Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014-16: cross sectional analysis

Huseyin Naci,1,2 Courtney Davis,3 Jelena Savović,4,5 Julian P T Higgins,4,5,6 Jonathan A C Sterne,4,6 Bishal Gyawali,2,7 Xochitl Romo-Sandoval,1 Nicola Handley,3 Christopher M Booth7

ABSTRACT

OBJECTIVE
To examine the design characteristics, risk of bias, and reporting adequacy of pivotal randomised controlled trials of cancer drugs approved by the European Medicines Agency (EMA).

DESIGN
Cross sectional analysis.

SETTING
European regulatory documents, clinical trial registry records, protocols, journal publications, and supplementary appendices.

ELIGIBILITY CRITERIA
Pivotal randomised controlled trials of new cancer drugs approved by the EMA between 2014 and 2016.

MAIN OUTCOME MEASURES
Study design characteristics (randomisation, comparators, and endpoints); risk of bias using the revised Cochrane tool (bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result); and reporting adequacy (completeness and consistency of information in trial protocols, publications, supplementary appendices, clinical trial registry records, and regulatory documents).

RESULTS
Between 2014 and 2016, the EMA approved 32 new cancer drugs on the basis of 54 pivotal studies. Of these, 41 (76%) were randomised controlled trials and 13 (24%) were either non-randomised studies or single arm studies. 39/41 randomised controlled trials had available publications and were included in our study. Only 10 randomised controlled trials (26%) measured overall survival as either a primary or coprimary endpoint, with the remaining trials evaluating surrogate measures such as progression free survival and response rates. Overall, 19 randomised controlled trials (49%) were judged to be at high risk of bias for their primary outcome. Concerns about missing outcome data (n=10) and measurement of the outcome (n=7) were the most common domains leading to high risk of bias judgments. Fewer randomised controlled trials that evaluated overall survival as the primary endpoint were at high risk of bias than those that evaluated surrogate efficacy endpoints (2/10 (20%) v 16/29 (55%), respectively). When information available in regulatory documents and the scientific literature was considered separately, overall risk of bias judgments differed for eight randomised controlled trials (21%), which reflects reporting inadequacies in both sources of information. Regulators identified additional deficits beyond the domains captured in risk of bias assessments for 10 drugs (31%). These deficits included magnitude of clinical benefit, inappropriate comparators, and non-preferred study endpoints, which were not disclosed as limitations in scientific publications.

CONCLUSIONS
Most pivotal studies forming the basis of EMA approval of new cancer drugs between 2014 and 2016 were randomised controlled trials. However, almost half of these were judged to be at high risk of bias based on their design, conduct, or analysis, some of which might be unavoidable because of the complexity of cancer trials. Regulatory documents and the scientific literature had gaps in their reporting. Journal publications did not acknowledge the key limitations of the available evidence identified in regulatory documents.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Most new cancer drugs approved by the European Medicines Agency (EMA) have been studied in randomised controlled trials, considered to be the “gold standard” for evaluating treatment efficacy. Design characteristics, risk of bias, and reporting of randomised controlled trials that support recent EMA cancer drug approvals have not been evaluated.

WHAT THIS STUDY ADDS
Around half of randomised controlled trials that supported European cancer drug approvals from 2014 to 2016 were assessed to be at high risk of bias based on characteristics of their design, conduct, or analysis; trials that evaluated overall survival were at lower risk of bias than those that evaluated surrogate measures of clinical benefit. Risk of bias judgments differed when using information available from the scientific literature and European regulatory documents separately, which highlights persistent limitations in information available in regulatory documents and published papers. European regulators frequently raised questions about the appropriateness and applicability of the available evidence on new cancer drugs, which were not acknowledged in the scientific literature.
of new drugs approved by the EMA were associated with a single pivotal study.1

Recently, cancer drugs have comprised the single largest category of new drug approvals in Europe. In 2017, more than a quarter (24/92) of EMA approvals were for cancer drugs.4 There is considerable debate and controversy about the therapeutic and economic value of these drugs.5-10 Our recent research showed that most new cancer drugs were approved by the EMA without evidence of benefit on overall survival or quality of life.11 In recent years there has been a substantial shift towards use of surrogate endpoints such as progression free survival.12 There is growing recognition that the correlation between surrogate endpoints and overall survival is often poor.13

About a third of “positive” randomised controlled trials of cancer drugs report treatment effects that are considered to be clinically meaningful according to the European Society of Medical Oncology Magnitude of Clinical Benefit Scale.1 14 Moreover, there is no association between magnitude of benefit and drug price.15 Because cancer drugs are responsible for most of the recent increases in pharmaceutical spending across healthcare systems,16 the evidence base that supports their market entry warrants close scrutiny.

Previous work described the characteristics of pivotal studies supporting new cancer drug approvals in Europe and the United States. Regulators in both settings generally review the same set of clinical studies when approving new drugs.17 In a large evaluation that focused on US Food and Drug Administration approvals, clinical studies of cancer drugs were less likely to be randomised and double blinded than clinical studies of drugs in other therapeutic areas.18 In another US study, cancer drugs with orphan (rare disease) designations were less likely to be randomised and double blinded than non-orphan cancer drugs.19 In Europe, most of the new cancer drug approvals between 2009 and 2013 were supported by at least one randomised controlled trial.20 However, an increasing proportion of new cancer drugs are approved on the basis of non-randomised, single arm studies.5

Randomised controlled trials are widely considered to be the “gold standard” for evaluating the clinical efficacy of new drugs.20 However, flaws in the design, conduct, analysis, or reporting of randomised controlled trials can produce bias in estimates of treatment effect, potentially jeopardising the validity of their findings. A large body of literature documents these biases, which could be substantial in magnitude.21-27 For example, in a large meta-epidemiological study of 1973 randomised controlled trials, lack of blinding was associated with an average 22% exaggeration of treatment effects among trials that reported subjectively assessed outcomes.22 Such non-trivial differences could affect how trial results are interpreted and used in regulatory settings and clinical practice. Therefore, it is imperative to systematically examine the validity of randomised controlled trials that support the approval of new drugs through assessment of the risk of bias in their results.28

In this study, we examined the characteristics of randomised controlled trials that supported approval of cancer drugs by the EMA from 2014 to 2016. We focused on three aspects of cancer drug trials. The first aspect was trial design. A key feature of cancer drug trials is whether they are designed to demonstrate a benefit on overall survival or quality of life.12 29 30 We determined whether recent randomised controlled trials of cancer drugs included overall survival or quality of life outcomes as endpoints. The second aspect was risk of bias. Previous studies primarily focused on crude metrics of trial quality such as blinding of participants and investigators.18 19 31 Although these aspects are important, they are not an adequate measure of a trial’s validity because randomised controlled trials with blinding might still be at high risk of bias (conversely, trials without blinding could produce valid results).32 We aimed to perform risk of bias assessments that more thoroughly evaluated deficits in the design, conduct, analysis, and reporting of randomised controlled trials.28 The third aspect was the adequacy, completeness, and consistency of reporting across different sources. Trial reporting has improved substantially over the past few decades.33 Yet, discrepancies can occur between regulatory documents and scientific publications,34 and might lead to different interpretations. We investigated such discrepancies.

Methods

Identification of cancer drug approvals
Two researchers (XRS and NH) independently searched the publicly available EMA database of European public assessment reports from 1 January 2014 to 31 December 2016. They used Anatomical Therapeutic Chemical Classification (ATC) codes L01-04 to identify “antineoplastic and immunomodulating” agents for solid tumours and haematological malignancies that received “first marketing authorisations”. A third researcher (HN) independently confirmed the sample of cancer drug approvals during this period. We excluded “type 2 variations,” which are additional marketing authorisations of already approved drugs in new therapeutic indications.

