2	Change of bowel habit	21	Chest pain	6	Effusion (none)
2	Flatulence (*passing gas*)	21	Flare	4	Recurrent falls
2	Increased appetite	16	Nephrolithiasis (*renal colic*)	3	Hospitalized
2	Stinging	16	Urticarial (*hives*)	3	Induration (none)
2	Tendon pain	15	Insomnia (*difficulty sleeping*)	3	Optic neuritis (none)
1	Ear pain	13	Pleurisy (none)	1	Abdominal hernia, obstructive (none)
1	Feeling of warmth	11	Gastroenteritis (*stomach flu*)	1	Abdominal wall abscess
1	Hallucination (*sensing things that are not real*)	10	Flushing	1	Alopecia (*hair loss*)
1	Hyperesthesia (*increased sensitivity of any sense*)	6	Angina pectoris (*angina*)	1	Anal fistula (none)
1	Hypoesthesia (*reduced sensitivity of any sense*)	6	Palpitations	1	Blepharitis (*eyelid inflammation*)
1	Lack of appetite	4	Dental pain	1	Increased body weight
1	Pain in rectum	3	Gastritis	1	Infected tophus (none)
1	Restless legs syndrome (*restless legs*)	2	Abdominal distension (*bloating*)	1	Inguinal hernia (none)
1	Straining	2	Anxiety attack	1	Mastitis (*inflamed breast*)
		2	Muscular weakness (*muscular weakness in the area around the study joint*)	1	Menometrorrhagia (*abnormally heavy, prolonged, and irregular uterine bleeding*)
		1	Asthma	1	Ptosis (*droopy eyelid*)
		1	Ataxia (*impaired coordination*)	1	Yellow discoloration of urine
		1	Constipation-related bloating		
		1	Cystitis (*bladder inflammation*)		
		1	Irritable bowel syndrome		
		1	Neuralgia (*nerve pain*)		
		1	Skin peeling		
		1	Syncope (*fainting, losing consciousness*)		
		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 exits, 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.

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Severity of Harms

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

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)	Life threatening (7)
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)	
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.

Harm Domains

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

DISCUSSION

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

Building on the premise that patients' and clinicians' different perspectives on a disease might influence the assessment of effects in RCTs (43), we feel patients should assess harms and their severity when the harm involves "felt" components. Likewise, clinicians should 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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AUTHOR CONTRIBUTIONS

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

Study concept and design: Berthelsen and Christensen.

Acquisition: Berthelsen with support from Christensen.

Extraction: Berthelsen and Woodworth.

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

Drafting of the manuscript: Berthelsen and Christensen.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Berthelsen and Christensen.

