**Full Infuse Timeline, including links**

(To create a link, highlight the text and then hit CTRL+K, and paste the link into the field)

**Note: the Cervical Fusion (ACDF) timeline entries below are highlighted in this yellow.**

**1980** -- [The Genetics Institute is founded](http://biotechhistory.org/timeline/gi/) in Boston as a private company to develop “therapeutic proteins” for health care. One of its key breakthroughs is isolating [bone morphogenic proteins](http://www.ncbi.nlm.nih.gov/pubmed/1637554) that can trigger “osteogenesis,” or the growth of new bone, in humans.

**1992** -- Wyeth Pharmaceuticals (then known as American Home Products, or AHP), [acquires a controlling interest](http://www.fundinguniverse.com/company-histories/wyeth-history/) in the Genetics Institute. (Wyeth buys the remainder of the private company and the rights to BMP in 1996.)

**1995** -- Sofamor Danek, a publicly traded healthcare company based in Memphis, acquires exclusive rights to rhBMP-2 from Wyeth for a [net payment of $50 million](http://www.sec.gov/Archives/edgar/data/873730/0000950123-98-000853.txt).

**1996** -- The [Safe Medical Devices Act of 1990](http://www.ncbi.nlm.nih.gov/pubmed/10129209) goes into effect, requiring device-makers to report when they become aware of information from any source that one of their marketed devices “may have caused or contributed to a death or serious injury; or has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.”

**1998** -- Researchers begin enrolling 279 patients with degenerative disc disease in [a pivotal randomized, controlled study](https://clinicaltrials.gov/show/NCT01491386) on use of rhBMP-2 with the ACS sponge and LT Cage. In October 2002, the study “proved rhBMP-2 to be equivalent to autograft,” according to [Medtronic’s description posted online](http://www.infusebonegraft.com/healthcare-providers/about-infuse-bonegraft/history-of-rhbmp-2/index.htm) years later. Medtronic doesn’t officially post the data on clinicaltrials.gov until Dec. 12, 2011, the same day that it posts data from [13 other studies](https://clinicaltrials.gov/ct2/results?term=rhBMP-2&show_flds=Y) of Infuse for DDD patients.

**September 1999** -- **ACDF trial starts** -- The first cervical-fusion patient is treated with BMP in an FDA-approved trial, making ACDF one of the original procedures in which BMP is tested on humans. Patient 1 receives 0.4 ml of BMP solution at a concentration of 1.5 mg/ml on a 1.5x2-cm collagen sponge placed inside a piece of fibular allograft bone that is “tapped gently” into the disc space. The patient, like all the patients in the Medtronic-sponsored trial, is reported to have a successful fusion and no device-related complications.

**Jan. 27, 1999** -- Medtronic acquires Sofamor Danek in a roughly [$3 billion, all-stock deal](http://www.marketwatch.com/story/sofamor-danek-shares-soar-after-medtronic-deal-11-02-98). The deal is part of an $8 billion corporate buying spree that included five companies through 1999. [The deal is structured as a merger](http://www.sec.gov/Archives/edgar/data/873730/0000950144-99-000492.txt).

**Jan. 10, 2002** -- **Off-Label Concerns raised** -- Medtronic-paid doctors present the first pivotal study data on Infuse, urging for a narrow approval of the product, in the anterior lumbar spine using the LT Cage. The FDA experts are warned that doctors will use BMP off-label if it’s approved for any procedure, and in fact Medtronic/Sofamor Danek is already actively testing experimental applications like ACDF. Yet the FDA experts are not presented with safety data on uses besides anterior lumbar LT Cage placement. When the question comes up, FDA director [Dr. Celia Witten](http://worldstemcellsummit.com/speakers/celia-m-witten-md-phd/), whose division is overseeing Infuse’s approval, tells the FDA panel, “We're really asking you to focus your discussion on this product and its safety and effectiveness as the label indication … and not, you know, speculate on what other uses might not be safe of, you know, a portion of the product or some other product.”

**July 2, 2002** -- The FDA’s Office of Device Evaluation [grants Medtronic’s premarket approval (PMA) application](http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058a.pdf) for the InFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device. The device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. The devices are to be implanted via an anterior open or an anterior laparoscopic approach. The approval requires Medtronic to file a post approval report that looks at “6 years of post operative data” from patients who got the device during studies or those implanted after FDA approval. The conditions of approval also require Medtronic to retrieve and analyze any bone that is removed in subsequent surgeries and to do a post-approval study on the effects of Infuse “on tumor promotion.” FDA tells Medtronic that failure to comply with the conditions “invalidates this approval order” and commercial distribution of a non-compliant device violates the law.

