Grave fraudulence in medical device research: a narrative review of the PIN seeding study for the Pinnacle hip system

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ABSTRACT
In 2001, DePuy, a wholly-owned subsidiary of Johnson & Johnson (J&J/DePuy), initiated a seeding study called the “Multi-center, Prospective, Clinical Evaluation of Pinnacle Acetabular Implants in Total Hip Arthroplasty” (PIN Study). J&J/DePuy designed this study to develop new business opportunities during the launch of their Pinnacle Hip System (PHS) and generate survivorship data for marketing. This article, the first review of a seeding trial for a medical device, examines internal company documents relating to the PIN Study; the analysis herein focuses on the integrity of J&J/DePuy’s research practices in conception, implementation, and analysis. J&J/DePuy violated the study protocol and manipulated data; consented participants in violation of standards protecting human subjects; and did not secure Institutional Review Board approval for all study sites. J&J/DePuy used PIN Study results as the “fundamental selling point” for the PHS. Medical device seeding trials are distinct from previously-documented pharmaceutical seeding trials because companies can profit directly from device sales and because these studies may be the first clinical evaluation of the device (as was the case for the PIN Study). Seeding trials are malleable marketing projects, not rigorous scientific studies. Regulatory bodies, physicians, and others should be vigilant for persuasive marketing accounts disguised as science.

KEYWORDS
DePuy; FDA; Johnson & Johnson; Pinnacle hip system; medical ethics; research ethics; seeding trial; total hip arthroplasty

Introduction
Seeding trials are clinical trials designed by pharmaceutical and medical device companies to promote the use of their products. They are typically conducted as part of a marketing strategy for products that are either under review, cleared, or recently approved by the U.S. Food and Drug Administration (FDA) (Hill et al. 2008; Krumholz, Egilman, and Ross 2011; Sox and Rennie 2008). Hill et al. recognize that “[s]eeding trials are...
designed to appear as if they answer a scientific question but primarily fulfill marketing objectives” (Hill et al. 2008). Seeding trials typically demonstrate four traits as follows (Hill et al. 2008; Kessler et al. 1994):

(1) Marketing objectives influence study conception and design.
(2) Marketing objectives influence data collection and analyses.
(3) The study’s marketing goals are concealed from doctors, patients, and Institutional Review Boards (IRBs).
(4) The study sponsor implements unscientific research practices.

In a recent descriptive study, Barbour et al. also found that seeding trials tended to recruit patients from a large number of study sites so that the average number of patients per site was very small (Barbour et al. 2016). These researchers concluded that 21% of clinical trials published in high-impact general medicine journals were motivated by marketing purposes rather than scientific objectives (Barbour et al. 2016).

There are several systematic reviews of company documents regarding the use of seeding trials to promote pharmaceuticals (Hill et al. 2008; Krumholz, Egilman, and Ross 2011). This is the first study of a seeding trial that was designed to promote the sale of a medical device.

Confidential internal documents made public as a result of recent litigation against Johnson & Johnson and its subsidiary DePuy Synthes, offer an insight into a seeding trial conducted with the Pinnacle Hip System (PHS) implant. The PHS is a four-part modular artificial hip for total hip replacement surgeries, including metal, polyethylene, and ceramic liners (see Figure 1). The metal-on-metal (MoM) configuration of the PHS was the subject of recent litigation against J&J/DePuy alleging product liability and personal injury for this product.

This analysis focuses on J&J/DePuy’s clinical trial of the PHS: the “Multi-center, Prospective, Clinical Evaluation of Pinnacle Acetabular Implants in Total Hip Arthroplasty” (PIN Study). J&J/DePuy’s previously-confidential internal documents were systematically reviewed for characteristics of a seeding trial, and it was found to display all four features described above. Internal documents show that J&J/DePuy’s marketing department conceived of the PIN Study in 1999 and subsequently had an integral role in the design, funding, implementation, analysis, and dissemination of the findings. Document review and analysis also revealed the impact of marketing participation in the study conception, design, data collection and analysis, IRB, and informed consent. This systematic review contributes to the literature on seeding trials and litigation-generated data on corporate and regulatory behavior.
Methods

More than 50 million pages of documents produced by J&J/DePuy in response to discovery requests in the DePuy Orthopaedics, Inc. Pinnacle Metal-on-Metal Hip Implant Liability Litigation trials (MDL Docket No. 3:11-MD-2244-K) were archived in a database maintained by the plaintiffs’ attorneys. Most of the documents were created between 1990 and 2013, with recent production extending into 2016, and included as follows: internal email correspondences; internal reports; unpublished drafts of papers and presentations; protocols and project plans; and correspondence with external study investigator-surgeons, including consulting agreements, data reports, and individual case report forms. One researcher (EAF) completed a primary review of all PIN Study case report forms; all investigators participated in the systematic review of additional documents. The vast majority of the 6.5 million records available remain confidential under a protective order. Although all 6.5 million documents were accessible to authors, this analysis
is limited to the testimony and documents that became public during the litigation.  

Systematic search techniques in combination with a grounded theory approach were employed. Grounded theory is an inductive method which allows analytical categories to emerge from the data presented (Pope, Ziebland, and Mays 2000). With this approach, analysis begins at the time of first data collection and research frameworks must responsively evolve over the course of data collection to continually ground the analyses in the reality of the data. As described by Corbin and Strauss, “…the hypotheses are constantly revised during the course of the research until they hold true for the phenomena under study, as evidence in repeated interviews, observations, or documents” (Corbin and Strauss 1990). This approach has been used in analyses of corporate documents, which require the synthesis of a wide variety of information (Steinman et al. 2006). The entire database was initially searched for key terms identified by the authors, including: Pinnacle, metal-on-metal, PIN Study, seeding, metalosis/metallosis, ARMD (Adverse Reaction to Metal Debris), ALVAL (Aseptic Lymphocyte-dominated Vasculitis-Associated Lesion), and metal ions. After the emergent subset of documents was reviewed, key themes and concerns were identified including documents specifically pertaining to the PIN Study. Additional searches were conducted to explore the PIN Study, focusing on terms associated with interim analyses, survivorship, protocol, consent, IRB, and the names of certain investigators or employees. Additionally, over 20 depositions of individuals connected to J&J/DePuy or the PIN Study and all trial transcripts of this case were reviewed. All researchers maintained close communication over the course of data collection and analysis. In accordance with grounded research theory, ongoing, open discussions kept researchers informed of the data collection and emerging analyses of other researchers; this allowed for the synthesis of findings from multiple sources and perspectives. Disagreements in analysis were resolved through open discussion until a consensus was achieved.