Our study period ended in 2016, which allowed a minimum of one year for trials to be published in the peer reviewed literature after authorisation. We excluded approvals for the treatment of benign tumours, supportive treatments, and generic products, which was consistent with our previous study.11 We noted when a drug received a “conditional marketing authorisation” from the EMA. Conditional marketing authorisations are granted for drugs aimed at treating serious or life threatening conditions with an unmet medical need.35 Such approvals rely on less comprehensive data than those required for regular marketing authorisations, and pharmaceutical companies are required to conduct additional studies to evaluate the clinical benefit of their products after market entry.36 37 We also noted if a drug received an “orphan drug” designation, which is granted for the treatment of rare diseases.
Identification of pivotal trials supporting cancer drug approvals
We included the pivotal studies that formed the basis of cancer drug approvals during our study period. Two researchers (XRS and NH) independently identified the pivotal studies, which were defined as those labelled as “main studies” in the European public assessment reports on the EMA website. A third researcher (HN) confirmed the list of pivotal studies. European public assessment reports are summaries of documents compiled by rapporteurs from European member states by using data submitted by pharmaceutical companies. These reports include publicly available information on the characteristics, findings, and EMA’s appraisal of pivotal and supportive clinical studies that support marketing authorisation decisions of new products.

Regulatory approval could precede the publication of trial results in the scientific literature. We searched publicly available clinical trial registries in Europe (European Clinical Trials Database: EudraCT) and the US (US National Library of Medicine database of clinical trials: ClinicalTrials.gov) to identify published accounts of pivotal studies in the scientific literature. The latest search date was 15 May 2018. ClinicalTrials.gov routinely searches PubMed and automatically retrieves the peer reviewed publications associated with each record in the registry (study sponsors can also manually enter information on trial publications in ClinicalTrials.gov). Therefore, we primarily relied on ClinicalTrials.gov to identify the publications of pivotal studies supporting EMA approvals during our study period. We cross checked EudraCT to capture any studies which might have been missed in ClinicalTrials.gov. If available, we also identified the protocols and supplementary appendices of pivotal studies. When the protocol was not available, we contacted the corresponding authors and requested access to their study protocol.

Data collection on study design characteristics
We documented the therapeutic indications for which cancer drugs received EMA first marketing authorisations. Pivotal studies were then characterised in terms of their design (randomised v non-randomised), study arms (experimental treatment and comparators), and primary and secondary endpoints. We categorised pivotal studies as randomised controlled trials if participants were randomly allocated to different treatment arms. We noted if trial endpoints included overall survival, health related quality of life, progression free survival, disease response rates or response duration. In addition to recording the primary endpoint of each study, we noted whether the secondary endpoints included overall survival or quality of life outcomes. All data were collected independently by two researchers (XRS and NH) and verified by a third (HN).

Risk of bias assessment in randomised trials
We used the revised Cochrane risk of bias assessment tool (RoB 2.0, version 2016, available at www.riskofbias.info) to examine the internal validity of randomised controlled trials. The Cochrane risk of bias tool was initially published in 2008 and has been widely used in systematic reviews of randomised controlled trials. The updated version considers five bias domains: (a) bias arising from the randomisation process; (b) bias owing to deviations from intended interventions; (c) bias caused by missing outcome data; (d) bias in measurement of the outcome; and (e) bias in selection of the reported result. Risk of bias judgments were based on answers to a series of signalling questions in each of the five bias domains. We relied on the tool’s standard algorithms to map our responses to signalling questions to risk of bias judgments. As recommended in the guidance document, if a trial was judged to be at “high risk of bias” in one domain, we considered it to be at high risk of bias overall. In addition, a trial judged to have “some concerns” in three or more domains was considered to be at high risk of bias overall.

Our assessment focused on the primary endpoint of each pivotal randomised controlled trial. If a trial had clinical and surrogate measures as coprimary endpoints, we relied on the clinical outcome (for example, risk of bias assessment was based on overall survival if a trial included overall survival and progression free survival as coprimary endpoints), unless data were only available for the surrogate measure at the time of EMA approval.

On the first domain, trials were judged to be at low risk of bias if they adopted appropriate methods to generate and conceal the allocation sequence. We also examined whether there were imbalances in group sizes, baseline characteristics, or key prognostic factors that suggested a problem with the randomisation process. Previous meta-epidemiological studies have shown that trials with inadequate or unclear sequence generation and allocation concealment have on average 7-10% exaggerated treatment effects compared with trials with adequate methods.

On the second domain, our assessment was based on the effect of assignment to the interventions at baseline (the “intention to treat” effect). Studies were at low risk of bias if there were no deviations from intended interventions. We judged trials to be at high risk of bias if there were clear deviations from the intervention that was intended in the trial protocol; if such deviations were not balanced between the experimental and control groups; and if these deviations likely influenced the outcome. Trials were also judged to be at high risk of bias on this domain if some participants were not analysed in the group to which they were randomised and if there was potential for a substantial impact on study findings. Open label trials were not automatically at high risk of bias owing to deviations from intended interventions; similarly, trials with blinding were not immune to bias by default. In trials that masked participants, carers, and trial personnel, we carefully considered whether blinding could be compromised because of major differences in drug adverse events. However, compromised blinding led to high risk of bias judgments for this domain only.
if there were deviations from intended interventions that were not balanced between groups and potentially influenced the outcome.

On the third domain, studies were at low risk of bias if outcome data were available for all or nearly all randomised participants, as reported in the CONSORT (Consolidated Standards of Reporting Trials) flow diagram.46 Unless there was evidence that results were robust to missing outcome data in sensitivity analyses, we considered trials to be at high risk of bias if the proportions of, or reasons for, missing outcome data differed between experimental and control groups (potentially resulting in an imbalance in censoring rates).47 48 For time to event analyses, trials were judged to be at high risk of bias if, firstly, the proportions of participants who withdrew their consent to take part in the study differed between trial arms, and participants were censored when they withdrew consent; or secondly, participants who discontinued treatment were censored. In these cases, missingness could depend on the true value of the outcome. In some trials, patients who withdrew their consent continued to be followed up and contribute outcome data, unless they specifically withdrew their consent for further tumour assessments. In such cases, we judged the trials to be at low risk of bias.

On the fourth domain, studies were at low risk of bias if outcome assessors were unaware of the intervention received by the study participants. We judged trials to be at high risk of bias if outcome assessors were not masked (or if blinding could be compromised) and outcome assessment could be influenced by knowledge of the intervention received. According to previous meta-epidemiological reviews, lack of blinding of outcome assessors in randomised controlled trials is associated with 36% exaggerated treatment effects for subjective outcomes.49

On the fifth domain, studies were at low risk of bias if the results were unlikely to have been selected on the basis of either multiple outcome measurements or multiple analyses of the data.

Two trained researchers (XRS and NH) independently assessed the risk of bias in each pivotal randomised controlled trial. Areas of disagreement were resolved by discussion and consensus in face to face meetings, first between the two researchers and then with other members of the project team (HN and CD). Two researchers reached the same overall risk of bias judgment for 74% of trials when using the published articles and for 85% of trials when using the European regulatory documents. A third researcher (HN) independently reviewed and confirmed the accuracy of all assessments. Difficult cases were also discussed among team members with methodological (JS, JPTH, and JACS) and clinical (BG) expertise.

