

DISCUSSION

Conflict of interest and bias in publication

RUTH MACKLIN

In his excellent article about commercial conflict of interest (1), Mark Wilson quotes Dennis Thompson, a political scientist who provided a searching analysis of the concept of conflict of interest (Col). Using Thompson's analysis, Wilson writes: "Determining whether factors such as ambition, the pursuit of fame and financial gain had biased a judgment was challenging. Motives are not always clear to either the conflicted party or to an outside observer." In this commentary, I aim to broaden the discussion beyond the narrowly commercial aspects of Col. I argue that bias can be introduced in major scientific journals by the editors' choices and policies. The context is a controversy that erupted in 2013 over the adequacy of informed consent in a clinical trial involving extremely premature infants. In this, as in Wilson's example, the players included the *New England Journal of Medicine (NEJM)*, as well as the highest officials of the US National Institutes of Health (NIH).

The SUPPORT controversy

The controversy focused on the ethics of informed consent for a study researching treatments for extremely premature newborns. The study, called SUPPORT, was carried out between 2004 and 2009. It compared different oxygen levels given to the newborns in an attempt to determine the optimal level for this high-risk group. The results of the study were published in the *NEJM* in 2010 (2). The Office of Human Research Protections (OHRP), a federal agency for oversight, criticised the informed consent forms for the research carried out in more than 20 neonatal intensive care units in prestigious university medical centres in the US (3). The OHRP imposed a mild sanction on the University of Alabama at Birmingham, the lead institution coordinating the SUPPORT trial, claiming that the consent documents failed to properly disclose the risks posed by the research to the infants involved in the study. In response, the *NEJM* published four articles defending the consent documents and chastising the OHRP for "overreaching" itself by sanctioning the lead institution. With some apparent reluctance, the journal published one article that agreed with

the OHRP's contention that the consent forms were flawed and also defended the OHRP's role in sanctioning the investigators.

The first article that appeared in the *NEJM* was authored by two bioethicists, Magnus and Caplan (4). They began by defending the importance of the type of study being conducted by SUPPORT – a trial of the comparative effectiveness of two different treatment regimens that were allegedly the "standard of care" in neonatal intensive care units in the US. At the time that the article was written, there was no ethical controversy on the methodology of the trial or on whether the two treatment regimens were actually the "standard of care". [Controversy arose over the latter aspect later and an empirical study documented the fact that one of the two treatment arms of the trial was very rarely used in neonatal intensive care units (5)]. Magnus and Caplan wrote: "With regard to SUPPORT, the OHRP is asking that research be described as riskier than it really is and is suggesting that the parents were duped into enrolling their frail infants in dangerous research. Not only is that not true, but it also poses substantial risk to the conduct of valuable comparative effectiveness research." It is worth noting that Magnus is on the faculty of Stanford University, which was one of the SUPPORT trial sites.

The second article in the *NEJM* on this controversy was an editorial authored by Jeffrey M Drazen, the journal's Editor-in-Chief, and colleagues (6). The editorial began with a heart-rending account of the death of the premature baby of President John F Kennedy back in 1963. The authors then addressed the reader as if the reader had just given birth to a premature baby with lung disease, just like Kennedy's baby. The gist of the editorial, like that of Magnus and Caplan's article, was a strong defence of the importance of research. It ended with this statement: "We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress."

Two weeks later, two more pieces appeared in the *NEJM*. One was a long letter signed by 46 bioethicists and paediatricians (7), while the other was an article by three top officials at the NIH, including Francis S Collins, the NIH Director, and Alan E Guttmacher, the head of the NIH Institute of Child Health and Human Development, which sponsored the SUPPORT study (8). Like the first two articles, these two upheld the importance of studying extremely premature newborns, lamented the damage that the OHRP's action could do to future research, and defended the wording of the consent forms because the

Author: Department of Epidemiology and Population Health. **Albert Einstein College of Medicine**, 1300 Morris Park Avenue, Bronx, NY 10461, USA – Ruth Macklin (ruth.macklin@einstein.yu.edu), Professor of Bioethics.

To cite: Macklin R. Conflict of interest and bias in publication. *Indian J Med Ethics*. 2016 Oct-Dec;1(4)NS:219-22.

Published online on August 8, 2016.

© *Indian Journal of Medical Ethics* 2016

procedures in the research were all “standard of care” for these patients.

