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Reporting of harms in oncological clinical study reports submitted to the European Medicines Agency compared to trial registries and publications—a methodological review

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Abstract

Background: An accurate and comprehensive assessment of harms is a fundamental part of an accurate weighing of benefits and harms of an intervention when making treatment decisions; however, harms are known to be underreported in journal publications. Therefore, we sought to compare the completeness of reporting of harm data, discrepancies in harm data reported, and the delay to access results of oncological clinical trials between three sources: clinical study reports (CSRs), clinical trial registries and journal publications.

Methods: We used the EMA clinical data website to identify all trials submitted to the EMA between 2015 and 2018. We retrieved all CSRs and included all phase II, II/III or III randomised controlled trials (RCTs) assessing targeted therapy and immunotherapy for cancer. We then identified related records in clinical trial registries and journals. We extracted harms data for eight pre-specified variables and determined the completeness of reporting of harm data in each of the three sources.

Results: We identified 42 RCTs evaluating 13 different drugs. Results were available on the EMA website in CSRs for 37 (88%) RCTs, ClinicalTrials.gov for 36 (86%), the European Clinical Trials Register (EUCTR) for 20 (48%) and in journal publications for 32 (76%). Harms reporting was more complete in CSRs than other sources. We identified marked discrepancies in harms data between sources, e.g. the number of patients discontinuing due to adverse events differed in CSRs and clinical trial registers for 88% of trials with data in both sources. For CSRs and publications, the corresponding number was 90%. The median (interquartile range) delay between the primary trial completion date and access to results was 4.34 (3.09–7.22) years for CSRs, 2.94 (1.16–4.52) years for ClinicalTrials.gov, 5.39 (4.18–7.33) years for EUCTR and 2.15 (0.64–5.04) years for publications.

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Conclusions: Harms of recently approved oncological drugs were reported more frequently and in more detail in CSRs than in trial registries and journal publications. Systematic reviews seeking to address harms of oncological treatments should ideally use CSRs as the primary source of data; however, due to problems with access, this is currently not feasible.

Keywords: Systematic reviews, Reporting bias, Clinical study reports, Adverse events, Harms, Registries

Background

Systematic reviews of randomised controlled trials (RCTs) are considered the gold standard for evaluating the effectiveness and harms of interventions [1]. However, results of many completed RCTs are not published, which leads to reduced power and potential publication bias in reviews [2–4]. Moreover, peer-reviewed publications are not always an accurate reflection of how trials were planned, conducted and analysed. A lack of transparency or missing information on harms is common [3, 5].

One potential source of unpublished data is clinical study reports (CSRs): extensive reports prepared by pharmaceutical companies and submitted to regulatory authorities as a part of an application for marketing authorisation. The structure of CSRs is outlined in a guideline from the International Conference on Harmonisations [6]. Access to CSRs has historically been difficult [7], but since 2015, the European Medicines Agency (EMA) has launched an initiative (policy 0700) to increase transparency of information on medicinal drugs by providing access to CSRs submitted to the agency. However, the EMA has not published any CSRs since December 4, 2018, when the initiative was paused indefinitely during the EMA's move to Amsterdam [8]. Although several systematic reviews have included CSRs [9–12] and a questionnaire study found that respondents consider CSRs valuable for systematic reviews [13], a 2014 study found that most systematic reviews continue to rely on publications as the primary source of data [14].

Several studies have compared reporting in publications, trial registries and CSRs; for example, a study found that CSRs had higher reporting quality than did registry reports and publications [15], a finding that was confirmed in several other studies [16–20]. However, no study has systematically compared reporting of harms in trial registries and publications with a large sample of recent CSRs from oncological trials.

Targeted therapy and immunotherapy for cancer have revolutionised the care of most patients with cancer. Several of these specific oncologic drugs have recently been approved by the US Food and Drug Administration and EMA. Evaluating the harms of these new drugs is essential. Thus, we aimed to compare the delay to access results of oncological RCTs, the completeness of reporting harm data and discrepancies in harm data reported between the three sources: CSRs available on the EMA Website, clinical trial registries and journal publications.

Methods

We identified all trials evaluating targeted therapy and immunotherapy for cancer available on the EMAs clinical data Website and retrieved the related CSRs. Then, we systematically searched for the related records in clinical trial registries and related publications. Finally, we compared the delay to access results, the completeness of reporting of harm data and discrepancies in harm data reported between the three sources.

Identification of trials

In November 2019, we used the EMA's clinical data website (https://clinicaldata.ema.europa.eu) to identify all submissions for marketing authorisation or extension of indication under the EMA policy 0070. We updated the search in June 2020 and identified no new submissions. For all submissions, we extracted the product name, active substance, marketing authorisation holder and Anatomical Therapeutic Chemical (ATC) code. We selected the ATC codes for monoclonal antibodies (L01XC) and protein kinase inhibitors (L01XE) corresponding to targeted therapy and immunotherapy.