Although IRB approval and informed consent were needed for the PIN Study clinical trial as performed by J&J/DePuy, these were deemed unnecessary for this article because the analysis relies on a secondary review of public, de-identified, existing data on PIN Study patients. The full collection of PIN Study Case Report Forms was made public under a judge’s order in October 2016 with the following redactions: patient name, surgeon name, surgery date, medical institution, date of consent, and age at time of surgery (Kinkeade 2016).

1Although the vast majority of documents reviewed for this study remain confidential, an author’s expert report (DSE) in this case has become public. This article cites the author’s expert report in instances where the source documents remain confidential.
Results

Key features of medical device regulation

The FDA Center for Devices and Radiological Health (CDRH) oversees medical device regulation in the United States. New artificial hip implants must undergo the FDA process for either 510(k) clearance or Pre-Market Approval based on device classification (FDA 2015).

In 2000, J&J/DePuy brought the PHS to market under the less-stringent, expedited 510(k) process. The 510(k) process allows for FDA clearance of some medical devices without pre-market clinical testing. According to the FDA, “A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent” (Ardaugh, Graves, and Redberg 2013; FDA 2015).

Since J&J/DePuy did not perform any pre-market clinical testing of the PHS, study subjects enrolled in the PIN Study were among the first to receive the device.

Background on the PIN Study

J&J/DePuy listed the PIN Study on clinicaltrials.gov as “Multi-center, Prospective, Clinical Evaluation of Pinnacle Acetabular Implants in Total Hip Arthroplasty” (J&J/DePuy 2014). The company first listed the trial on March 23, 2006; the primary outcome measure was described as survivorship at five years, and the secondary outcome measures included the “Harris Hip Score,” Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Short Form-36 (SF-36), each at pre-operative, six month, and one, two, three, four, and five years. The study investigators enrolled 1,593 patients between July 2000 and June 2007, with patient follow-up extending to December 2012 (Exhibit PLT-03517 0000; J&J/DePuy 2014). The study protocol proscribed any interim report and called for five-year follow-up data. Thus had J&J/DePuy followed the protocol, the study would not have been available until 2012. Six publications have relied on PIN Study data from 2007 to present (Barrett, Kindsfater, and Lesko 2012; Dowd et al. 2008; Kindsfater 2014; Kindsfater et al. 2007; Kindsfater and Lesko 2017; Kindsfater et al. 2012).

Footnote: In many cases, these “predicate” devices also have not been assessed for safety and efficacy or may even have demonstrated poor clinical outcomes. The metal-on-metal configuration of the PHS, for example, relied on a chain of predicate devices leading back to three hip implants (the McKee-Farrar, the Ring, and the Sivash metal-on-metal implants), all of which had been previously removed from the market due to poor performance. The 510(k) process does not evaluate safety and effectiveness of new devices; instead, the 510(k) regulatory pathway evaluates the substantial equivalence of the new device to one previously sold in the United States (a “predicate” device).
The unblinded and uncontrolled PIN Study was poorly designed and implemented, (Deposition Exhibit Forster-02 2004; Deposition Exhibit Kindsfater-25 2001). Although the protocol proscribed any interim analysis, J&J/DePuy presented interim data in a poster presentation at the American Academy of Orthopaedic Surgeons (AAOS) Conference in February 2007 (Figure 2). The company made the following untrue claims related to the PIN Study (Deposition Exhibit Forster-24 2006; Kindsfater et al. 2007; Plouhar 2016f):

- The study was prospective.
- The study enrolled consecutive patients.
- The study involved 1,183 patients.
- The average follow-up was twenty-four months.
- The study primary outcome measure was cup survival.
- The five year acetabular cup survival was 99.9 by Kaplan-Meier (KM) analysis.
- The study was IRB approved (which presumably entailed informed patient consent).

J&J/DePuy subsequently utilized the 99.9% survivorship at five years—which the Worldwide Vice President of Clinical Research admitted did “not accurately reflect the data that was at the [surgeon investigator] sites”—in marketing materials to claim that their hip implant had a nearly perfect success rate (Plouhar 2016f).

Review of the Pinnacle documents revealed that the study was conceived, developed, funded, and ultimately terminated prematurely by the company’s marketing department. Since the study objectives were unscientific in nature,

Figure 2. Primary contents of the PIN Study poster presented at the 2007 AAOS conference. The false statements are boxed in red.
the trial design and implementation was subject to unscientific research practices. This review revealed three such practices: protocol violations, data manipulation, and ethics violations.

**The PIN Study as a marketing tool**

In 2005, the United States Department of Justice (DOJ) began an investigation of J&J/DePuy’s use of kickbacks to surgeon consultants to market artificial hip and knee reconstruction products to surgeons (Feder 2008). Some of these surgeon consultants included clinical research investigators contracted by J&J/DePuy to participate in clinical studies. The DOJ-appointed monitor noted, “Because investigators are usually paid for each case form submitted, the more DePuy products they use, the more case report forms they can submit, and thus the more compensation they can collect” (Exhibit PLT-00049 2008). After the initiation of the DOJ investigation in 2005, J&J/DePuy developed an alternative marketing strategy based on the publication of interim PIN Study results.