**October 2002** -- Medtronic’s [pivotal study of 279 patients](https://clinicaltrials.gov/ct2/show/NCT01491386?term=BMP2+pivotal&rank=5&submit_fld_opt=) is completed. The data from this study were the basis of the FDA’s approval of Infuse.

**2003** - Medtronic praises Infuse in its annual report, saying, “Due to convincing clinical results and compelling patient benefits, INFUSE Bone Graft is generating significant patient demand and high rates of surgeon adoption. While still early, uptake among key opinion leaders has been particularly strong, and INFUSE Bone Graft is rapidly becoming the standard of care at our nation's premier spine centers.”

**June 15, 2003** – **1st ACDF Study Published** - The 1999 pilot study of Infuse in cervical fusions, [published this month in Spine](https://www.ncbi.nlm.nih.gov/pubmed/12811263), concludes there were **zero** device-related adverse events or complications among 18 Infuse anterior cervical diskectomy fusion (ACDF) patients. The Medtronic-sponsored study, published in Spine, concludes that it’s safe to continue studying Infuse for cervical fusions. The paper is widely cited, [rated #86 all-time](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4733372/table/TB1500003-1/) among the most influential cervical spine papers. By 2007, BMP is used in at least 18% of all U.S. cervical fusions. Yet the Senate Finance Committee later concludes that Medtronic’s Neil Beals helped edit this paper to emphasize a perceived major shortcoming (donor graft site pain pain) in the control-group procedure. The Spine Journal meanwhile cites this study as one of the early papers sponsored by Medtronic that “disturbingly” underestimated the risks from rhBMP-2 use and helped drive early off-label use in the medical community.

**April 8, 2004** -- ‘**Concerns’ email to Boden** -- Medtronic Senior Vice President Rick Treharne emails key Medtronic consultant Dr. Scott Boden at Emory University in Atlanta to ask Boden’s opinion about the 30 complaints Medtronic had received about Infuse, including 13 complaints from seven different hospitals related to off-label use in the cervical spine. Treharne says there are 452 known cases of BMP cervical fusion at those sites, showing an overall rate of swelling events of between 1.7% and 3.8%, which he suggests is roughly consistent with rates from other sources. Two days later Boden responds, “I have begun hearing ‘concerns’ out in the field about swelling in BMP cases as well. While statistically your numbers do not suggest an increased incidence, I think there is a possibility that could be a misleading conclusion.” Boden writes that one person has told him about a “golf-ball size mass” in an ACDF patient with BMP, which he has never seen in any non-BMP ACDF procedure. Boden also mentions one “death in the literature.” “These patients are clearly at higher risk of swelling … it would be helpful to know if the other BMP cases had visible swelling and what it looked like. GI has some sense that it may be related to overconcentrating the BMP on the sponge, or putting too much total sponge in a small area. I am not sure we have the data to support this contention either. … I think continued warning needs to be advised to surgeons about off-label use, especially in the cervical spine.” (*Source: Senate Finance Committee exhibits, pgs 2119-2121*)

**June 14, 2004** -- **‘Our No. 1 complaint’ email** -- Treharne emails another key Medtronic consultant, Dr. Kenneth Burkus, to say that “swelling in the cervical spine” has become Medtronic’s “No. 1 complaint” about BMP. Treharne also emails Burkus “confidential analyses” of the swelling rates. Yet Treharne’s email says the company still isn’t convinced. He says the rates and the severity of swelling in cervical BMP patients is consistent with the rates of swelling seen in cervical non-BMP patients, and that earlier data from product inventor Wyeth “makes a compelling and convincing case that there is no issue here in regard to rates of edema.” (He uses “edema” interchangably with “swelling.”) “In sum, I just do not, at this time, see anything here to worry about,” Treharne writes. (*Source: SFC pgs 2122-2126*)

