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Annals of Oncology 28: 688–695, 2017
doi:10.1093/annonc/mdw682
Published online 28 December 2016

SPECIAL ARTICLE

Statistical controversies in clinical research: comparison of primary outcomes in protocols, public clinical-trial registries and publications: the example of oncology trials

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Background: Protocols are often unavailable to peer-reviewers and readers. To detect outcome reporting bias (ORB), readers usually have to resort to publicly available descriptions of study design such as public clinical trial registries. We compared primary outcomes in protocols, ClinicalTrials.gov and publications of oncology trials and evaluated the use of ClinicalTrials.gov as compared with protocols in detecting discrepancies between planned and published outcomes.

Method: We searched for phase III oncology trials registered in ClinicalTrials.gov and published in the *Journal of Clinical Oncology* and *New England Journal of Medicine* between January 2014 and June 2015. We extracted primary outcomes reported in the protocol, ClinicalTrials.gov and the publication. First, we assessed the quality of primary outcome descriptions by using a published framework. Second, we evaluated modifications of primary outcomes between each source. Finally, we evaluated the agreement, specificity and sensitivity of detecting modifications between planned and published outcomes by using protocols or ClinicalTrials.gov.

Results: We included 65 trials, with 81 primary outcomes common among the 3 sources. The proportion of primary outcomes reporting all items from the framework was 73%, 22%, and 75% for protocols, ClinicalTrials.gov and publications, respectively. Eight (12%) trials presented a discrepancy between primary outcomes reported in the protocol and in the publication. Twelve (18.5%) trials presented a discrepancy between primary outcomes registered at ClinicalTrials.gov and in publications. We found a moderate agreement in detecting discrepant reporting of outcomes by using protocols or ClinicalTrials.gov [$\kappa = 0.53$, 95% confidence interval (0.25–0.81)]. Using ClinicalTrials.gov to detect discrepant reporting of outcomes showed high specificity (89.5%) but lacked sensitivity (75%) as compared with use of protocols.

Conclusion: In oncology trials, primary outcome descriptions in ClinicalTrials.gov are often of low quality and may not reflect what is in the protocol, thus limiting the detection of modifications between planned and published outcomes.

Key words: clinical trials, methodology, outcome reporting bias, protocols

Introduction

Outcome reporting bias (ORB) refers to unacknowledged changes in trial outcomes from protocol to publication depending on the nature and direction of the results [1]. It involves a diverse group of practices that include under-reporting (not reporting planned outcomes), over-reporting (reporting unplanned outcomes), or misreporting (changing the definition and measures of outcomes) [2]. For ~40%–62% of trials, at least one primary outcome is omitted, introduced or changed between what was planned in the protocol and what was published [3, 4]. ORB distorts the evidence available in the literature by favoring positive results [3].

Oncology trials are not safe from such practices. Although overall survival is the gold standard for demonstrating clinical

benefit, many trials use different endpoints such as progression-free survival, tumor size, biologic markers, symptom control, quality of life or economic evaluations [5]. Studies have shown that 12%–14% of clinical trials in oncology modified pre-specified primary outcomes and that 38% reported an unplanned analysis [2, 6]. Such discrepant outcome reporting is important in oncology trials because such trials often assess new treatments that are both expensive and have a tight risk–benefit balance.

Detection of modifications between planned and published outcomes is complex. Protocols constitute the most comprehensive description of the study design before trial inception, but they often are confidential documents, unavailable to peer-reviewers and readers [7]. To overcome this problem and improve transparency in clinical research for patients, clinicians, researchers and policy makers, the International Committee of Medical Journal Editors requires access to key protocol information by registration of trials in public clinical-trial registries such as ClinicalTrials.gov before enrollment of the first participant [8]. However, use of these public registries to identify discrepant outcome reporting is possible only if outcomes are fully and clearly registered before the beginning of the trial [9]. When examining ClinicalTrials.gov, only 63% of registered outcomes were precise enough for comparison with published findings [4]. This was also the case in oncology trials, for which only 37% of registry entries in ClinicalTrials.gov provided a sufficiently clear outcome description for comparison with publications [6].

