

FEATURE

HIDDEN DATA

Putting GlaxoSmithKline to the test over paroxetine

Blockbuster antidepressant paroxetine is no stranger to headlines. The drug is now back centre stage as requests for clinical data from one of its trials are testing manufacturer GlaxoSmithKline's commitment to full transparency, **Peter Doshi** reports

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When the *Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP)* published study 329 in 2001,¹ its editors could have had no idea that the paper would spark a controversy, not only about the use of the antidepressant paroxetine in children but also about secrecy in clinical trials. It is a controversy that rages to this day and that goes to the heart of recent campaigns to gain access to drug companies' trial data.

By most accounts, GlaxoSmithKline is leading the pack in its efforts to liberate access to its clinical trial data. It was the first major pharmaceutical company to sign up to the international AllTrials petition calling for all trials to be registered with the full methods and the results reported.² Whereas companies like AbbVie and InterMune have lodged lawsuits aiming to block access to clinical trial data,³ GSK has forged ahead with a new website enabling third party access to deidentified participant level data "because it is the right thing to do, both scientifically and for society."⁴ GSK's website states that five requests have been approved up to 20 September. None have been rejected. One is under review.

But one group's request for data is testing the limits of GSK's commitment to full transparency. Jon Jureidini, clinical professor of psychiatry at the University of Adelaide, is leading a team to reanalyse and republish the results of GSK's study 329—a randomised, double blind, placebo controlled trial of paroxetine for the treatment of depression in adolescents. For over a decade, Jureidini has been critical of how the study was reported in *JAACAP* in 2001. In 2003, Jureidini and Tonkin wrote to *JAACAP*: "We believe that the Keller et al study shows evidence of distorted and unbalanced reporting that seems to have evaded the scrutiny of your editorial process."⁵ They noted that "on neither of [the study's two primary outcome] measures did paroxetine differ significantly from placebo"—yet the Keller et al paper concluded that "paroxetine is generally well tolerated and effective for major depression in adolescents."¹

Jureidini was subsequently contracted to provide expert advice as part of a class action lawsuit against GSK in 2004. Through this legal action, some internal company documents were released into the public domain, and Jureidini and colleagues reported that study 329 had an additional six secondary outcomes specified in the protocol.⁶ Paroxetine was not more effective than placebo on any of these outcomes either.

Troubled history

Paroxetine was a blockbuster antidepressant, known by its trade names Paxil in the United States and Seroxat in the United Kingdom, and was widely prescribed "off label" for use in children and adolescents. The drug came under heightened attention in the early 2000s, after a decade of rising antidepressant use among youths,⁷ over concerns about a link between paroxetine and suicidality in children.

In 2003, the UK Committee on Safety of Medicines recommended that paroxetine not be used in children and adolescents for the treatment of depressive illness because of concerns about an increased risk of self harm and potentially suicidal behaviour. And in 2004, the US Food and Drug placed a boxed warning, its most serious type of warning, on all antidepressants, stating that they increase the risk of suicidal thinking and suicidal behaviour in these age groups.⁸

In 2012, GSK agreed to pay \$3bn (£2bn; €2.4bn) in a fraud settlement with the United States government. In a statement connected with the lawsuit, the Department of Justice declared that "the centerpiece of GSK's efforts to market Paxil for childhood depression was the GSK funded Study 329," about which the published *JAACAP* "article distorted the study results and gave the false impression that the study's findings were primarily positive, when they were, in fact, primarily negative."⁹ Jureidini and colleagues have led a long campaign to compel the journal to correct or retract the article, which was authored by both academics and GSK employees.¹⁰ Earlier this year,

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Correspondence relating to data requests for study 329 (see <http://www.bmj.com/content/347/bmj.f6754?tab=related#webextra>)

Jureidini presented GSK's chief executive, Andrew Witty, with a final plea to help correct the scientific record. "Your corporation has so far failed to take responsibility for a published report that has harmed young patients who were prescribed paroxetine on the basis of this misleading article. As the CEO of GSK, you have the opportunity to correct the scientific record. I respectfully urge you to do so," Jureidini wrote (see data supplement on bmj.com).

But GSK defended the integrity of the 2001 publication. "GSK does not agree that the article is false, fraudulent or misleading," John E Kraus, head of medical governance, wrote to Jureidini.