**August 16, 2004** -- **ACDF warning deemed premature** -- Dr. Charles Mick writes Dr. Boden an email asking if the North American Spine Society should warn surgeons about a potential association between BMP-ACDF and serious swelling in the neck. Boden says no. “There aren’t enough (data) to say for sure whether it is dose-related, technique-related, exposure-related, or what. I think it may be premature for any ‘official’ warning, but it should remain a topic of discussion of podium symposia and presentations until we are more sure of the mechanism, frequency, and impact.” The next day, [Medtronic Biologics Marketing Director Neil Beals](https://www.linkedin.com/in/neil-beals-65471a10) responds: “reasonable position taken by Scott - action is needed on this ASAP.” The following year, Boden’s payments from Medtronic jump ten-fold, from $138,500 in 2004 to $1.36 million in 2005. All told, Boden received $28.8 million in payments from Medtronic between 1996 and 2008. (*Source: SFC pgs 2127-28*)

**Sept. 14, 2004** -- **Medtronic Safety Alert** -- Medtronic sends doctors a one-page “Safety Alert,” signed by Treharne, reporting an undisclosed number of cases of “localized soft tissue edema” following off-label surgeries using Infuse in anterior cervical fusions. Three of the cases of throat swelling were severe enough to require reoperations; one required a tracheotomy. “These occasional complaints have not been associated with neurological deterioration … Since these complaints have also been reported after cervical surgery without the use of INFUSE Bone Graft, in the absence of complete data, it is unknown whether these incidences are solely related to the use of INFUSE Bone Graft. … Our investigation is still ongoing … Swelling complaints after on-label use in the spine have not been reported. In fact, this product has an excellent safety record confirming the safety profile established with extensive pre-clinical testing.” The number of off-label cervical-spine fusions with Infuse in the U.S. soars after this letter was sent, doubling between 2004 and 2006.

**Dec. 7, 2004** -- **Label warning added** -- The FDA places a warning about concerns about Infuse on the product label, according to the SFC report. The FDA would wait another four years before issuing its Public Health Notification warning against ACDF with BMP.

**Dec. 15, 2004 -** **Toning down a negative study** -- Medtronic’s Treharne emails Medtronic-paid expert Dr. Steven Glassman to try to tone down language in a retrospective study report finding significant risks associated with using a high dose of BMP in ACDF. Glassman’s draft article said, “The high complication rate is alarming and warrants intense scrutiny.” But Treharne wrote, “I think what you are trying to say is that the occurrence [of] adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation.’’ The final paper, published in March 2005 [in Spine](https://www.researchgate.net/profile/Lisa_Shields/publication/257613254_103482_Adverse_effects_associated_with_high_dose_rhBMP-2_use_in_anterior_cervical_spine_fusion/links/00b4952a135863af7e000000.pdf), included the original language, not Treharne’s watered-down suggestion. The paper concluded by saying, “the rate of complications in this series **implies a causal relationship** to the use, or potentially misuse, of INFUSE. This study emphasizes the risk associated with application of new technologies in areas in which extensive clinical experience is not available. Further investigation is necessary to determine the optimal surgical technique and dose of rhBMP-2 that will effectively enhance anterior cervical fusion, but minimize complications.” The study was not financially supported by Medtronic. The 135 ACDF-with-BMP patients received doses of 1.4 mL per level fused at a concentration of roughly 1.5 mg/ml on a collage sponge that was 2.5x5-cm placed inside a resorbable Hydrosorb cage made by Medtronic. That was almost quadruple the dose of BMP used in the 1999 pilot study.

**May 2005** -- **Another positive ACDF study** -- [A retrospective study of 24 cases](http://thejns.org/doi/abs/10.3171/spi.2005.2.5.0521) of off-label BMP use in ACDF at Emory University in Atlanta finds “ACDF involving an rhBMP-2-filled PEEK spacer leads to good clinical outcome and solid fusions (even in multilevel cases) while avoiding the complications associated with harvesting iliac crest bone grafts.” An assessment of this article in The Spine Journal later criticized the “industry-associated author” of the study and report’s false conclusion that the results demonstrated the safety and efficacy of the procedure with 100% fusion rate and “no significant morbidity.”

**March 30, 2006** -- **IDE Study denial** -- The Food and Drug Administration denies Medtronic’s Feb. 1, 2006 application to begin a prospective, non-randomized pivotal IDE study of Infuse and PEEK interbody spacers in ACDF surgery in 225 patients with cervical degenerative disc disease at one level. The study was supposed to support a full PMA application for FDA approval of ACDF with Infuse and PEEK spacers. The FDA denied permission because, among other deficiencies, Medtronic failed to set up “stopping rules” that would have halted the trial in the event of adverse events including death and severe edema. The study is conditionally approved by the FDA later in 2006, after Medtronic agrees to stop enrollment if it encounters specific device-related and life-threatening events, including life-threatening cervical edema. The study had [a start date of June 8, 2007](https://clinicaltrials.gov/ct2/show/study/NCT00485173?term=Pivotal+Infuse+Cervical+PEEK&rank=1). (The final results of the study, including its finding of a high rate of dysphagia, come out in December 2012.)