To our knowledge, no study has compared the reporting of outcomes between protocols, public clinical-trial registries and publications. Studies usually compared publications with (i) protocols available from ethics committees [3, 10, 11], (ii) protocols publicly available as supplemental material from journals [2] or (iii) public clinical-trial registry entries [4, 6, 12]. One study compared reporting of outcomes between clinical study reports and publicly available materials in publications and ClinicalTrials.gov [13, 14]. The authors found that study reports were more complete than public clinical-trial registry entries and publications, but they did not describe in detail the quality of outcome reporting or the nature of outcome modifications.

In this study, we compared the primary outcomes reported in protocols, ClinicalTrials.gov registries and publications of oncology trials. Then we evaluated the use of ClinicalTrials.gov as compared with protocols in detecting modifications between planned and published outcomes.

Methods

We carried out a methodological review of phase III oncology trials published in 2014–2015 in the *Journal of Clinical Oncology* and *New England Journal of Medicine* and compared the description of primary outcomes reported in published articles, ClinicalTrials.gov and protocols. Then we evaluated the use of ClinicalTrials.gov as compared with protocols in detecting modifications between planned and published outcomes.

Study search

One investigator (AP) searched Medline via PubMed for articles published between 1 January 2014 and 29 June 2015 by using the keywords *Cancer OR Oncol** and the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in two journals, *Journal of Clinical Oncology* and *New England Journal of Medicine*. We chose these journals because they publish study protocols as supplementary material.

Selection of relevant studies

We included phase III randomized controlled trials in the field of oncology for which both an online protocol and a ClinicalTrials.gov registration were available. We excluded studies that involved a pediatric population (<18 years old) or hematologic malignancies, reported pooled data from two or more trials or were secondary reports of previously published trials. Two investigators (V-TT, AP) confirmed the eligibility of trials included in the selection.

Extraction of general characteristics

One investigator (AP) used a standardized extraction form to collect: (i) publication details (journal name, year of publication), (ii) disease site, (iii) type of the intervention (chemotherapy, targeted therapy, radiation therapy, surgery, supportive care or screening and/or diagnosis), (iii) trial design (superiority, non-inferiority, or equivalence), (iv) number of study groups and (v) funding source (funding by industry or not as reported in ClinicalTrials.gov).

Extraction of primary outcomes from the three sources

For each trial, two investigators (V-TT, AP) independently extracted the primary outcome(s) reported in the (i) the study protocol (including all amendments), (ii) the entry in ClinicalTrials.gov at the time of publication and (iii) the published reports (including outcome modifications reported in methods as recommended by the CONSORT [15]).

We considered as primary outcomes only those explicitly reported as such [4]. If no primary outcome was explicitly reported in publications or protocols, we used the outcome reported in sample size calculations. For each outcome extracted, we assessed results, which were considered positive if they significantly supported the superiority or non-inferiority of the intervention over the control.

Assessment of quality of description of outcomes

Two investigators (V-TT, AP) assessed the quality of the description of each primary outcome reported in the three sources (excluding safety outcomes reported as primary outcomes), by using seven items inspired by the framework of Zarin et al. [16]. These seven items are standard protocol items according to the SPIRIT guidelines [17] (supplementary Table S1, available at *Annals of Oncology* online):

1. *Domain*, defined as a clear description of what is being measured.
2. *Specific measurement*, defined as a clear description of how it is being measured.
3. *Specific metric*, defined as a description of how change was quantified (e.g. change from baseline, end value).
4. *Method of aggregation of data*, defined as a description of how data were managed (e.g. continuous value, proportion of patients achieving a given value).

