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SHORT RESEARCH ARTICLE

Prevalence of primary outcome changes in clinical trials registered on ClinicalTrials.gov: a cross-sectional study [v1; ref status: indexed, <http://f1000r.es/34I>]

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Abstract

Background: An important principle in the good conduct of clinical trials is that a summary of the trial protocol, with a pre-defined primary outcome, should be freely available before the study commences. The clinical trials registry ClinicalTrials.gov provides one method of doing this, and once the trial is registered, any changes made to the primary outcome are documented. The objectives of this study were: to assess the proportion of registered trials on ClinicalTrials.gov that had the primary outcome changed; to assess when the primary outcome was changed in relation to the listed study start and end dates and to assess whether the primary outcome change had any relation to the study sponsor.

Methods: A cross-sectional analysis of all interventional clinical trials registered on ClinicalTrials.gov as of 25 October 2012 was performed. The main outcome was any change made to the initially listed primary outcome and the time of the change in relation to the trial start and end date.

Findings: Our analysis showed that 28229 of 89204 (31.7%) registered studies had their primary outcome changed. Industry funding was associated with all primary outcome changes, odds ratio (OR)= 1.36, 95% confidence interval (CI)=1.31-1.41, p<0.001; with primary outcome changes after study start date OR=1.37, 95% CI=1.32-1.42, p<0.001; with primary outcome changes after primary completion date OR=1.84, 95% CI=1.75-1.94, p<0.001 and with primary outcome changes after study completion date OR=1.82, 95% CI=1.73-1.91, p<0.001.

Conclusions A significant proportion of interventional trials registered on ClinicalTrials.gov have their primary outcomes altered after the listed study start and completion dates. These changes are associated with funding source.

Article Status Summary

Referee Responses

Referees	1	2	3
v1 published 26 Mar 2014	 report	 report	 report

- Janet Wale**, Cochrane Collaboration
Consumer Network Australia
- Deborah Korenstein**, Mount Sinai
Hospital USA
- Steven A Julious**, University of Sheffield
UK

Latest Comments

No Comments Yet

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Introduction

Clinical trials provide the principal method with which to assess the effectiveness of therapeutic strategies¹. An important principle in the good conduct of clinical trials is that a summary of the trial protocol, with a pre-defined primary outcome, should be freely available before the study commences¹. In February 2000, the United States (US) Food and Drug Administration (FDA) created an online clinical trials registry named ClinicalTrials.gov². From 2005, the International Committee of Medical Journal Editors (ICMJE) required that clinical trials should be listed in a clinical trial registry to qualify for publication³. The registration of a clinical trial usually involves reporting information on 20 items proposed by the World Health Organization (WHO) registration advisory group, including the primary outcome of the study⁴. One reason for the creation of this registry was to help to reduce the risk of selective reporting of outcomes that had been previously identified. For example, a cohort study using protocols and published reports of randomized trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg in Denmark in 1994–1995 found that 62% of trials had at least one primary outcome that was changed, introduced, or omitted⁵. A more recent study looking at trials that were registered on trial websites (such as ClinicalTrials.gov), found that 31% of trials displayed some evidence of discrepancies between the outcomes registered and the outcomes published⁶. Therefore, even trial registration may not be a complete barrier to selective outcome reporting.

ClinicalTrials.gov tracks all changes made to registered protocols. The objectives of this study were: to assess the proportion of registered trials on ClinicalTrials.gov that had the primary outcome changed; to assess when the primary outcome was changed in relation to the listed study start and end dates and to assess whether the primary outcome change had any relation to the study sponsor.

Methods

Data source

ClinicalTrials.gov is a publicly available trial registry and results database developed and maintained by the US National Library of Medicine on behalf of the US National Institutes of Health.

