

## Special Communication

# Litigation Seeking Access to Data From Ongoing Clinical Trials

## A Threat to Clinical Research

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Researchers conducting randomized clinical trials may find themselves subject to legal subpoenas for interim data. When a subpoena demands premature disclosure of unblinded data, there is potential for damage to the scientific integrity and reputation of the on-going trial. We describe herein general issues raised by subpoenas for trial data and the particular case of a 2012 subpoena served on investigators from Yale University who were successful in winning reprieve from Connecticut Superior Court.

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**F**unded by the National Institute of Neurological Disorders and Stroke (NINDS) and coordinated by Yale University, the Insulin Resistance Intervention after Stroke (IRIS) trial (clinicaltrials.gov Identifier: NCT00091949) is a randomized, double-blind, clinical study to test the effectiveness of pioglitazone (Actos; Takeda Pharmaceuticals) for secondary prevention of ischemic stroke. Pioglitazone is a thiazolidinedione; the medication is approved by the US Food and Drug Administration (FDA) as an adjunct to diet and exercise for improvement of glycemic control in adults with type 2 diabetes mellitus. After the IRIS trial began in 2004, 2 epidemiologic studies described a possible increased risk for bladder cancer among patients with diabetes who were using pioglitazone.<sup>1-3</sup> Product liability litigation followed.

In October 2012, the plaintiff in one of the liability lawsuits,<sup>4</sup> Sara J. Kincaid, served a subpoena,<sup>5</sup> or court-authorized request, on Yale University for IRIS documents, including unblinded adverse event reports of incident bladder cancer. Kincaid was not a participant in the IRIS trial. In response, Yale provided nearly 5000 pages of documents but not the unblinded reports. The IRIS trial was ongoing, and premature disclosure of unblinded data would have violated the study protocol and FDA research guidelines,<sup>6</sup> which permit unblinding only to protect the safety of a participant. Kincaid's legal team never questioned the safety of the IRIS trial, and all parties to the litigation understood that an independent data and safety monitoring board (DSMB) was monitoring the safety of participants.

In February 2013, Yale University filed an objection to the request for unblinded data in Connecticut Superior Court. In September 2013, Judge Robert E. Young of Connecticut Superior Court<sup>5</sup> denied Kincaid's request. The judge concluded that the likely damage to the study that would have been caused by the disclosure of the information was greater than the possible benefit to the plaintiff. Although Yale's litigation was successful, the case is a troubling demonstration of the potential for plaintiffs' attorneys and other outside parties to disrupt clinical research. Moreover, the case raised important issues about research integrity, academic freedom, and the role of researchers in court.

### Harms of Disclosing Interim Data From a Clinical Trial

When unblinded interim data from a clinical trial are released in response to a subpoena, only the recipient typically stands to benefit. The challenge to a researcher who receives a subpoena, therefore, is to gauge if this benefit outweighs the potential harms to everyone else involved, including researchers, research participants, and the public. In the Yale case,<sup>5</sup> the plaintiff asserted that she was entitled to the unblinded IRIS adverse event data because it might help her establish a link between pioglitazone and bladder cancer. If data from IRIS were not definitive on their own, her attorneys argued, they might be supported by data from older studies<sup>7-9</sup> to achieve greater statistical power. Serving the subpoena was, in fact, a gamble for the plaintiff because the IRIS data could have helped or hurt her case, depending on the number of participants with bladder cancer in each treatment group. Only an imbalance toward cancer in the pioglitazone group could have helped her case, but a large or statistically significant imbalance between groups was unlikely because the DSMB was monitoring these data closely.

The disclosure of interim results of ongoing clinical trials in legal proceedings is problematic. First, public release of interim data deprives researchers of the opportunity to offer the initial interpretation of their findings. They cannot specify strengths, weaknesses, or meaning in the context of existing knowledge. Instead, the initial interpretation is provided by litigants who reach conclusions that are based on immature data and who may lack the scientific perspective required for a dispassionate appraisal of the evidence.<sup>10</sup> Second, public release effectively bypasses peer review, which is essential for the credibility of the research process and to ensure that data are appropriately vetted, analyzed, and interpreted before dissemination.<sup>11</sup> Third, because major medical journals may not consider for publication research that has already been publicized, public release may disqualify research from even undergoing peer review. Fourth, public release of immature data may al-

ter the behavior of research participants and investigators and interfere with the conduct of a clinical trial. Trial participants may stop using the study drug or stop adhering to the protocol in other ways because of unfounded inferences about the safety or efficacy of the medication. Investigators may alter their efforts to enroll new participants or change how they counsel those already enrolled. Finally, dissemination of unblinded findings could undermine the extensive review of data and emerging trends by the DSMB. Public interpretation of less comprehensive data by persons with insufficient experience or conflicts of interest could compromise a board's objectivity and pressure it to change a protocol or stop a study.