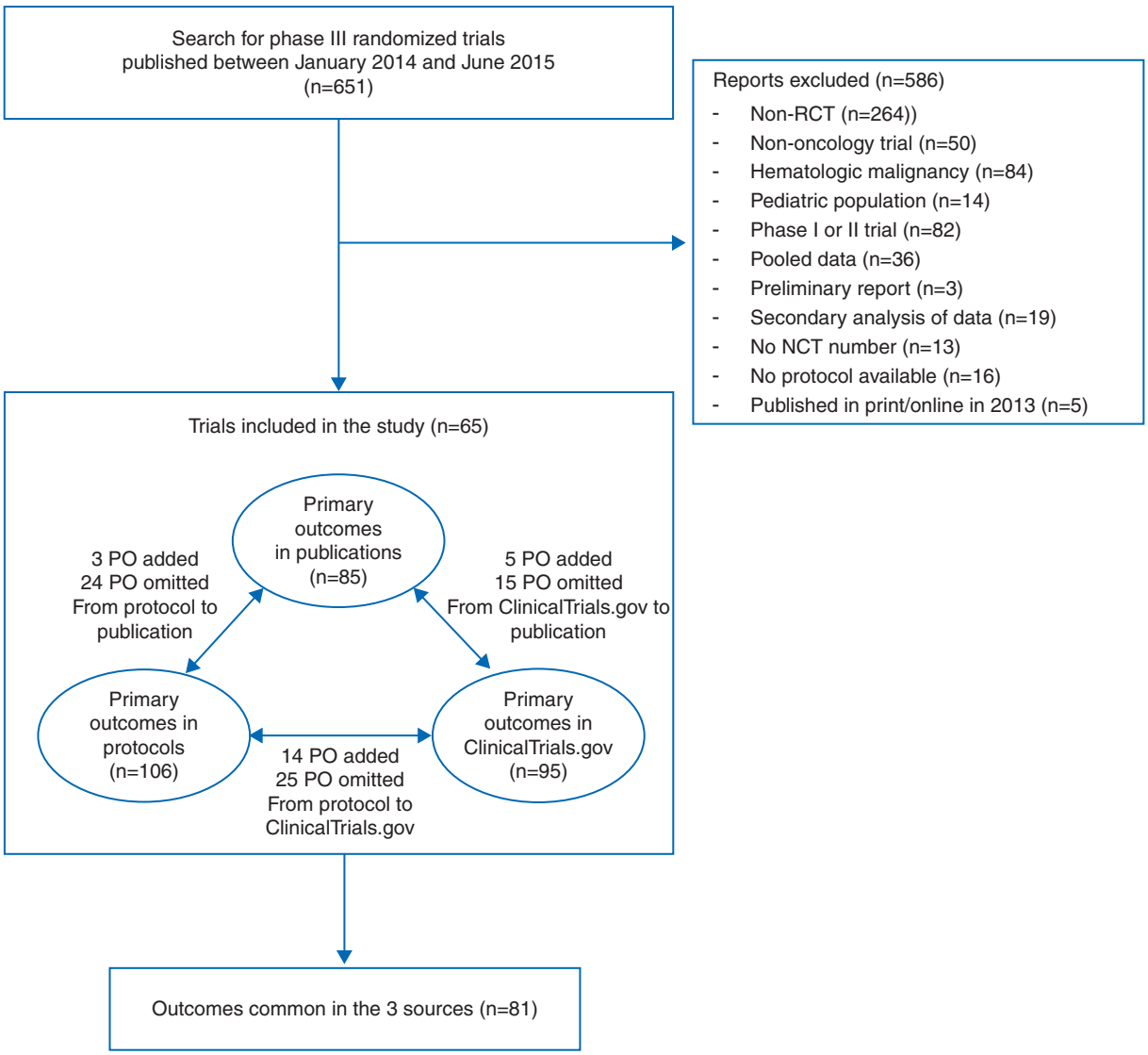

Figure 1. Flow chart of articles in the study. PO: primary outcome.

5. *Time frame*, defined as a description of when the outcome was assessed.
6. *Identity of outcome assessors*, defined as the presence of information on the identity and/or training of outcome assessors.
7. *Blinding of outcome assessors*, defined as the presence of information on whether assessors were blinded to the intervention received, and how.

