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Industry-Sponsored Ghostwriting in Clinical Trial Reporting: A Case Study

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INDUSTRY-SPONSORED GHOSTWRITING IN CLINICAL TRIAL REPORTING: A CASE STUDY

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In this case study from litigation, we show how ghostwriting of clinical trial results can contribute to the manipulation of data to favor the study medication. Study 329 for paroxetine pediatric use was negative for efficacy and positive for harm. Yet the ghostwritten publication from this study concluded that paroxetine provided evidence of efficacy and safety and continues to be influential. Despite the role of named authors in revisions of the manuscript, the sponsor company remained in control of the message.

Keywords: *Central Medical Affairs Team, clinical trials, conflict of interest, final clinical report, GlaxoSmithKline, industry-sponsored ghostwriting, key opinion leader, off-label prescriptions, paroxetine (Paxil, Seroxat), Paxil Team, primary efficacy variables, secondary efficacy variables, Scientific Therapeutics Information, serious adverse events, SmithKline Beecham*

Industry-sponsored ghostwriting continues to be an item of debate in the medical and bioethics journals. The most recent concerns have focused on pharmaceutical ghost-marketing or ghost-management (Moffatt and Elliott, 2007). With increasing concerns about selective reporting of data in the clinical trials, it has been alleged that the real purpose of ghostwriting is to conceal conflicts of interest and facilitate misrepresentation of research in the literature (Ngai et al, 2005). In what follows, we expose the details from a newly-discovered case from litigation that is consistent with these allegations.

Documents from *Beverly Smith vs. SmithKline Beecham* reveal that the medical communications agency, Scientific Therapeutics

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Information (STI), was commissioned by SmithKline Beecham (SKB) in 1998 to create a draft article for submission to a medical journal from a report of its Study 329 on antidepressants for adolescent depression. Study 329 was published in the *Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP)* in 2001 under the name of Martin Keller and twenty-one other authors. We reviewed: approximately 10,000 pages of SKB (now GlaxoSmithKline, GSK) internal documents; publications and poster presentations arising out of Study 329; and depositions of GSK employees, the medical writer and named authors of the published article. The relevant documents were released into the public domain after Baum Hedlund challenged GSK's claim to confidentiality by the Trade Secrets Act. They are available at www.healthyskepticism.org/documents/PaxilStudy329.

Origin of the Study 329 Manuscript

The initiative for Study 329 came from Martin Keller (considered a “key opinion leader” by SKB) who led a group of psychiatrists and psychologists, including seven of the first eight authors of the published article (SKB, 1992). Keller and his colleagues successfully pitched the study to SKB. SKB staff then implemented the project in consultation with some or all of Keller's co-investigators. As recruiting problems demanded more sites, so were more “principal investigators” added to the team.

Study 329 was one of three clinical trials (along with studies 377 and 701) conducted by SKB aimed at gaining a new indication with the FDA for paroxetine (Paxil, Seroxat) use in pediatric depression. Paroxetine failed to demonstrate superiority over placebo on primary outcome measures in all three studies, and SKB abandoned the effort to gain regulatory approval. But there was concern that failure to demonstrate efficacy in the pediatric population would undermine the profile of paroxetine more generally. SKB's Central Medical Affairs Team (CMAT) set the following as a target in a 1998 position article: “To effectively manage the dissemination of these data in order to minimize any potential negative commercial impact.” As part of this strategy, “Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed” (SKB, 1998a).

After SKB staff had written up a “Final Clinical Report” of the acute phase of Study 329 (SKB, 1998b), they contracted STI to prepare the article for publication in a psychiatry journal. STI advertises itself on its website as “a full-service medical publishing group specializing in the development of scientific literature and other resource media with direct application to clinical therapeutics” with a staff that “is intimately familiar with the drug development process and the best possible use of print material to create and sustain awareness for a given concept, drug, or group of drugs, using a fair, balanced approach that maximizes credibility” (STI, 2006). In their pitch to win this contract, STI offered, for \$17,250 to “provide all necessary resources to complete this manuscript including writing, editing, library research and retrieval, copy editing, proof reading, word processing, art work, and the needed co-ordination with author(s), sponsor, and journal.” The contract specified that STI would produce “up to six drafts of the manuscripts with the sixth being the journal submission draft.” The first draft was to be reviewed only by the sponsor, the second by the primary author and sponsor, the third by the primary author, sponsor, and two others (review by more authors would increase the cost to SKB). Not until the fourth draft was there a plan to send out the article to all authors and only “for comment” (SKB, 1998c). As things played out in this case, “authors” provided revisions after draft one and continued doing so up to draft eleven.