In 2007, J&J/DePuy accepted responsibility for its illegal conduct and paid the government $84.7 million dollars in exchange for a deferred prosecution agreement (USDOJ 2007). The terms of the Deferred Prosecution Agreement and Corporate Integrity Agreement signed by J&J/DePuy in 2007 called for commitment to “exemplary corporate citizenship” and updated policies and procedures to ensure compliance with the Anti-Kickback Statute (Exhibit PLT-03416 0000; Exhibit PLT-03821 2007). These agreements also required adherence to the Advanced Medical Technology Association (AdvaMed 2009) Code of Ethics on Interactions with Health Care Professionals (Exhibit PLT-03416 0000; Exhibit PLT-03821 2007). Under this AdvaMed code, companies “may not interfere with a Health Care Professional’s independent clinical decision-making or provide coverage, reimbursement and health economics support as an unlawful inducement” (AdvaMed 2009). AdvaMed provides additional guidance on avoiding unlawful inducements in a research context, as follows (AdvaMed 2009):

> A Company may provide research and educational grants and charitable donations. However, a Company may not provide such grants or donations as an unlawful inducement. Therefore, a Company should: (a) adopt objective criteria for providing such grants and donations that do not take into account the volume or value of purchases made by, or anticipated from, the recipient …

Although J&J/DePuy’s mismanagement of the PIN Study seemingly violated these requirements (see below) and the DPA monitor recognized the potential for kickback schemes in clinical research, the monitor either did not uncover or chose not to cite the company for this misconduct during an oversight period in 2008 and 2009.
Beginning in the late 1990s, J&J/DePuy’s marketing department originated the PIN Study, influenced the study design, and selected the clinician investigators. In an internal project summary memorandum, J&J/DePuy listed “U. S. Hip Marketing” as the originator for the PIN Study (Exhibit PLT-02933 2008). J&J/DePuy marketing provided input on site/investigator selection, data collection, interim analyses, and PIN Study publications (Deposition Exhibit Egilman-02 2015; Exhibit PLT-03244 1999). J&J/DePuy assigned a “Clinical Research Associate,” who was a recent graduate with Bachelors of Science in Physiology and Life Sciences, to design and manage the PIN Study (Deposition Exhibit Kindsfater-25 2001; Exhibit PLT-00015 2000; LinkedIn 0000). The Clinical Research Associate recognized that the PIN Study was not a research priority, stating that “… every Pinnacle meeting that I catch wind of never has clinical as part of the agenda …” (Deposition Exhibit Egilman-02 2015). She said that there was no point in J&J/DePuy spending more money to look at outcomes when the Pinnacle design surgeons were already following their own patients closely; she emphasized that marketing department needs had driven the study: “If Sales [sic] needs to have someone do outcomes, then sales can pay for it” (Deposition Exhibit Egilman-02 2015).

J&J/DePuy marketing used the PIN Study as a marketing tool and profit-making venture. Since the 510(k) process does not require premarket clinical safety testing, J&J/DePuy could profit directly from a seeding trial initiated immediately following FDA clearance (Exhibit PLT-00015 2000). During the study’s conception, J&J/DePuy wrote that the PIN Study would have a “New Business Focus” with a “Focus on key accounts” and an opportunity for “New Business Building” (Exhibit PLT-03244 1999; Exhibit PLT-03245 1999). Since the PHS was already cleared for use, the company estimated that the study would cost $345,000 in fees paid to physicians for “filling out annual reports,” but would generate an estimated $4.2 million in sales revenue (based on an estimate of about $4,200 per PHS implanted), more than a 1,000% profit margin (Exhibit PLT-00015 2000). J&J/DePuy decided to close PIN Study enrollment in 2007, despite falling 1,500 subjects short of target enrollment, in order to save money and focus on other business needs. J&J/DePuy wrote as their “Business Justification” for this decision that they “Need to focus on the newly launched, larger diameter heads; therefore, business will close enrollment of Pinnacle study and will continue to follow up subjects only” (Exhibit PLT-02933 2008).

J&J/DePuy’s Area Vice Presidents of the sales force chose and recruited surgeon investigators (Exhibit PLT-00015 2000; Barrett 2015b). These surgeons were incentivized to implant Pinnacle hips for the PIN Study: the terms of these agreements varied from surgeon to surgeon with payments ranging from $100 for enrolling a subject to $1,275 for subjects with complete ten-year follow-up (Deposition Exhibit Kindsfater-25 2001). However,
some arrangements allowed surgeons to profit much more substantially. For example, J&J/DePuy paid the investigator at site six $31,601.25 and paid his practice $602,362.50 for clinical research services from 2003 to 2012 (Deposition Exhibit Egilman-02 2015). The investigator at site two was also a “design surgeon” and received royalties from each PHS that other physicians implanted (Barrett 2015b). The investigators at site two and site six, who enrolled 454 and 277 patients, respectively, were also paid to assist in marketing the PHS through published papers and presentations (Barrett, Kindsfater, and Lesko 2012; Exhibit PLT-03517 0000; Kindsfater 2014; Kindsfater et al. 2007, 2012).

**Research practices in the PIN Study**

J&J’s Vice President of Clinical and Pre Clinical Research and Development, who oversaw the PIN Study, testified that the study violated almost all of J&J/DePuy’s guidelines for good clinical research practices, including following the study protocol, informing investigators and staff of their research obligations, ensuring IRB approval, reporting of adverse events in a timely fashion, preparing and maintaining accurate records, and meeting consent and IRB requirements (Exhibit PLT-03535 0000; Plouhar 2017). Flaws in protocol compliance, data collection, and record-keeping, and research ethics are described in what follows.

**Protocol violations**

All versions of the PIN Study protocols called for complete patient follow-up of at least five years and proscribed an interim analysis: “No interim analysis is planned in this study other than standard monitoring of adverse event rates” (Deposition Exhibit Forster-02 2004). However, J&J/DePuy published several interim analyses intended to support marketing of the PHS (Deposition Exhibit Egilman-02 2015). Surgeons were listed as authors of analyses of PIN Study data, including one paper in 2008, two papers in 2012, and poster presentations in 2007 and 2014 (Barrett, Kindsfater, and Lesko 2012; Dowd et al. 2008; Kindsfater 2014; Kindsfater et al. 2007, 2012). J&J/DePuy also included data from two of these interim publications in their presentation on MOM hip implants to the FDA in 2012 (Voorhorst 2012).