There is nothing wrong with the heads of agencies or organisations defending an activity they have conducted or sponsored, especially in the face of criticism. That is an acceptable exercise of freedom of speech and the right to publish, so long as the publication does not constitute slander or libel. Interestingly, it is evident that Collins had been in touch with Drazen, the editor of the *NEJM*, about this matter. In an e-mail message dated June 4 (obtained through the US Freedom of Information Act), sent to colleagues in the NIH and officials from the Department of Health and Human Services, Collins wrote: “This all seems to be coming together well. Thanks for everyone’s hard work. *NEJM* has confirmed that they will post the NIH essay at 5 PM on Wednesday.” The next day, the NIH authors’ article, “In Support of SUPPORT– A View from the NIH”, was published in the *NEJM* (8).

Remarkably, in the Col disclosure form required to be filled in by the authors, Doctors Hudson, Guttmacher and Collins answered “no” to all conflict of interest questions, including: “Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?” (The Col disclosure forms submitted by authors are made available by the *NEJM* on request.) In contrast, Benjamin Wilfond, the lead author of the letter signed by the bioethicists and paediatricians, reported receiving a grant from the NIH related to the SUPPORT study. Some of his co-authors also reported working at sites that participated in SUPPORT, and having relationships with the National Center for Advancing Translational Sciences and the NIH, among others (9).

After these articles were published in the *NEJM*, I and two colleagues, to whom I had recently been introduced in connection with the SUPPORT controversy, took up the other side of the issue. Lois Shepherd, Alice Dreger and I examined the OHRP’s determination letter to the researchers, the NIH-sponsored research protocol for the study, and all the consent forms used by the medical centres where the research was conducted. We found that those consent forms were uniformly flawed. They failed to disclose the foreseeable risks of the study that the parents of the premature infants should have been told about before deciding to enter their babies in the study. Working together, the three of us began to round up bioethicists and other scholars willing to sign a letter to the *NEJM*, countering the claims made by the 46 bioethicists in the latest salvo. In the end, our letter opposing the one by the first group of bioethicists was published in the *NEJM* and had 45 signatories (10).

The struggle to publish in the *NEJM*

However, getting our one-page letter published in the *NEJM* was no easy task. The first hurdle was what to call the piece. It seemed appropriate to seek publication in the same category as the one in which the letter by Benjamin Wilfond, the lead author, and the 45 others who had defended the SUPPORT

consent forms and criticised the OHRP for “overreaching” had appeared (7). That letter appeared in the journal under the heading “Correspondence”. We decided to submit a letter similar to the one written by Wilfond and colleagues. On June 13, 2013, I wrote the following letter of inquiry to the editor of the *NEJM*.

Dear Dr Drazen,

We have drafted a letter to the editor in response to the Commentary by Benjamin S. Wilfond, which was signed by a group of bioethicists and pediatricians and published online June 5, 2013. We note that instructions for letters to the editor say that “Letters in reference to a Journal article must not exceed 175 words (excluding references)... Letters not related to a Journal article must not exceed 400 words (excluding references).” Since our letter is related to a previously published letter to the editor, and not to a Journal article, we are uncertain whether our letter may exceed the 175-word limit. We note further that the Wilfond et al letter contained 528 words. Therefore, we respectfully request that our letter, with a word count equivalent to that of the published letter, be considered for publication.

The instructions also say that a letter can be signed by no more than three authors. In addition to Dr Wilfond, who signed the published letter, 45 other names appear at the end of the letter. We have obtained an equivalent number of signatures from prominent bioethicists, physicians, law professors, and scholars in allied fields. Although the undersigned are the three authors of our letter, the additional signatures represent individuals who endorse the contents of the letter. They have all declared no conflict of interest.

We would be grateful for a response to this query so that we may submit our letter within the three-week period for responses.

Later the same day, the editor replied:

Dear Professor Macklin,

We consider the Wilfond letter to be a publication; our policy concerning a 175 word limit for letters applies.

Best,

jmd

After consulting Dreger and Shepherd, I wrote back to Dr Drazen, thanking him and saying, “We will submit our article as a publication.” His reply to my letter was:

Dear Professor Macklin,

Just to be sure I was clear. Your letter to the editor will be about the Wilfond letter and limited to 175 words.

We look forward to your submission.

Best,

Jmd

This was not acceptable. Now what to do? We consulted again. Lois Shepherd wrote: "Their letter starts 'To the editor' and is published under 'Correspondence'. So, it seems we don't care what they call it, we just want them to publish it." Alice Dreger added: "I think Lois is right –tell him we'd like to know how theirs was categorised and we'll take that category."

The next day, the three of us signed and sent the following letter to Dr Drazen:

Dear Dr Drazen,

We have considered your reply to our query about publication. We are rather troubled by your response to our request to publish our view (and that of the many other bioethicists, physicians and other scholars who have agreed to join us as signatories) with equal space given to the initial Wilfond letter. You mentioned that the Wilfond letter signed and published in the NEJM was not, in fact, a letter. Because it was published under the heading 'Correspondence', was addressed 'To the Editor', and contains an equivalent word count and number of signatories, we do not see how it differs materially from our letter, other than that ours represents a differing opinion.

