## Appendix. Themes of responses from journals.

<table>
<thead>
<tr>
<th>Theme and Subthemes</th>
<th>Quote</th>
<th>Issue</th>
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<tr>
<td><strong>Conflicts with CONSORT</strong></td>
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<td>Failure to recognise that post-commencement changes are acceptable under CONSORT, but should be declared in the paper reporting the results of the trial.</td>
<td>“The basis of our long experience reviewing research articles, we have learned that prespecified outcomes or analytic methods can be suboptimal or wrong” “Although prespecification is important in science, it is not an altar at which to worship… [COMPare’s] assessments appear to be based on the premise that trials are or can be perfectly designed at the outset… and that any changes investigators make to a trial protocol or analytic procedures after the trial start date indicate bad science.” (Annals Editors critique, 01/03/16)</td>
<td>COMPare uses CONSORT as the gold standard. CONSORT item 6b requires that trial reports should declare and explain &quot;any changes to trial outcomes after the trial commenced, with reasons&quot; in the paper reporting the results of the trial. Changes are not forbidden, however they should be declared in the trial report.</td>
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<td>“The Centre for Evidence-Based Medicine Outcome Monitoring Project’s assessments appear to be based on the premise that trials are or can be perfectly designed at the outset” (Annals Editors critique, 01/03/16)</td>
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<td>“Prespecification can be misused to sanctify both inappropriate endpoints, such as biomarkers, when actual health outcomes are available and methods that are demonstrably inferior.” [sic] (Annals Editors critique, 01/03/16)</td>
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<td>Stating that outcome switching doesn’t matter if the main results of the study are unlikely to be affected.</td>
<td>“We reviewed materials associated with the articles and concluded that the information reported in the articles accurately represented the scientific and clinical intent detailed in the protocols… We found no inconsistencies between the audited articles and their related protocols that would justify changes in trial interpretation, corrections, or warnings to readers.” (Trial 45, Annals, 06/04/16)</td>
<td>CONSORT requires all outcomes to be correctly reported; it does not distinguish between circumstances when this would, or would not, affect the overall interpretation of the intervention being trialled. It is unlikely that all outcome misreporting would change the direction or size of an overall finding; however a culture of permissiveness around correct outcome reporting does permit misrepresentation more broadly.</td>
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<td>“This is true [secondary outcome SVR24 not reported in publication] but justifiable. In NEJM letters to editor about this paper (in press), the authors reported that they have analyzed the SVR24 data and results are equivalent to SVR12 (i.e. there were no relapses between week 12 and week 24 post treatment) (NEJM first comments on trial 22 (3))</td>
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<td>Statement describing journal practices that contradict CONSORT guidance.</td>
<td>“We support transparent and accurate reporting and, in particular, require the reporting of the most clinically relevant outcomes used to justify claims of efficacy or harm.” (Trial 45, Annals, 06/04/16)</td>
<td>CONSORT item 6b requires that trial reports should declare and explain &quot;any changes to trial outcomes after the trial commenced, with reasons&quot; in the paper reporting the results of the trial.</td>
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<td>“We view each piece individually and add the data as appropriate based on the judgment of the peer reviewers, the statistical reviewers, and the editors.” (NEJM emails 1, 17/11/15)</td>
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<td>Statement that failure to report prespecified secondary outcomes is not of interest.</td>
<td>“We will not ordinarily consider letters that simply... point out unpublished secondary outcomes.” (JAMA emails, 09/12/15)</td>
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<td>Denial of endorsing CONSORT, despite appearing on CONSORT’s list of endorsing journals.</td>
<td>“The New England Journal of Medicine finds some aspects of CONSORT useful but we do not, and never have, required authors to comply with CONSORT.” (NEJM emails 1, 17/11/15)</td>
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## Criticisms of COMPare methods and data