Reporting adequacy in regulatory documents and scientific literature

We assessed the risk of bias in each randomised controlled trial twice to compare the completeness and consistency of trial reporting in the regulatory documents and scientific literature.50 Firstly, we relied on the published articles, and if available, their protocols and supplementary appendices. Secondly, we repeated the assessments by using information available in European public assessment reports alone (without consulting the trial publication, its protocol and supplementary appendix, or clinical trial registry records). There was a minimum “wash out” period of four weeks between assessments. If our risk of bias judgment differed when we used information from regulatory documents versus publications, we noted the reasons for the observed discrepancies. A third version of each risk of bias assessment was derived using the totality of information available for each trial by combining the scientific literature and regulatory documents (“combined information”).

Finally, one researcher (HN) documented the additional limitations of the available evidence highlighted in European public assessment reports and whether these were acknowledged in trial publications. These issues were related to the appropriateness and generalisability of the available evidence and focused on trial features that were not included in the five domains of the Cochrane risk of bias tool. For example, regulators often commented on the magnitude of clinical benefit, choice of comparators, and endpoints because these could affect the relevance of trial findings to clinical practice. Similarly, “maturity” of statistical analyses was routinely discussed because early termination of trials could affect the reliability and interpretation of findings, especially when interim analyses are not prespecified.51 52

Patient and public involvement

No patients or members of the public were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients or members of the public were asked to advise on interpretation or writing up of results. We plan to involve patients and members of the public when disseminating the study results on a publicly available website. We plan to disseminate the findings of this work to patient organisations.

Results

Cancer drug approvals

Figure 1 shows the process that led to identification of our study sample. Of 64 potentially relevant marketing authorisations granted by the EMA between 1 January 2014 and 31 December 2016, 48 were for cancer products. After we excluded 16 generic and supportive care drugs, our sample consisted of 32 cancer drug approvals. A total of five (16%) approvals were indicated for the treatment of multiple myeloma, four (13%) for melanoma, and four (13%) for lung cancer (appendix table 1). During this period, 13 (41%) cancer drugs were approved for orphan indications and five (16%) received conditional marketing authorisations.

Characteristics of pivotal trials

Thirty two cancer drug approvals were supported by 54 pivotal studies. Of these, 41 (76%) were randomised...
controlled trials (two of which randomised patients to different doses of the experimental treatment), 11 (20%) were single arm studies that evaluated the experimental treatment alone without a comparator, and 2 (4%) were non-randomised comparative studies. Only seven cancer drug approvals were supported by two or more randomised controlled trials. Two of 13 cancer drugs (15%) with orphan designation were supported by single arm studies alone compared with 2 of 19 non-orphan drugs (11%). Two of 5 cancer drugs (40%) with conditional marketing authorisations were supported by single arm studies alone, whereas 2 of 27 drugs (7%) with regular approvals had only single arm studies.

We were able to identify published accounts of 39 of 41 randomised controlled trials. The two unpublished randomised controlled trials were for pegaspargase, which was previously approved by national health authorities in several European countries. European public assessment reports were available for all 39 randomised controlled trials. Trial protocols were publicly available for 21 randomised controlled trials and we gained access to two additional protocols.

Only 10 of 39 randomised controlled trials (26%) evaluated overall survival as either a primary or coprimary endpoint (appendix table 2). Progression free survival was the primary endpoint in 21 randomised controlled trials (54%), whereas the remaining trials evaluated disease response, event free survival, or safety endpoints.

### Risk of bias

Figure 2 shows the risk of bias in pivotal randomised controlled trials of cancer drugs by using combined information obtained from regulatory documents and the scientific literature. Based on our answers to signalling questions (appendix table 3), we judged two trials to be at high risk of bias that arose from the randomisation process. Four trials were at high risk of bias owing to deviations from intended interventions. Twenty three randomised controlled trials had some concerns because of deviations from intended interventions, which reflected either lack of blinding or risk of compromised blinding; however, none of these was responsible for a high risk of bias judgment overall. Ten trials were judged to be at high risk of bias owing to missing outcome data and seven because of measurement of the outcome. All randomised controlled trials were at low risk of bias in selection of the reported result.

Taken together, 19 randomised controlled trials (49%) were at high risk of bias overall, 2 (5%) had some concerns, and 18 (46%) were at low risk of bias according to our assessments using the revised Cochrane tool. Of the 19 randomised controlled trials that were at high risk of bias overall, 13 had one domain at high risk of bias, 5 had two domains at high risk of bias, and 1 had three domains with some concerns. Detailed justifications for our judgments are included in appendix table 3.

Fewer randomised controlled trials that evaluated overall survival as the primary or coprimary endpoint were at high risk of bias than those that evaluated surrogate efficacy endpoints (2/10 (20%) v 16/29 (55%), respectively). Of the 16 randomised controlled trials with surrogate endpoints that were at high risk of bias, our judgments were informed by concerns about missing outcome data for six randomised controlled trials; measurement of the outcome for three randomised controlled trials; and a combination of domains for seven randomised controlled trials.

### Reporting adequacy

Figure 3 shows the domain specific risk of bias judgments when we considered information reported in the scientific literature (trial publication, protocol, appendix, clinical trial registry record) and European public assessment reports separately. Our judgments differed for at least one domain in 26 out of 39 randomised controlled trials (table 1). Most of these differences did not change the overall risk of bias judgments, however our conclusions changed for eight randomised controlled trials (21%).

Table 1 lists the reasons for observed differences. Overall, the content and consistency of reporting varied between the two sources. For example, the methods adopted in generating and concealing the allocation sequence were more readily available in the scientific literature than in regulatory documents (n=15). In contrast, major protocol deviations were only explicitly reported in regulatory documents, albeit inconsistently (n=3). Although protocols were available for 23/39 randomised controlled trials in our sample, we could not spot major deviations without explicit acknowledgment and discussion of such deviations in the reports. For the remaining bias domains, there was no discernible pattern. While some regulatory documents had more complete reporting in terms of missing outcome data, this information was...
<table>
<thead>
<tr>
<th>Drug name (generic)</th>
<th>Name of study</th>
<th>Primary efficacy endpoint</th>
<th>Randomisation</th>
<th>Deviation from intended interventions</th>
<th>Missing data</th>
<th>Measurement of outcome</th>
<th>Selection of reported results</th>
<th>Overall risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>XL184-301</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Trametinib</td>
<td>MEK114267</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Trametinib</td>
<td>B81113220</td>
<td>Response, PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Trametinib</td>
<td>MEK115306</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>B021004/ CLL110</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>GS-US-312-0116</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Study 1112</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>LUME Lung 1–1199.13</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Olaparib</td>
<td>D0910C00019</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>HT-IE (VRD)</td>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>HT-IE (RAINBOW)</td>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>E7080-G000-303</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>CA209-066</td>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>CA209-037</td>
<td>Response, OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Study P002</td>
<td>PFS, OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Study P006</td>
<td>PFS, OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>CLDE225A2201</td>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>CBHS8902308</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Cartizomib</td>
<td>PX-171-009</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>G028141</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Taltimogene laherparepvec</td>
<td>Study 005/05</td>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>DFCI-87-001</td>
<td>EFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>DFCI-91-01</td>
<td>EFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>DFCI-05-001</td>
<td>DFS, OS, HRQoL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>AALL07P4</td>
<td>No efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>ASP-304</td>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Neotumumab</td>
<td>1XJ-IE (SQUIRE)</td>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Trifluridine/tipiracil</td>
<td>TPI-TAS-102-301</td>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Ektumorub</td>
<td>CA204-004</td>
<td>PFS, Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Ektumorub</td>
<td>CA204-009</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>MMY2002</td>
<td>Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>E7080-G000-205</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>XL184-308</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Ilnotecnac hydrochloride trihydrate</td>
<td>NAPOLI-1</td>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Olatumumab</td>
<td>ISB-IE (EGG)</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>1023 (PALOMA-3)</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>1008 (PALOMA-2)</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>C16010</td>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