**July 14, 2006** – Medtronic agrees [to pay $40 million to settle](http://www.justice.gov/sites/default/files/civil/legacy/2014/04/18/MedtronicJUL2006.pdf) a federal False Claims Act lawsuits including one filed in 2003 by a former employee, Jacqueline Kay Poteet, and another filed by former Medtronic lawyer Ami Kelly, who allege a massive program to pay doctors under lavish sham consulting, training and royalty-sharing agreements that induced them to use Medtronic Sofamor Danek devices. “The government had alleged that, between 1998 and 2003, Medtronic paid kickbacks in a number of forms, including sham consulting agreements, sham royalty agreements and lavish trips to desirable locations. The Justice Department contended that [these kickbacks violated](http://www.justice.gov/archive/opa/pr/2006/July/06_civ_445.html) the Anti-Kickback Statute and the False Claims Act.” Medtronic admits no wrong-doing as part of the settlement. ([The case history of the Poteet action](http://caselaw.findlaw.com/us-6th-circuit/1011748.html) is long.) The settlement includes a [five-year corporate integrity agreement](https://www.scribd.com/doc/274533162/Medtronic-Sofamar-Danek-CIA-2009), also dated July 14, 2006 but taking effect in 2009. The agreement says Medtronic must create a database of all of its financial arrangements with physicians to help evaluate whether they violate the Anti Kickback Statute.

**Nov. 16, 2006** -- **MOAS begins** -- An Infuse patient signs an informed consent affirmation form to take part in a Medtronic-sponsored project titled, “A Retrospective Study of the Use of Infuse Bone Graft In Clinical Practice.” The patient becomes one of 3,647 people at more than 20 hospitals whose records are included in the study, including more than 100 ACDF patients. The massive retrospective study, which is known informally as the “Mother of All Submissions” (MOAS), examines Infuse patients who were treated between 2002 and 2006. Virtually all of this “real-world” use is off-label. The person running the study is [Jim Van Hoeck](https://www.linkedin.com/in/jimvanhoeck).

**March 30, 2007** -- **MOAS data** -- The first report of a MOAS patient with complications is received. It’s a lumbar-fusion patient who had to have a reoperation. Ultimately, more than 1,100 surgeries in the study are followed by patient complications, deaths or device malfunctions.

**April 13, 2007 -- 1st ACDF in MOAS** -- The first report of a MOAS ACDF patient with complications is received. It’s a patient who had a “neurological deficit/dysfunction” following a C5-C6 anterior fusion with a small kit of BMP (2.8 ml max dose.)

**April 2007** -- Dental/oral indication for Infuse approved: “In April 2007, we began to market INFUSE Bone Graft for certain oral maxillofacial and dental regenerative bone grafting procedures. It is [estimated that more than 350,000 bone grafting procedures](http://www.sec.gov/Archives/edgar/data/64670/000089710109001266/medtronic092639s2_10k.htm) of this type are performed in the U.S. each year. Medtronic has also submitted a PMA with the FDA for a posterolateral spinal indication for Amplify rhBMP-2 Matrix.”

**June 8, 2007 -- IDE study begins** -- Medtronic’s IDE study for Infuse in PEEK cervical spacers begins. The trial will include up to 225 patients who get either 0.6 mg of BMP or 1.05 mg of BMP, depending on the size of the PEEK spacer. The last patient in the trial is treated in 2010, and the final post-op evaluation of the final patient is in December 2011. **These results are never published in a journal**. But t[he tabulated results](https://clinicaltrials.gov/ct2/show/results/NCT00485173?term=Pivotal+Infuse+Cervical+PEEK&rank=1&sect=X4301256#othr), posted at clinicaltrials.gov in 2012, show five patient deaths and high rate of dysphagia.