Study sample

We wrote scripts in R to download all interventional clinical studies registered with ClinicalTrials.gov as of 25 October 2012. Data from the ‘tabular view’ for all studies (*e.g.* <http://clinicaltrials.gov/ct2/show/record/NCT00548405?term=alemtuzumab+multiple+sclerosis&rank=2>) were downloaded, and the information was automatically extracted from each field and used to populate a spreadsheet for analysis. This spreadsheet is available in *figshare* (doi: 10.6084/m9.figshare.967827). We downloaded data from all interventional studies registered with ClinicalTrials.gov as of 25 October 2012 preventing any bias in study selection (please contact the corresponding author for details on the scripts).

The following information was collected from each study: study registration date (the date the study is registered with ClinicalTrials.gov); the study start date (defined as the date that enrollment to the protocol begins); the primary completion date (defined as the anticipated or actual date the final subject was examined or received

an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated); study completion date (defined as the final date on which data was collected); original primary outcome (defined as a specific key measurement(s) or observation(s) used to measure the effect of experimental variables in a study) and date submitted; current primary outcome and date submitted; study phase (phase of investigation as defined by the US FDA), data monitoring committee (whether an independent group of scientists has been appointed to monitor the safety and the scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the termination of the trial for efficacy, for harm or for futility); study sponsor (defined as the primary organization that oversees the implementation of the study and is responsible for data analysis) and collaborators (defined as other organizations (if any) providing support, including funding, design, implementation, data analysis and reporting).

For studies to be included in this analysis a primary outcome had to be registered. A study was classified as not having a primary outcome changed if the original primary outcome was listed as ‘same as current’. For a subset of interventional trials, specifically those that had ‘multiple sclerosis’ or ‘diabetes’ in the title, we looked for primary outcomes that had a significant change, as the authors have experience in these fields. We defined a discrepancy between primary outcomes if the two were clearly different (*e.g.* in one study the primary outcome was changed from ‘expanded disability status scores assessed every 12 weeks’ to ‘annualized relapse rate’). Two authors (SVR and JP) independently assessed whether or not the studies had significant changes; then they met to compare results. For any discrepancies they met with another author (LH) and a consensus was reached. The kappa statistic for agreement between the first two observers was 0.87.

ClinicalTrials.gov stores funding organization information using two data elements: lead sponsor (defined as the organization or person who oversees the clinical study and is responsible for analyzing the study data) and collaborator (defined as an organization other than the sponsor that provides support for a clinical study). We derived probable funding source from the lead sponsor and collaborator fields using the following algorithm: if the lead sponsor and any collaborators were from industry and no non-industry sponsors or collaborators were listed, then the study was categorized as industry funded; if the lead sponsor and/or collaborator included industry and non-industry sources, then the study was categorized as mixed; finally if the lead sponsor and any collaborators were not from industry and no industry sponsors or collaborators were listed, then the study was categorized as non-industry funded. Two authors (SVR and JP) independently appraised the funding status of all studies; then they met to compare results. For any discrepancies they consulted another author (LH) and a final consensus was reached. The kappa statistic for agreement between the first two observers was 0.76.

Statistical analysis. We used logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CI) for comparisons between outcome changed and non-outcome changed groups, using registration date and funding source as explanatory variables.

In a full model, we included study phase and data monitoring committee as additional explanatory variables. The p -values <0.05 were interpreted as significant. Statistical analyses were conducted using the STATA 12.0.0 software.

Data set of primary outcome changes in interventional clinical trials registered on ClinicalTrials.org

<http://dx.doi.org/10.6084/m9.figshare.967827>

Results

Study sample

As of 25 October 2012, 97,668 interventional trials were registered with ClinicalTrials.gov. These trials were registered between 1999 and 2012; the distribution of registrations by year is shown in [Table 1](#). There were 46,803 (52.5%) trials classed as non-industry funded, 11,986 (13.4%) as mixed and 30,415 (34.1%) as industry funded ([Table 1](#)). There were 39,992 studies registered as completed.

Primary outcome changes

We found that 28,129 studies (31.7% of 89,204) had their primary outcome changed. Funding source and registration year were associated with trials that had their primary outcome changed ([Table 2](#)). Restricting analyses to completed trials (39,992 trials) did not materially change these associations (mixed funding odds ratio (OR)=1.02; 95% confidence interval (CI)=0.95–1.10, $p=0.63$; industry funding OR=1.30, 95% CI=1.24–1.36, $p<0.001$).