All versions of the protocol specified that subjects were to be enrolled prospectively; however, J&J/DePuy retrospectively enrolled patients at two sites (Plouhar 2016a). In June 2001, the J&J/DePuy Clinical Research Associate instructed the investigator at site two to “continue retrospectively collecting data on the cases that you have already done, and to begin prospectively enrolling patients” (Exhibit PLT-00633 2001). The site two investigator, a design surgeon for the Pinnacle cup, retrospectively enrolled seventy-four patients into the study after their date of surgery (Exhibit PLT-
00633 2001; Exhibit PLT-03245 1999; Barrett 2015a; Forster 2015b; J&J/DePuy “Move Ahead With Confidence—Choose your hip replacement from DePuy Orthopaedics” 2011b). Overall, 93 PIN subjects signed informed consent or medical release forms after their date of surgery (Deposition Exhibit Jewell-06 2006; Exhibit PLT-03517 0000). At site ten, J&J/DePuy retrospectively transferred 31 patients from another study (C-Stem) into the PIN Study without patient consent (see IRB approval and informed consent section) (Deposition Exhibit Forster-27 2003; Exhibit PLT-03517 0000; Forster 2015a).

All versions of the protocol stated that every patient who met the PIN Study’s “inclusion criteria” was to be enrolled, but at least two investigators did not enroll subjects consecutively. The investigator at site six performed an average of six hundred Pinnacle system implants a year (Plouhar 2016c). Had he enrolled patients consecutively, he would have enrolled 4,200 patients over the course of seven years (Plouhar 2016c). In fact, he did not enroll any patients from October 2003 through March 2006 and only enrolled 277 patients over the course of the study (Exhibit PLT-03517 0000; Plouhar 2016c). J&J/DePuy noted that the investigator at site ninety-eight “is doing the surgeries, but his staff just aren’t entering them in the study” (Deposition Exhibit Egilman-02 2015).

Additionally, approximately 25% (112/454) of patients at site two received a stem type that the study protocol proscribed (Deposition Exhibit Forster-02 2004). J&J/DePuy included 111 of these 112 patients with stem protocol violations on the 2007 PIN Poster (representing 9.4% out of the 1,183 patients cited) (Exhibit PLT-03517 0000).

J&J/DePuy also violated the PIN Study protocol’s IRB requirement, as discussed in the “IRB approval and informed consent” section below.

**Data manipulation**

The 2007 PIN Study poster stated that 1,183 patients were included in the analysis. The 1,183 count included two duplicate patients, one patient who did not have a Pinnacle hip and thirty-one patients whose data was copied from another study and added to the PIN Study (Deposition Exhibit Jewell-06 2006; Exhibit PLT-02933 2008; Exhibit PLT-03517 0000).

The average follow-up on June 1, 2006, the date J&J/DePuy submitted the abstract to AAOS, was 1.45 years (Deposition Exhibit Jewell-07 2006). However, J&J/DePuy reported in their abstract submission that the average follow-up was 24 months (Deposition Exhibit Forster-24 2006). In early May

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3The PIN Study protocol limited the investigators to a combination of only one line of cemented and one line of cementless implants (“for example: only S-ROM and Luster implants, not S-ROM, Luster, and Endurance”) (Deposition Exhibit Forster-02). The investigator at site two violated this requirement by implanting two types of cementless stems.
2006, a J&J/DePuy statistician created a PIN Study dataset wherein subjects were listed in order by the amount of potential follow-up years that could be added if those patients were seen (Deposition Exhibit Egilman-02 2015). He told the PIN Study clinical manager that those patients with the most “Add_Time” were patients to target for follow-up. He also offered to “…track this for you periodically on a weekly basis if need be, so you will know when we have reached or exceeded the target of mean = > 24 mo” (Deposition Exhibit Egilman-02 2015). The J&J/DePuy statistician calculated average follow-up twelve times between May 4 and October 18, 2006 in an attempt to achieve the desired two-year follow-up time (Deposition Exhibit Egilman-02 2015). J&J/DePuy’s aggressive targeting proved inadequate to meet the two-year average follow-up time. To misrepresent the average follow-up as greater than two years, J&J/DePuy excluded 147 enrolled patients who had never had a follow-up visit and re-calculated the follow-up time based on the remaining 1,036 patients (Deposition Exhibit Jewell-06 2006). The average follow-up for the 1,183 patients was actually 1.76 years as of October 2006 when J&J/DePuy performed the final average follow-up calculation (Deposition Exhibit Jewell-06 2006).

Additionally, J&J/DePuy hoped to report a five-year survivorship by Kaplan-Meier (KM) analysis. J&J/DePuy relied on an article by Dorey and Amstutz on KM survivorship analysis, which stated that a number greater than 20 patients must survive for the time period of the analysis to establish a valid KM statistic and that there must be minimum of ten failures (Dorey and Amstutz 1986). However, when J&J/DePuy initially submitted the poster to the AAOS in May 2006, only four patients had five years of follow-up. After targeted follow-up on patients who had longest potential “Add_Time” and continuously rerunning the analysis of the cohort by October 2006, 21 patients were purportedly followed for five years prior to the 2007 AAOS presentation (Deposition Exhibit Jewell-06 2006). However, none of the patients used to extend the survivorship curve to five years met study inclusion criteria, which included site IRB approval, a signed informed consent form, and prospective enrollment (Deposition Exhibit Forster-02 2004; Deposition Exhibit Kindsfater-25 2001). As discussed above, the investigator at site two operated on eighteen of these patients before J&J/DePuy initiated his site into the PIN Study, and he added them retrospectively after the study began (Deposition Exhibit Jewell-06 2006; Exhibit PLT-00633 2001; Barrett 2015a). J&J/DePuy added the other three patients from another study that was in progress at site ten (Deposition Exhibit Forster-27 2003; Deposition Exhibit Jewell-06 2006; Exhibit PLT-03517 0000). Neither site had IRB approval when these patients were enrolled (discussed in IRB approval and informed consent section).