Fig 2 | Risk of bias assessment for the pivotal randomised controlled trials supporting European Medicines Agency cancer drug approvals using information available in the scientific literature (trial publications, protocols, supplementary materials, and clinical trial registry records) and regulatory documents. Risk of bias assessments were based on the primary efficacy endpoints. DFS=disease free survival; EFS=event free survival; HRQoL=health related quality of life; OS=overall survival; PFS=progression free survival.
more routinely and comprehensively reported in the scientific literature in other cases. Regulatory reviewers identified additional limitations in the evidence base beyond the domains captured in the risk of bias assessments for 10 drugs (32%). These limitations focused on the appropriateness and generalisability of the available data and included choice of comparators, study endpoints, interim analyses, or a combination of factors (box 1). In five cases, the committee questioned either the consistency or magnitude of the observed clinical benefit. The regulatory reviewers raised concerns that were substantial enough to warrant a divergent committee opinion in four cases, all of which were judged to be at low risk of bias according to our risk of bias assessment. None of these regulatory concerns were fully disclosed and discussed as limitations or uncertainties in the scientific literature (appendix box 1).

**Results summary**

Table 2 summarises our findings at the cancer drug level. Of 32 new cancer drugs approved by the EMA from 2014 to 2016, 27 entered the European market with at least one randomised trial. Of the cancer drugs with randomised controlled trials, only seven were evaluated in trials powered to measure overall survival as a primary or coprimary endpoint. Half (n=16) of cancer drugs had at least one randomised controlled trial at low risk of bias. European regulators identified other concerns for 7 of the 16 drugs that had at least one randomised controlled trial at low risk of bias.

Figure 4 summarises our findings according to approval characteristics. Of 13 cancer drugs approved in orphan conditions, 4 (31%) had at least one randomised controlled trial at low risk of bias and without major regulatory concerns. The corresponding number was 5 among the subset of 19 drugs (26%) approved in non-orphan conditions. A lower proportion of cancer drugs with conditional marketing authorisations had at least one randomised controlled trial at low risk of bias and without major regulatory concerns compared with drugs with regular EMA approvals (1/5 (20%) v 8/27 (30%), respectively).

**Discussion**

**Summary of findings**

In this study, we evaluated the evidence base underpinning the EMA’s recent cancer drug approvals. Between 2014 and 2016, a quarter of pivotal studies supporting cancer drug approvals were not randomised designs. Of the 39 randomised controlled trials that formed the basis of new cancer drug approvals, almost three quarters did not measure overall survival or quality of life outcomes as primary endpoints. Using the revised Cochrane tool, we judged 49% of randomised controlled trials to be at high risk of bias. Our judgments changed in either direction for a fifth of randomised controlled trials when we relied on information reported in regulatory documents and scientific publications separately. Regulators identified additional deficits beyond the domains captured in risk of bias assessments for several trials, which were not disclosed as limitations in scientific publications.

The three key findings of this study warrant further discussion. Firstly, our evaluation characterises the design features of contemporary cancer drug trials. Although randomised controlled trials accounted for about 90% of pivotal studies from 2009 to 2013,11 such designs accounted for 75% of studies from 2014 to 2016. A growing proportion of recent cancer drug approvals were based on single arm studies, which are more likely to receive conditional marketing authorisations that target indications with unmet medical need.53 Even when trials had comparators, their appropriateness was at times questionable.
Table 1 | Reasons for differences in risk of bias judgments according to scientific literature and regulatory documents (only randomised controlled trials with different risk of bias judgments are listed)

<table>
<thead>
<tr>
<th>Drug name (generic)</th>
<th>Name of study</th>
<th>Observed discrepancy</th>
<th>Reason for discrepancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>XL184-101</td>
<td>Deviation from intended interventions: some concerns in published reports and high risk of bias in EPAR</td>
<td>EPAR reported more detail on major protocol deviations</td>
</tr>
<tr>
<td>Trametinib</td>
<td>BRF113220</td>
<td>Randomisation: low risk of bias in published reports and high risk of bias in EPAR</td>
<td>EPAR lacked information on randomisation methods. EPAR provided additional detail on (non-event related) censoring of participants</td>
</tr>
<tr>
<td>Trametinib</td>
<td>MEK115306</td>
<td>Randomisation: low risk of bias in published reports and high risk of bias in EPAR</td>
<td>EPAR reported findings of sensitivity analyses that tested different censoring rules. EPAR did not report these results</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>GS-US-312-0116</td>
<td>Missing outcome data: low risk of bias in published reports and high risk of bias in EPAR</td>
<td>Numbers of participants who withdrew their consent do not match between the participant disposition reported in EPAR and supplementary appendix of publication</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Study 1112</td>
<td>Randomisation: low risk of bias in published reports and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>LUME Lung 1 – 1199.13</td>
<td>Randomisation: low risk of bias in published reports and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Olaparib</td>
<td>D0810C00019</td>
<td>Randomisation: low risk of bias in published reports and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>I4T-IE-JVBD ( REGARD)</td>
<td>Randomisation: low risk of bias in published reports and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>CLDE225A22201 (BOLT)</td>
<td>Randomisation: low risk of bias in published reports and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>CLBH5892D2308 (Panorama I)</td>
<td>Missing outcome data: low risk of bias in published reports and high risk of bias in EPAR</td>
<td>Supplementary appendix of published report included results from sensitivity analyses that tested different censoring rules. EPAR did not report these results</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>PX-171-009 (ASPIRE Study)</td>
<td>Deviation from intervention intended interventions: some concerns in published reports and high risk of bias in EPAR</td>
<td>EPAR reported the proportion of participants with major protocol deviations, which differed across trial arms</td>
</tr>
<tr>
<td>Talimogene laherparevpec</td>
<td>Study 005/05</td>
<td>Missing outcome data: high risk of bias in published reports and low risk of bias in EPAR. Measurement of the outcome: low risk of bias in published reports and some concerns in EPAR</td>
<td>EPAR reported findings of sensitivity analyses that tested different censoring rules (not available in publication). EPAR provided additional information on outcome assessment</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>CCG-1962</td>
<td>Missing outcome data: some concerns in published report and low risk of bias in EPAR</td>
<td>EPAR provided more information about study and treatment discontinuations</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>DFCI-87-001</td>
<td>Randomisation: low risk of bias in publication and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods. Number of randomised and assessed participants did not match between publication and EPAR</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>DFCI-91-01</td>
<td>Randomisation: low risk of bias in publication and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>DFCI-05-001</td>
<td>Randomisation: low risk of bias in published report and some concerns in EPAR</td>
<td>Published report provided additional information about availability of outcome data</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>AALL07P4</td>
<td>Missing outcome data: high risk of bias in published report and some concerns in EPAR</td>
<td>Published report provided additional information about availability of outcome data</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>ASP-304</td>
<td>Missing outcome data: some concerns in published report and low risk of bias in EPAR</td>
<td>EPAR provided more detailed information about outcome data availability</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>CA204-009</td>
<td>Randomisation: some concerns in published reports and low risk of bias in EPAR. Deprivation from intended intervention: some concerns in publication and low risk of bias in EPAR. Missing outcome data: low risk of bias in published reports and high risk of bias in EPAR</td>
<td>EPAR reported more information on randomisation methods. EPAR reported that major protocol deviations were balanced between trial arms. Findings of sensitivity analyses that tested different censoring rules were available only in published reports</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>MMY2002</td>
<td>Randomisation: low risk of bias in published reports and high risk of bias in EPAR</td>
<td>EPAR reported more detail on different parts of the trial, which were not randomised</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>E7080-G000-205</td>
<td>Deviation from intended intervention: some concerns in published report and low risk of bias in EPAR. Missing outcome data: high risk of bias in published report and low risk of bias in EPAR. Measurement of the outcome: high risk of bias in published report and low risk of bias in EPAR</td>
<td>EPAR reported that protocol deviations were balanced across trial arms. EPAR also reported the findings of sensitivity analyses testing different censoring rules. Results of outcome assessment by an independent panel were reported in EPAR</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>XL184-108</td>
<td>Randomisation: low risk of bias in published report and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods. EPAR provided information on protocol deviations, which appeared balanced across trial arms</td>
</tr>
<tr>
<td>Olaratumab</td>
<td>ISB-IE-JGDG (JGDG)</td>
<td>Missing outcome data: high risk of bias in published report and low risk of bias in EPAR</td>
<td>EPAR reported findings from sensitivity analyses that tested different censoring rules</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>1023 (PALOMA-3)</td>
<td>Randomisation: low risk of bias in published report and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>1008 (PALOMA-2)</td>
<td>Randomisation: low risk of bias in published report and some concerns in published report and high risk of bias in EPAR</td>
<td>EPAR lacked information on randomisation methods. EPAR reported major protocol deviations, which differed across trial arms</td>
</tr>
<tr>
<td>ixazombib</td>
<td>C16010</td>
<td>Randomisation: low risk of bias in published report and some concerns in EPAR</td>
<td>EPAR lacked information on randomisation methods</td>
</tr>
</tbody>
</table>