Jureidini has responded by assembling a team to reanalyse and republish study 329. In July they publicly declared their intention to produce a new journal report of study 329, written in accordance with the *BMJ* endorsed restoring invisible and abandoned trials (RIAT) initiative, which calls for third party authors to publish or republish unpublished and misreported clinical trials.¹¹ The team's starting place is a trove of over 6000 pages from a previously internal clinical study report written by SmithKline Beecham in 1998 that was forced into the public domain as a condition of a consent order GlaxoSmithKline agreed to in the settlement of a 2004 lawsuit with the New York State Attorney General.¹² (SmithKline Beecham and Glaxo Wellcome merged in 2000 forming GSK.) The pages include a report of the trial, the study protocol, statistical analysis plan, blank case report forms, and numerous data tables, which Jureidini's team will use for its analysis.

But GSK's public posting of its internal report on study 329 is incomplete, lacking an unknown number of pages containing original case report forms from Appendix H. Jureidini and colleagues have therefore asked GSK for access to the deidentified case report forms and the corresponding deidentified electronic participant level data, "so that we can restore the publication of trial 329 in a fair, complete and publicly transparent way."

"With regard to the electronic database," James Shannon, GSK's chief medical officer, wrote to Jureidini on 11 October, "I would ask that you do indeed submit an analysis plan via the website and sign a data sharing agreement." Jureidini had initially rejected submitting an analysis plan arguing that "such a plan is irrelevant when restoring a publication where our primary focus is the original analysis plan drawn up and implemented by your own statisticians." Nonetheless, Jureidini complied, and submitted an analysis plan—mostly a direct copy and paste from the protocol contained in the company's 1998 clinical study report—placing GSK's independent review panel in the unusual position of refereeing the appropriateness of the manufacturer's own analysis plan.

As for the case report forms, GSK initially rejected Jureidini's request, explaining, "We do not publicly disclose Case Report Forms (CRFs) and we do not provide them to other researchers. Complete CRFs are available to regulatory authorities for audit and for them to assure the integrity of the data sets and CSRs." However, last week the company suggested a phone call with Jureidini, "to explore with you how we can help with this."

Commitment to transparency

GSK's wavering responses contrast with the many upbeat public proclamations by its executives about the company's commitment to transparency. "Increasing transparency about our research is a critical area we've been pursuing at GlaxoSmithKline for almost a decade," Shannon wrote in a September editorial in the *Huffington Post*.¹³ "We've also launched a new website allowing scientists to request access to

the very detailed, anonymised patient-level data sitting behind the results of our clinical trials. This will mean independent researchers, with a fresh perspective, can conduct further research which could advance medical science and improve patient care."

Transparency is "at the core of how we work," Shannon explains. "People have asked me, 'what if a new side effect comes to light for one of your medicines? Or what if a scientist discovers that you made a mistake in your research?' My answer back is 'why wouldn't we want that to happen? Isn't it better that we know? There is always the potential for us to find a better way to do things.'"¹³

Last month, Witty took it one step further in a television interview with the US *Fox News*. "We're not simply going to publish data on trials still to come, but we're going to go back, and we're going to publish all the data for all the trials that have been done since the company was formed."¹⁴

Witty's phrase "all the data" sounds straightforward, but the company's 11 October response to Jureidini implied that "all the data" would not include case report forms from study 329—or, it would seem, any other study. Nor, it seems, is GSK going to "publish" any of the deidentified patient level data on its new website, if "publish" means to make something public and freely accessible.

Caveats

A more careful reading of GSK's stance is that it believes in what it calls a "closed-access system,"¹⁴ in which only approved researchers are permitted to query (but not download) data in preapproved ways. To gain access to GSK's participant level data, requestors must first submit and have their analysis plan approved by an "independent review panel" and sign a data sharing agreement. A sample agreement posted on GSK's website indicates that researchers are expected to run only preapproved analyses: "GSK and Researcher agree that GSK will provide the Researcher with access to patient level data from the GSK-sponsored clinical studies listed in Exhibit A for the sole purpose of analysis according to Researcher's approved research plan (the "Analysis") attached as Exhibit B and for no other purpose."¹⁵

GSK suggests that such a system is necessary to protect the privacy of research participants. It is not enough to simply remove personally identifiable information from the participant level dataset. "It may be possible to combine deidentified data with other information to identify individuals. To minimize any such risk, our approach will be to provide access to anonymous patient-level data on a password-protected website that has controls in place to prevent data from being downloaded or transferred."¹⁴

This concern is underscored in an editorial, published in the *Lancet*, coauthored by Patrick Vallance, GSK president of pharmaceuticals research and development, and Iain Chalmers, one of the founders of the Cochrane Collaboration and now coordinator of the James Lind Initiative.¹⁶ They write that "the protection of privacy is vital in IPD [individual participant data] analyses," but point out that the process of deidentification can be carried out so thoroughly as to render the scientific value of the data useless. Deidentify the data insufficiently, and trial participants may be re-identified, violating their privacy. Vallance and Chalmers posit that a "controlled system" of restricted access offers a possible solution to the reidentification problem.¹⁶

It is therefore unsurprising that GSK initially refused Jureidini and colleagues access to the case report forms on grounds of protecting the privacy of trial participants. “The content of Appendix H is not posted on our website because it contains information (such as names) that can be used to readily identify the patients concerned.”