Once we had identified all eligible active substances, we downloaded all documents from the EMA website (i.e., CSRs and related documents) and used these to create a list of all trials submitted to the EMA. We included phase II, II/III or III RCTs that were part of a submission for a targeted therapy or immunotherapy. We excluded trials that compared only different dosages of the same treatment.

Two reviewers (ASP-M and PC) independently identified trials from the documents for one-quarter of the eligible active substances. Because of no discrepancies in this identification, the remaining identifications involved one reviewer (ASP-M).

Identification of related clinical-trial registry records for the identified RCTs

One reviewer (ASP-M) systematically searched Clinical-Trials.gov and the European Clinical Trials Register

(EUCTR) by using (1) the trial registry identifier or ID number if mentioned in the CSR or (2) the name of the experimental drug (or its international non-proprietary name). If we were still unable to identify the corresponding trial, we used other keywords (e.g. treatment comparator and indication). The records identified were systematically checked by a second reviewer (PC). Then we checked whether results were posted on the trial registries identified. If the study was registered in both registries, we extracted data from both.

Identification of results publications for identified RCTs

We first searched for citations listed in trial registries. For ClinicalTrials.gov, the only registry to give access to citations, we used the citations listed under "publication of results" and "publications automatically indexed to this study by ClinicalTrials.gov identifier (NCT Number)". We included all publications reporting results for the trial identified. We did not include publications of reviews or publications that presented pooled analyses of several trials and did not include data from the individual trial. If no publications were indexed in the registry record, we searched MEDLINE and EMBASE by using the name of the experimental drug, treatment comparator, indication and name of the principal investigator.

Data extraction

For each trial, we extracted information from the CSR available on the EMA Website, the clinical trial registry records (both ClinicalTrials.gov and EUCTR) and all related publications. The extracted information was entered in a data extraction spreadsheet. Two reviewers (ASP and PC) independently extracted data for 10% of trials. Because of only minor disagreements, one reviewer (ASP-M) extracted the data for the remaining trials. All extractions were then checked by a second reviewer (PC). All discrepancies were resolved by discussion.

We extracted the following information for each trial:

1) *General characteristics*: name of trial, name of studied drug, clinical development phase, condition; number of centres, number of arms, number of participants randomised, whether the trial was a non-inferiority trial, the primary outcome, funding and whether the trial was blinded.
2) *Delay in access to trial results:* The CSRs included in this project are released under the EMA policy 0070 [21], which dictates that clinical data submitted to the EMA as part of a marketing authorisation application or a post-authorisation procedure shall be released once the concerned procedure (hereafter EMA procedure) has been finalised. We recorded the date of finalisation of the

procedure for all included submissions by using the European Commission's register [22] and determined the delay between the finalisation of the procedure and publication of CSRs on the EMA website.

To determine the time between completion of the study and release of results in each source, we recorded the primary trial completion date (i.e. the date of the last participant's final follow-up visit for measurement of the primary outcome) from ClinicalTrials.gov. If this was not available, we checked the other sources (CSRs, publications, and EUCTR) for a primary completion date. We also recorded for each source the date when the results were released and available. For trials with multiple publications, we used the earliest publication date. We then calculated the delay between primary trial completion date and availability of results for each source.

3) *Completeness of reporting harm data and discrepancies in harm data*: We extracted the following information from all three sources of data for each trial: number of patients randomised, whether a definition of safety population was provided, number of patients in the safety population, threshold for reporting adverse events (e.g. 10%, 5% or none), number of patients experiencing at least one adverse event, total number of adverse events, number of patients experiencing at least one serious adverse event, total number of serious adverse events, number of patients experiencing at least one adverse event judged to be grade 3–5 according to the Common Terminology Criteria for Adverse Events (CTCAE), total number of adverse events judged to be grade 3–5 according to the CTCAE, number of patients discontinuing the trial due to adverse events, number of deaths due to adverse events, and whether a description of the process of determining whether a death was due to adverse events, including whether the person(s) making the judgement were blinded, was provided. For all variables, we recorded the numbers per arm. Some sources reported CTCAE grade 3–4 events rather than grade 3–5 events. If the number of grade 5 events was reported separately, we added the numbers. If the number of grade 5 events was not reported, we still gave the trial a "yes" for the question, extracted the number of grade 3–4 events and noted this.