EPAR=European public assessment report.
Box 1: Major concerns raised in European regulatory documents (appendix box 1 includes a more detailed narrative overview of these cases)

Idelalisib: early termination of trial
- The pivotal study was terminated early owing to efficacy. According to the EPAR, “the magnitude of the treatment effect is therefore not well defined and further follow-up is needed.”
- This need was acknowledged in the published article for safety evaluation but not to confirm clinical benefit.

Olaparib: non-preferred outcome; retrospective subgroup analysis
- Regulators had previously advised the manufacturer to evaluate overall survival as the trial’s primary endpoint; however, this recommendation was not followed.
- The target patient population for which approval was sought was retrospectively defined. In addition, “the SA6 was uncertain about the true effect of olaparib in this [target] patient population due to the shortcomings of the pivotal study being a small phase II randomised study with a large percentage of censored observations for PFS analysis, and in view of the absence of improvement in OS.”
- These limitations were not acknowledged in the published article. However, the published article reported that: “Our data cannot address differences that might exist between patients with BRCA germline mutations and those with a BRCAness phenotype.”

Ramucirumab: inconsistent effects across settings and demographic characteristics; divergent committee opinion
- According to the EPAR, there was a differential OS outcome across regions in the REGARD study. “Inconsistency was also observed regarding gender (ramucirumab effective in men, but potentially detrimental in women).”
- In addition, some CHMP members “considered that the effect associated with ramucirumab as single agent was too marginal and possibly even inferior to single agent chemotherapy that are used in this setting.”
- In contrast, the published article for the REGARD study stated that: “the survival benefit with ramucirumab was consistent across almost all subgroups. Although the effect on OS was attenuated in women, the PFS estimate in women favoured ramucirumab.”

Nivolumab: unplanned early termination of trial due to observed efficacy; non-preferred outcome; potential imbalances in baseline characteristics
- According to the EPAR, “the trial was terminated early owing to efficacy. According to the published article, “baseline characteristics were similar in the nivolumab and [investigators’ choice chemotherapy group], with the exception of history of brain metastases and high lactate dehydrogenase, which were higher in the nivolumab arm than the [investigators’ choice chemotherapy group].” findings on OS were not reported.

Panobinostat: questionable clinical benefit
- According to the EPAR, the CHMP concluded that “the benefit in PFS has not been translated into a similar relative benefit in OS.” A SAG meeting was convened to discuss whether the clinical benefit of panobinostat was “sufficient to justify exposing these patients to the severe adverse event profile of the drug.”
- Some members of the SAG concluded that “the clinical benefit cannot be considered established.” Such concerns were not disclosed or discussed in the published article.
- While the EPAR showed that “the results from the EORTC QLQ-C30 captured a consistently negative effect by the experimental regimen compared to the control arm,” these results were not reported in the primary publication of the trial.

Cobimetinib: appropriateness of comparator arms
- According to the EPAR, “the CHMP expressed some concern over the lack of a cobimetinib only treatment arm.”
- Appropriateness of the comparator arm was not discussed in the published article.

Talimogene: appropriateness of comparator arms; questionable clinical benefit; questionable study endpoints; divergent committee opinion
- According to the EPAR, there were several concerns with the pivotal study supporting this approval.
- The CAT expressed concerns over the comparator; questioned “the validity of using DRR as the primary endpoint for the pivotal trials as opposed to using other more robust endpoints such as PFS or OS”; and questioned the clinical relevance of the magnitude of treatment effect on DRR.
- In addition, “although there appeared to be an effect on OS in the subgroup of patients with Stage IIIIB-IVM1a disease, OS was a secondary endpoint and the effect was based on exploratory subgroup analyses, after the analysis in the full analysis set was not statistically significant, and without a pre-specified strategy for multiplicity adjustment.”
- These concerns led to a divergent opinion on the approval decision.
Box 1: Continued

• Despite the statement in the EPAR that “it cannot be concluded that an effect on OS has been established for talimogene,” the published article reported that it was “well tolerated and resulted in a higher DRR (P<0.001) and longer median OS (P=0.051) ...” The discussion section added, “combined with the limited toxicity observed, these are clinically important results.”

Necitumumab: questionable clinical benefit; divergent committee opinion
• The magnitude of clinical benefit was questioned by the CHMP, which led to a divergent opinion on the approval decision.
• In contrast, the study publication reported that “the addition of a targeted agent to a platinum-based doublet improves survival. These efficacy data and the acceptable safety profile of necitumumab suggest a favourable benefit-to-risk ratio for this combination treatment.”

Daratumumab: appropriateness of comparator arms
• According to the EPAR, “the design of the study with no comparative arm is of concern ...”
• This was not highlighted in the published account of the trial. Instead, the publication reported: “although this study did not have a control arm, patients with the degree of treatment refractoriness in our study historically have poor outcomes.”

Ixazomib: problematic interim analyses; questionable clinical benefit; divergent committee opinion
• The EMA initially refused granting a marketing authorisation to ixazomib, but this decision was subsequently overturned. Ultimately, ixazomib received a conditional marketing authorisation.
• There were several concerns regarding the single pivotal trial submitted by the manufacturer. Notably, there was a “worsening of results between the initially submitted analysis and the updated analysis.”
• The CHMP therefore concluded that ixazomib “was not approvable based on the efficacy grounds ...”
• In response to the manufacturer’s request for reexamination, a SAG meeting was convened. The SAG “considered that on the basis of the primary PFS analysis, which was conducted according to the pre-specified statistical considerations, the trial met its objective of showing a statistically and clinically significant improvement in PFS.” Although the CHMP still maintained that “the total available evidence on efficacy is not as comprehensive as normally would be required,” a conditional marketing authorisation was ultimately granted.
• There was a divergent opinion on the approval decision (signed by nine members of the CHMP).
• The published article only reported the first set of interim results, which were initially submitted to the EMA and stated that “in accordance with the statistical analysis plan in the protocol and the principle of group sequential design, this was the final statistical analysis of progression free survival” despite providing more mature data on progression free survival data to the European regulators.