| Misrepresentation of COMPare’s methods | “The initial trial registry data… serve as COMPare’s “gold standard.”” (Annals Editors critique, 01/03/16) | This is untrue. As explained in our publicly accessible operations manual, COMPare used the registry entry where there was no pre-commencement protocol publicly available, as CONSORT 6b requires that changes after commencement are noted in the trial report. Notably, no Annals trial had a publicly accessible pre-commencement protocol. |
| | COMPare’s method is a “simple check for an exact word match between outcomes entered in a registry and those reported in a manuscript, but that oversimplifies a highly nuanced process.” (Annals to BMJ). | This is untrue. COMPare did not seek literal word matches; each prespecified outcome was manually checked and re-checked, as per previous research on outcome misreporting, using CONSORT as gold standard. |
| Invalid criticism of COMPare data point. | “Our review indicates problems with COMPare’s methods. For one trial COMPare apparently considered the protocol published well after data collection ended.” (Annals Editors critique, 01/03/16) | This is untrue. COMPare used the registry entry for this trial, because the protocol was published after the trial started, and after data collection ended, as is clear on the data sheet. |
Timing of prespecification

"We disagree with COMPare’s contention that registry data are superior to protocol information because of the timing of the former..." (Trial 45, Annals, 06/04/16)

Prespecification of outcomes should take place before trial commencement. CONSORT item 6b requires that trial reports should declare and explain "any changes to trial protocol that were not prespecified..." is false. Protocol indicates safety and tolerability as second of 2 primary objectives, and registration lists incidence of AEs leading to discontinuation as 1 of 2 primary outcome measures. First line of Table 3 and first sentence of Safety section (p. 2604) reports that 1 of 624 patient treated with sofosbuvir–velpatasvir discontinued due to AE. (NEJM first comments on trial 22 (1))

This is invalid. The outcome in question was prespecified as a primary outcome, but incorrectly reported by NEJM as a secondary outcome. COMPare therefore coded it as reported, but incorrectly reported. This is clearly denoted in the COMPare assessment sheet for this trial, and the COMPare letter reads "There were 2 pre-specified primary outcomes, of which one is reported in the paper; while one is incorrectly reported as a secondary outcome."

Claim that COMPare coding incorrect on specific outcomes

NEJM gave journalists a detailed review of COMPare’s assessment of one trial, which NEJM stated had identified six errors in COMPare’s assessment. This was reviewed, and NEJM were wrong on all six counts, full details are given in the table above and in the correspondence appendix (NEJM first comments on trial 22). Another NEJM review of a COMPare letter was also factually wrong on all three issues raised. The editors were wrong on all nine issues raised. The document they sent exemplified misunderstandings around the importance of reporting all prespecified timepoints for each prespecified outcomes.

Warning readers against COMPare’s assessments

Until the COMPare Project’s methodology is modified to provide a more accurate, complete and nuanced evaluation of published trial reports, we caution readers and the research community against considering COMPare’s assessments as an accurate reflection of the quality of the conduct or reporting of clinical trials. (Annals Editors critique, 01/03/16), (Trial 25, Annals, 14/12/15), (Trial 44, Annals, 15/12/16), (Trial 45, Annals, 15/12/15), (Trial 68, Annals, 30/12/15).

Following this comment no trialists engaged with any of our evidence of failure to correctly report prespecified outcomes. We regarded this as a breach of ICMJE guidance as per Table 3 and discussion.
The claim that space constraints prevent all prespecified prespecification after trial outcomes prespecified in Dismissal of registry data discrepencies between Stating or implying that constraints prevent all those reported in the registry. (JAMA emails, 9/12/15)

"The letters you submitted are for the most part not consistent with the approach outlined in your website, "comparing the clinical trials registry and trial protocol with the trial report." Most of the letters have noted discrepancies between the trial registry and trial report, but it appears that you have not always checked for discrepancies with the trial protocols, which have been included as a supplement with each trial published in JAMA since mid-2014." (JAMA emails, 9/12/15)

Registries

**Dismissal of registry data**

"The initial trial registry data... often include outdated, vague or erroneous entries." (Annals Editors critique, 01/03/16)

"We check the registries, but as both authors’ responses attest, registry information can be incomplete or lack sufficient detail, and we rely more heavily on the protocol that guided the actual conduct of the trial." (Trial 45, Annals, 06/04/16).