Analysis

We compared reporting of the different variables defined above in CSRs with that in clinical trial registries and

publications, separately. We performed Kaplan-Meier analysis on the delay from primary trial completion date to the publication of the CSR, the first publication of results in trial registries, and a publication in a medical journal. If a trial had not been published in a source, we calculated the delay between the primary completion date and June 29, 2020 and considered the trial right censored. For numerical variables reported in at least two of the data sources, we examined whether the numbers reported were the same. For this analysis, we pooled results from Clinical-Trials.gov and EUCTR. If results were available from both registries, we used the data from ClinicalTrials.gov for the analysis of discrepancies.

Patient involvement
No patients were involved in the planning or conduct of this study.

Results
Selection of trials
We identified 142 submissions through the EMA clinical data Website. These submissions corresponded to 124 unique substances: 22 concerned oncology drugs and 13 of these corresponded to targeted therapy and immunotherapy (Additional file 1). For these 13 drugs included in the study, we identified 164 unique trials, of which 42 met our eligibility criteria (phase II, II/III or III RCTs). The inclusion process is shown in Fig. 1.

The drugs included and the number of trials for each drug are in Table 1. The median number of randomised patients in the included trials was 364 (range 142–666) (Table 2). The primary outcome was progression-free survival for 27 of the 42 (64%) included trials, overall survival for eight (19%) and both for three (7%). The remaining four trials (7%) had other primary outcomes. Additional characteristics of included studies are in the Additional file 1: Table S1. Publications matched to individual trials are presented in Additional file 1: Table S2 [23–112].

Availability of sources
The EMA's Website had complete CSRs for 37 of the 42 (88%) included trials. For the remaining five (12%) trials, the EMA Website did not contain full CSRs and only documents such as summaries, pharmacokinetic data or periodic safety reports were available; the EMA Website did not explain why full CSRs are not available for these trials, but three trials were ongoing at the time of the application for marketing authorisation. Among the 42 included trials, trial results were posted on ClinicalTrials.gov for 36 (86%) and on the EUCTR for 20 (48%). We were able to identify

publications with results for 32 of the 42 (76%) included trials (all included publications are in the Additional file 1). Trial results were available in the three sources for 25 (60%) trials and in two sources for 13 (31%) (i.e. CSR and clinical trial registry for six trials, in CSR and publication for three trials, in clinical trial registry and publications for four trials). Results were available in only one source for three (7%) trials (two in CSRs and one in a clinical trial registry) and one (2%) trial had no results available.

Delay in access to trial results
The median delay between finalisation of the EMA procedure and availability of CSRs was 1.21 years (range 0.91–1.78). The median (interquartile range) delay between primary completion data and result availability was 4.34 (3.09–7.22) years for CSRs, 2.94 (1.16–4.52) years for ClinicalTrials.gov, 5.39 (4.18–7.33) years for the EUCTR and 2.15 (0.64–5.04) years for publications. Figure 2 shows Kaplan-Meier curves for the delay between primary trial completion dates and publication of the different sources.

Reports of harms in each source
Table 3 shows the proportion of trials for which we could obtain data on our pre-specified variables from each of the four sources of data. For most variables, results were more frequently reported in CSRs than both trial registries and publications. The number of patients with at least one serious adverse event was reported for all trials in both CSRs and Clinical-Trials.gov and in 19/20 (95%) trials in the EUCTR but only 16/32 (50%) trials with publications. The number of patients with any adverse events was reported in all CSRs but was not available for any trials or registries because the number of patients with serious and non-serious adverse events are reported separately. The number of patients with any adverse events was available for only 13/32 (41%) trials with publications. The number of patients with CTCAE grade 3–5 events was available in 36/37 (97%) CSRs but only 14/32 (44%) publications. The CTCAE grade was not reported in either of the trial registries.

The total number of serious adverse events, any adverse events, and CTCAE grade 3–5 events was available in 9/37 (24%), 12/37 (32%) and 6/37 (16%) CSRs, respectively; 10/36 (28%), 10/36 (28%) and 0/36 (0%) records at ClinicalTrials.gov; and 17/20 (85%), 17/20 (85%) and 0/20 (0%) records at the EUCTR. For publications, only 1/32 (3%) reports gave the total number of serious adverse events. The number of total adverse events and grade 3–5 adverse events was not available in publications for any trial.