Sally Laden, the associate editorial director from STI, prepared the drafts of the manuscript. In sworn depositions, Ryan, the second author, claimed that Keller prepared the first draft (Ryan, 2006, p. 77). Keller said that his ideas generated the first draft, with Laden’s contribution being “typing the words follow[ing] discussion as to what words will be typed” (Keller, 2006, p. 248). Laden, however, contradicts Keller’s testimony in that she asserted that she alone created the first draft and had no conversations with Keller until after that draft was written (Laden, 2007, p. 111). Strober, the third author, confirmed this point (Strober, 2007, p. 88). Moreover, Laden states that she was involved in interpreting the data from the Final Study Report (Laden, 2007, p. 115). SKB’s McCafferty (Director, Neuroscience Therapeutic Team, Clinical Research and Development) confirms this in his deposition: “Laden [. . .] took the clinical study

report and prepared the first draft” (McCafferty, 2006, p. 313). In fact, the title page of draft one of the manuscript reads: “Manuscript prepared by: Sally K. Laden, M.S., Scientific Therapeutics Information, Inc., Springfield, New Jersey. Manuscript prepared for: James P. McCafferty, SmithKline Beecham Pharmaceuticals, Collegetown, Pennsylvania” (SKB, 1998d). This was removed from the submission copies. In the fine print of the published article, it reads: “Editorial assistance was provided by Sally K. Laden, M.S.” When asked why Laden was only acknowledged for “editorial assistance,” McCafferty said: “She never attended any of the teleconferences during the [. . .] conduct of the study” (McCafferty, 2006, p. 463). Laden, however, claims that she did (Laden, 2007, p. 291). Moreover, her deposition and other documents show that her role was not restricted to producing drafts. She coordinated the publication process including: responses to the peer-reviews in both submissions, first to *JAMA* and then *JAACAP* (SKB, 1999a; 2000a,b); the response to the *JAACAP* editor’s comments in producing subsequent revisions in collaboration with “authors” (SKB, 2001a); proof reading galleys (SKB, 2001e); and providing submission packages to Keller that included draft cover letters for the editors of the journals (SKB, 2001b).

Ownership of the Data and Control of the Message

Despite claims that the “authors” determined the content of the article (Strober, 2007, p. 265), we believe SKB and STI maintained careful control over the entire drafting and publication process. Laden needed McCafferty’s signature on an STI release form that was sent to him in November 2001 to authorize a draft of the article “be released to Martin Keller, M.D. to submit for publication” to *JAACAP* (SKB, 2000c). Typically, pharmaceutical companies release manuscripts after internal “medico-legal review” since the data from the clinical trials they sponsor are their “intellectual property.” Keller and his co-authors were not precluded from making their own statements and interpretations about the study (SKB, 1999b), but any publication resulting from the clinical trial data required SKB approval. The investigator agreement between SKB and the 329 investigators specifically identifies the research data as the property of the company and prohibits any publication without the company’s approval (Ryan, 1993).

Laden testified that the source of her first draft of the manuscript was “the clinical study report from Study 329” (Laden, 2007, p. 100). However, since the clinical study report was over fourteen hundred pages (SKB, 1998b), SKB provided her with a synopsis of the report as a basis for her first draft (Laden, 2007, pp. 107–108). The clinical study report, while generous in its conclusions about paroxetine, did not systematically create the misleading impression of efficacy and safety characteristic of Laden’s first draft. The first draft contained a significant distortion of outcome whereby the list of primary outcomes was expanded from two to eight, four of which separated paroxetine from placebo. This change gave plausibility to the claim that “paroxetine is effective.” When questioned about the problem of how her first draft failed to distinguish between primary and secondary efficacy variables when the study report had clearly defined them, Laden replied, “this may have been my interpretation of the data” (Laden, 2007, pp. 114–115). However, when asked “Do you know why you said there were eight primary efficacy variables when the study report said there [were] only two?” she claimed not to know (Laden, 2007, pp. 128–129). Aside from working with the synopsis of the study report, she testified that she relied upon SKB’s McCafferty for accurate information, but denied that SKB had asked her “to put lipstick on that pig” (Laden, 2007, pp. 171, 175). What is not clear from the available documents is who was responsible for the manipulation of the data. This is the risk of using a ghostwriter to prepare a manuscript. As former *JAMA* editor, Drummond Rennie, has noted in connection with another Laden project gone awry: “It is very bad scientific and ethical practice to have a nonauthor write the first draft” (Holden, 2006; see also Armstrong, 2006).