We would like to give you another chance to accept our letter. If we do not publish it with NEJM, we will certainly publish it elsewhere. Your denial of the request for equal space can only be seen as a suppression of viewpoint in the light of the following: that your journal published the original SUPPORT study results, an editorial defending the informed consent documents, the Wilfond letter, and a commentary by NIH officials defending the study's consent process, all without significant publication of contrary viewpoints.

We hope you will reconsider your initial decision regarding publication of our letter.

The editor replied the same day, saying:

Dear Dr Macklin,

We consider the Wilfond piece an article. Our policies are firm on this matter.

Best,

Jmd

After this response, we went back and forth trying to decide what our next step should be. We agreed that the best strategy would be to simply ask outright under what category the Wilfond article was published and request that our piece be published in the same category. There was a catch, however. As already noted, a letter to the editor must not exceed 175 words and may refer to articles published in the *NEJM*. However, an article (or letter) in the 400-word category may not have references to articles previously published in the journal. This latter restriction meant that we could not refer

to the Wilfond article – at least directly – in our piece. After considerable strategising, we decided to let the matter rest over the weekend and on Monday morning (June 17), I sent the following e-mail message to Dr Drazen.

Dear Dr Drazen,

We've become aware there may be a misunderstanding in our communications. We propose to submit a general letter ("article") agreeing with the OHRP's determination that the SUPPORT consent documents were flawed. It will not reference a prior publication by the Journal. It will be under 400 words. The only remaining question about submission, then, would be whether the Journal will include the 40+ signatures of a number of prominent bioethicists, physicians and law professors who agree with the contents of the article (letter). We assume that will not be a problem, since this was permitted for the Wilfond article. Please advise as to this last point, as we would like to move forward with submission soon.

Thank you.

In his reply, which arrived the same day, the editor said:

Dear Professor Macklin,

Your proposal is acceptable.

On June 20, we received an e-mail accepting our piece, worded as follows: "I am pleased to inform you that your Letter to the Editor entitled, 'The OHRP and SUPPORT: another view', has been accepted for online-only publication in edited form at *NEJM.org*."

Thinking this was the end of the process, we made sure that everyone who signed the letter submitted conflict of interest forms and consent to publish. I received a PDF file of the article in the form in which it was to be published. To my surprise, in addition to the references we provided, none of which mentioned the articles previously published in the *NEJM* on SUPPORT, there were now references to the editorial by Drazen and colleagues (6), the article by Magnus and Caplan (4), the letter by Wilfond and colleagues (7), and the one by Francis Collins and his two senior colleagues from the NIH (8) – all of which had been published previously in the journal. This clearly violated the journal's own policy. At this late stage, I was dealing with the copyeditor by telephone, clearing up some details. When I pointed out that those citations had not been there in the manuscript we had submitted and that the journal's rule precluded including such references, the copy editor replied that it was one of the top editors who had insisted on putting in those citations. I said we wanted to ensure that the editors knew that we had not made those references, and she said, "It came from the very top." I replied to the copy editor by e-mail as follows: "My co-authors and I are quite disappointed about the addition of the four citations and the associated sentence. I know you said the decision was made by the top editors, but my co-authors believe it changes the content of what we wrote originally. We played

by the rules, but it appears that the rules have changed.” The copy editor’s reply was: “I forwarded your message to the editor who had requested the addition. We have now deleted ‘recently discussed in the *Journal*’ and have deleted references 1 to 4 (leaving, now, only the former reference 5, which is now reference 1).” As it turned out, the editors still could not resist referring in some manner to the previously published articles in the *NEJM*. Using the prerogative of the editor of a journal, they added an “Editor’s note” that referenced all four of the articles.

Non-financial Col

This saga clearly illustrates how powerful figures can influence publications in highly reputed scientific journals. Top figures at the NIH – the Director, Collins, and the Deputy Director, Hudson – and the head of the institute that sponsored the SUPPORT study, Guttmacher, had a strong interest in defending the study. All Collins had to do was to get in touch with the editor of the *NEJM* and prompt publication would be virtually guaranteed. It must be recalled that these three authors answered “no” to all of the conflict of interest questions on the Col form. For Drazen, the Editor-in-Chief, the journal’s reputation was at stake. The *NEJM* had published the results of the SUPPORT clinical trial (2). If the trial was determined to be unethical in some way, even if only in terms of inadequate informed consent documents, it would reflect adversely on the journal. According to international standards, the publication of unethical research is unacceptable. Drazen had also defended the consent forms in the SUPPORT study in his editorial, thereby putting his own views on the line.