Fig. 1 Flowchart of inclusion of trials
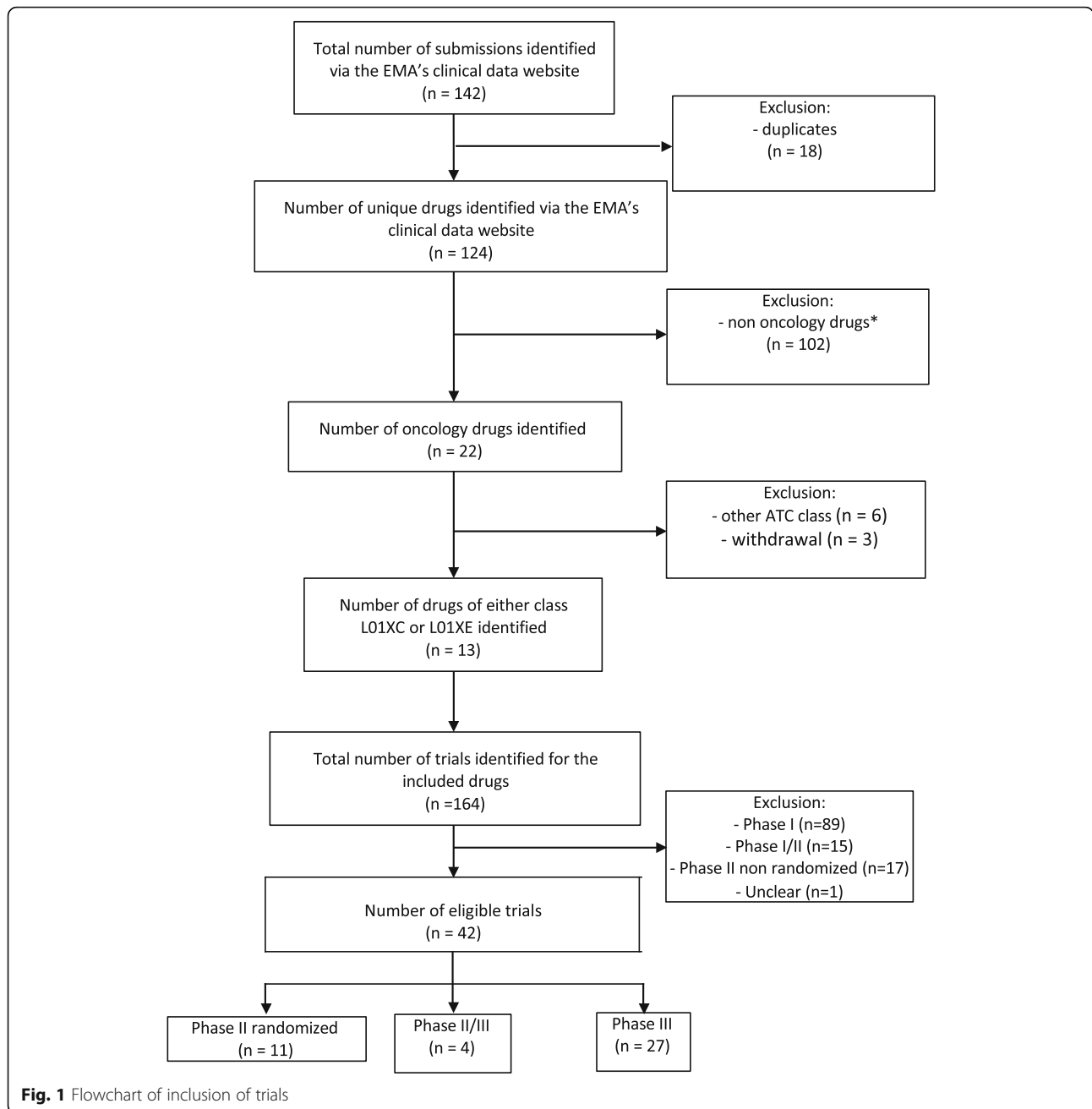
The number of deaths due to adverse events was available in CSRs for 34/37 (92%) trials, from ClinicalTrials.gov for no trials, from EUCTR for 15/20 trials (75%) and from publications for 12/32 (38%) trials. Only 10/37 (27%) trials in CSRs and no trials in other sources had a detailed explanation of how it was decided whether a death was due to an adverse event or progressive disease.

Discrepancies between sources
For trials for which results were available for a variable in a minimum of two sources of data, we compared the data and noted any discrepancies. The proportion of trials with discrepancies are in Table 4. Figure 3 shows discrepancies for each variable in each included trial.

We found marked discrepancies in harms data between CSRs, trial registry entries and publications. The number of patients who discontinued the treatment due to adverse events was particularly problematic, with discrepancies in 88% and 90% of trials for CSRs as compared with registries and publications, respectively. The number of deaths due to adverse events differed between CSRs and clinical trial registers in 92% of trials with data