**Sept. 20, 2007** -- “Beginning on September 20, 2007, the Company has received letter requests from Senator Grassley of the U.S. Senate Finance Committee requesting information on a variety of subjects, including … financial ties between the Company and physicians who use INFUSE Bone Graft; .... and certain communications regarding INFUSE Bone Graft and the Company’s clinical research projects with the U.S. military and compensation paid to physicians working for the U.S. military. The Company has cooperated, and will continue to cooperate with, the Senator’s requests.”

**Oct. 17, 2007 -- ACDFs hit MOAS** -- This is the worst day for cervical fusions in MOAS, with 16 separate reports received this day of ACDFs followed by complications. All the patients but one had the smallest dose, 2.8 ml or less. The one-day cohort includes six dysphagias plus a case of severe “swelling.”

**Nov. 5, 2007** -- **Last ACDF in MOAS** -- The final cervical fusion in MOAS is recorded. Medtronic has now catalogued 118 cases of cervical fusions with complications, including at least 92 ACDFs (anterior cervical fusions). Rather than heed the repeated calls from the medical community for further investigation of ACDF with BMP, Medtronic opts to stop collecting data in the study and shut it down study prematurely, without ever publishing its results. The data would incorrectly archived in company files until early 2013. Reviewing the data in 2016, Infuse critic Dr. Eugene Carragee concludes that if cervical fusions in the study population were as common as cervical fusions with BMP in the “real world” at the time, Medtronic would have recorded a 13 percent rate of serious inflammations, which was double the rate of serious inflammations seen in the control group of a different Medtronic ACDF study done at the same time. Medtronic says it did not analyze the data in that level of detail in 2007.

**Oct. 1, 2007** -- FDA inspectors issue a [Warning Letter](http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076522.htm) to Medtronic Spine for publishing marketing materials on its Satellite Spinal System that explicitly encourage doctors to use the device in an unapproved way.

**July 1, 2008** -- **FDA warning** -- [The FDA warns](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm) of “life-threatening complications associated with recombinant human Bone Morphogenetic Protein (rhBMP) when used in the cervical spine.” The alert notes that this is an off-label use, and its safety has not been demonstrated or approved by the FDA. This warning triggers a drop-off in Infuse sales growth so significant that Medtronic discloses it to shareholders in its next [quarterly earnings report](https://www.sec.gov/Archives/edgar/data/64670/000089710108002439/medtronic084960_10q.htm).

**July 25, 2008** -- **Smaller Infuse Sizes** -- Sales of Biologics including Infuse rise 16% to $221 million, driven mainly by the introduction of “extra small” and “double extra small” Infuse kits “for use in spinal and oral maxilliofacial procedures. “These smaller kits expand the potential user population,” the company tells investors [in a 10-Q filing](https://www.sec.gov/Archives/edgar/data/64670/000089710108001858/medtronic083633_10q.htm). Then-CEO Hawkins [tells investors](http://seekingalpha.com/article/91660-medtronic-inc-f1q09-qtr-end-07-25-08-earnings-call-transcript?part=single), “During the quarter, we announced approval to market two smaller kit sizes of INFUSE Bone Graft for use in certain spinal fusion and oral/maxillofacial procedures which helped contribute to the largest revenue quarter ever for INFUSE. We estimate the OMF market potential for INFUSE to be in the $200 to $250 million range.” Hawkins tells investors, somewhat disingenuously, that “Strong performance in Biologics continued again this quarter with growth of 16%.” The seeds of a 10 percent sales decline in the following quarter were already planted when he made this comment.

**Oct. 6, 2008** – **Boston DOJ Subpoena** -- Prosecutors in Boston subpoena Medtronic’s Infuse information for a criminal investigation for false claims and off-label promotion: “On October 6, 2008, Medtronic received a subpoena from the United States Attorney’s Office for the District of Massachusetts pursuant to the Health Insurance Portability & Accountability Act of 1996 requesting production of documents relating to Medtronic’s INFUSE Bone Graft product. Medtronic is in the process of responding to that subpoena and will comply as required with the terms of the subpoena.” ([source](https://www.sec.gov/Archives/edgar/data/64670/000089710108002439/medtronic084960_10q.htm).)