J&J/DePuy’s study also did not meet Dorey and Amstutz’s second criteria to perform a KM survivorship analysis, which stated that “If
there have been very few failures (<10), there is very little that can be said statistically about the survivorship curve, because the statistics generated are highly suspect” (Dorey and Amstutz 1986). J&J/DePuy ignored Dorey and Amstutz admonition and, after excluding liner failures, calculated their KM five-year survivorship with a single cup failure (Kindsfater et al. 2007).

The PIN Study protocol version 2.3 (the version in use at the time of the poster submission) and the protocol described on ClinicalTrials.gov stated: “For the purposes of determining survival rate of the Pinnacle™ cup system, failure will be defined as the surgical removal of either the cup or the liner for any reason” [Emphasis added] (Deposition Exhibit Forster-02 2004; J&J/DePuy 2014). However, J&J/DePuy excluded liner revisions in the interim survivorship analysis after they unblinded the results (Deposition Exhibit Jewell-06 2006; Kindsfater et al. 2007). The PIN poster reported only one cup failure, but there were actually cup and liner failures (8 cups, 12 liners) prior to January 2, 2007, the date when J&J/DePuy last updated the results that they presented at AAOS (Exhibit PLT-02960 2013; Plouhar 2016b). After excluding the liner failures and failing to locate seven of the eight cup failures, J&J/DePuy reported that the five-year acetabular cup survival was 99.9% (by KM analysis) (Deposition Exhibit Jewell-06 2006; Kindsfater et al. 2007).

Furthermore, the same month J&J/DePuy submitted the AAOS abstract, they submitted another report on the PIN Study outcomes to the French regulatory authority (Deposition Exhibit Egilman-02 2015). J&J/DePuy reported eleven failures to the French regulatory authority (although at this time there had been sixteen failures) (Exhibit PLT-02960 2013). Based on the eleven failures, J&J/DePuy reported a survival estimate of 96.6% at four years, compared to the AAOS poster which claimed 99.9% survival at five years (Deposition Exhibit Egilman-02 2015).

IRB approval and informed consent
J&J/DePuy violated the PIN Study protocols’ IRB requirement, as follows (Deposition Exhibit Forster-02 2004; Deposition Exhibit Kindsfater-25 2001):

It is the primary investigator’s responsibility to submit a copy of the investigational plan and secure approval of the IRB of every institution under consideration for the study. Upon review, a copy of the letter from the IRB must be forwarded to DePuy to indicate whether or not approval has been granted to perform the study at each institution.

J&J/DePuy emphasized the importance of IRB approval and informed consent during a 2014 investigator training presentation for a different study on the PHS; a slide titled “Informed Consent Document (ICD)” included a
photograph of the Nuremberg trials with the following note (Exhibit PLT-00014 2014):

In 1947, twenty-six Nazi physicians were tried at Nuremberg, Germany for research atrocities performed on prisoners of war. This resulted in the Nuremberg code, the first internationally recognized code of research ethics, issued by the Nazi War Crimes Tribunal and adopted by the United Nations in 1948.

Despite the requirement for IRB approval, the PIN Study protocol had not been reviewed or approved by any IRB when enrollment began (Exhibit PLT-03482 2006).

In trial testimony, J&J/DePuy’s director and then vice president of clinical research originally claimed that the PIN Study did not require IRB approval because J&J/DePuy did not intend to submit the results to the FDA: “we believed that there was—at the time we started the study that there was not necessarily a requirement for IRB approval (Plouhar 2016d).” During another trial six months later, she changed her testimony, stating as follows (Plouhar 2016e):

You know—you know, when I started in the department I—the study had been started and—and it was—I—to be honest, I was appalled that we were conducting a study without IRB approval. And I think that—and when I started digging into this, there were other studies that were postmarket studies similar to Pinnacle that were being conducted without IRB approval . . . .

Although the first patient was enrolled on October 23, 2000, IRB approval was not granted for any site until 2004 and four sites never received IRB approval (Exhibit PLT-03482 2006; Exhibit PLT-03517 0000). Site six did not receive IRB approval until December 8, 2004, after enrolling 181 patients (Deposition Exhibit Jewell-06 2006; Exhibit PLT-03482 2006; Exhibit PLT-03517 0000). Site two received “retrospective approval” from Western IRB, also in December 2004 (Exhibit PLT-03482 2006). In total, J&J/DePuy enrolled 806 subjects from sites that had not yet secured IRB approval (Table 1) (Deposition Exhibit Forster-20 2013; Deposition Exhibit Forster-21 2013; Deposition Exhibit Forster-22 2013; Deposition Exhibit Forster-23 2013; Exhibit PLT-03482 2006; Exhibit PLT-03517 0000).

Additionally, at least three IRBs refused to approve the study (Exhibit DEMO-03385 2015; Exhibit PLT-00648 2005; Exhibit PLT-02957 2005). Comments from the Mayo Clinic IRB, which voted twelve to zero to disapprove the study at one potential site, were prescient (Exhibit DEMO-03385 2015):

The Board was primarily concerned that there was not a sound scientific basis for conducting the study and that the sponsor’s main aim might be to foster use of the implant in preference to other implants. This opinion is reinforced because it is not clearly stated in the protocol if other devices can be used and how the decision to use the study device is made (e.g. Is there any coercion to use the study device?)
and Dr. Duffy mentions that other devices have a good track record and can be used for > 10 years (raises another question of why the follow-up is only 5 years). Also it is not clearly stated in the protocol what is being analyzed . . . .

The IRB at a hospital in Florida denied retrospective approval at site seven in 2005 after three years of study enrollment (Exhibit PLT-00648 2005; Exhibit PLT-03517). They wrote (Exhibit PLT-00648 2005):

At the Institutional Review Committee meeting today, you stated the above-mentioned study has been conducted at your institution for three years. For three years this has been going on with no IRB approval. Because IRB approval has never been granted, this is a direct violation of Baptist Medical Center, IRC, and OHRP, (Office for Human Research Protection) policy. Please be advised you are to cease all activities associated with this study, until such time as the IRC can make an informed decision about whether or not this study should be approved. This includes accepting new subjects and collecting data on the subjects you have already “enrolled.”