Primary outcome changes in relation to study start date

The dates of primary outcome changes were first compared in relation to the registered study start date. This analysis showed that 26,457 studies (30.3% of 87384 studies with a registered start date)

had their primary outcome changed after the study had supposedly started. Funding source and registration year were associated with trials that had their primary outcome changed after the study start date ([Table 2](#)). Restricting analyses to completed trials (39236 trials) did not affect the associations with funding (mixed funding OR=1.01; 95% CI=0.94–1.09, $p=0.70$; industry funding OR=1.29, 95% CI=1.23–1.35, $p<0.001$).

Primary outcome changes in relation to study end date

The dates of primary outcome changes were then compared to the listed study end dates. The results showed that 11,834 studies (30.4% of 38,974 studies with a registered primary completion date) had their primary outcome changed after the primary completion date and 10,623 (26.2% of 40,615 studies with a registered study completion date) studies had their primary outcome changed after the study completion date. Funding source and registration year were associated with trials that had their primary outcome changed after either study completion dates ([Table 2](#)). Restricting analyses to completed trials (32,124 trials with a primary completion date and 35,719 trials with a study completion date) rendered the associations with mixed funding non-significant (primary completed trials mixed funding OR=1.10; 95% CI=0.99–1.19, $p=0.057$; completed trials mixed funding OR=1.08, 95% CI=0.99–1.17, $p=0.085$); the associations with industry funding remained (primary completed trials industry funding OR=1.94; 95% CI=1.83–2.05, $p<0.001$; completed trials industry funding OR=1.81, 95% CI=1.72–1.91, $p<0.001$).

Inclusion of study phase and use of a data monitoring committee

In a full model we included study phase and the use of a data monitoring committee (DMC) as additional explanatory variables. There were 48,471 trials that provided information for all four variables,

Table 1. Number of interventional studies registered on ClinicalTrials.gov by year, funding status and primary outcome change.

Year	Publicly funded		Mixed funding		Industry funded	
	Unchanged	Changed	Unchanged	Changed	Unchanged	Changed
1999	286	142	19	1	3	6
2000	88	91	17	6	1	0
2001	85	141	6	1	3	7
2002	127	186	26	22	137	94
2003	139	333	15	20	125	108
2004	152	460	17	30	250	248
2005	2017	2775	767	860	1817	1717
2006	1519	2402	437	696	1223	1897
2007	2055	2798	563	885	1168	2473
2008	4761	1304	1170	360	2882	1750
2009	5042	1146	1337	314	2742	1254
2010	5609	890	1412	254	2868	850
2011	6184	548	1458	146	3367	463
2012	5241	282	1088	59	2752	210

Table 2. Association of funding status and registration year with primary outcome change for a) all primary outcome changes, b) primary outcome changes after listed study start date, c) primary outcome changes after listed primary completion date on ClinicalTrials.gov and d) primary outcome changes after listed study completion date on ClinicalTrials.gov. OR=odds ratio.