**Nov. 28, 2008: Sales Growth Stops:** [quarterly earnings report](https://www.sec.gov/Archives/edgar/data/64670/000089710108002439/medtronic084960_10q.htm): “Continued regulatory scrutiny of off-label use in medical devices. During the three months ended October 24, 2008, the FDA issued a public health notice regarding use of BMP in cervical procedures, which was received negatively by both physicians and payors. As a result, sales of our INFUSE Bone Graft slowed in the quarter. It is uncertain if this trend will continue in subsequent quarters. … Spinal Biologics net sales for the three and six months ended October 24, 2008 were $198 million and $419 million, respectively. Net sales for the three months ended October 24, 2008 were flat in comparison to the same period of the prior fiscal year, whereas net sales for the six months ended October 24, 2008 increased 8 percent over the same period of the prior fiscal year. For the three months ended October 24, 2008, **we believe growth was negatively impacted by physician and payor response to a FDA public health notice regarding use of bone morphogenetic protein (BMP) in cervical procedures and the overall regulatory scrutiny of off-label use in medical devices**. The increase in net sales for the six months ended October 24, 2008 was driven from the three months ended July 25, 2008. INFUSE Bone Graft contains a recombinant human bone morphogenetic protein, or rhBMP-2, that induces the body to grow its own bone, eliminating the need for a painful second surgery to harvest bone from elsewhere in the body.”

**June 5, 2009**: The [New York Times](http://www.nytimes.com/2009/06/06/business/06surgeon.html?_r=0) reports, “Discredited Research Study Stuns an Ex-Army Doctor’s Colleagues.” -- “An apparent case of falsified research by a doctor who had befriended Dr. Andersen when they both worked at Walter Reed, treating American soldiers severely injured in Iraq. The full report of that Army investigation, recently obtained by The New York Times, provides an unusually detailed anatomy of a suspected case of medical research fraud — one all the more disturbing because it occurred at the nation’s premier military research hospital.”

**July 1, 2009 -- JAMA study** -- In the first-ever national analysis of BMP use in the U.S., researchers conclude [in a paper in JAMA](http://jamanetwork.com/journals/jama/fullarticle/184181) that ACDF procedures with BMP in 2006 were associated with longer hospital stays, higher odds of serious complications like dysphagia, and higher overall inpatient costs. The JAMA researchers found a 50% higher rate of complications in ACDF with BMP versus the same surgery without BMP (7% odds of a complication with BMP vs. 4.68% without it.) The study also examined lumbar, thoracic, and posterior-cervical fusions with BMP, and found the odds of complications was either roughly equal to or less than the traditional procedure.

**Oct. 30, 2009 -- The ACDF portfolio** -- Medtronic tells investors that it has a “market-leading anterior cervical portfolio” of devices, including the PEEK Prevail cervical cage. But spine sales may be negatively implacted by “Continued regulatory, legal and media scrutiny of off-label use in medical devices.” ([source](https://www.sec.gov/Archives/edgar/data/64670/000089710109002528/medtronic095603_10-q.htm))

**Aug. 28, 2010** -- The [Milwaukee Journal-Sentinel reports](http://www.jsonline.com/news/health/101732923.html) that the FDA has growing concerns about Infuse. The story mentions a clinical trial that was stopped early because of concerns about ectopic bone growth. Cancer concerns also mentioned.

**September 2010** -- Off-label use of Infuse has skyrocketed. [A study report published in Spine](http://www.ncbi.nlm.nih.gov/pubmed/?term=Off-label+use+of+bone+morphogenetic+proteins+in+the+United+States+using+administrative+data) finds that 85 percent of the 340,251 BMP surgeries between 2003 and 2007 were for off-label indications.

**December 2010** -- Medtronic CEO Bill Hawkins announces [his intention to retire](http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1769975) at the end of Medtronic’s fiscal year, in April 2011. Hawkins, who became CEO in August 2007, is 56 at the time of the announcement.

**May 25, 2011** -- The [New York Times reports](http://www.nytimes.com/2011/05/25/business/25spine.html?_r=0) that a new study on Infuse complications “suggests that one of Medtronic’s best-selling spinal products poses a risk of male sterility.” The finding contradicts results from earlier studies authored by Medtronic-sponsored investigators.

**June 13, 2011** -- Omar Ishrak [becomes CEO](http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1770466) of Medtronic, succeeding Bill Hawkins.

**June 21, 2011** -- Senate Finance Committee members Chuck Grassley and Max Baucus [send a letter to Medtronic CEO Omar Ishrak](http://www.finance.senate.gov/newsroom/chairman/release/?id=a7e974b6-b4b6-4e2c-a738-edefac30fcb6) asking for, “All documents and communications pertaining to adverse postoperative events and/or medical complications relating to the use of recombinant human bone morphogenetic protein 2 (rhBMP-2) treatments” and all payments Medtronic made to Infuse clinical investigators, including corporate entities. The request cites concerns raised in the Journal-Sentinel and New York Times stories.