"We carefully check for discrepancies between the protocol and the manuscript... In our experience, the trial registration may not always accurately reflect the protocol, especially if clearly documented, justified, and approved revisions to the protocol have occurred." (JAMA emails, 9/12/15)

"Registries include only extracted information, do not routinely monitor whether the data in the registry match the protocol, and may not be updated when the protocol changes. We therefore rely primarily on the protocol" (Annals Editors critique, 01/03/16)

"We will not ordinarily consider letters that simply note discrepancies with the trial registration." (JAMA emails, 09/12/15)

"Inaccuracies in the trial registration documents are more of an issue for the individuals overseeing the trial registries." (JAMA emails, 9/12/15)

"The letters you submitted are for the most part not consistent with the approach outlined in your website, "comparing the clinical trials registry and trial protocol with the trial report." Most of the letters have noted discrepancies between the trial registry and trial report, but it appears that you have not always checked for discrepancies with the trial protocols, which have been included as a supplement with each trial published in JAMA since mid-2014." (JAMA emails, 9/12/15)

Rhetoric

**Stating that space constraints prevent all outcomes being reported**

"Space constraints for articles published in the Journal do not allow for all secondary and other outcomes to be reported" (NEJM emails 1, 21/11/15)

The claim that space constraints prevent all prespecified outcomes being reported conflicts with the finding of...
We cannot verify whether Annals ask authors to do this; “We carefully check for discrepancies between the protocol and the manuscript,” (JAMA emails, 9/12/15) pre-specified outcomes being reported. JAMA: “authors are not always required to report all secondary outcomes and all pre-specified exploratory or other outcomes in a single publication, as it is not always feasible given the length restrictions to include all outcomes in the primary report.” (JAMA emails, 9/12/15) COMPare, and prior research on outcome misreporting, that non-prespecified additional outcomes were routinely added (mean 5.4 outcomes added per trial in COMPare, range 2.9-8.3 by journal).

General statement about supporting goals of COMPare. Though we share COMPare’s overarching goals to assure the validity and reporting quality of biomedical studies, we do not agree with their approach. (Trial 44, Annals, 15/12/16)

While the goal of the COMPare project (http://www.compare-trials.org) is noble, my colleagues and I have outlined concerns with COMPare’s approach (1). (Trial 45, Annals, 09/04/16)

“We share COMPare’s overarching goals to assure the validity and reporting quality of biomedical studies, but we differ on how to best achieve those aims.” (Annals Editors critique, 01/03/16)

All such statements were accompanied by caveats, generally references to methodological criticisms that were invalid, statements that explicitly or implicitly undermined the journals’ commitment to CONSORT, or incorrect statements about specific data points.

Reasons for rejecting COMPare letters. “In addition, some of the information in your letters is vague, containing only numbers and not specific outcomes, making it difficult to understand the specific issues or reply to them. Moreover, the last 2 paragraphs of the letters you have submitted, concerning CONSORT and the COMPare project, are identical.” (JAMA emails, 09/12/15)

All correction letters linked to the COMPare online repository where all underlying data was shared in full. This letter was received halfway through the study period. To address the reasons given for letter rejection, all subsequent letters had no repetition and extensive detail within the text on specific misreported outcomes. However none of these subsequent letters were published and we received no further replies, as per Table 3.

We cannot verify JAMA’s internal processes; however we can confirm that trials reported in Annals are routinely non-compliant with CONSORT, a finding which is consistent with previous research. COMPare found that in Annals trials: 6% of novel outcomes added to trial reports were correctly indicated as novel; a mean of 4.1 novel undeclared outcomes were added per trial; 44% of primary outcomes were correctly reported; and 31% of secondary outcomes correctly reported.

We cannot verify whether Annals ask authors to do this; however we can confirm that trials reported in Annals are routinely non-compliant with CONSORT, a finding which is consistent with previous research. COMPare found that in Annals trials: 6% of novel outcomes added to trial reports were correctly indicated as novel; a mean of 4.1 novel undeclared outcomes were added per trial; only 82% of primary outcomes were correctly reported; and 70% of secondary outcomes correctly reported.