	a) OR (95% confidence interval)	p value	b) OR (95% confidence interval)	p value	c) OR (95% confidence interval)	p value	d) OR (95% confidence interval)	p value
Funding								
Non-industry	1		1		1		1	
Mixed	1.01 (0.96–1.06)	0.33	1.01 (0.96–1.07)	0.60	1.08 (1.00–1.17)	0.04	1.10 (1.02–1.18)	0.019
Industry	1.36 (1.31–1.41)	<0.001	1.37 (1.32–1.42)	<0.001	1.84 (1.75–1.94)	<0.001	1.82 (1.73–1.91)	<0.001
Registration Year								
1999	1		1		1		1	
2000	1.90 (1.36–2.66)	<0.001	1.62 (1.15–2.28)	0.006	1.14 (0.71–1.82)	0.59	1.41 (0.79–2.53)	0.25
2001	3.26 (2.36–4.50)	<0.001	3.02 (2.16–4.21)	<0.001	1.79 (1.13–2.82)	0.012	1.95 (1.11–3.45)	0.021
2002	1.92 (1.49–2.48)	<0.001	1.62 (1.25–2.10)	<0.001	1.69 (1.16–2.47)	0.007	1.81 (1.18–2.77)	0.007
2003	3.13 (2.45–4.00)	<0.001	2.74 (2.13–3.53)	<0.001	2.37 (1.64–3.42)	<0.001	2.74 (1.80–4.17)	<0.001
2004	3.22 (2.56–4.06)	<0.001	2.74 (2.17–3.47)	<0.001	2.37 (1.67–3.36)	<0.001	2.59 (1.73–3.87)	<0.001
2005	2.17 (1.78–2.65)	<0.001	1.86 (1.51–2.28)	<0.001	2.61 (1.90–3.58)	<0.001	2.02 (1.39–2.94)	<0.001
2006	2.91 (2.38–3.56)	<0.001	2.47 (2.01–3.04)	<0.001	2.29 (1.67–3.15)	<0.001	2.24 (1.54–3.26)	<0.001
2007	3.03 (2.48–3.70)	<0.001	2.41 (1.96–2.96)	<0.001	1.61 (1.17–2.21)	0.003	2.00 (1.38–2.90)	<0.001
2008	0.71 (0.58–0.87)	0.001	0.58 (0.47–0.71)	<0.001	0.68 (0.50–0.94)	0.019	1.10 (0.76–1.60)	0.62
2009	0.55 (0.45–0.68)	<0.001	0.43 (0.35–0.53)	<0.001	0.52 (0.38–0.71)	<0.001	0.89 (0.61–1.29)	0.54
2010	0.38 (0.31–0.46)	<0.001	0.27 (0.22–0.34)	<0.001	0.32 (0.23–0.45)	<0.001	0.56 (0.39–0.83)	0.003
2011	0.20 (0.16–0.24)	<0.001	0.12 (0.10–0.15)	<0.001	0.14 (0.10–0.20)	<0.001	0.24 (0.16–0.36)	<0.001
2012	0.11 (0.09–0.14)	<0.001	0.06 (0.04–0.07)	<0.001	0.16 (0.11–0.23)	<0.001	0.27 (0.18–0.42)	<0.001

47,748 trials that also had a study start date, 23,080 that also had a primary completion date and 21,747 that also had a study completion date. Funding source was associated to all primary outcome changes, primary outcome changes after listed study start date and primary outcome changes after listed primary completion date following adjustment for study phase and presence of a DMC (Table 3). Study phase and use of a DMC were also associated to primary outcome changes. All associations remained similar when restricting to completed trials, although the associations of mixed funding with all primary outcome changes and primary outcome changes after study start date became non-significant.

Significant primary outcome changes in multiple sclerosis interventional trials

A subset of interventional trials in multiple sclerosis was investigated to assess the actual change in primary outcome. Fifty out of 422 (11.9%) registered trials were deemed to have a significant change in the primary outcome, 49 out of 416 (11.8%) were changed after the study start date, 32 out of 187 (17.1%) were changed after the primary completion date and 26 out of 191 (13.6%) were changed after the study completion date. After adjusting for study registration year, industry funding was associated with all primary outcome changes (OR=4.92, 95% CI 2.12–11.41, $p<0.001$), primary

outcome changes after listed study start date (OR=4.75, 95% CI 2.04–11.05, $p<0.001$), primary outcome changes after listed primary completion date (OR=14.3, 95% CI 1.87–109.3, $p=0.01$), and primary outcome changes after listed study completion date (OR=14.52, 95% CI 1.90–111.06, $p=0.01$). These associations remained also when adjusting for presence of DMC and study phase and when looking at completed trials.