Table 1 Included drugs and trials

Drug name	Number of trials	Pharmaceutical company	Type of cancer	Trial name available
Afatinib	6	Boehringer Ingelheim	Head and neck squamous cell carcinoma, non-small cell lung cancer	LUX-Head and Neck 1, LUX-Lung 5, LUX-Lung 6, LUX-Lung 8, LUX-LUNG 1
Bevacizumab	6	Roche	Non-small cell lung cancer	ATLAS, EURTAC, BeTa
Cabozantinib	4	Exelixis	Medullary thyroid cancer, renal cell carcinoma, prostate cancer	EXAM, METEOR, COMET-1, COMET-2
Cediranib	5	AstraZeneca	Ovarian cancer, colorectal cancer, renal cell carcinoma, glioblastoma	ICON6, HORIZON III, HORIZON II, REGAL
Cediranib	2	NCIC Clinical Trials Group	Non-small cell lung cancer	
Erlotinib	1	Roche	Non-small cell lung cancer	
Everolimus	1	Novartis	Neuro-endocrine tumour (gastro-intestinal or lung origin)	RADIANT-4
Lenvatinib	4	Eisai	Non-small cell lung cancer, glioma, differentiated thyroid cancer, hepatocellular carcinoma	SELECT
Nivolumab	4	Bristol-Myers Squibb	Renal cell carcinoma, non-small cell lung cancer, melanoma	CheckMate 025, CheckMate 057, CheckMate 067, Checkmate 069
Olaratumab	3	ImClone Systems	Ovarian cancer, non-small cell lung cancer, prostate cancer	
Palbociclib	3	Pfizer	Breast cancer	PALOMA-2, PALOMA-3, PALOMA-4
Pembrolizumab	3	Merck	Melanoma, non-small cell lung cancer	Keynote-006, Keynote-010, Keynote-024

from both sources, the corresponding number was 40% for CSRs and publications. Similarly, the total number of serious adverse events differed between CSRs and clinical trial registers for all five trials whereas the numbers matched in the single trial that had data in both a CSR and a publication.

Table 2 Characteristics of included trials

Clinical development phase	**N (%)**
Phase II	12 (29)
Phase II/III	4 (10)
Phase III	26 (61)
Blinding	**N (%)**
Open label	22 (52)
Double blind	20 (48)
Primary outcome	**N (%)**
Progression-free survival	27 (64)
Overall survival	8 (19)
Progression-free survival and overall survival	3 (7)
Other	4 (7)
Superiority design	40 (95%)
	Median (IQR)
Number of participants randomised	364 (142–666)
Number of centres	99 (42–142)

IQR interquartile range

Discussion

Our study shows that data on harms in RCTs evaluating targeted therapy and immunotherapy for cancer are reported more frequently and in more detail in CSRs than in registries and publications. However, reporting is not perfect. CSRs were missing for five (12%) trials. Three of these trials were ongoing at the time of submission of documents to the EMA which might explain the missing CSRs. The two remaining trials were completed before the submission and it is unclear why CSRs were missing for these trials. Furthermore, important data were incompletely reported; for example, the total number of serious adverse events and all adverse events was available in only 9/37 (24%) and 12/37 (32%) CSRs. Although data should be available at the date the EMA procedure is completed, we showed a median of 1.21 years between the finalisation of the procedure and publication of CSRs on the website. Additionally, the delay from primary completion of a trial until results were available was longer for CSRs than for other sources. We also demonstrated discrepancies in harms data between CSRs and other sources. One possible explanation for such discrepancies could be different selection criteria for which events to include in which reports, e.g., clinicaltrials.gov use a 5% threshold for non-serious adverse events and similar thresholds are also commonly used in journal publications. Routinely reporting all events, without thresholds, would both improve reporting and potentially solve some discrepancies.
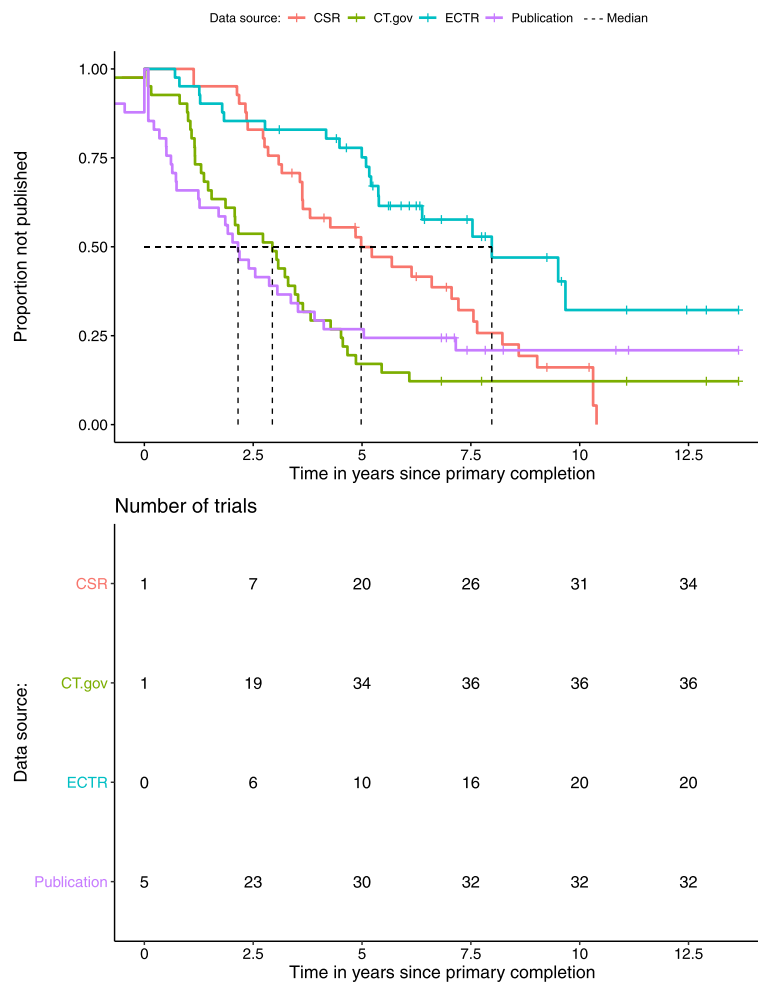
Fig. 2 Delay between primary trial completion day and availability of results from sources in days. CSR, clinical study report; CT, ClinicalTrials.gov; ECTR, European Clinical Trials Register