But Jureidini and company are challenging GSK. “As a group we do not accept your argument about patient confidentiality . . . The blank case report forms (CRFs) in the Clinical Study Reports (CSRs) make it clear that the only patient identifiers in any CRF not contained in the CSRs were initials. Redacting initials is the work of minutes.” Jureidini adds that reidentification of patients “is not our intention. We think anyone in our group attempting to do this would do significant damage to the data access cause. We are happy to sign agreements that there will be no effort to identify anyone and that the de-identified CRFs will not be shared with anyone outside the 329 group, with access limited to two to three designated individuals within our group.”

Jureidini also questioned GSK’s commitment to its patients: “noting the concern you expressed in your letter for the wellbeing of patients who participate in clinical trials, can we enquire as to GSK’s follow-up of patients who were in Study 329? For instance, were those who became suicidal or violent on Paxil subsequently advised of the possible role of the drug in their dangerous and distressing feelings/actions and counselled that it may be better for them to avoid SSRIs [selective serotonin reuptake inhibitors] in future?”

Perhaps most concerning, Jureidini explained to GSK that his team has concerns about how some of the adverse event data were reported in the 1998 clinical study report and therefore needs the additional requested data.

Recently, GSK has softened its position and seems willing to discuss the possibility of rethinking its previous position. “I recognize, however, that you believe you need to see the CRFs and I would like to explore with you how we can help with this,” Shannon wrote. “Please could we arrange a telephone call to discuss this more fully and agree a way forward?”

Jureidini has declined the telephone call, and requested keeping the interactions by email. “I would be grateful if you could indicate what in your opinion is the safest way of getting all CRFs from study to me, suitably de-identified, but otherwise complete with narrative elements intact.”

“Responsible” data sharing

Jureidini’s quest to access the complete participant level data for study 329 highlights some of the anxieties surrounding disclosure of clinical trial data.

Looming large are concerns about misuse of data. “We believe that there are public health risks if the proposed analyses are not scientifically robust and give rise to erroneous concerns about safety or false hopes of a potential benefit for patients,” GSK has declared.⁴ This fear of misleading analyses is embodied in an adjective gaining popularity among discussions over data sharing: “responsible.” The Institute of Medicine has named its ongoing consensus study on the topic “Strategies for Responsible Sharing of Clinical Trial Data” and a recent essay in the *New England Journal of Medicine* entitled Preparing for Responsible Sharing of Clinical Trial Data, warns that “poor-quality analyses can harm rather than advance public health, it must ensure responsible use of data.”¹⁷

Irony of study 329

There is a certain irony in the story of study 329 and its 2001 publication in *JAACAP*. In a letter to Jureidini, GSK explained that the *JAACAP* publication “was subjected to peer review on three occasions” and “accurately reflects the honestly-held views of the clinical investigator authors.” But a more pertinent question is whether the published article accurately reflects the trial.

In their most recent letter to GSK, Jureidini and his colleagues reiterate their need for the study 329 case report forms and their intention to analyse study 329 “following the original analytic plan.” As such, Jureidini’s team’s efforts to independently analyse and publish the results of study 329 can be viewed as perhaps the most “responsible” of all analyses—and one that it seems may yet overturn the *JAACAP* publication that GSK continues to defend.

Competing interests: I have read and understood the BMJ policy on declaration of interests and declare the following interests: I am the first author of the RIAT declaration, which was co-authored by David Healy, who is part of Jureidini’s team. I am providing the Jureidini team with unpaid advice on the RIAT process. I am also a member of a Cochrane review of neuraminidase inhibitors that is based in part on clinical study reports provided by GSK for zanamivir. I initiated an inquiry in 2012 that resulted in an additional 38 781 pages from the clinical study reports of study 329 and eight other studies to be publicly posted on GSK’s website.