DECLARATION OF INTEREST

Berthelsen: none

Woodworth: none

Ioannidis: none

Tugwell: none relevant

Devoe: none relevant

Williamson: none

Terwee: none

Suarez-Almazor: none

Strand: none relevant

Leong: none

Goel: none relevant

Conaghan: none relevant

Boers: none relevant

Shea: none relevant

Brooks: none relevant

Simon: none relevant

Furst: none relevant

Christensen: none relevant

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APPENDIX A

SUPPLEMENTARY MATERIAL

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

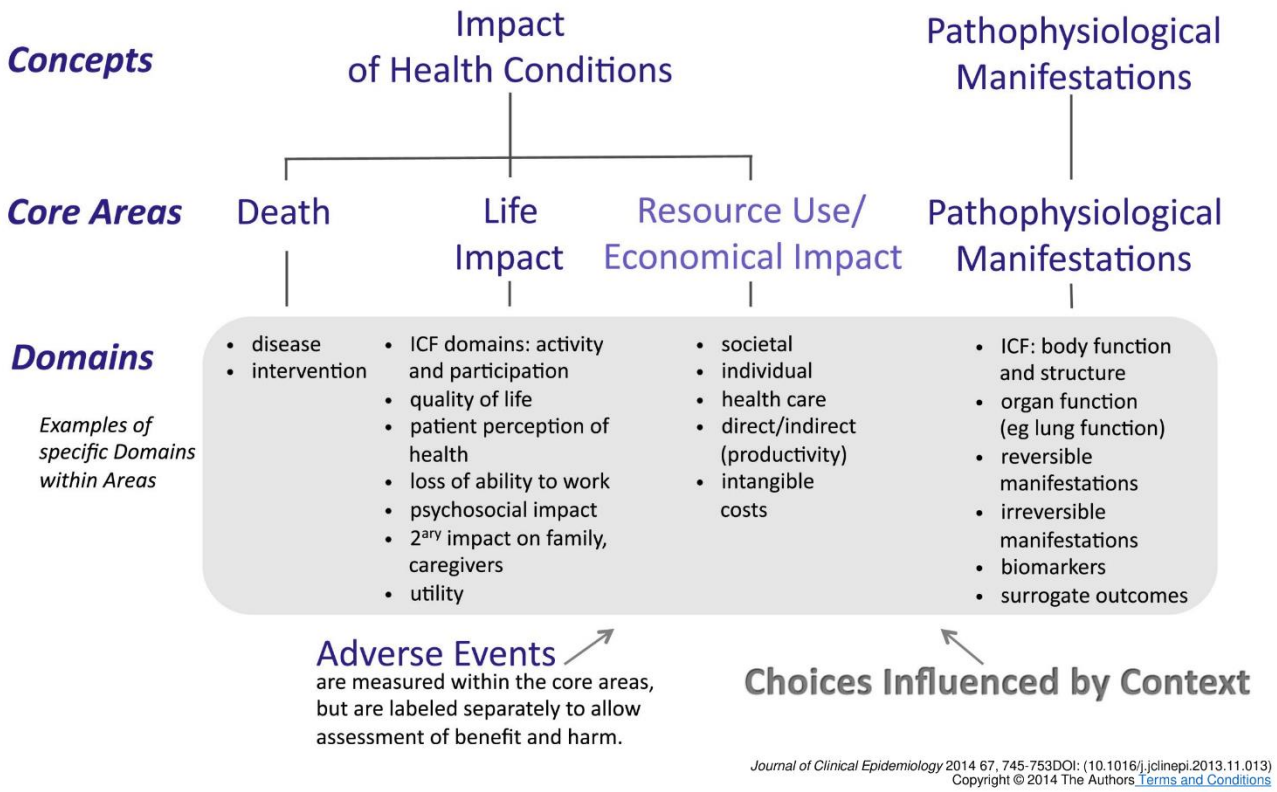

Fig A.1. Conceptual framework of Core Areas for outcome measurement in the setting of health intervention studies.
Resource Use has a lighter shade to indicate it is currently strongly recommended, but not mandatory for inclusion. The choice of specific Domains within an Area depends on the context for 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