Our results are consistent with other findings. In 2013, Wieseler et al. examined a sample of 86 trials with both a CSR and a publicly available source of data and found that serious adverse events, adverse events and withdrawals due to adverse events were more frequently reported in CSRs than another source [16]. In 2014, Maund et al. found that for nine antidepressant trials, CSRs were a more reliable source of information on harms than were journal articles [17]. In 2016, two reports described the reporting of harms of orlistat in CSRs and journal publications: both concluded that reporting of harms was more extensive in CSRs than in journal publications [18, 19]. In 2019, a study compared six CSRs for gabapentin and two for quetiapine with publications and found that in CSRs all adverse events were reported, whereas no publications reported all adverse events [20].

Our finding of non-publication of RCTs and poor reporting of harms in publications is also in accordance with previous findings [113]. The CONSORT statement outlines items that should be reported in journal publications describing RCTs and is endorsed by 585 journals [114]. However, the CONSORT statement only has one item addressing harms. An extension for harms exists and some of the items outlined in this extension are the number of participants discontinued due to harms, the frequency of all adverse events with separate information about the severity, and the number of both affected participants and the number of events [115]. Unfortunately, to our knowledge, submission of the CONSORT harms extension is not mandated by any journal, and of the *Lance*t, *New England Journal of Medicine*, *BMJ* and *JAMA*, only the *Lancet* makes specific reference to the extension in their guidance to authors [116]. Had the extension been endorsed by the journals included in this study, and thus been followed, publications would likely have fared much better.