We defined as an optimal outcome description the reporting of all seven items. We defined as an acceptable outcome description the reporting of all of the following five items: domain, specific measurement, specific metric, method of data aggregation, and time frame.

Assessment of outcome modifications

Two investigators (V-TT, AP) independently looked for any modification to the primary outcomes between (i) protocols and published articles, (ii) protocols and ClinicalTrials.gov, (iii) ClinicalTrials.gov and published articles. Modifications could involve (i) a change from a primary outcome to a secondary outcome, (ii) a change from a secondary outcome to a primary outcome, (iii) introduction of a new primary outcome, (iv) omission of a previously stated primary outcome, or (v) change in measurement method or time frame.

We considered as outcome modifications only flagrant discrepancies between the different sources. As a result, we did not consider the lack of precision in reporting outcomes as an outcome modification. For example, we considered that an outcome reported as 'Progression-free Survival' in ClinicalTrials.gov and 'Progression-free Survival using RECIST criteria, measured every 8 weeks, as determined by blinded independent imaging review' in a publication, contained no flagrant outcome modification.

Analysis

Data are presented as number (percentage) for qualitative data and median [interquartile range (IQR)] for continuous data.

First, we described the quality of primary outcome descriptions. We assessed the proportion of outcomes with an optimal description and an acceptable description in each source. We

Table 1. Characteristics of randomized trials included in the study (n = 65)

Characteristic	Value
Journal—*n* (%)	
New England Journal of Medicine	22 (34%)
Journal of Clinical Oncology	43 (66%)
Type of tumor—*n* (%)	
Breast	12 (18%)
Colon/rectum	4 (6.1%)
Gastro intestinal (excluding colon/rectum cancer)	8 (12%)
Female reproductive tract	9 (14%)
Head and neck (including thyroid cancer)	7 (11%)
Kidney	2 (3.1%)
Lung	6 (9.2%)
Prostate	3 (4.6%)
Skin	7 (11%)
Any site	7 (11%)
Type of intervention—*n* (%)	
Chemotherapy	9 (14%)
Targeted therapy	33 (51%)
Radiation and chemotherapy	2 (3%)
Surgery and/or radiation therapy	8 (12%)
Supportive care	11 (17%)
Screening and/or diagnostic	2 (3%)
No. of study groups—*n* (%)	
2	60 (92%)
>2	5 (8%)
No. of patients included – median (IQR)	452 (253–704)
Funding source—*n* (%)	
Industry	32 (49%)
Non-industry	33 (51%)
Outcomes reported in the three sources—*n* (%)	
Total	81 (100%)
Overall survival	23 (28%)
Time-to-event[a]	30 (37%)
Response rate	2 (2%)
Patient-reported outcome	17 (21%)
Other	9 (11%)

[a]Time-to-event includes progression-free survival, disease-free survival, event-free survival, relapse-free survival, time to disease progression.

looked for the association between an acceptable outcome description and presence of modifications between the protocol and the published study by using Fisher's exact test. $P < 0.05$ was considered statistically significant. Second, we described the modification of primary outcomes among each data source. Third, we evaluated the ability of ClinicalTrials.gov to detect modifications between planned and published outcomes as compared with protocols. We assessed the agreement in identifying discrepant reporting of outcomes by using the protocol or ClinicalTrials.gov with Cohen's Kappa (κ), then evaluated the sensitivity and specificity of using ClinicalTrials.gov to detect discrepant reporting of outcomes as compared with protocols.

All analyses involved use of R v3.2.2 (http://www.R-project.org), the R Foundation for Statistical Computing, Vienna, Austria).

Results

Our literature search yielded 651 references, from which 65 were included (Figure 1). Trials enrolled a median of 452 patients [IQR (253–704)]. Approximately half of the trials were funded by industry ($n = 32$, 49%) and half evaluated a targeted therapy ($n = 33$, 51%) (Table 1). At the time of assessment, only 29 (44%) studies had results posted at ClinicalTrials.gov.