Changes to the First Draft

Our analysis of the progression of drafts shows that there are few substantial differences between the final published article and the first draft prepared by Laden (Jureidini, 2007). Large portions of the introduction and discussion were re-written, but these changes add little to the substance of the article, and most other changes are little more than copy editing. Throughout the many drafts of this article, the conclusion persists that paroxetine

is safe and effective for adolescent depression despite the fact that it failed on both primary and most secondary outcome measures. The only critical difference between Laden's first draft and the final article comes from changes in the manner in which efficacy and safety results are reported. SKB statistician Oakes objected that the claim that there were eight primary outcomes was misleading the reader, but this only led to substituting the label "Depression Related" for "Primary" (SKB, 1999c). Only when the manuscript underwent peer review with *JAACAP* were the primary outcomes re-introduced. Even then, the primary outcomes were reported in a way that subtly and deceptively made one of the primary outcomes appear positive, allowing the claim for efficacy to be retained (see Jureidini et al, 2008). It is also unclear who was responsible for this later distortion.

Similarly, the dramatic downplaying of Serious Adverse Events (SAEs) in the first draft could not be sustained, and SKB's McCafferty complained about this inaccuracy (SKB, 1999d). This resulted in his preparing an additional paragraph to acknowledge these effects. Just prior to publication, McCafferty's contribution was changed in a way that made paroxetine look less dangerous. This late change appears to have come from within SKB rather than from any of the named authors, but again its source is unclear.

Contributions of Named Authors

The lack of change from the first draft leaves little space for the named authors to have made a meaningful contribution. Keller and a few of his colleagues were responsible for the initial idea for the study and had made at least some contribution to the planning and implementation of the trial, but none of them are amongst the named authors of SKB's write-up of Study 329; nor as we have seen did they contribute to its transformation into the first draft. A letter from Keller to Laden regarding his response to an early draft states: "You did a superb job with this. Thank you very much. It is excellent. Enclosed are rather minor changes from me, Neal, and Mike [. . .]" (SKB, 1999e). Other correspondence shows that the first three named authors, Keller, Ryan, and Strober, made numerous minor contributions to revisions of the manuscript, as did McCafferty and Oakes from SKB. Klein,

Kutcher, Wagner, Geller, Carlson, Clarke, and Birmaher made minimal contributions at one point to draft three, but several SKB employees who were not acknowledged made more substantial contributions. It is plausible that many of the 22 authors made no significant intellectual contribution to the design of the study or the resultant article, but merely administered treatments and collected data (or oversaw those processes). According to the documents, Sweeney gained authorship status at the suggestion of Klein on the grounds that he “coordinated, recruited” at two sites (SKB, 1999f); Clarke advocated for Winters to become an author because she had given “much of [her] time to medication treatment sessions in the hope of some acknowledgment” (SKB, 1999g). The role of most authors is perhaps best captured by STI’s offer to distribute “the final draft to the listed authors as a courtesy” (SKB, 1998c). Our examination of the drafts of the article and their margin notes suggests that at least ten of the clinicians whose names appeared on the article made no recognizable contribution to the content of the article.

Marketing, PR, and Promotion

Consistent with its advertised mission, it is clear that marketing considerations drove STI’s involvement in the 329 project from the start. In addition to preparation of the manuscript, the firm set up Advisory Board meetings, Continuing Medical Education symposia at national meetings, and worked actively with SKB’s “Paxil Marketing Team” (Laden, 2007, p. 39). Laden claimed that STI’s purpose was “to further scientific discourse” and that they were not engaged in promotion (Laden, 2007, pp. 28–32). Correspondence, however, shows that STI also worked with the New York public relations firm, Cohn & Wolfe, in preparing the “launch” in anticipation of an FDA approval of the pediatric indication for Paxil. When, for example, the manuscript for Study 329 was accepted for publication, Laden wrote to the Paxil Marketing Team: “At long last, the Journal of the American Academy of Child and Adolescent Psychiatry has accepted the manuscript [. . .]. This news comes in time for Karen Wagner to present the data as ‘in press’ at next week’s Forum 2001 meeting [. . .]” (SKB, 2001c). Another sequence of email communications between Laden, SKB’s marketing, and Cohn & Wolfe shows that SKB