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- Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 2001;40:762-72.
- Kmietowicz Z. GSK backs campaign for disclosure of trial data. *BMJ* 2013;346:f819.
- Hawkes N. Industry and drug regulators disagree on which data should remain confidential. *BMJ* 2013;347:f5390.
- Nisen P, Rockhold F. Access to patient-level data from GlaxoSmithKline clinical trials. *N Engl J Med* 2013;369:475-8.
- Jureidini J, Tonkin A. Paroxetine in major depression. *J Am Acad Child Adolesc Psychiatry* 2003;42:514, author reply 514-5.
- Jureidini JN, McHenry LB, Mansfield PR. Clinical trials and drug promotion: selective reporting of study 329. *Int J Risk Saf Med* 2008;20:73-81.
- Zito JM, Safer DJ, dosReis S, Gardner JF, Soeken K, Boles M, et al. Rising prevalence of antidepressants among US youths. *Pediatrics* 2002;109:721-7.
- Olsson M, Marcus SC, Druss BG. Effects of food and drug administration warnings on antidepressant use in a national sample. *Arch Gen Psychiatry* 2008;65:94-101.
- United States ex rel. Greg Thorpe, et al v. GlaxoSmithKline plc, and GlaxoSmithKline llc. United States’ complaint. C.A. No. 11-10398-RWZ. 2011 www.justice.gov/opa/documents/gsk/us-complaint.pdf.
- Newman M. The rules of retraction. *BMJ* 2010;341:c6985.
- Doshi P, Dickersin K, Healy D, Vedula SS, Jefferson T. Restoring invisible and abandoned trials: a call for people to publish the findings. *BMJ* 2013;346:f2865.
- Civil Action No 04-V-5304 MGC. People of the State of New York against GlaxoSmithKline, plc and SmithKline Beecham Corporation. Consent order & judgment. 2004. www.ag.ny.gov/sites/default/files/press-releases/archived/aug26a_04_attach1.pdf.
- Shannon J. Unlocking access to clinical trial data— what are we afraid of? *Huffington Post* 2013 Sep 9. www.huffingtonpost.co.uk/james-shannon/clinical-trial-data_b_3859734.html.
- GlaxoSmithKline CEO on increasing transparency of clinical trials. *Fox Business* 2013 Oct 10, http://video.foxbusiness.com/v/2735629915001/glaxosmithkline-ceo-on-increasing-transparency-of-clinical-trials/.
- GlaxoSmithKline. Data sharing agreement. https://clinicalstudydata.gsk.com/Documents/DATA-SHARING-AGREEMENT.pdf.
- Vallance P, Chalmers I. Secure use of individual patient data from clinical trials. *Lancet* 2013;382:1073-4.
- Mello MM, Francer JK, Wilenzick M, Teden P, Bierer BE, Barnes M. Preparing for responsible sharing of clinical trial data. *N Engl J Med* 2013;369:1651-8.
- US Department of Justice. GlaxoSmithKline to plead guilty and pay \$3 billion to resolve fraud allegations and failure to report safety data. 2012. www.justice.gov/opa/pr/2012/July/12-civ-842.html.

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Story of study 329

- **1994-98:** SmithKline Beecham conducts study 329, a study of 275 adolescents with depression
- **24 November 1998:** Date of SmithKline Beecham's internal clinical study report for study 329, which was made public by the 2004 consent order
- **July 2001:** Keller et al publish study 329 in the *Journal of the American Academy of Child and Adolescent Psychiatry*¹
- **26 August 2004:** GSK signs consent order with the New York State Attorney General, agreeing to pay \$2.5m and publicly post clinical study reports for GSK sponsored trials of paroxetine in children and adolescents
- **2 July 2012:** US Department of Justice announced that GSK "agreed to plead guilty and to pay \$3 billion to resolve its criminal and civil liability arising from the company's unlawful promotion of certain prescription drugs, its failure to report certain safety data, and its civil liability for alleged false price reporting practices"¹⁸
- **26 April 2013:** Jureidini writes to GSK chief executive requesting his help in retracting the Keller et al *JAACAP* article
- **3 May 2013:** GSK responds that "GSK does not agree that the article is false, fraudulent or misleading"
- **13 June 2013:** *BMJ* publishes the restoring abandoned and invisible trials (RIAT) declaration¹¹
- **25 June 2013:** GSK expresses support for RIAT, stating that "by making the Clinical Study Reports available we are very happy for others to publish on the records if they wish to and if journals consider the work to be of scientific merit"
- **15 July 2013:** Jureidini publicly announces his team's intent to republish study 329 in accordance with the RIAT initiative
- **28 October 2013:** Jureidini and colleagues formally submit a request for deidentified electronic participant level data through GSK's website. The result of their request is pending review by GSK's independent review panel