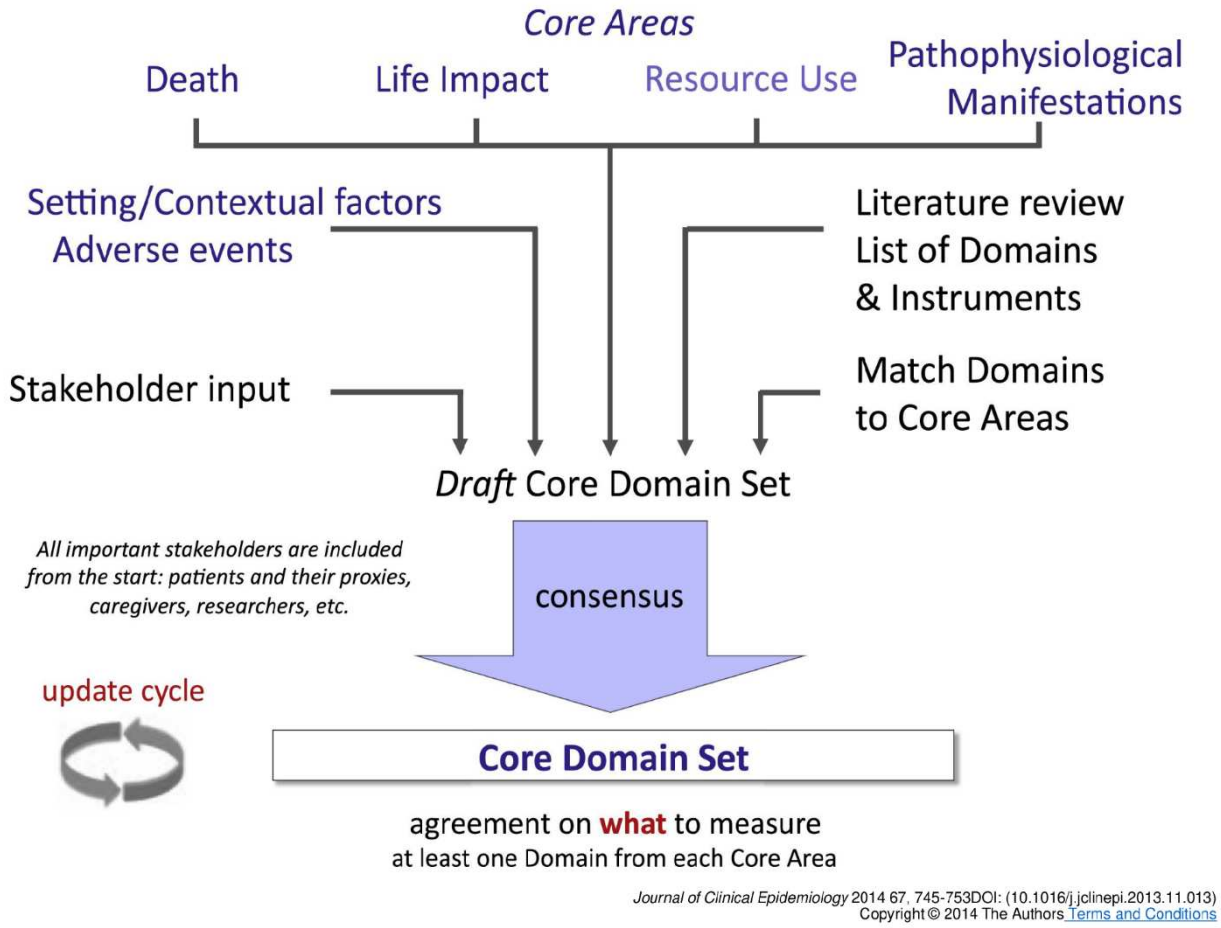

Fig A.2. Development of a Core Domain Set from the Core Areas of measurement.
A Core Domain Set is defined as the minimum set of Domains and Subdomains necessary to adequately cover all Core Areas, that is, fully measure all relevant concepts of a specific health condition within a specified setting.

Supplementary Fig B

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

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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 (*liver function tests abnormal*)	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					

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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 (*increase in total cholesterol level*)	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 week24					
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 (*common cold*)	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					