requested that Laden provide the PR firm with copies of the proofs of the 329 publication. Matt Battin of SKB also suggested that Cohn & Wolfe be given a “heads up” on the timing of the publication for media opportunities (SKB, 2001d). Holly White of Cohn & Wolfe wrote: “Originally we had planned to do extensive media relations surrounding this study until we actually viewed the results. Essentially the study did not really show Paxil was effective in treating adolescent depression, which is not something we want to publicize. However, we should prepare Q&A and key messages in case reporters do cover this study. The proofs would definitely come in handy” (SKB, 2001e).

A letter from Laden shows that the reprints were distributed to SKB’s Zach Hawkins for the Neuroscience sales force (SKB, 2001f). Hawkins attached the reprints to a memo to sales representatives selling Paxil. The memo states: “This ‘cutting-edge,’ landmark study is the first to compare efficacy of an SSRI and a TCA with placebo in the treatment of major depression in adolescents. *Paxil* demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression” (SKB, 2001g). Battin had noted that because Paxil prescribing to children was off-label, SKB’s marketing would not be able to use the article in promotion; however, reprints might be sent out as part of a response to medical queries on the use of Paxil in children (SKB, 2001d). Accordingly, the Keller et al. reprints were also attached to medical query letters sent to physicians who inquired about Paxil after visits from their SKB sales force. While the letters state Paxil is not FDA-approved for use in children, and that GSK may not offer any recommendations regarding the use of Paxil in these patients, it discusses the Keller et al. article as having demonstrated that Paxil was superior to placebo by several assessment methods. Page 12 of this medical query letter reads: “Please add reprint Keller et al. PX2808 Thank you” (SKB, 2002).

Role of the Journal

The publication of misleading articles constitutes a failure of the editorial process (see Jureidini and Tonkin, 2003). Who should take responsibility for the journal publishing an incompetent report? *JAACAP* had no way of knowing the full extent of manipulation in the reporting of Study 329, but in our view the draft

submitted to them contained sufficient information to show that its conclusions were misleading. At least one of the reviewers noted inconsistencies between the data and the strong claims for efficacy, but these concerns were not acted on (SKB, 2000d). When questioned about publishing Study 329 in a 2007 BBC Panorama Programme, "The Secrets of the Drug Trials," the editor of *JAACAP*, Mina Dulcan, replied that she had no regrets about publishing the study, and that it served its purpose of generating all sorts of useful discussion on the issue of pediatric SSRI use (BBC, 2007). When McHenry inquired via email about whether *JAACAP* was aware of having been infiltrated by SKB's marketing efforts, the editors replied: "The types of papers that we publish are never written by PR firms, and since our Instructions for Authors cover the issue of authorship criteria anyway, there is no need for a specific prohibition." And, "[u]nless there is a specific accusation of research fraud, it is not the role of scientific journals to police authorship" (Available on request). Yet the International Committee of Medical Journal Editors (ICMJE) statement on which *JAACAP* bases its own authorship policy clearly places responsibility with the journal: "Editors should ask authors to disclose whether they had writing assistance and to identify the entity that paid for this assistance" (ICMJE, 2001).

Impact of the Keller et al. Article

Study 329 continues to be cited as positive, right up to 2008. We found 226 published articles that cited it and retrieved 207 of the 211 that were in English (see Jureidini and Jureidini, 2008, for a full list of the articles and their citations to Study 329). We examined all comments on the Keller et al. article in these 207 articles; 153 made reference to efficacy in Study 329. False claims about the efficacy of paroxetine for adolescent depression were reproduced in 68 of these 153 articles (44%), with the reader being at risk of concluding that Study 329 was positive in another 54 articles (35%).

The 68 articles that perpetuated the false claims did so by one or more of:

1. Explicitly designating Study 329 positive:
"paroxetine has one positive trial" (Boylan et al., 2007);

2. Claiming that Study 329 demonstrated the efficacy of paroxetine: “Recent trials for pediatric MDD have shown the effectiveness of paroxetine in adolescents” (Shoaf, 2004);
3. Falsely reporting statistical significance on a primary outcome in Study 329: “Significant efficacy on one of the two primary endpoints and three of the five secondary endpoints” (Moreno et al, 2007);
4. Including Study 329 in a group of positive trials indicating the efficacy of SSRIs: “Despite the controversy, several studies have demonstrated that SSRIs are more effective than placebo in treating depressed adolescents” (Steele and Doey, 2007).