**June 28, 2011** – The Spine Journal devotes an entire issue to articles exposing a pattern of academic surgeons with financial ties to Medtronic omitting mention of serious side effects associated with Infuse. Led by Dr. Eugene Carragee at Stanford University, the analysis identifies 13 studies sponsored by Medtronic where there was no reporting of adverse events associated with Infuse. [A systematic review of the Infuse literature](http://www.ncbi.nlm.nih.gov/pubmed/21729796) “suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications.”

(Another source of the summary info is here: <http://www.finance.senate.gov/newsroom/chairman/release/?id=b1d112cb-230f-4c2e-ae55-13550074fe86>)

**June 29, 2011** -- The [Wall Street Journal](http://www.wsj.com/articles/SB10001424052702303627104576413663395567784) reports: “In a written statement, Medtronic's new chief executive, Omar Ishrak, conceded that Dr. Carragee's study raised "questions about researchers' conclusions in their published peer-reviewed literature," but added that it didn't tarnish the credibility of the clinical-trial data Medtronic submitted to the FDA. For his study, Dr. Carragee went back and examined that data and found some of the unreported complications in it. Mr. Ishrak, who took the company's helm just two weeks ago, added that Medtronic would "investigate questions surrounding researchers' potential conflicts of interest, refine our policies as warranted, and strive to lead the industry in ethical and transparent business practices." In a phone interview, Richard Kuntz, Medtronic's chief scientific officer, said Mr. Ishrak asked him to put together a team of internal and external researchers to review all the issues raised by Dr. Carragee's study and report back to him within 90 days.”

**August 2011** -- [Medtronic says that it has paid $2.5 million to commission](http://www.infusebonegraft.com/healthcare-providers/about-infuse-bonegraft/the-yale-study/index.htm) Yale University to conduct “an independent review of data related to Infuse bone graft.” Medtronic says it “provided data from 17 completed clinical trials related to INFUSE Bone Graft and recombinant human bone morphogenetic protein-2, as well as post-market adverse event (safety) reports that were submitted to the U.S. Food and Drug Administration. The analyses also included data from published literature as late as 2012. Yale independently assembled a panel of experts and selected Oregon Health & Sciences University (OHSU) and University of York in the United Kingdom (York) to conduct separate analyses of the data. The report of the completed review was published in the June 18, 2013 issue of the Annals of Internal Medicine.” The project is part of the [Yale Open Data Access](http://yoda.yale.edu/) (YODA) project. Medtronic says the analyses showed Infuse “is a safe and effective bone graft treatment when used as indicated.” . [Full report here](http://www.infusebonegraft.com/healthcare-providers/about-infuse-bonegraft/the-yale-study/key-findings/index.htm).

The article in the Annals of Internal Medicine reports “in spinal fusion, rhBMP-2 has no proven clinical advantage over bone graft and may be associated with important harms, making it difficult to identify clear indications for rhBMP-2. Earlier disclosure of all relevant data would have better informed clinicians and the public than the initial published trial reports did.”

**2012** -- Medtronic reports that Infuse has been used on [more than 500,000 patients](http://www.finance.senate.gov/newsroom/chairman/release/?id=b1d112cb-230f-4c2e-ae55-13550074fe86) since its introduction.

**January 2012** -- The number of spinal-fusion surgeries in the U.S. [increased by 138%,](http://www.ncbi.nlm.nih.gov/pubmed/21311399) much faster than other types of surgeries, between 1998 and 2008, an article in Spine reports. The national bill for spinal fusion surgery increased much faster -- the 2-fold increase in surgeries was accompanied by an 8-fold increase in the national healthcare bill for spinal fusion.

**March 2012** - Medtronic pays $85 million to settle shareholders lawsuit stemming from charges that it failed to disclose that Infuse was used off-label 85 percent of the time. [Reuters story](http://www.reuters.com/article/us-medtronic-settlement-idUSBRE82T1A920120330).