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25	Hematopoietic cytopenias					
10	Leucopenia					
1	Agranulocytosis					
344	Vomiting					
96	Nausea and vomiting symptoms	Vomiting	520	Life impact	Mostly felt AEs with observed components	Gastrointestinal
71	Nausea/vomiting/decreased appetite					
9	Vomiting (all occurrences)					
188	Injection-site reactions					
78	Injection site reaction					
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	Injection-site reactions	507	Life impact	Mostly observed AEs with felt components	Dermatologic
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					
172	Gastrointestinal	Gastrointestinal disorders (none)	501	PM	Clinically/measurable observable AEs	Gastrointestinal
33	Various gastrointestinal aes					
10	Gastro-intestinal disorders					
1	Gastrointestinal inflammation					
208	Hypertension					
134	Vascular hypertensive disorders	Hypertension (*increased blood pressure*)	419	PM	Clinically/measurable observable AEs	Cardiac
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					
27	Neurologic signs and symptoms (dizziness)	Dizziness	401	Life impact	Mostly felt AEs	Neuropsychiatric
1	Dizziness and flushing					
1	Postural dizziness					
213	Musculoskeletal and connective tissue disorders					
103	Musculoskeletal and connective tissue	Musculoskeletal and connective tissue disorders (none)	352	PM	Clinically/measurable observable AEs	Musculoskeletal
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					
75	Anti-certolizumab pegol antibodies	Antibodies to biologics	319	PM	Laboratory/biomarker based AEs	Allergic/ immunologic
48	Antibodies to golimumab					
31	Antibody to pegloticase					

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17	Anti-czp antibodies					
9	Antibodies to certolizumab pegol					
5	Anti-tocilizumab antibodies					
114	Ra	RA flare	303	Life impact	Mostly observed AEs with felt components	Musculoskeletal
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	Injury, poisoning, and procedural complications	288	Life impact	Mostly felt AEs with observed components	General (constitutional)
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	Skin and subcutaneous tissue disorders (none)	282	PM	Clinically/measurable observable AEs	Dermatologic
111	Skin and subcutaneous tissue					
7	Skin disorders					
268	Fatigue	Fatigue	268	Life impact	Mostly felt AEs	General (constitutional)
207	Gout flare	Gout flare	266	Life impact	Mostly observed AEs with felt components	Musculoskeletal
33	Gouty arthritis					
17	Gout flares					
8	Worsening of gout/gouty arthritis					
1	Gout (only severe intensity)					
157	Nervous system disorders	Nervous system disorders (none)	257	PM	Clinically/measurable observable AEs	Neuropsychiatric
98	Nervous system					
2	Nervous system disorders (alzheimer;cerebrovascular accident)					
255	Somnolence	Somnolence (*sleepiness*)	255	Life impact	Mostly felt AEs with observed components	Missing
224	Rash	Rash	243	PM	Mostly observed AEs with felt components	Dermatologic
14	Rashes, eruptions and exanthems					
2	Skin rash					
2	Rash/skin reactions					
1	Lupus erythematosus rash					
142	Lower respiratory tract and lung infections		241	PM	Mostly observed AEs with felt components	Pulmonary
81	Bronchitis					
7	Lower respiratory tract/lung infection					
6	Lower respiratory tract infection NOS					

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

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

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2 Pneumonia mycoplasmal 1 Bronchopneumonia 1 Broncho-pneumonia 1 Lobar pneumonia 1 Lung infection pseudomonal 1 Necrotising pneumonia 1 Organized pneumonia 1 Pneumonitis					Clinically/measurable observable AEs	
31 Death 16 Deaths 12 Died 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	Death	72	Death	Clinically/measurable observable AEs	General (constitutional)
47 Cough 23 Cough increased	Cough	70	Life impact	Mostly felt AEs with observed components	Pulmonary
64 Skin injuries 1 Skin laceration	Skin injuries	65	Life impact	Mostly felt AEs with observed components	Dermatologic
61 Erythema 1 Facial redness	Erythema (*redness*)	62	Life impact	Mostly observed AEs with felt components	Dermatologic
59 Infusion reaction 2 Infusion site reaction 1 Infusion-related reaction	Infusion reaction	62	PM	Mostly observed AEs with felt components	Allergic/ immunologic
52 Stomatitis 10 Mouth ulcers	Mouth ulcers	62	Life impact	Mostly observed AEs with felt components	Ear/nose/throat
57 Gastrointestinal atonic and hypomotility disorders	Gastrointestinal atonic and hypomotility disorders (none)	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	Pain	56	Life impact	Mostly felt AEs	General (constitutional)
16 Neoplasms benign, malignant, and unspecified 12 Malignancy 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)	Cancer	47	PM	Clinically/measurable observable AEs	General (constitutional)
4 Psychiatric disorders 35 Psychiatric 1 Psychosis	Psychiatric disorders (none)	41	Life impact	Mostly observed AEs with felt components	Neuropsychiatric