Table 3 Proportion of trials for which data, including harms data, could be obtained from the sources examined (n = 42)
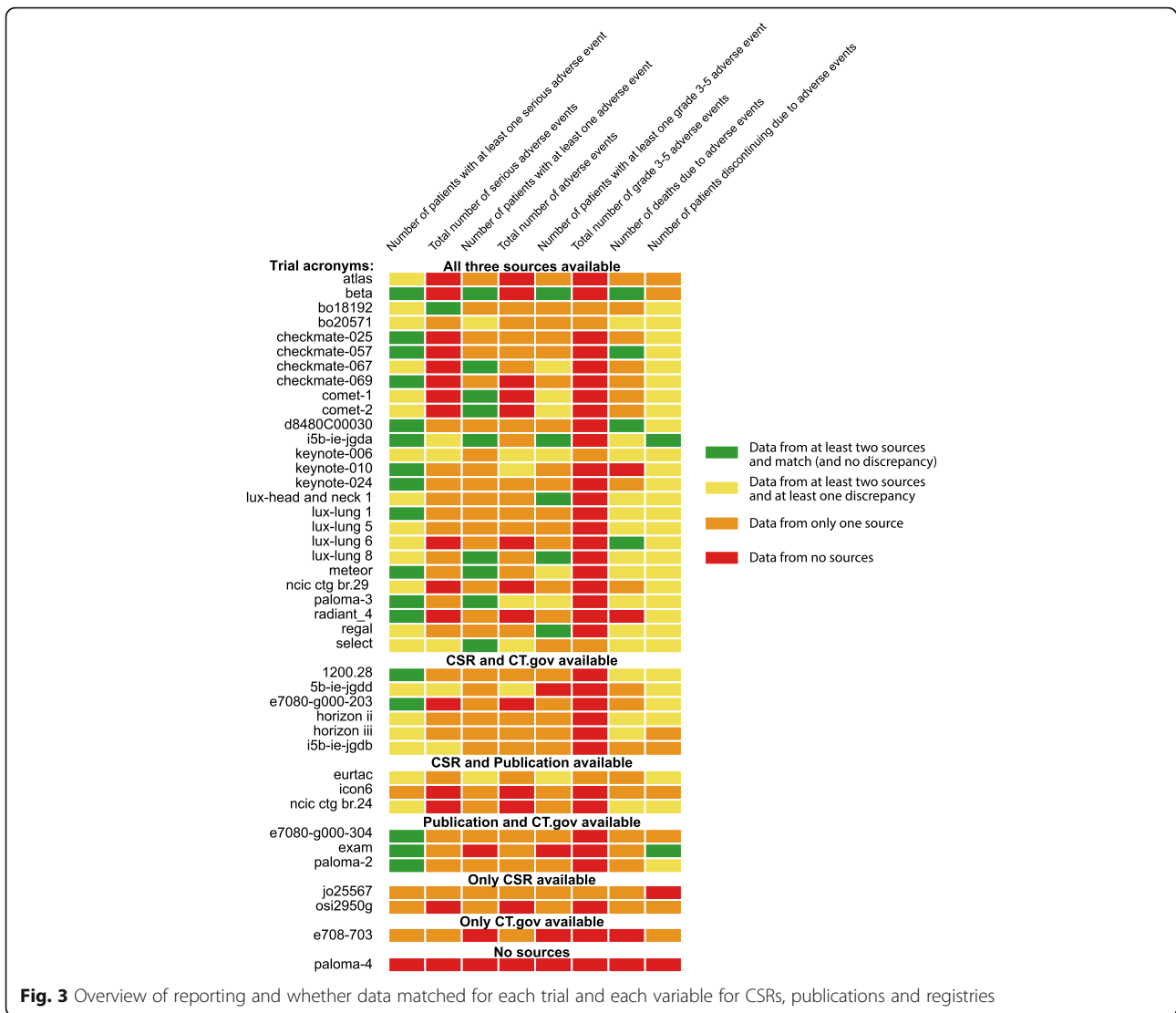
	CSR	ClincalTrials.gov	EU Clinical Trials Register	Publications
Source of data identified	37 (88%)	36 (86%)	20 (48%)	32 (76%)
Reporting of				
Included participants				
Number of participants randomised	37 (100%)	36 (100%)	19 (95%)	32 (100%)
Number of participants in safety population	37 (100%)	36 (100%)	19 (95%)	32 (100%)
Serious adverse events (SAEs)				
Number of patients with at least one SAE	37 (100%)	36 (100%)	19 (95%)	16 (50%)
Total number of SAEs	9 (24%)	10 (28%)	17 (85%)	1 (3%)
Any adverse events (AEs)				
Number of patients with at least one AE	37 (100%)	0 (0%)	0 (0%)	13 (41%)
Total number of AEs	12 (32%)	10 (28%)	17 (85%)	0 (0%)
CTCAE grade 3–5 AEs				
Number of patients with at least one Grade 3–5 AE	36 (97%)	0 (0%)	0 (0%)	14 (44%)
Total number of Grade 3–5 AEs	6 (16%)	0 (0%)	0 (0%)	0 (0%)
Deaths due to AEs				
Number of deaths due to AEs	34 (92%)	0 (0%)	15 (75%)	12 (38%)
Information on how it was decided whether a death was considered due to an AE	10 (27%)	0 (0%)	0 (0%)	0 (0%)
Discontinuations due to AEs				
Number of patients who discontinued trial due to AEs	32 (86%)	28 (78%)	17 (85%)	25 (78%)

CSR clinical study report, *CTCAE* Common Terminology Criteria for Adverse Events

Table 4 Discrepancies in harms data between CSRs, trial registries, and publications for variables that were reported in two sources

	CSR and trial registries	CSR and publications	Publications and trial registries
Discrepancies			
Number of patients with at least one SAE	15/32 trials (47%)	5/13 trials (38%)	8/14 trials (57%)
Total number of SAEs	5/5 trials (100%)	0/1 trial (0%)	No trials with data from both sources
Number of patients with at least one AE	No trials with data from both sources	2/11 trials (18%)	No trials with data from both sources
Total number of AEs	5/5 trials (100%)	No trials with data from both sources	No trials with data from both sources
Number of patients with at least one Grade 3–5 AE	No trials with data from both sources	7/12 trials (58%)	No trials with data from both sources
Total number of Grade 3–5 AEs	No trials with data from both sources	No trials with data from both sources	No trials with data from both sources
Number of deaths due to AEs	12/13 trials (92%)	4/10 trials (40%)	4/4 trials (100%)
Number of patients who discontinued trial due to AEs	23/26 trials (88%)	18/20 trials (90%)	11/18 trials (61%)

CSR clinical study report, *AE* adverse event, *SAE* serious adverse event

Fig. 3 Overview of reporting and whether data matched for each trial and each variable for CSRs, publications and registries

The substantial delay between completion of trials and availability of CSRs is an important barrier to access to all data. Several teams have highlighted the need to access trial results through posting on trial registries. For example, a report from TranspariMED states that in a 2013 cohort of cancer drug trials, two thirds of trials had not posted results to ClinicalTrials.gov 3 years after completion [117]. Interventions have been proposed to improve access to results [118] and similar strategies to increase access and reduce delays for CSRs should be developed.