The investigator at site seven told the IRB that he would no longer participate in the study and was “soured” by the process of dealing with the committee (Exhibit PLT-00646). He sent copies of the IRB letter along with his response to J&J/DePuy (Exhibit PLT-00646 2005). Despite the IRB’s directive to halt all study activities, the surgeon submitted new enrollment data on nineteen additional patients and continued to send follow-up data to J&J/DePuy.

| Site number | Date of Earliest IRB Approval | Time from Earliest Patient Implant Date to IRB Approval | Number of Patient Implants Before IRB Approval | Number of Total Patient Implants Enrolled in Study |
|-------------|--------------------------------|--------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| 1           | None                           | Never Approved                                        | 50                                            | 50                                               |
| 2           | 12/21/2004                      | ~2.5 years                                             | 398                                           | 454                                              |
| 3           | 1/6/2005                        | ~1.5 years                                             | 31                                            | 120                                              |
| 4           | 1/6/2005                        | ~1.5 years                                             | 15                                            | 40                                               |
| 5           | 12/21/2004                      | n/a                                                    | 0                                             | 30                                               |
| 6           | 12/8/2004                       | ~3.25 years                                            | 181                                           | 277                                              |
| 7           | Rejected 9/14/2005              | Never Approved                                        | 71                                            | 71                                               |
| 8           | 1/26/2005                       | n/a                                                    | 0                                             | 50                                               |
| 9           | 12/21/2004                      | n/a                                                    | 0                                             | 88                                               |
| 10          | None                            | Never Approved                                        | 32                                            | 32                                               |
| 11          | 3/17/2005                       | n/a                                                    | 0                                             | 68                                               |
| 12          | 4/6/2005                        | n/a                                                    | 0                                             | 49                                               |
| 13          | 6/22/2005                       | n/a                                                    | 0                                             | 111                                              |
| 14          | 7/12/2005                       | n/a                                                    | 0                                             | 59                                               |
| 17          | 6/1/2006                        | n/a                                                    | 0                                             | 16                                               |
| 98          | None                            | Never Approved                                        | 28                                            | 28                                               |
| 99          | Unknown                         | ?                                                      | ?                                             | 50                                               |
| TOTAL       |                                 |                                                        | 806                                           | 1,593                                            |
J&J/DePuy was aware of and participated in circumvention of the IRB decision (Deposition Exhibit Egilman-02 2015). Not all patients in the PIN Study provided informed consent, despite the fact that the protocol called for a “Signed Informed Patient Consent form” as an inclusion criterion (Deposition Exhibit Forster-02 2004; Deposition Exhibit Kindsfater-25 2001). J&J/DePuy did not use informed consent forms at any site until 2003, three years after the study began; prior to this, participants signed one-page medical release forms (Exhibit PLT-03517 0000). At site two, for example, 254 patients were enrolled using a medical release, rather than an IRB-approved informed consent form (Exhibit PLT-03517 0000; Forster 2015c). J&J/DePuy was aware that some medical release forms were post-dated by the investigator-surgeon at site two: in at least 15 cases, J&J/DePuy sent undated forms back to the investigator and received a post-dated version of the same form in return (Exhibit PLT-03517 0000). At site ten, J&J/DePuy photocopied the top of the PIN Study Case Report Forms onto 31 forms patients filled out for a different study (the “C-stem Study) (Deposition Exhibit Forster-27 2003). The patients did not sign medical release forms or informed patient consent forms for the PIN Study; instead, J&J/DePuy crossed out “C-stem” on the medical release form and wrote “PIN Study” (see Figure 3) (Deposition Exhibit Forster-27 2003; Exhibit PLT-03517 0000; Forster 2015a).

**PHS marketing based on PIN Study data**

On the eve of the AAOS poster abstract submission, J&J/DePuy also discussed “seeding” the market and developing white papers to “support the launch” (Deposition Exhibit Egilman-02 2015). J&J/DePuy’s head of Hip Marketing, originally proposed using the 99.9% survivorship figure in the actual poster title, but J&J/DePuy’s outside consultants advised against it, calling it akin to selling “snake oil” (Exhibit PLT-00858 2007). The head of Hip Marketing then complained: “so much for pushing the envelope. We plan to make a change [to

![Figure 3. Header for altered patient medical release from site ten (Exhibit PLT-03517).](image)
remove 99.9% from the title. But I ain’t backing off my marketing focus in general” (Exhibit PLT-00858 2007). The final AAOS poster was entitled “Midterm Survival of the Pinnacle Multi-Liner Acetabular Cup in a Prospective Multi-Center Study” (Kindsfater et al. 2007). However, J&J/DePuy frequently incorrectly cited the title as “99.9% Midterm Survival of the PINNACLE Multi-Liner Acetabular Cup in a Prospective Multi-Center Study” when they used the results in marketing pieces (Exhibit PLT-00026 2010; Exhibit PLT-00041 2008; Exhibit PLT-00046 2013; Exhibit PLT-00057 2008; Exhibit PLT-00116 2011; Exhibit PLT-00801 2009; J&J/DePuy 2011b). Dr. Kindsfater, the first author and presenter of the poster at AAOS, gave a presentation in 2014 that includes the PIN poster with the 99.9% in the title; this presentation is currently available online (Kindsfater 2014).

J&J/DePuy has used the 99.9% survivorship claim from the PIN Study as their “fundamental selling point” for the PHS since the study poster was published in 2007 (Exhibit PLT-03242 2009). For example, J&J/DePuy printed 112,500 copies of a brochure in 2011 that stated (J&J/DePuy “Move Ahead With Confidence—Choose your hip replacement from DePuy Orthopaedics” 2011b):

Solutions from DePuy orthopaedics

The PINNACLE Hip from DePuy Orthopaedics is a modular hip replacement system with a range of components that allows your surgeon to choose the combination that’s right for you. The PINNACLE Hip has been used for 10 years, with nearly one million implanted worldwide. Five years after surgery, 99.9% of PINNACLE Hips are still in place.