Significant primary outcome changes in diabetes interventional trials

A subset of interventional trials in diabetes was also investigated to assess the actual change in primary outcome. Two hundred and forty eight out of 2836 (8.7%) registered trials were deemed to have a significant change in the primary outcome, 225 out of 2786 (8.1%) were changed after the study start date, 158 out of 1475 (10.7%) were changed after the primary completion date and 147 out of 1561 (9.4%) were changed after the study completion date. After adjusting for study registration year, industry funding was associated to all primary outcome changes (OR=1.76, 95% CI 1.31–2.36, $p<0.001$), primary outcome changes after listed study start date (OR=1.75, 95% CI 1.28–2.38, $p<0.001$), primary outcome changes after listed primary completion date (OR=1.83, 95% CI 1.20–2.77 $p=0.005$), and primary outcome changes after listed study completion

Table 3. Association of funding status, registration year, use of a data monitoring committee and study phase with a) all primary outcome changes, b) primary outcome changes after listed study start date, c) primary outcome changes after listed primary completion date on ClinicalTrials.gov and d) primary outcome changes after listed study completion date on ClinicalTrials.gov.
OR=odds ratio.

	a) OR (95% confidence interval)	p value	b) OR (95% confidence interval)	p value	c) OR (95% confidence interval)	p value	d) OR (95% confidence interval)	p value
Funding								
Non-industry	1		1		1		1	
Mixed	1.07 (1.00–1.15)	0.04	1.08 (1.01–1.16)	0.024	1.01 (0.91–1.12)	0.84	1.08 (0.97–1.19)	0.15
Industry	1.65 (1.56–1.73)	<0.001	1.69 (1.60–1.78)	<0.001	1.73 (1.61–1.86)	<0.001	1.74 (1.62–1.88)	<0.001
Registration Year								
1999	1		1		1		1	
2000	1.38 (0.82–2.34)	0.23	1.35 (0.80–2.29)	0.26	1.15 (0.63–2.08)	0.65	0.95 (0.47–1.92)	0.88
2001	2.73 (1.57–4.72)	<0.001	2.67 (1.54–4.64)	<0.001	3.00 (1.65–5.44)	<0.001	2.19 (1.11–4.31)	0.024
2002	2.69 (1.73–4.19)	<0.001	2.61 (1.68–4.07)	<0.001	2.55 (1.57–4.13)	<0.001	1.82 (1.06–3.14)	0.03
2003	7.01 (4.55–10.8)	<0.001	6.76 (4.39–10.43)	<0.001	5.92 (3.68–9.50)	<0.001	4.27 (2.57–7.12)	<0.001
2004	8.80 (5.76–13.45)	<0.001	8.56 (5.60–13.09)	<0.001	5.99 (3.81–9.41)	<0.001	4.88 (2.97–8.02)	<0.001
2005	12.33 (8.61–17.66)	<0.001	11.64 (8.13–16.69)	<0.001	5.82 (3.94–8.59)	<0.001	4.69 (3.04–7.24)	<0.001
2006	16.34 (11.37–23.47)	<0.001	14.91 (10.38–21.43)	<0.001	4.22 (2.86–6.23)	<0.001	3.84 (2.49–5.93)	<0.001
2007	5.26 (3.70–7.47)	<0.001	4.73 (3.32–6.73)	<0.001	2.21 (1.50–3.25)	<0.001	1.82 (1.18–2.81)	0.006
2008	1.11 (0.78–1.58)	0.56	1.01 (0.71–1.43)	0.97	0.93 (0.63–1.36)	0.70	0.94 (0.61–1.45)	0.79
2009	0.85 (0.60–1.21)	0.36	0.74 (0.52–1.05)	0.096	0.70 (0.48–1.04)	0.076	0.78 (0.50–1.20)	0.26
2010	0.58 (0.41–0.83)	0.002	0.47 (0.33–0.67)	<0.001	0.43 (0.29–0.64)	<0.001	0.49 (0.31–0.76)	0.001
2011	0.30 (0.21–0.43)	<0.001	0.21 (0.15–0.30)	<0.001	0.16 (0.10–0.24)	<0.001	0.17 (0.10–0.27)	<0.001
2012	0.16 (0.11–0.23)	<0.001	0.09 (0.06–0.13)	<0.001	0.22 (0.14–0.36)	<0.001	0.24 (0.15–0.41)	<0.001
Phase								
0	1		1		1		1	
1	1.37 (1.05–1.78)	0.02	1.37 (1.04–1.80)	0.027	1.05 (0.68–1.63)	0.83	1.10 (0.68–1.76)	0.71
2	1.53 (1.18–1.99)	0.001	1.54 (1.17–2.02)	0.002	1.67 (1.08–2.58)	0.02	1.70 (1.06–2.73)	0.028
3	1.63 (1.26–2.13)	<0.001	1.62 (1.23–2.13)	0.001	2.22 (1.43–3.44)	<0.001	2.22 (1.38–3.57)	0.001
4	1.23 (0.94–1.60)	0.125	1.25 (0.95–1.65)	0.109	2.06 (1.33–3.20)	0.001	2.00 (1.25–3.22)	0.004
DMC								
No	1		1		1		1	
Yes	1.17 (1.12–1.23)	<0.001	1.13 (1.07–1.19)	<0.001	0.82 (0.77–0.88)	<0.001	0.81 (0.75–0.86)	<0.001