Our study is the first to compare reporting of harms in CSRs released under EMA policy 0070 with publications and trial registries for oncological trials. The automatic release of the CSRs might have led to better reporting of harms in other sources of data, but this does not seem to be the case. Additionally, we systematically examined pre-defined variables in a relatively large sample of trials.

Our study has some limitations. First, we focused on oncology trials, and our findings might not be applicable to other fields of medicine. However, our results, together with results from previous studies, suggest that the reporting of harms is better in CSRs than trial registries and journal publications across all specialities. Second, we examined only two clinical trial registries, and more information might be available from other registries; however, ClinicalTrials.gov and EUCTR are two of the most-used registries, and information available elsewhere is unlikely to substantially alter our conclusions.

Our study has important implications for both research and practice. Our results suggest that any systematic review or other assessment of harms associated with oncological treatments would have to rely on CSRs for making the soundest conclusions. If such an assessment relies on data from only publications

and trial registries, it will only be able to include a subset of the available data. This is problematic for several reasons, namely reduced power to detect differences between groups and the fact that the data reported in registries and publications might vary systematically from data not reported. Additionally, we have shown marked discrepancies in data reported in CSRs and other sources, especially for withdrawals due to adverse events; therefore, we consider results based on CSRs more reliable. However, while we believe that CSRs are currently the most reliable source of data on harms, using CSRs might currently not be feasible. First, even though CSRs contained more data than other sources, important information was still missing in a significant number of CSRs. Secondly, we identified a substantial delay between the completion of trials and the availability of a CSR. To solve the problem of missing data in CSRs, we suggest that regulatory authorities make stricter requirements to the quality of submitted CSRs. The issue of delay in access is complicated by the fact that the EMA does not release CSRs until the procedure for which they were submitted is completed; however, we identified substantial delay from completion of the procedure to availability of CSR. By decreasing this delay to the absolute minimum, the overall delay could be reduced substantially. Currently, the EMA are not releasing any CSRs due to the agency's move to Amsterdam, and in a reply to an open letter from IQWIQ and Cochrane the agency would not commit to reinitiating publication of CSRs [119].

In addition, improving reporting of harms in journal publications would be valuable, as this is a very accessible source of information and as publications are often available earlier than CSRs. By actively enforcing the CONSORT statement and the extension for harms, journals could help improve the reporting of harms. Also, the CONSORT extension for harms, which was released in 2004, could be updated to better reflect new opportunities for data-sharing and new knowledge on reporting of harms.

In addition, current estimates of the harms of oncological treatments based on published data might not be accurate and not able to inform clinical practice. Because oncological treatments are generally toxic, the harms profile is an important piece of information for assessing the benefit/harm balance, and true informed consent is only possible if the estimate of harms is accurate.

We suggest that future studies comparing reporting of harms in different sources should focus on more detailed aspects of harms reporting, e.g. whether information on adverse events by System Organ Class and Preferred Term levels are available.

Conclusions

Harms in trials evaluating targeted therapy and immunotherapy for cancer are reported in more detail and more reliably in CSRs than in trial registries and journal publications. This finding confirms previous results and suggests that CSR would provide more complete data on harms of oncological treatments and ideally systematic reviewers should have access to CSRs for providing accurate evidence synthesis. Thus, we consider it vital that regulators start routinely releasing CSRs.

Abbreviations
ATC: Anatomic therapeutic chemical; CSR: Clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; EMA: European Medicines Agency; EUCTR: European Clinical Trials Register; RCT: Randomised controlled trial

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-01955-0.

Additional file 1. Characteristics of included trials.

Authors' contributions
All authors had complete access to the data in the study. ASP, PC and IB contributed to the study concept and design and wrote the protocol. ASP and PC acquired and extracted the data for the study; ASP, PC and IB contributed to the analysis. ASP, PC and IB contributed to the interpretation of the data. ASP developed the first draft of the manuscript and the other authors critically revised. The authors read and approved the final manuscript.

Availability of data and materials
The CSRs used for this study are available at the EMA's clinical data Website. All data files and the code for the statistical analysis are available from the Open Science Framework database (link: https://osf.io/mabyu/?view_only=d58aea7810234c229e593549569bc42d).

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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