The disclosure of interim data could also be harmful if it resulted in the identification of research participants, their treatment assignments, or the release of other protected health information. Even with careful redaction, data selection and editing, trial data that are under intense legal scrutiny may inadvertently reveal clues to the identities of individuals. One potential consequence is surveillance bias (ie, differential detecting, reporting, or adjudicating outcome events between treatment groups). Another is breaches of confidentiality; such breaches are never acceptable and courts have been willing to quash subpoenas that involve this risk.<sup>12</sup>

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## Public Interests in the Confidentiality of Interim Clinical Trial Data

Data from clinical trials are arguably a public good, particularly when the government funds a trial. Why, then, should the data be kept from plaintiffs in court and from the public who might argue that secrecy (eg, maintaining the blind) is rarely in the public interest? There are several reasons. When a trial is ongoing, maintaining the blind of treatment assignment is at the heart of the scientific process. Keeping data confidential is justified by the public's considerable interest in clinical research that is conducted properly and science that may advance medical care. Thus, the NINDS deputy director wrote to the court in Connecticut to support Yale's objection to the *Kincaid* subpoena<sup>13</sup> and stated that breaking the blind "would violate the public interest in securing sound and unbiased data in publicly-funded scientific research."<sup>13</sup> A clinical trial that fails because of deviation and poor execution, he wrote, exposes study participants to avoidable risk and inconvenience.<sup>13</sup>

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## Related Court Cases

Although the Yale case<sup>5</sup> involved a subpoena, data from federally funded trials have also been sought through the Freedom of Information Act (FOIA). In 1980, however, the US Supreme Court sidestepped the issue of access to government data when it held that investigators for the University Group Diabetes Program, which was funded by the National Institutes of Health (NIH), were not required to turn over data under the FOIA because the records resided with the investigators and were not "agency records."<sup>14</sup>

Federal and state courts have usually upheld the interests of researchers in freedom of inquiry, including the testing of hypotheses according to the study protocol and publication of a first inter-

pretation of results. In *Dow Chemical Co vs Allen*, for example, Dow Chemical sought raw data from the University of Wisconsin regarding an ongoing animal toxic effects study.<sup>10,12</sup> The university was testing 2 doses of a chemical, which Dow Chemical distributed as an herbicide, to determine if the chemical should continue to be publicly available.<sup>12,15</sup> Dow sought the interim data after the Environmental Protection Agency attempted to stop production of the chemical, partly based on the emerging data from the Wisconsin study. A federal court recognized that the release of interim data could jeopardize the success of the study, burdening both the researchers and the taxpayers who funded the research. The court also noted the concern "which invariably accompanies governmentally authorized intrusions into the intellectual life of the university."<sup>10(p1278)</sup>

Starting in 2004, the Women's Health Initiative (WHI) investigators sought judicial relief from several subpoenas issued by Wyeth Pharmaceuticals.<sup>16</sup> After a 2002 report from the WHI investigators<sup>17</sup> showed an increased risk of breast cancer and vascular events among postmenopausal women assigned to combination treatment with medroxyprogesterone and estrogen (Prempro), Wyeth faced product liability litigation. The company argued that it needed the trial database and documents to prepare its legal defense. The investigators did not want to release trial information until they published additional reports. In addition, some women in the hormone trial were also enrolled in 2 ongoing WHI trials of dietary modification and calcium supplementation<sup>18</sup>; the investigators argued that information about the randomization assignments associated with the ongoing trials for coregistered participants should not be released until the research was completed (Garnet Anderson, WHI Clinical Coordinating Center, personal e-mail and telephone communication between May 5, 2014, and June 3, 2014). In a partial victory for the investigators, the US District Court in the Eastern District of Arkansas ruled that the investigators were not required to disclose the diet and calcium treatment assignments for women who were coregistered in the ongoing trials, but that they could not delay release of hormone treatment assignments and trial data collected for all patients enrolled in the previously published hormone therapy trials (with the exception of personal identifiers).<sup>19</sup>

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## Lessons From the Court Cases

The *Kincaid*,<sup>5</sup> *Dow Chemical*,<sup>10</sup> and *Prempro*<sup>16</sup> cases are examples of the general rule that courts may grant relief when subpoenas are overbroad, involve trade secrets or other confidential information, or when compliance with the subpoenas would create an undue burden.<sup>11,15,20</sup> Courts have recognized time, expense, lost academic opportunity, confidentiality, and infringement on academic freedom as reasons to side with investigators in considering whether to grant subpoenas that include requests for research data.<sup>12,15</sup> The court in the *Prempro* case,<sup>16</sup> however, declared a tight limit on the withholding of data; it essentially required the WHI investigators to release almost all data on the completed hormone trials after publication of the main results but before many secondary papers were published. Proponents of open science hold that greater availability of data encourages accurate reporting and improved surveillance of treatment safety, among other benefits.<sup>21</sup> Investigators, however, may hold diverse opinions on how soon data should be shared after the main results are published.