We found two randomised controlled trials in which participants were randomised to receive different doses of the same experimental treatment (without a control). In other cases, the comparator either precluded isolation of the effect of the experimental treatment or did not adequately reflect standard of care; these trials were subsequently criticised by the EMA. In terms of study endpoints, only a quarter of randomised controlled trials were powered to evaluate overall survival as the primary outcome. According to the recent EMA guidelines on the evaluation of anticancer treatments,“convincingly demonstrated favourable effects on overall survival are from both a clinical and methodological perspective the most persuasive outcome of a clinical trial.” Yet, most cancer drugs were approved on the basis of other endpoints, such as progression free survival and disease response. Recent systematic reviews showed that progression free survival and disease response do not consistently translate to survival gains or quality of life benefits. Cancer drugs that appear effective on these surrogate measures could even turn out to be harmful.

Secondly, the evidence base underpinning EMA approvals of new cancer drugs has methodological weaknesses. In this study, the primary domains responsible for the high risk of bias judgments were missing outcome data and measurement of the outcome (see box 2 for illustrative examples). In several trials, the proportions and reasons for missing outcome data differed, which probably resulted in unbalanced censoring and potentially favoured the experimental drug. Considerable differences in the toxicity profiles of drugs was another common issue. When such differences were substantial, we concluded that blinding of participants, carers, or investigators could be compromised. As recognised by EMA scientists, “the real effectiveness of the blinding for cancer drugs can always be questioned.” We judged trials to be at high risk of bias if a subjective primary outcome (such as progression free survival) was assessed by local investigators who we concluded might no longer be blinded to treatment allocation. This judgment was also supported by the recent US Food and Drug Administration guidelines that recommend independent verification of tumour assessment endpoints when the adverse event profiles of comparator treatments could substantially unblind the trial in practice.

Thirdly, the regulatory documents and scientific publications had limitations in their reporting. Some
of these limitations followed a discernible pattern. For example, key design elements of randomised controlled trials such as sequence generation and allocation concealment were consistently reported in trial publications, their protocols, or appendices. In contrast, regulatory documents seldom specified randomisation methods; instead, regulators often discussed potential imbalances in baseline characteristics to gauge the success of randomisation. Other discrepancies among regulatory documents and publications were less predictable. While both sources typically showed the flow of participants, strategies to deal with missing outcome data and the sensitivity of findings to censoring rules and assumptions were only haphazardly reported. Moreover, neither source consistently reported major deviations from intended interventions.

Comparison to other studies in the literature

Previous studies have documented the shift in cancer trials away from evaluating overall survival in the 1970s to measuring surrogates of clinical benefit in more recent decades. Of the trials in this study, the majority were assessing surrogate endpoints such as progression-free survival, overall response rate, or disease control rate. This shift in endpoint reporting is consistent with trends observed in the recent literature, where there is a growing emphasis on the use of surrogate endpoints as primary endpoints in cancer trials. The use of surrogate endpoints offers several advantages, including the ability to measure treatment effects earlier, reduce trial duration, and potentially provide a more accurate assessment of clinical benefit. However, it also raises important considerations related to the validity and reliability of surrogate endpoints, as well as the potential for selection bias.

Table 2 | Overview of findings at the drug level. For each cancer drug approval from 2014 to 2016, the table shows whether there was at least one randomised controlled trial supporting the EMA’s approval decision; whether there was at least one randomised controlled trial evaluating overall survival as a primary or coprimary endpoint; whether there was at least one randomised controlled trial at low risk of bias; whether EMA scientists and committee members raised additional concerns about the appropriateness of the available evidence according to factors that were not captured in risk of bias assessments; and whether EMA committee members issued a divergent opinion on the approval decision based on those concerns.

<table>
<thead>
<tr>
<th>Drug name (generic)</th>
<th>Approval characteristics</th>
<th>Has at least one RCT supporting EMA approval</th>
<th>Has at least one RCT evaluating OS for EMA approval</th>
<th>Has at least one RCT at low risk of bias</th>
<th>Other regulatory concerns raised prior to approval</th>
<th>Divergent regulatory opinion on the approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>Orphan; conditional</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Trametinib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Certitinib</td>
<td>—</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cabimetinib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Orphan; conditional</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Talimogene</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>—</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pegaspargase</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>—</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Necitumumab</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Trifluridine/tipiracil</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Orphan</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Imitotecan</td>
<td>Orphan</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Olaratumab</td>
<td>Orphan; conditional</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>—</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Orphan; conditional</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Orphan; conditional</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

EMA=European Medicines Agency; NA=not applicable; OS=overall survival; RCT=randomised controlled trial.

![Proportion of cancer drug approvals](image-url)
RESEARCH

Box 2: Illustrative examples of trials judged to be at high risk of bias because of missing outcome data and measurement of the outcome

Elotuzumab
We judged one of the pivotal trials of elotuzumab to be at high risk of bias. In trial CA204-009, which was open label, outcome assessors were aware of the intervention received by study participants, and assessment of the progression free survival outcome could have been influenced by knowledge of the intervention received. Because there was no blinded central assessment of outcomes, we concluded that this trial was at high risk of bias in measurement of the outcome. This potential limitation was also acknowledged in the trial publication.

Nivolumab
We judged one of the pivotal trials of nivolumab to be at high risk of bias because of missing outcome data. In trial CA209-037, outcome data were potentially missing for a considerable proportion of the population. In the investigator’s choice chemotherapy arm of the trial, 22/133 (16.5%) patients withdrew their consent, which meant withdrawing consent from the full protocol, including study treatment, study procedures, and survival follow-up. Proportions of missing outcome data and reasons for missing outcome data differed across intervention groups: 16.5% v 11% of patients withdrew their consent in the investigator’s choice chemotherapy and nivolumab arms of the trial, respectively. Missingness in the outcome could be related to both the intervention group and the true value of the outcome. Also, there were no sensitivity analyses conducted to test the robustness of study results to different assumptions about missing outcome data.

Trametinib
We judged the pivotal trial of trametinib to be at high risk of bias. In trial BRF113220, there was potential evidence of unbalanced censoring. According to the European public assessment report, there were relatively large proportions of censored participants in both trial arms. The censoring method included censoring for extended loss to follow-up, new anticancer therapy, and excluding symptomatic progression. While 31% of participants who received dabrafenib 150 mg were censored, 11% were censored among participants receiving trametinib. In the absence of evidence that results were robust to the presence of potentially missing outcome data (we were unable to find the results of “eight sensitivity analyses planned to investigate the robustness of progression-free survival against these censoring rules”), we concluded that this trial was at high risk of bias due to missing outcome data. In addition, local investigators in trial BRF113220 were unblinded and therefore aware of the intervention received by study participants. Because the assessment of the progression free survival outcome could be influenced by knowledge of the intervention received, the trial was also at high risk of bias owing to measurement of the outcome. The authors reported local results as their main analysis, although the results from the blinded review committee were also available in the main body of the publication. Results obtained from blinded assessment were less pronounced (hazard ratio for progression free survival was 0.39, 95% confidence interval 0.25 to 0.62, according to local assessment, compared with 0.55, 0.33 to 0.93).