Supplementary Table B

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

Supplementary Table B

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

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	Fracture	17	PM	Clinically/measurable observable AEs	Musculoskeletal
2	Hip fracture					
1	Facial bone fracture					
1	Femur fracture					
1	Femoral neck fracture					
1	Fractured coccyx					
1	Radius fracture					
1	Thoracic vertebral fracture					
1	Traumatic patella fracture					
1	Ulnar fracutre					
17	Haematological	Haematological (none)	17	PM	Laboratory/biomarker based AEs	Laboratory data: hematology
10	Herpes simplex	Herpes simplex (none)	17	PM	Clinically/measurable observable AEs	Ear/nose/throat
5	Herpes viral infections					
2	Herpes viral infection					
16	Bone loss	Bone loss (none)	16	PM	Clinically/measurable observable AEs	Musculoskeletal
9	Hypotension	Hypotension (none)	16	PM	Clinically/measurable observable AEs	Cardiac
7	Decreased blood pressure					
9	Joint effusion	Joint effusion (*joint swelling*)	16	Life impact	Mostly observed AEs with felt components	Musculoskeletal
7	Joint swelling					
15	Nephrolithiasis	Nephrolithiasis (*renal colic*)	16	Life impact	Mostly felt AEs with observed components	General (constitutional)
1	Renal colic					
16	Urticaria	Urticarial (*hives*)	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 (*difficulty sleeping*)	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 (*stomach flu*)	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 (*bruise*)	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 1	Myalgia Myalgia/muscle stiffness	Myalgia (*muscle pain*)	8	Life impact	Mostly felt AEs	Musculoskeletal
4 2 1 1	Acute pyelonephritis Pyelonephritis Kidney infection Pyelonephritis acute	Pyelonephritis (none)	8	PM	Clinically/measurable observable AEs	General (constitutional)
4 2 1 1	Stroke Nonfatal stroke Ischaemic stroke Lacunar infarction	Stroke	8	PM	Clinically/measurable observable AEs	Neuropsychiatric
8	Tendon rupture	Tendon rupture	8	PM	Clinically/measurable observable AEs	Musculoskeletal
4 2 1 1	Transient ischemic attack Transient ischaemic attack Tia Transit ischaemic attack	Transient ischemic attack (*TIA*)	8	PM	Clinically/measurable observable AEs	Neuropsychiatric
2 1 1 1 1 1	Bacterial arthritis Infective arthritis Infectious arthritis Salmonella arthritis Streptococcal infections Staphylococcal polyarthritis	Bacterial arthritis (none)	7	PM	Clinically/measurable observable AEs	Musculoskeletal
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 1 1 1	Lymphoma Hodgkin's lymphoma Follicle centre lymphoma Extranodal marginal-zone b cell lymphoma	Lymphoma (none)	7	PM	Clinically/measurable observable AEs	Missing
6	Pain in extremity					

Supplementary Table B

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

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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	Dysphagia (*difficulty in swallowing*)	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 1 1	Elevation of serum creatinine Increased blood creatinine/increased blood urea Investigations (creatinine increased)	Elevation of serum creatinine (none)	4	PM	Laboratory/biomarker based AEs	Laboratory data: chemistry
2 1 1	Tongue neoplasms Malignant tongue neoplasm Epidermoid cancer of the tongue	Malignant tongue neoplasm (none)	4	PM	Clinically/measurable observable AEs	Ear/nose/throat
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 1	Hepatobiliary disorders (cholecystitis) Acute cholecystitis	Acute cholecystitis	3	PM	Clinically/measurable observable AEs	Gastrointestinal
3	Burning	Burning	3	Life impact	Mostly felt AEs	General (constitutional)
1 1 1	Coronary artery disease Coronary artery arteriosclerosis Ischemic coronary artery disorders	Coronary artery disease (none)	3	PM	Clinically/measurable observable AEs	Cardiac
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