Quality of outcome descriptions

Accounting all outcome modifications (e.g. addition, omission and/or change from secondary to primary outcomes), we found a total of 81 primary outcomes common to the three sources (Figure 1). Approximately two-thirds (66%) were overall survival or time-to-event outcomes (e.g. progression-free survival, disease-free survival, etc.; Table 1), and 48 (59%) were positive.

The proportion of primary outcomes with acceptable descriptions (i.e. reporting all elements of the Zarin et al. framework) was 59 (73%), 18 (22%), and 61 (75%) in protocols, ClinicalTrials.gov and publications, respectively (Table 2; Figure 2). Few outcome descriptions could be considered optimal, with 30%, 4%, and 26% of outcomes reporting all seven framework elements from protocols, ClinicalTrials.gov and publications, respectively. Information about the blinding of outcome assessors was the least frequently reported information, with <45% of outcome descriptions reporting it in each source.

In our sample, less precise primary outcome descriptions in ClinicalTrials.gov was significantly associated with modifications of outcomes ($P = 0.03$). Quality of outcome descriptions in protocols or publications was not associated with modification of outcomes nor with positive or negative results.

Outcome modifications

Comparison between protocols and publications. A total of eight trials (12%) had at least one discrepancy between primary outcomes in the publication and the protocol (Figure 3; supplementary Table S2, available at *Annals of Oncology* online). Discrepancies involved the omission in the publication of one or several planned endpoints ($n = 2$), the addition in the publication of one or several unplanned primary outcome ($n = 1$), the change from one or several secondary outcomes in the protocol to primary outcomes in the publication ($n = 1$), the change from a primary outcome in the protocol to a secondary outcome in the publication ($n = 2$), and the modification of the measurement method of one or several outcomes ($n = 6$). For example, in the published report of a trial evaluating early versus delayed initiation of palliative care, a new primary outcome 'Resource Use,' absent from the protocol, was introduced in the publication [18].

Comparison between protocols and ClinicalTrials.gov. We found 12 (18%) studies with at least one discrepancy between primary outcomes in the protocol and in ClinicalTrials.gov (supplementary Table S3, available at *Annals of Oncology* online). In four cases, secondary outcomes in the protocol and publication were registered as primary outcomes.

Comparison between ClinicalTrials.gov and publications. We found 12 (18.5%) studies with at least one discrepancy between primary outcomes reported in ClinicalTrials.gov and the

Table 2. Quality of outcome descriptions in each data source (n = 81) according to the Zarin et al. framework [11]

Item	Protocols	ClinicalTrials.gov	Publications
(1) Domain	81 (100%)	80 (99%)	81 (100%)
(2) Specific measurement	68 (84%)	50 (62%)	77 (95%)
(3) Specific metric	72 (89%)	71 (88%)	77 (95%)
(4) Method of aggregation of data	68 (84%)	63 (78%)	72 (89%)
(5) Time frame	71 (88%)	48 (59%)	70 (86%)
(6) Identity of outcome assessor	40 (49%)	14 (17%)	40 (49%)
(7) Blinding of outcome assessor	34 (42%)	28 (34%)	34 (42%)
Minimal acceptable reporting of outcome[a]	59 (73%)	18 (22%)	61 (75%)
Optimal reporting of outcome[b]	24 (30%)	3 (4%)	21 (26%)

[a]Minimal acceptable reporting of outcome involves the reporting of the five elements from the Zarin et al. framework [11].
[b]Optimal reporting of outcome involves the reporting of the five elements from the Zarin et al. framework and information about the blinding and the identity of the outcome assessor.