What has been described above raises the question of a reputed journal’s ability to bias its readers by the sheer number of publications on one side of a controversial issue. Two articles in support of SUPPORT were opinion pieces, published in the journal’s “Perspectives” section. A third was the editorial written by the Editor-in-Chief. The fourth was the “Correspondence” authored by Wilfond and colleagues, which was supported by many prominent bioethicists. The only published piece on the other side of the controversy was the one by Macklin and colleagues, and that letter was published online only; it did not appear in the printed version of the *NEJM*. The top editors ended up referencing the four published articles that defended SUPPORT and criticised the OHRP, thereby finding a way around the rule that prohibited our correspondence from referencing articles published in the

journal. Although this sort of potential bias does not constitute a direct conflict of interest, it may very well fall into another ethically suspect category: publication bias.

Note

¹ The paragraphs describing my communications with the *NEJM* are excerpted and slightly adapted from my chapter, “Working with Public Citizen”, to appear in Baylis F, Dreger A (eds), *Bioethics in Action* (Cambridge University Press, forthcoming).

References

1. Wilson M. *The New England Journal of Medicine*: commercial conflict of interest and revisiting the Vioxx scandal [Internet]. *Indian J Med Ethics*. Published online on June 15, 2016 [cited 2016 Jul 8]. Available from <http://ijme.in/index.php/ijme/article/view/2407/4974>
2. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Lupton AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sánchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O’Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959–69. doi: 10.1056/NEJMoa0911781.
3. OHRP Determination Letter to UAB, March 7, 2013 [cited 2016 Jul 8]. Available from: http://www.hhs.gov/ohrp/sites/default/files/ohrp/detrm_letters/YR13/mar13a.pdf
4. Magnus D, Caplan AL. Risk, consent, and SUPPORT. *N Engl J Med*. 2013;368(20):1864–5. doi: 10.1056/NEJMp1305086.
5. Cortés-Puch I, Wesley RA, Carome MA, Danner RL, Wolfe SM, Natanson C. Usual care and informed consent in clinical trials of oxygen management in extremely premature infants. *PLoS One*. 2016;11(5):e0155005. doi: 10.1371/journal.pone.0155005. eCollection 2016 [cited 2016 July 8]. Available from: <http://dx.doi.org/10.1371/journal.pone.0155005>.
6. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. *N Engl J Med*. 2013;368(20):1929–31. doi: 10.1056/NEJMe1304996.
7. Wilfond BS, Magnus D, Antommaria AH, Appelbaum P, Aschner J, Barrington KJ, Beauchamp T, Boss RD, Burke W, Caplan AL, Capron AM, Cho M, Clayton EW, Cole FS, Darlow BA, Diekema D, Faden RR, Feudtner C, Fins JJ, Fost NC, Frader J, Hester DM, Janvier A, Joffe S, Kahn J, Kass NE, Kodish E, Lantos JD, McCullough L, McKinney R Jr, Meadow W, O’Rourke PP, Powderly KE, Pursley DM, Ross LF, Sayeed S, Sharp RR, Sugarman J, Tarnow-Mordi WO, Taylor H, Tomlinson T, Truog RD, Unguru YT, Weise KL, Woodrum D, Youngner S. The OHRP and SUPPORT. *N Engl J Med*. 2013;368(25):e36. doi: 10.1056/NEJMc1307008.
8. Hudson KL, Guttmacher AE, Collins FS. In support of SUPPORT—a view from the NIH. *N Engl J Med*. 2013;368(25):2349–51. doi: 10.1056/NEJMp1306986.
9. Neale T. NIH backs consent process in preemie SUPPORT trial. *Med Page Today*, June 6, 2013 [cited 2016 July 8]. Available from: <http://www.medpagetoday.com/publichealthpolicy/clinicaltrials/39682>
10. Macklin R, Shepherd L, Dreger A, Asch A, Baylis F, Brody H, Churchill LR, Coleman CH, Cowan E, Dolgin J, Downie J, Dresser R, Elliott C, Epright MC, Feder EK, Glantz LH, Grodin MA, Hoffman W, Hoffmaster B, Hunter D, Iltis AS, Kahn JD, King NM, Kraft R, Kukla R, Leavitt L, Lederer SE, Lemmens T, Lindemann H, Marshall MF, Merz JF, Miller FH, Mohrmann ME, Morreim H, Nass M, Nelson JL, Noble JH Jr, Reis E, Reverby SM, Silvers A, Sousa AC, Spece RG Jr, Strong C, Swazey JP, Turner L. The OHRP and SUPPORT: another view. *N Engl J Med*. 2013;369(2):e3. doi: 10.1056/NEJMc1308015.