Statements about journal processes

Statement that authors are required to declare changes to outcomes. “When the review process generates requests for authors to report outcomes not specified in the protocol or the authors choose themselves to present such outcomes, we ask authors to indicate these as post hoc or exploratory analyses.” (Annals Editors critique, 12/02/16)

“We agree that it is important for researchers to pre-specify primary and secondary outcomes before conducting a trial and to report outcomes accurately in their publications. In fact, we carefully monitor this during editorial review.” (JAMA emails, 9/12/15)

“We carefully check for discrepancies between the protocol and the manuscript”, (JAMA emails, 09/12/15)

We cannot verify whether Annals ask authors to do this; however we can confirm that trials reported in Annals are routinely non-compliant with CONSORT, a finding which is consistent with previous research. COMPare found that in Annals trials: 6% of novel outcomes added to trial reports were correctly indicated as novel; a mean of 4.1 novel undeclared outcomes were added per trial; only 82% of primary outcomes were correctly reported; and 70% of secondary outcomes correctly reported.

Statement that journal has a process to ensure correct outcome reporting

“‘To be consistent with CONSORT recommendations, we ask authors to describe, either in the manuscript or in an appendix, any major differences between the trial registry and protocol, including changes to trial endpoints or procedures.” (Annals Editors critique, 01/03/16)

“We we share COMPare’s overarching goals to assure the validity and reporting quality of biomedical studies, but we differ on how to best achieve those aims.” (Annals Editors critique, 01/03/16)

We cannot verify whether Annals ask authors to do this; however we can confirm that trials reported in Annals are routinely non-compliant with CONSORT, a finding which is consistent with previous research. COMPare found that in Annals trials: 6% of novel outcomes added to trial reports were correctly indicated as novel; a mean of 4.1 novel undeclared outcomes were added per trial; only 82% of primary outcomes were correctly reported; and 70% of secondary outcomes correctly reported.

Placing responsibility on others (e.g., trialists or reader)

Passing responsibility to trialists, rather than journals or editors. The Lancet published 15/20 letters, mostly with accompanying responses from trialists: the majority of author responses expressed further misunderstandings about what constitutes correct outcome reporting, as reported in the accompanying paper on trialists’ responses. The Lancet made no comment themselves [all correspondence]. We asked the journal to clarify their position in our follow-up correspondence: “Since The Lancet have a longstanding positive commitment to improving reporting standards, lead the REWARD campaign on research integrity, and endorse CONSORT, we would welcome their perspective on why undeclared outcome switching in PETIT2 (and others) was apparently not addressed prior to publication; whether they now view outcome switching as acceptable; or whether they disagree that it has happened here.” We received no reply and our letter was not published. (Trial 9, Lancet, 05/02/16). Where a journal is listed as endorsing the CONSORT guidelines on trial reporting it is reasonable to expect that they will take responsibility for ensuring trials are reported consistently with these guidelines.

Passing responsibility on trial registry staff

“Inaccuracies in the trial registration documents are more of an issue for the individuals overseeing the trial registries.” (JAMA emails, 9/12/15)

As above, if there are discrepancies between the outcomes prespecified and the outcomes reported in the paper, then the paper is discrepant, not the source of prespecified outcomes.
| Stating that readers can see for themselves if outcomes reported are discrepant with those pre-specified. | NEJM “Any interested reader can compare the published article, the trial registration and the protocol (which was published with the article) with the reported results to view discrepancies” (NEJM emails 1, 21/11/15) | COMPare found that accessing documents and assessing trials for correct outcome reporting took between one and seven hours per trial. |
| Issuing a correction. | The BMJ issued a 149 word correction on the REEACT trial after receiving COMPare's correction letter (REEACT correction, BMJ, 12/01/16). | Out of 756 breaches of CONSORT identified by COMPare across 58 trials these were the only two corrections issued. |
| After COMPare attempted to access a protocol for a trial published in Annals from the lead author, we received an email from the sponsor telling us access was only possible if we signed a confidentiality agreement. This conflicted with the written transparency commitment made in the Annals publication to share the protocol on request. Annals issued a correction. “The “Reproducible Research” statement accompanying the article was incomplete. It indicated that the protocol was available by contacting the authors but should also have stated that signature of a confidentiality agreement was necessary to obtain the protocol.” (Trial 45, Annals, 12/04/16) | |

**Notes**

References throughout are to COMPare-trials.org/data, containing the full correspondence on all trials, organised by Trial ID and date, or Journal Name for general correspondence.