This brochure was still available online in 2016 (J&J/DePuy 2011b). Aside from touting the inaccurate and misleading 99.9% survivorship figure, the brochure’s language suggests that 99.9% of all Pinnacle hips were still functioning in 2011, omitting the fact that these numbers 1) were based on a KM estimate rather than complete five year follow-up, 2) represented cup survivorship, not survivorship of the entire hip construct, and 3) relied on just twenty-one subjects with five year follow-up who were enrolled despite protocol violations. J&J/DePuy used the 99.9% success claim in various other print and web advertising from 2008 to the present (DePuy-Synthes 2015; Exhibit PLT-00041 2008; Exhibit PLT-00046 2013; J&J/DePuy 2007, 2008e, 2008f, 2008g, 2008h, 2008i, 2008j, 2008k, 2008d, 2008l, 2008a, 2008b, 2008c; “ALTRX Altra-Linked Polyethylene Product Overview” 2011a; “Never Stop Moving Hip replacement solutions from DePuy Orthopaedics” 2011c, 2012, 2013, 2016; J&J/DePuy-Synthes 2014). They also included the 2007 PIN poster in the 2010 “Pinnacle POWERPLAY AID, INC. Selling Guide” distributed to J&J/DePuy sales representatives (Exhibit PLT-00026 2010). J&J/DePuy’s marketing department indicated that “[the 2007 poster] is the fundamental selling point for Pinnacle” (Exhibit PLT-03242 2009; Kindsfater et al. 2007).
Discussion

Litigation has become a rich source of information on pharmaceutical company malfeasance. In a review of drug risks that were revealed through discovery in tort litigation, Kesselheim and Avorn concluded as follows (Kesselheim and Avorn 2007):

Clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products. In each instance, the litigation process revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior.

Similarly, documents classified as “confidential” by J&J/DePuy during litigation discovery became public during trials and depositions; these documents provided a basis for this first review of a seeding trial for a medical device. Despite the importance of corporate documents for public health as described above and demonstrated in this article, plaintiff lawyers have agreed to a restrictive protective order in this case. This protective order maintains the confidentiality of millions of pages of documents produced by J&J/DePuy and prevents the disclosure of information contained therein (Kinkeade 2012).

This review provides evidence that confidentiality agreements in public trials subvert public health. Plaintiff lawyers agree to these orders without the knowledge or consent of their clients. In our experience, some clients are more interested in exposing the corporate misconduct that caused their injury than they are in recovering monetary damages. Protective orders like the one issued in this case allow companies to designate entire document productions as confidential. Rather than identifying documents with legitimate claims to protection (such as technical drawings or patient information) these orders extend confidentiality to include emails, presentation slides, and publicly-available material such as advertisements and published articles. It is unethical for plaintiff attorneys to secretly waive their clients’ right to object to confidentiality orders in their own cases.

Although titled a “Multi-center, Prospective, Clinical Evaluation of Pinnacle™ Acetabular Implants in Total Hip Arthroplasty,” the PIN Study was not intended to fill a gap in the scientific literature, but to generate revenue for J&J/DePuy. The PIN Study was conceived, funded, designed, implemented, and disseminated in large part by the J&J/DePuy marketing department. This review suggests that medical device seeding trials are unique compared to previously documented pharmaceutical seeding trials because (1) they allow the company to profit directly from the trial and (2) the seeding trial data may be (as is the case for the PIN Study) the first clinical study data collected by a company. In previously published pharmaceutical seeding trials, the sponsor (manufacturer) provided the medication...
free of charge (Hill et al. 2008; Krumholz, Egilman, and Ross 2011). In this case, the investigators charged the patients for surgery and the cost of the device. By using the 510(k) clearance process, J&J/DePuy sold the Pinnacle Hip System without pre-market clinical testing, thus J&J/DePuy used the PIN Study to develop clinical data after the Pinnacle Hip System had already reached the market.

Although the PIN Study was not specifically implicated in the Deferred Prosecution Agreement signed in 2007, both the DOJ and J&J/DePuy agreed that the company used illegal kickbacks to sell to surgeons over the period of PIN Study enrollment (USDOJ 2007). The DOJ-appointed monitor also recognized the potential for abuse of research consultancy payments (Exhibit PLT-00049 2008). The findings reported here suggest that J&J/DePuy may have used the PIN seeding trial to incentivize PHS sales among participating surgeons in violation of the company’s agreements with the DOJ and DHHS (AdvaMed 2009; Exhibit PLT-03416 0000; Exhibit PLT-03821 2007). Investigators who used more Pinnacle hips were able to enroll more patients and receive larger consulting payments; J&J/DePuy also received payment from patients and insurance companies for each study device implanted. Since medical device seeding trials allow for companies to reap the profits of study device sales, these studies deserve extra scrutiny for their potential to serve as illegal kickback schemes.

Unscientific research practices are a major cause for concern in seeding trials (Hill et al. 2008; Kessler et al. 1994; Sox and Rennie 2008). In the PIN Study, protocol violations, data manipulation, and the absence of proper IRB approval and informed consent all suggest unscientific research practices that call into question the integrity of corporate-sponsored research. A 2013 Cochrane Review publication found that industry-funded published studies were more likely to report favorable efficacy results and favorable conclusions compared to studies with other funding sources (Lundh et al. 2017). Publications of industry-sponsored clinical trials can be even more valuable tools for product promotion than other forms of advertising as readers of medical journals tend to treat published clinical trials as compelling evidence; the tacit endorsement by peer reviewers and journal editors also lends credibility to favorable publications (Avorn, Chen, and Hartley 1982). Smith reviews some corporate strategies for ensuring agreeable study results, including two used in the PIN Study: 1) the use of multiple endpoints to select those with the most favorable results (i.e., mining interim analyses for publishable data) and 2) the selection of reported results based on their marketing appeal (i.e., reporting survivorship for cups only, versus for both cups and liners) (Smith 2005). Unfortunately, unscientific findings like those reported in the PIN Study can spread through the literature like ink in milk. According to the Web of Science as of July 2017, 27 publications directly cite PIN Study publications (Bernasek et al. 2013; Burge et al. 2015; Dhotare et al. 2016;
Greiner et al. 2016; Hosny et al. 2013; Klingenstein et al. 2012, 2013; Lainiala et al. 2014; Langton et al. 2016; Liudahl et al. 2013; Lohmann et al. 2013; Lombardi et al. 2015; Maloney, Ha, and Miller 2015; Matharu et al. 2014; Mihalko et al. 2014; Plummer et al. 2016; Reito et al. 2016; Ricciardi et al. 2016; Schmitz et al. 2013; Singh et al. 2013, 2015; Stihsen et al. 2013; Stryker et al. 2015; Tsukagoshi et al. 2015; Tvermoes et al. 2015; Wagner et al. 2012; Wyles et al. 2014). J&J/DePuy also included PIN Study publications in their 2012 presentation to the FDA on the safety of Metal-on-Metal hip implants, suggesting the potential for mismanaged and manipulated seeding trials to influence regulatory decision making (Voorhorst 2012).