Many articles are still reporting Study 329 as positive in 2006–2008; 12 of the 68 were published in these years.

Another 54 of the 153 were more ambiguous in their reporting of the Keller et al. article, but would lead the majority of readers to form a more positive view of the outcome for paroxetine in Study 329 than is justified by the data. Articles in this category include ones in which the reader would be likely to conclude that the study was positive, even though there was no explicit claim. For example, Study 329 was reported to have “provided evidence suggestive of efficacy;” “found the effectiveness of paroxetine on several secondary outcome measures;” or to have been amongst studies that “support positive effects of SSRIs” in depressed adolescents. Other articles included in this category report Study 329 as positive, but with contradictory statements in the same article. For example, Cohen et al. (2004) claimed that Study 329 “showed that the SSRI paroxetine was significantly superior to placebo in treating adolescent depression” but also reported that “no statistical difference was found between paroxetine and placebo on the primary outcome measure.” Only 31 articles (20% of those 153 that commented on efficacy) accurately reported the efficacy outcomes of Study 329. Only 12 of these 31 were critical of Keller et al.’s reporting of Study 329.

Conclusion

It is by now standard practice for clinical trial investigators to engage a medical writer in the production of a manuscript. In

principle, this should be no more problematic than engaging a statistician to analyze the data and evaluate the results of efficacy and safety. For the published version of Study 329, however, there is a peculiar role reversal in the meanings of “author” and “editor.” The majority of the 22 named authors provided no more than minor text editing of the manuscript. Of greater concern is the manner in which Study 329 reveals the pervasive influence of pharmaceutical marketing objectives and other corporate considerations on the preparation and publication of a “scientific” manuscript, so that any benefit from the use of a “medical writer” is outweighed by the significant health risks of allowing a manipulation of outcomes. The critical misleading claims in the Keller et al. article were that “Paroxetine is generally well-tolerated and effective for major depression in adolescents.” This was created in the translation of the Final Report into the first draft, even though it was not supported by the data. The fact that the article was ghostwritten meant that individuals unknown, presumably from within SKB, could intervene without the named authors being encouraged to step in to correct any manipulation of data.

Without litigation, the conflicts of interest and the extensive role of STI in the promotion of Paxil in pediatric use would have remained concealed. While financial support from SKB is identified in the published article, there is no mention of the fact that SKB engaged STI, paid for the manuscript, and then released it to Keller et al. We uncovered: meetings with investigators in which marketing purpose was clearly identified; contact between the medical writer and SKB marketing; changes between the Final Study Report and the first draft of the manuscript that could not be accounted for; and a deceptive presentation of outcomes. All of these activities go well beyond the simple use of a medical writer in the production of the manuscript. In our view, it is unacceptable that Laden’s true role as the primary writer of the drafts and her relation to STI and to SKB were concealed. This type of ghostwriting (perhaps more precisely “ghost-marketing”) is not adequately addressed by authorship criteria identified by the medical journal editor societies. As Moffatt and Elliott argue: “Ghostwritten articles are useful as marketing tools precisely because they appear to come from a disinterested source. In fact, the entire program of ghostwriting is designed to give articles

written by people with a direct financial interest in promoting a product the appearance of disinterestedness” (Moffatt and Elliott, 2007).

The deceptive report of Study 329 was published in a major medical journal and was subsequently used to promote Paxil pediatric use off-label. While off-label promotion is illegal for pharmaceutical companies, a legal loophole allows their key opinion leaders to deliver the message for them. This was accomplished, as the CMAT position article makes clear, by publishing parts of the positive data and by the many presentations given around the world by Keller, Ryan, Wagner, and others.

This publication is still cited in the medical literature as a positive result, when in fact the study was negative for efficacy and positive for harm.

The medical profession and the public rely on the accuracy of research reported in the peer-reviewed medical literature. While bias and manipulation of data can be created without ghostwriters, our case study demonstrates the additional risk. If no named author takes full responsibility for the development and content of the article, unattributed distortions can flourish. Medical editor organizations such as ICMJE have formulated conflict of interest policies to address appropriate credit and accountability for medical journals, but these policies have not been uniformly adopted or followed. Disguised authorship and industry control over the production of manuscripts undermines the scientific integrity of the literature and has serious consequences for both prescribing physicians and patients.

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