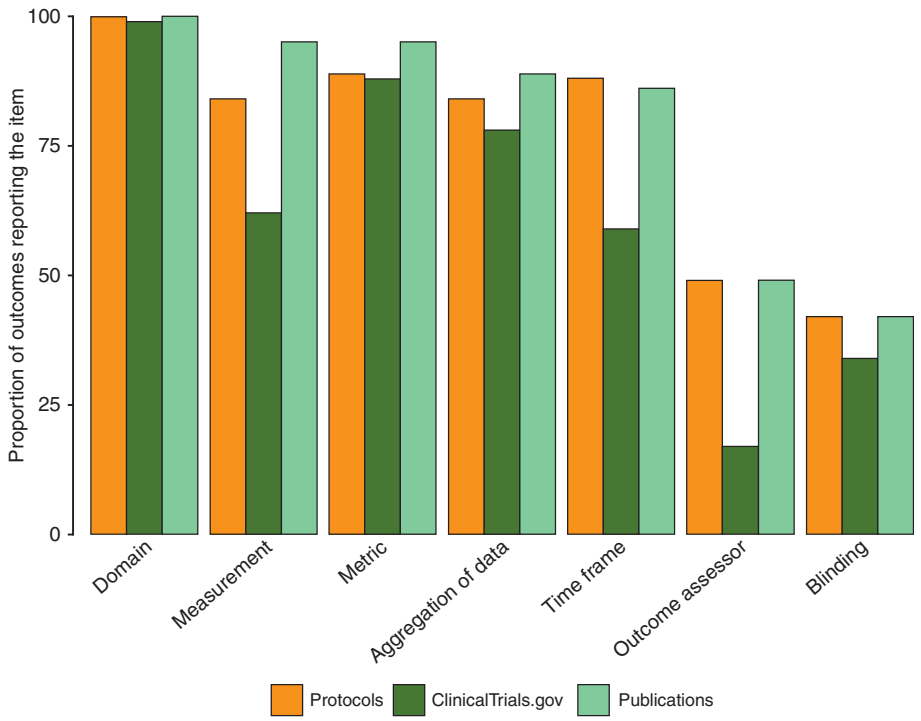

Figure 2. Outcome descriptions in each data source ($n = 81$).

publication (Figure 3; supplementary Table S4, available at *Annals of Oncology* online). Discrepancies involved the omission in the publication of one or several planned endpoints ($n = 5$), the addition in the publication of one or several unplanned primary outcomes ($n = 3$), a change from a primary outcome in ClinicalTrials.gov to a secondary outcome in the publication ($n = 4$), modification of the measurement method of one or several outcomes ($n = 3$) and an unclear entry in ClinicalTrials.gov preventing the assessment of outcome modification ($n = 1$).

Comparison of identification of ORB by using protocols or ClinicalTrials.gov. We found moderate agreement in identifying studies with discrepant reporting of outcomes by using protocols or ClinicalTrials.gov, with $\kappa = 0.53$ [95% confidence interval (0.25–0.81)]. This finding was due to both false-positive identifications of discrepant reporting of outcomes in ClinicalTrials.gov ($n = 9$) (e.g. registration as primary outcomes of measurements reported as secondary outcomes in both the protocol and registration) and false-negative identification of discrepant reporting of outcomes ($n = 7$) (e.g. modification of the measurement method between the protocol and the publication covered by an imprecise entry in the public clinical-trial registry [19]) (supplementary Table S5, available at *Annals of Oncology* online). Using ClinicalTrials.gov to detect discrepant reporting of outcomes showed high specificity (89.5%) but lacked some sensitivity (75%) as compared with use of protocols.