IRBs and journal editors are poised to play a vital role in weeding out seeding trials. J&J/DePuy concealed the PIN Study’s marketing motive and obscured the true nature of the trial, thereby undermining both IRB approvals and informed patient consent (Hill et al. 2008; Krumholz, Egilman, and Ross 2011; Sox and Rennie 2008). Still, the Mayo Clinic IRB recognized the marketing motives of the PIN Study and denied approval. It is recommended that IRBs remain cautious of research that may be seeding trials by looking for “red flags” identified in Table 2. Furthermore, IRBs should ask study sponsors whether other IRBs rejected the protocol and for documentation of such rejections. It is also recommended that journal editors ask for the underlying scientific data associated with a corporate-sponsored submission that is a suspected seeding trial.

The PIN Study provided physicians and consumers with a false sense of security regarding the PHS. The 99.9% survivorship claim was used to market the Pinnacle Metal-on-Metal hip system, which is no longer on the market and has a failure rate 4.5 times greater than the Pinnacle Metal-on-Polyethylene system (13th Annual Report 2016, 2016 National Joint Registry for England, Wales, Northern Ireland, and the Isle of Man 2016). Previous research shows that direct-to-physician marketing and industry gifts affect physician prescribing habits. Steinman et al. revealed that 61% of doctors felt that industry gifts and promotions did not affect their own prescribing choices, but only 16% felt that these practices did not affect their colleagues (Steinman, Shlipak, and McPhee 2001). In 2012, more than 24 billion dollars were spent on direct-to-physician marketing

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**Table 2. “Red Flags” to aid in the identification of seeding trials.**

| Examples of “Red Flags” for seeding trials |
|-------------------------------------------|
| ● Study design may incentivize investigators to use one drug or device over another |
| ● Study initiated just before or shortly after a drug or device reaches the market (Sox and Rennie 2008) |
| ● Protocols lacking clear indication of what is being analyzed |
| ● Research that is un-blinded and/or lacking a control (Sox and Rennie 2008) |
| ● Studies with a short follow-up time (Sox and Rennie 2008) |
| ● Studies with a high number of study sites and a low number of patients per site (Barbour et al. 2016) |
| ● Studies with company employees as authors (Barbour et al. 2016) |
(Fugh-Berman and Ahari 2007; “Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on and Patients” 2013); the Wall Street Journal reported that pharmaceutical companies spent billions more on advertising than research and development in 2013 (Swanson 2015). A 2010 review on the effect and role of direct-to-physician marketing concluded that “with rare exceptions, studies of exposure to information provided directly by pharmaceutical companies have found associations with higher prescribing frequency, higher costs, or lower prescribing quality or have not found significant associations” (Spurling et al. 2010). A “treating” physician in the most recent Pinnacle hip litigation testified that he relied partially on the PIN Study 99.9% survivorship claim for reassurance in his decision to implant the PHS (Howe 2016):

... when I do read the JBJS article and I see it—one of my peer-reviewed journals, the Pinnacle cup with their success rate written in it, that does bias me in terms of, like, it makes me feel, like, okay. I’m using the right thing. . . . I don’t remember the exact [advertisement]. It was a Pinnacle outcomes that was in JBJS about 99 percent or high 90s success rate and survivorship. It was in JBJS. It was in their—they have these little, you know—every article will have a couple advertising parts . . . So as an orthopaedic surgeon, when you’re using something and you get some data, whether it be an advertising thing or not, that says that kind of percentage, I felt pretty good about it.

Despite evidence of the inaccuracy of the 99.9% survivorship claim, J&J/DePuy continues to rely on these falsified PIN Study results to market the PHS (J&J/DePuy 2011a; “Move Ahead With Confidence—Choose your hip replacement from DePuy Orthopaedics” 2011b; J&J/DePuy 2011c, 2012, 2013, 2016).

Seeding trials are malleable marketing projects, not rigorous scientific studies. Regulatory bodies, physicians, journal editors, IRB members, and others should be vigilant for persuasive marketing accounts disguised as science.

Limitations

Plaintiffs’ lawyers had agreed to J&J/DePuy’s request, without the knowledge or permission of their clients, to keep secret all of the documents cited herein. This report is limited to public documents that became public during court proceedings, including four trials and hundreds of depositions that J&J/DePuy did not designate as confidential. There are still millions of pages of documents that remain “confidential.” Due to a court-issued protective order agreed upon by both counsel representing the plaintiffs and counsel representing the defendants, we cannot in any way comment on the contents of these “confidential” documents and depositions.
Conflict of interest

David Egilman served as an expert witness in litigation at the request of people who were injured as the result of having total hip replacement with the Pinnacle Metal on Metal Hip System. Joan Steffen and Kevin Reardon worked for Dr. Egilman on this litigation. Ella Fassler served as a consultant on the same litigation. None of these authors were compensated for work on this paper and the lawyers for the injured plaintiffs did not review this paper and had no input into the content of the paper. The authors provided J&J/DePuy lawyers a draft copy of this manuscript one month before publication with a request for comments and corrections; no response has been received.

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