date (OR=2.63, 95% CI 1.68–4.11, $p<0.001$). These associations remained also when adjusting for presence of DMC and study phase and when looking at completed trials.

Discussion

Summary

We assessed the proportion of primary outcome changes for interventional trials registered on ClinicalTrials.gov from 1999 to 2012, when these changes occurred and whether these changes related to funding source. Industry funding was associated with primary outcome changes. These associations remained even after adjusting for the phase of the study and the presence of a DMC. The changes

appeared to peak in the period between 2004 and 2007. This may suggest that a lower number of trials were registered before this time period and perhaps that there was not enough time to accrue for changes to be made in more recently registered trials (or that the changes made to the protocol decrease over time). When looking at significant primary outcome changes, the proportion of trials with their outcome changed was much less than all changes; nevertheless, industry funding was still associated with significant primary outcome changes.

There are many reasons for departures from the initial study protocol. Authors should identify and explain any such changes, however

no such information is given on ClinicalTrials.gov and thus we have no explanation for our results. The results obtained here may suggest that industry funded trials are more diligent in reporting changes to protocols. Indeed, the primary outcome measure data element was not available in ClinicalTrials.gov until late 2004 and it was considered an optional data element until December 2012. There are implications of the data reported here for medical journals, reviewers and drug approval agencies.

Limitations of this study

A limitation for our study is the scope of the data. We used data from only one trial website, and thus the generalisability to other registration sites is unclear. We have also assumed the data entered regarding study start and completion dates were accurate. We have no information on the reasons for the changes being made. We also did not assess the significance of the primary outcome change for the vast majority of changes; the sub-studies in multiple sclerosis and diabetes suggested that significant changes may only occur in approximately 8% of all registered trials, but this may or may not be applicable to trials for other disorders. Some primary outcome changes may be typographical/semantic and may not reflect actual changes to the nature of the outcome (although one would expect these to occur equally regardless of funding source).

Background from other studies

Previous reports have not investigated changes to a primary outcome as entered on a registration website, but they have compared trial protocols to published studies. Four previous studies have shown that in 47–74% of studies the primary outcome stated in a protocol was the same as in a subsequent publication; between 13 and 31% of primary outcomes specified in the protocol were omitted in the publication and between 10 and 18% of reports introduced a primary outcome in the publication that was not specified

in the protocol⁷. The proportion of primary outcome changes that we found was perhaps lower than that found previously, but this may be due to the different methodology used in this study. The relationship between protocol changes and funding has not been thoroughly investigated. Chan and colleagues found that 61% of the 51 trials with major discrepancies between the study protocol and publication were funded solely by industry sources compared to 49% of the 51 trials without discrepancies⁵.

Conclusions

Primary outcome changes are made to study protocols registered on ClinicalTrials.gov and these changes are associated with funding source.