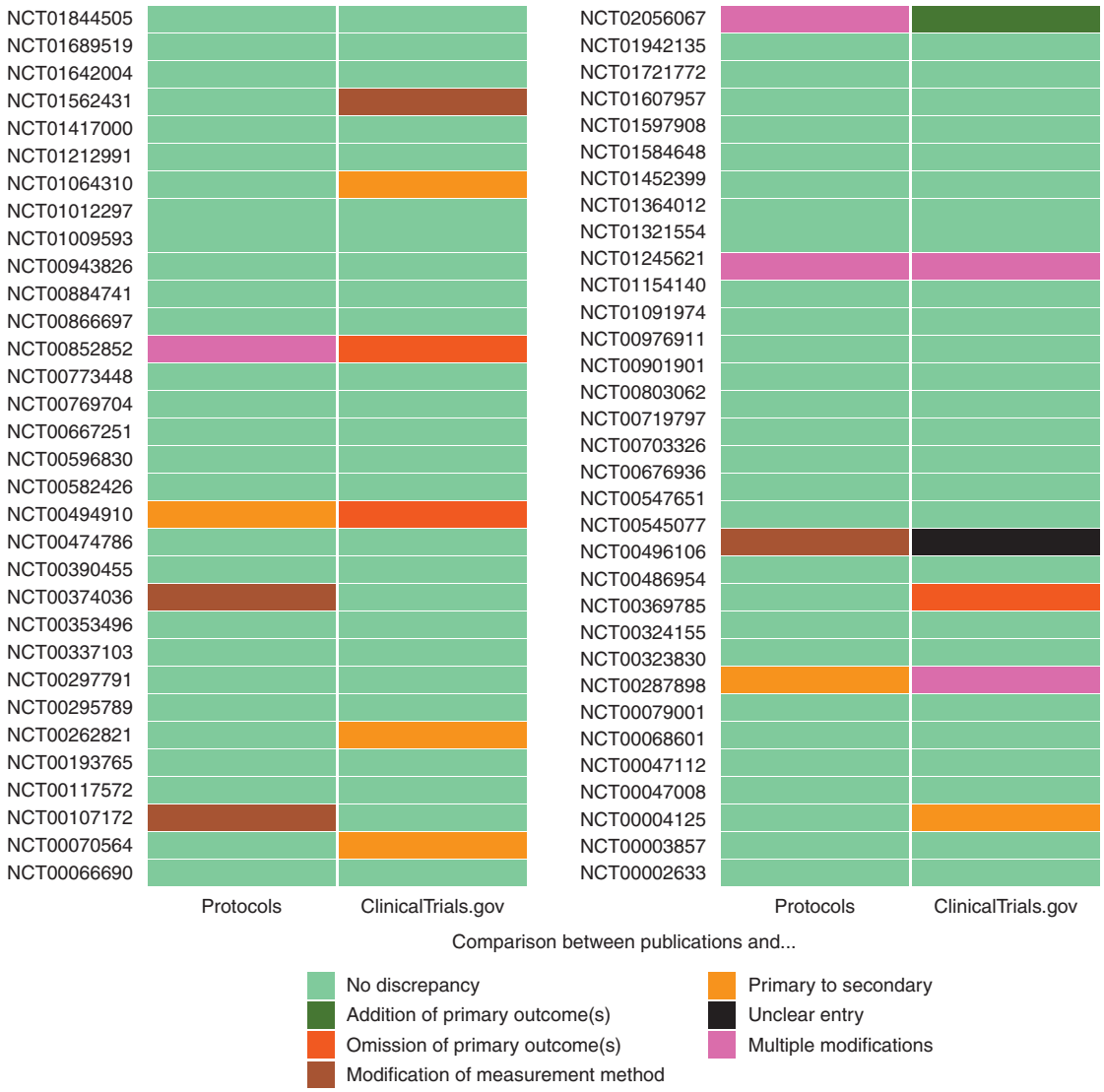

Figure 3. Discrepancies between primary outcomes in protocols and publications and in ClinicalTrials.gov and publications ($n = 65$).

Discussion

In the present study, we systematically compared primary outcomes reported in protocols, ClinicalTrials.gov and publications. We found evidence of distortion between protocols and published reports in 12% of trials. When using ClinicalTrials.gov to identify ORB, 18.5% of trials had at least one discrepancy between what was presented in the registry and published report. Using ClinicalTrials.gov to detect modifications between planned and published outcomes resulted in both false-positive identification of discrepant reporting of outcomes (e.g. protocol amendments not reported in ClinicalTrials.gov) and false-negative identification of discrepant reporting of outcomes (e.g. discrepancy between protocols and publications covered by imprecise outcome descriptions in ClinicalTrials.gov).