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3	Induration	Induration (none)	3	PM	Mostly observed AEs with felt components	Dermatologic
1 1 1	Malaise Abnormal feeling Malaise and/or fever	Malaise (*feeling badly*)	3	Life impact	Mostly felt AEs	General (constitutional)
2 1	Optic neuritis Optical neuritis	Optic neuritis (none)	3	PM	Mostly observed AEs with felt components	Eye/ophthalmologic
2 1	Otitis media Chronic otitis media	Otitis media	3	PM	Clinically/measurable observable AEs	Ear/nose/throat
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 1	Knee arthroplasty Total knee replacement	Total knee replacement	3	PM	Clinically/measurable observable AEs	Musculoskeletal
2	Abdominal distension	Abdominal distension (*bloating*)	2	Life impact	Mostly felt AEs with observed components	Gastrointestinal
2	Acute renal failure	Acute renal failure (none)	2	PM	Clinically/measurable observable AEs	General (constitutional)
1 1	Anxiety attack Worsening of anxiety	Anxiety attack	2	Life impact	Mostly felt AEs with observed components	Neuropsychiatric
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 1	Change of bowel habit Bowel movements	Change of bowel habit	2	Life impact	Mostly felt AEs	Gastrointestinal
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 1	Elective surgery Scheduled cataract surgery	Elective surgery	2	PM	Clinically/measurable observable AEs	General (constitutional)
1	Esophageal carcinoma					

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1	Oesophageal squamous cell carcinoma	Esophageal carcinoma (none)	2	PM	Clinically/measurable observable AEs	Missing
2	Flatulence	Flatulence (*passing gas*)	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 1	Meningitis Meningitis fungal	Meningitis	2	PM	Clinically/measurable observable AEs	Neuropsychiatric
2	Muscular weakness in the area around the study joint	Muscular weakness (*muscular weakness in the area around the study joint*)	2	Life impact	Mostly felt AEs with observed components	Musculoskeletal
1 1	Pancreatitis Acute pancreatitis	Pancreatitis	2	PM	Clinically/measurable observable AEs	Gastrointestinal
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 1	Small-bowel obstruction Intestinal blockage	Small-bowel obstruction (none)	2	PM	Clinically/measurable observable AEs	Gastrointestinal
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 1	Uterine cancer Uterine sarcoma	Uterine cancer	2	PM	Clinically/measurable observable AEs	General (constitutional)
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

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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 (*hair loss*)	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 (*impaired coordination*)	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 (*eyelid inflammation*)	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

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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 (*bladder inflammation*)	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

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1	Hallucination	Hallucination (*sensing things that are not real*)	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 (*increased sensitivity of any sense*)	1	Life impact	Mostly felt AEs	Neuropsychiatric
1	Hypoesthesia	Hypoesthesia (*reduced sensitivity of any sense*)	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

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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 (*inflamed breast*)	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 (*abnormally heavy, prolonged, and irregular uterine bleeding*)	1	Life impact	Mostly observed AEs with felt components	General (constitutional)
1	Neuralgia	Neuralgia (*nerve pain*)	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 (*droopy eyelid*)	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

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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 (*restless legs*)	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 (*fainting, losing consciousness*)	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 exits, 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 (*itching*)	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
Dysphagia (*difficulty in swallowing*)	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 (*'pins and needles'*)	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 (*bloating*)	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 *(impaired coordination)*	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 (*bladder inflammation*)	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 (*droopy eyelid*)	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 exits, 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.