## The Ruling in *Kincaid vs Yale University*<sup>5</sup>

Although clinical research data are subject to subpoena,<sup>12</sup> to our knowledge, the subpoenas served on Yale<sup>5</sup> and the WHI investigators<sup>16</sup> are the only 2 subpoenas to involve ongoing NIH-funded clinical trials. The subpoena served on Yale is apparently the first to win a reprieve in a state court. In ruling in favor of Yale, the Connecticut Superior Court judge cited the risks of premature unblinding and the specific concerns of the NINDS before concluding that "the risk of jeopardizing the integrity of the study outweighs the potential benefit to the plaintiff."<sup>5(p8)</sup> His ruling was influenced by comments from Kincaid's lawyers suggesting that any protective order (ie, an order limiting how parties handle and disclose data) would

probably be difficult to follow and that dissemination of the unblinded data was likely. The federal court that ruled in the *Dow Chemical* case<sup>10</sup> expressed similar concerns.

## Conclusions

In conclusion, clinical investigators should consider each specific request for clinical data on its merits. However, they should vigorously contest requests that may undermine the interests of research participants, the public, or the broader academic and research enterprise. Despite Yale's success, subpoenas and related litigation that seek access to data from ongoing clinical trials will remain a threat to clinical research.

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### REFERENCES

- Lewis JD, Ferrara A, Peng T, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care*. 2011;34(4):916-922.
- Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia*. 2012;55(7):1953-1962.
- Takeda Pharmaceuticals America Inc. *Pioglitazone package insert*. 2011.
- Kincaid vs Eli Lilly et al*. 49D0312 06 CT 024661, Indiana Circuit Court of Marion County. 2013.
- Kincaid vs Yale University*. NNH CV-12 6035005, Connecticut Superior Court, Judicial District of New Haven. September 16, 2013.
- US Department of Health and Human Services; US Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER). Guidance for industry: E9 statistical principles for clinical trials. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf>. Accessed June 4, 2014.
- Dormandy JA, Charbonnel B, Eckland DJA, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366(9493):1279-1289.
- DeFronzo RA, Tripathy D, Schwenke DC, et al; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med*. 2011;364(12):1104-1115.
- Hanefeld M, Brunetti P, Scherthaner GH, Matthews DR, Charbonnel BH; QUARTET Study Group. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. *Diabetes Care*. 2004;27(1):141-147.
- Dow Chemical Co vs Allen*. 672 F2d 1262 (7th Cir). 1982.
- Wiggins EC, McKenna JA. Researchers' reactions to compelled disclosure of scientific information. *Law Contemp Probl*. 1996;59:67-94.
- Holder AR. The biomedical researcher and subpoenas: judicial protection of confidential medical data. *Am J Law Med*. 1986;12(3-4):405-421.
- Koroshetz WJ. Affidavit in the case of *Sara J. Kincaid vs Yale School of Medicine*. Superior Court, Judicial District of New Haven. Docket No. 12-6035005. 2013.
- Forsham vs Harris*. 445 US 169 (1980).
- Lopez DE. *The compelled disclosure of research data*. Presented at the Legal Issues Affecting Academic Medical Centers and Other Teaching Institutions conference; January 27, 2000; Arlington, VA.
- Prempro Products Liability Litigation*. MDL Docket No. 4:03-CV-1507-WRW, United States District Court for the Eastern District of Arkansas, Western Division. 2009.
- Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
- Jackson RD, LaCroix AZ, Gass M, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683.
- Confidentiality Order re WHI Study Data*. Prempro products liability litigation: MDL Docket No. 4:03-CV-1507-WRW, United States District Court for the Eastern District of Arkansas, Western Division. Filed February 1, 2005.
- Rapp RE. In re *Cusumano* and the undue burden of using the journalist privilege as a model for protecting researchers from discovery. *J Law Edu*. 2000;29:265-284.
- Mello MM, Franer JK, Wilenzick M, Teden P, Bierer BE, Barnes M. Preparing for responsible sharing of clinical trial data. *N Engl J Med*. 2013;369(17):1651-1658.