Data availability

figshare: Data set of primary outcome changes in interventional clinical trials registered on ClinicalTrials.org⁸. <http://dx.doi.org/10.6084/m9.figshare.967827>

Author contributions

SVR and BG conceived and designed the study. SVR, JP, LH, APS, MK and DM analysed the data. SVR and BG interpreted the data. SVR drafted the article. All authors revised the article and gave final approval for publication.

Competing interests

The authors declare no competing interests.

Grant information

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[Data Source](#)

Current Referee Status:

Referee Responses for Version 1



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Approved: 09 May 2014

Referee Report: 09 May 2014

doi:[10.5256/f1000research.4053.r4262](https://doi.org/10.5256/f1000research.4053.r4262)

This is an interesting report with some interesting results. Upon reading the report it did lead to the thinking of possible confounding factors which could explain some of the differences if not all.

Some of the confounding factors could not be easily investigated in the current data set and I will consider these first.

The first is whether the treatment being investigated in the trial is a licensed or unlicensed therapy. Though in theory "do-able" the authors can be forgiven for not investigating this. However, could it be proposed that a trial of a new unlicensed treatment where knowledge is emerging - and being published as the trial is ongoing - is more likely to have an endpoint changed than a licensed treatment with known properties?

The other consideration is therapeutic area. The authors to a degree looked into this by investigating two sub populations of MS and diabetes trials but it could be that certain therapeutic areas predominate in certain sectors?

One final consideration is if the endpoint change was pre-planned in some way in some form of adaptive design.

With respect to confounders which could be investigated the main consideration is study duration. Might a study that has gone on longer be more likely to have an endpoint change? This could be legitimate if, as mentioned previously this change is due to published work becoming available. It could also be (maybe) legitimate if, for completed studies, it has dragged on for an age with no chance to reach the target sample size. So to a degree there is a case of fitting tailoring the study to what can be answered with the sample size. The interaction between study duration and funder would also be interesting (as well as just allowing in the model)

There are two markers in the analysis which do suggest study duration may impact on endpoint change. The first is study registration year and the other is phase of development. In the case of phase of development the effect seems to be the reverse, it could be argued, to what one would expect. Early phase trials are learning trials not confirming trials. A consequence is the endpoints may change to reflect the properties of a treatment an investigator is learning about in an ongoing manner. It would be interesting with study duration in the model how it would effect the comparison of phase of development

Following on from the point in the previous paragraph therefore an analysis of just trials which are Phase

Ill would be of interest. These trials should have everything set and pre-specified in terms of analysis

One final point about the work is that I could not see mention of a protocol for the audit itself undertaken for the paper. In particular what the pre-specified primary endpoint and analysis population was. It is not the convention for audits to do this but it would have been optimal given the subject matter.

In summary therefore it would be optimal to comment on the potential limitations of the work and to undertake the suggested analyses. However, the work itself is of interest and will almost certainly feed debate.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



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Referee Report: 23 April 2014

doi:[10.5256/f1000research.4053.r4266](https://doi.org/10.5256/f1000research.4053.r4266)

This cross-sectional study of trials registered on Clinicaltrials.gov found that changes in primary outcome are common and are associated with industry funding. The study was appropriately done and reported. The reasons for the changes in primary outcomes and the explanation for the association with funding source are not clear, but it seems likely that changes to the primary outcome might be important for the sound interpretation of results.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



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doi:[10.5256/f1000research.4053.r4267](https://doi.org/10.5256/f1000research.4053.r4267)

This is a well written, competently undertaken, cross-sectional analysis. The study finds that changes to primary outcomes listed in a trials register, at any stage of the trial, are clearly associated with industry funding. Studying the extent of the changes in two disease areas is a practical way used by the authors to assess the changes and their significance (extensive in some 8%).

The authors point out that there are many reasons for changes from the initial study protocol. No information is given on ClinicalTrials.gov on the reasons for changes and thus they have no explanation for their results. The authors suggest that industry funded trials are more diligent in reporting changes to

protocols.

This is a possible area for change which has been provided in this article.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