Therefore, regulatory action is needed to ensure that pharmaceutical manufacturers routinely evaluate their products in randomised trials that collect data on meaningful outcomes. In the absence of such data, it remains difficult to know whether new cancer drugs meet the needs of patients, clinicians, and healthcare systems.

While some of the methodological problems identified in our study were avoidable (for example, by ensuring adequate sequence generation and allocation concealment), others could be less straightforward to address in complex cancer trials. For example, ensuring outcome data availability when participants withdraw their consent might not be possible. The proportions of participants who withdrew their consent frequently differed among trial arms, which likely reflected meaningful differences in toxicity profiles of comparator drugs. In such instances when missingness could depend on the true value of the outcome, it is essential to evaluate the sensitivity of trial findings to different assumptions about missing outcome data.76 However, some trials censored participants when they changed from their assigned treatment. This analysis strategy is not appropriate when estimating intention to treat effects and could lead to bias because of missing outcome data.

Addressing other methodological problems in cancer trials could be feasible, but they come at a cost. Strategies to prevent unblinding might add complexity to trial designs.23 For example, methods to avoid unblinding in randomised controlled trials include centralised dosage modification of treatments and centralised assessment of clinical side effects.77 Similarly, independent clinicians could perform blinded central evaluation of tumour assessment endpoints, but this might have major cost implications.78 In a recent review of randomised controlled trials in solid tumours, there was no systematic bias between the findings from blinded independent central review and local assessment, but there were statistical inconsistencies between the two sets of results in almost a quarter of trials.79 Moreover, previous meta-epidemiological reviews across different therapeutic areas have found that studies with non-blinded assessors of subjective outcomes generate biased findings.69 This research strengthens the argument in favour of implementing blinded centralised assessments of tumour endpoints despite the associated costs.

An important design consideration in cancer trials is the choice of primary endpoint. Surrogate measures of clinical benefit (eg, progression free survival and disease response) have important feasibility advantages because they can be assessed earlier and with smaller sample sizes (and therefore fewer resources) compared with overall survival. A recent study found that cancer drugs approved on the basis of surrogate measures had on average a 11 month shorter development duration compared with drugs approved on the basis of overall survival.80 However, the feasibility advantages of using surrogate measures...
Box 3: Recommendations to improve the design, conduct, analysis, and reporting of pivotal trials of new cancer drugs

- Because overall survival would be largely immune to several sources of potential bias, regulators should require overall survival to be the primary endpoint of pivotal trials.
- Other desirable trial endpoints include quality of life and measures with established surrogacy.
- The magnitude of benefit associated with new cancer therapies should be carefully considered in trial design.
- When subjectively assessed outcomes are used as primary endpoints, trial sponsors should implement blinded independent central review of tumour assessments.
- If the trial is blinded, trial sponsors and investigators should adopt strategies to avoid unblinding of investigators, for example centralised dosage modification of treatments; this is especially important when outcome assessment is not blinded.
- Trial sponsors and investigators should report the risk of unblinding in trials in which investigators are not aware of treatment allocation; this is especially important when outcome assessment is not blinded.
- Trial sponsors and investigators should conduct sensitivity analyses to evaluate the robustness of trial results to missing outcome data. Regulators and journal editors should require consistent reporting of the findings of these sensitivity analyses.
- Regulators and journal editors should require consistent reporting of any major deviations from intended interventions that arose from the experimental context; whether deviations are balanced between the groups; and whether deviations could affect the outcome.

should be weighed against their several disadvantages. Firstly, patients might misinterpret such endpoints and overestimate the magnitude of benefit associated with new cancer drugs. Secondly, the strength of the correlation between surrogate and clinical outcomes in cancer trials is unclear. Over the past decade, several drugs (eg, bevacizumab in metastatic breast cancer) approved on the basis of surrogate measures failed to demonstrate overall survival gains in subsequent trials. In the recent BELLINI trial, patients who received venetoclax had shorter survival than those who received a control treatment (even though venetoclax appeared more effective than the control on the basis of progression free survival and response rate). Thirdly, and as recommended by regulators, unblinded trials (or trials at risk of unblinding) with surrogate endpoints might require additional (costly) safeguards such as independent blinded endpoint review to minimise risk of bias. Finally, and perhaps most importantly, evidence of overall survival benefit might never emerge for cancer drugs approved on the basis of surrogate measures alone. In an earlier study, we found that data on overall survival did not emerge in the postmarketing period for more than 90% of indications for which there was no evidence of such a benefit at the time of marketing authorisation.

Taken together, these findings support more widespread use of overall survival as the primary endpoint in pivotal trials of new cancer drugs. Randomised controlled trials with overall survival endpoints were less likely to be at high risk of bias in our sample; this finding is consistent with an earlier assessment that showed that 66% of randomised controlled trials evaluating overall survival were at low risk of bias (the corresponding figure in our study was 80%). Overall survival would be largely immune to the risk of bias attributable to potential unblinding of outcome assessors and missing outcome data.

There is also an opportunity to further improve the reporting standards of regulatory documents and scientific publications. Publication of the CONSORT statement in 1996 (and its update in 2010) has led to major improvements in randomised controlled trial reporting in the scientific literature. Also, the 2015 revision of the European public assessment report template addressed some of the previous criticisms. Currently, publications and regulatory documents make it difficult to distinguish between trial deficits that can be avoided and those that are more difficult to address. When methodological shortcomings are inevitable (eg, missing outcome data owing to withdrawal of participant consent), more transparent reporting is warranted. In addition, key information required to perform risk of bias assessments is still inconsistently reported in regulatory documents, trial protocols, publications, supplementary appendices, and clinical trials registries. For example, neither journal articles nor regulatory documents discuss the possibility that trial investigators could be unblinded when the adverse event profiles of comparator treatments are substantially different. Similarly, these sources do not consistently report the occurrence of protocol deviations that arose from the experimental context; whether deviations are balanced between the groups; and whether deviations could affect the outcome. Journal editors and European regulators can take further action to facilitate more complete and consistent reporting of pivotal studies. Our recommendations for improving the design, conduct, analysis, and reporting standards of cancer trials are listed in box 3.

Limitations
Our study had several limitations. We did not include clinical study reports, which, according to previous reviews, might provide the most comprehensive set of information on randomised controlled trials. Because there is no established guidance on how to feasibly collect information from such reports, their use in systematic reviews remains limited. We focused on cancer drug trials, therefore the generalisability of our findings to trials in other therapeutic areas is unclear. Nevertheless, cancer drugs comprise the single largest category of recent drug approvals. Additionally our study included cancer drug approvals between 2014 and 2016; characteristics of randomised controlled trials that supported EMA approvals during our study period might not reflect the design, conduct, analysis, and reporting of cancer drug trials outside of this period. Furthermore, our risk of bias assessments were not blinded to study results because risk of bias assessments require examination of results. However, a systematic review of randomised trials did not identify evidence overall of a difference in risk of bias judgments between blinded and unblinded assessments.
We examined the risk of bias, rather than bias itself. Therefore, it remains a possibility that trial results are unbiased despite the methodological flaws identified in our assessments. According to previous studies, risk of bias judgments based on publications alone might rely on incomplete information,^9^ and might not reflect the true methodological rigour of underlying studies. To address this issue, we relied on a combination of regulatory documents, trial protocols, publications, supplementary materials, and clinical trials registries. In some cases, our judgments were substantiated with potential evidence of bias; for instance, when outcome measurements available from unblinded local investigators produced exaggerated findings compared with those obtained from an independent panel of masked assessors. For example, the magnitude of progression-free survival benefit reported in the BRF113220 trial was less pronounced when assessed by an independent committee than by investigators (hazard ratio 0.39 v 0.55).^9^ Notably, our findings do not imply that EMA decisions are biased, and they do not suggest that pharmaceutical manufacturers deliberately introduce bias into their trials. Instead, our findings identify methodological shortcomings in pivotal trials of new cancer drugs.