In addition, we highlighted the low quality of primary outcome descriptions in ClinicalTrials.gov. Although guidance for registration in ClinicalTrials.gov insists on the importance of a clear description of the measurement method and time frame in registry entries [20, 21], only 62% and 59% of trial outcomes described in ClinicalTrials.gov contained a description of how and when the outcome would be measured. Some outcome modifications could have been covered by these imprecise descriptions. In our study, 25% of outcomes in publications were imprecisely reported and thus could suggest selective reporting based on results, not ascertainable by using protocols or ClinicalTrials.gov.

The proportion of discrepant outcomes found in our study concurs with the literature in oncology, in which authors found 12% and 14% modifications of primary outcomes by using protocols [2] and ClinicalTrials.gov entries [6], respectively. Overall, modifications between planned and published outcomes seem less frequent in oncology trials than in other specialties [11], perhaps because of high standardization of methods to evaluate progression-free and overall survival. In our study, discrepant reporting of outcomes occurred mostly in studies involving patient-reported outcomes. Higher standardization of trial outcomes, as advocated by initiatives such as COMET may be a way to reduce the possibility of outcome modifications [22].

Our study is original because it is the first to compare primary outcome descriptions in protocols, public clinical-trial registries and publications and to show the limits of comparing published and registered outcomes to detect discrepant reporting of outcomes. Because trial protocols are often confidential documents not available to readers or peer-reviewers [7, 23], our results question the ability of peer-reviewers or readers to identify deviations from the protocol as advocated by many journals [24]. For example, we found instances where modification of outcome measurements from the protocol to publication were covered by imprecise outcome descriptions in ClinicalTrials.gov.

Of note, discrepant outcome reporting is not always based on the result and may be due to a variety of reasons including loss of funding, poor quality of data or the non-analysis of secondary data because of no difference in the primary outcome [25]. However, in these cases, authors must identify any changes to the primary and secondary outcome measures after the trial started and explain the reasons for these changes. This important rule for the transparency of research was highlighted in the modification of the CONSORT reporting guidelines in 2010 [15]. In our sample, among 10 reports with discrepant reporting of outcomes between publications and protocols, only two gave the reasons for not reporting all primary outcomes [26, 27].

Our study has some limitations. First, because we studied recent trials, most did not yet have results posted at ClinicalTrials.gov. Information provided in public registries when results are posted is often more accurate than previous entries in ClinicalTrials.gov and/or publications [28, 29]. Thus, more research is needed to assess how outcomes are reported in this data source and how it may be used to investigate discrepant reporting of outcomes. Second, we considered only a limited number oncology trials published in two high-impact-factor journals providing open access to protocols. In addition, our sample comprised a small number of trials from each different sub-specialty of oncology. Therefore, our results and estimates for the prevalence of outcome modifications may not be generalizable to other trials in oncology or other specialties and should be further investigated.

Because public clinical-trial registries may not precisely reflect protocols, and because peer editors and peer-reviewers often fail to detect discordance between planned and published outcomes in trials they assess, readers need to be allowed to evaluate the integrity of research themselves. Projects such as the COMPARE-trials initiative [30] require the public disclosure of all documents, including study protocols. Thus, the policy adopted by the *Journal of Clinical Oncology* or the *New England Journal of Medicine* to systematically append the study protocol to published reports [31] helps improve the identification of modifications between planned and published outcomes and should be considered by more journals.

Conclusion

Because protocols are confidential documents, public clinical-trial registries are the only option for readers and reviewers to compare primary outcomes reported in publications with a previous source. We have shown that outcome descriptions in public clinical-trial registries often lack precision and may not reflect what is in the protocol, thus limiting the ability to identify discrepancies between planned and published outcomes.

Funding

This study was funded by the French National Institute for Cancer Research (INCa) Ref: SHSESP14-080. Our team is supported by an academic grant from the program 'Equipe espoir de la Recherche', Fondation pour la Recherche Médicale, Paris, France (No. DEQ20101221475). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

The authors have declared no conflict of interest.

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