Finally, our assessments focused on the primary endpoints of randomised controlled trials; it remains possible that results for other outcomes could be at lower risk of bias. However, this is unlikely because pervasive limitations are well documented for secondary endpoints of cancer drug trials, including harms,^7^ quality of life outcomes,^10^ and other outcomes. Therefore, we might not have fully captured other important methodological shortcomings of randomised controlled trials that support cancer drug approvals.

Conclusions

Most pivotal studies that formed the basis of EMA approval of new cancer drugs between 2014 and 2016 used randomised designs. Despite the widely accepted strengths of such designs, we concluded that almost half of randomised controlled trials were at high risk of bias because of deficits in their design, analysis, and conduct. During our study period, European regulators identified other concerns for 7 out of 16 drugs that had at least one randomised controlled trial at low risk of bias. Journal publications did not acknowledge the key trial limitations identified in regulatory documents. Policymakers, investigators, and clinicians should carefully consider risks of bias in pivotal trials that support regulatory decisions, and the extent to which new cancer therapies offer meaningful benefit to patients.

AUTHOR AFFILIATIONS

1Department of Health Policy, London School of Economics and Political Science, London WC2A 2AE, UK
2Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
3Department of Global Health and Social Medicine, King's College London, London, UK
4Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
5The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West (NIHR CLAHR West) at University Hospitals Bristol NHS Foundation Trust, Bristol, UK
6National Institute for Health Research Bristol Biomedical Research Centre, Bristol, UK
7Cancer Research Institute, Queen’s University at Kingston, Kingston, Ontario, Canada

Contributors: HN conceived and designed the study. XRS, NH, and HN collected data and completed the risk of bias assessments. HN independently verified all collected data including risk of bias assessments, undertook the primary analysis, and drafted the manuscript. All authors contributed to subsequent iterations. All authors provided critical input on the manuscript and approved the final version for publication. XRS and NH contributed equally. HN is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: HN is a 2018-19 UK Harkness Fellow in Health Care Policy and Practice, funded by the Commonwealth Fund. HN and CD are supported by the Higher Education Funding Council in England. XRS and NH were funded in part by Health Action International. JPTH and JACS are National Institute for Health Research (NIHR) senior investigators, and are supported by NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol, and are members of the Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol. JS and JPTH were supported by the NIHR Collaboration for Leadership in Applied Health Research and Care West (CLAHR West) at University Hospitals Bristol NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health and Social Care. BG’s fellowship at the Program on Regulation, Therapeutics, and Law (PORTAL) was funded by Arnold Ventures. CMB is supported as the Canada Research Chair in Population Cancer Care. Funders did not have any role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: support from the Commonwealth Fund, Higher Education Funding Council in England, Health Action International (HAI), National Institute for Health Research (NIHR) Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust, and the University of Bristol, NIHR Collaboration for Leadership in Applied Health Research and Care West (CLAHR West) at University Hospitals Bristol NHS Foundation Trust, and Arnold Ventures for the submitted work; CD reports being a member of the non-profit organisation HAI, and occasionally attends meetings of the European Medicines Agency’s Patients and Consumers Working Party Group as HAI’s alternative representative; XRS reports grants from HAI during the conduct of the study and personal fees from Sanofi Aventis, outside the submitted work; NH reports grants from HAI during the conduct of the study; the other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data are available.

The lead author (HN) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.
patients from the analysis in randomised controlled trials: meta-
b3244

Abrahà l, Cherubini A, Cozzolino F, et al. Deviation from intention to
treat analysis in randomised trials and treatment effect estimates:
meta-epidemiological study. BMJ 2015;350:h2445. doi:10.1136/
bmj.h2445

Page MJ, Higgins JPT, Clayton G, Sterne JAC, Hrobjartsson A,
Savovic J. Empirical evidence of study design biases in randomized
trails: systematic review of meta-epidemiological studies. PLoS
One 2011;6:e159267. doi:10.1371/journal.pone.0159267

design characteristics on intervention effect estimates from
doi:10.7326/0003-4819-157-6-201209180-00537

Higgins JPT, Altman DG, Gøtzsche PC, et al. Cochrane Bias Methods
Group, Cochrane Statistical Methods Group. The Cochrane
Collaboration’s tool for assessing risk of bias in randomised trials.
BMJ 2011;343:d5928. doi:10.1136/bmj.d5928

Booth CM, Creson DW, Wang L, Tannock IF, Kryzanowski MK.
Evolution of the randomized controlled trial in oncology over
2008.16.5456

Fleming TR, Rothmann MD, Lu H. Issues in using progression-
free survival when evaluating oncology products. J Clin

Naci H, Smalley KR, Kesselheim AS. Characteristics of preapproval
and postapproval studies for drugs granted accelerated approval
by the US Food and Drug Administration. JAMA 2017;318:626-36.

Mansouria MA, Higgins JPT, Sterne JAC, Herrin MA. Biases in
randomized trials: a conversation between trialists and
doi:10.1136/jech-2016-206941

and inadequate methods over time in 2920 randomized controlled
trials included in Cochrane reviews: research on research study
doi:10.1136/bmj.j2490

Köhler M, Haag S, Bieter K, et al. Information on new drugs at market
eentry: retrospective analysis of health technology assessment reports
versus structured reports, journal publications, and registry reports.
BMJ 2015;350:h796. doi:10.1136/bmj.h796

Hoekman J, Boon W. Changing standards for drug approval: a
longitudinal analysis of conditional marketing authorisation in
 socscimed.2018.12.025

Banzì R, Gerardì C, Bertellì V, Garantìì S. Approvals of drugs
with uncertain benefit-risk profiles in Europe. Eur J Intern

Banzì R, Gerardì C, Bertellì V, Garantìì S. Conditional approval of
medicines by the EMA. BMJ 2017;357:j2062. doi:10.1136/bmj.
j2062

De Pauw S, Fain KM, Zarin DA. How to avoid common problems when
using ClinicalTrials.gov in research: 10 issues to consider.
BMJ 2018;361:k1452. doi:10.1136/bmj.k1452

risk of bias in randomised trials. Cochrane Database Syst
Rev 2016;10(Suppl 1):29-31

characteristics of systematic reviews of biomedical research: a
journal.pmed.1002028

doi:10.1136/bmj.l4898

Schulz KF, Grimes DA. Allocation concealment in randomised
doi:10.1016/S0140-6736(01)06704-5

risk of bias in randomised trials. Cochrane Database Syst
Rev 2016;10(Suppl 1):29-31

characteristics of systematic reviews of biomedical research: a
journal.pmed.1002028

doi:10.1136/bmj.l4898

Schulz KF, Grimes DA. Allocation concealment in randomised
doi:10.1016/S0140-6736(01)06704-5

risk of bias in randomised trials. Cochrane Database Syst
Rev 2016;10(Suppl 1):29-31


70 Barbis C, Baschirrotto C, Cipriani A. EMA must improve the quality of its clinical trial reports. BMJ 2011;342:d2291. doi: 10.1136/bmj.d2291


Web appendix: Supplementary material