**May 16, 2012 -- Infuse investigation closed** -- Medtronic announces that the US Attorney in Boston has [closed its federal criminal and civil investigation](http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1769480) into Infuse. Other investigations continue. The next quarterly report [in June](https://www.sec.gov/Archives/edgar/data/64670/000089710112001054/medtronic122599_10k.htm) also reveals, apparently for the first time, other ongoing Infuse probes: “The Company also received subpoenas or document requests from certain state government bodies in connection with the INFUSE bone graft product, including civil investigative demands from the Attorneys General in Massachusetts, California, Oregon, and Illinois.The Company is fully cooperating with these requests.”

**June 26, 2012** -- **Infuse sales sink** -- From the fiscal year-end 10-k: “Spinal sales growth was negatively impacted from the June 2011 articles in *The Spine Journal* and by inquiries from governmental authorities, relating to our INFUSE bone graft product. *The Spine Journal* articles suggested that some physicians’ peer-reviewed studies may have underreported complications and adverse events associated with INFUSE. These articles did not question the integrity of the data provided by Medtronic to the U.S. FDA for product approval or the disclosure of safety issues on the product’s Instructions for Use for approved indications. Medtronic believes that the safety data reported to the U.S. FDA supports the safe use of INFUSE bone graft for the approved indications. However, because questions have been raised about the peer-reviewed literature, we announced in August 2011 that we have given a grant to Yale University to oversee two independent, systematic reviews of all INFUSE-related clinical data. We expect results of the reviews to be concluded in the second quarter of fiscal year 2013 and we will make all of the INFUSE clinical data and results available to medical researchers. INFUSE bone graft global net sales have declined 18 percent as reported for fiscal year 2012.” ([source](https://www.sec.gov/Archives/edgar/data/64670/000089710112001054/0000897101-12-001054-index.htm))

**Aug. 21, 2012** -- **Infuse sales sink further** -- “BMP revenue of $141 million declined 19 percent, both as reported and on a constant currency basis.” ([source](https://www.sec.gov/Archives/edgar/data/64670/000119312512362631/d399964dex991.htm))

**September 2012** - FDA physician Emily Woo publishes article showing that 99.5 percent of Infuse adverse events reported from 2002-2011 were from off-label use.

**October 2012** – The Senate Finance Committee [publishes a 2,315-page report](http://www.finance.senate.gov/newsroom/chairman/download/?id=e54db17c-a475-4948-bd81-69c8740c6aaf) revealing Medtronic made $210 million in payments to doctors whose published research did not appropriately report all adverse events. In some cases, Medtronic staffers helped draft and edit the papers and prepare congressional testimony. “The Committee’s investigation discovered troubling evidence that Medtronic officials influenced the content of articles in peer-reviewed

scientific publications to present InFuse in the best possible light. As physicians depend on peer-reviewed literature when making clinical decisions, biased articles in professional publications

that downplay potential risks and exaggerate the benefits of a product have the potential to put patients’ lives at risk,” the report concludes. (emphasis added)

**January 2013** - Medtronic spine division vice president of clinical affairs James Kirwin finds unreported Infuse study conducted by company from 2006-2008. The study is called MOAS, which he says stands for “Mother Of All Studies.” The study reviewed medical records of more than 3,000 Infuse patients -- six times more subjects than any other Infuse study on file with the NIH. Kerwin says MOAS documented more than 1,000 adverse events that have never been assessed or revealed outside the company including more than 300 serious adverse events. He brings it to the attention of his bosses and says the company needs to do “a mea culpa with the FDA.” Kirwin says the bosses put the matter in special restricted discussion status for legal reasons.

**February - July 2013** - Kirwin continues to press Medtronic to do something about the unreported MOAS study, which he says was also not reported to Justice Department investigators, state attorneys general or Senate Finance Committee members looking into off-label promotion of Infuse and unreported adverse events.

**March 18, 2013 -- ACDF IDE results disclosed --** The results of the IDE study are reported on clinicaltrials.gov for the ACDF IDE study approved in 2006. The investigators report a total of 37 dysphagia events affecting 15% of the 224 investigational patients. That was more than double the 7% rate of dysphagias in a control group, according [to the results posted at](https://clinicaltrials.gov/ct2/show/results/NCT00485173?term=Pivotal+Infuse+Cervical+PEEK&rank=1&sect=X4301256#othr) clinicaltrials.gov. Dysphagia is classified as an “other adverse event,” not a “serious adverse event.” The prevalence of dysphagia in the IDE agrees with the sentiments in the “No. 1 complaint” email that Treharne sent about BMP-ACDF in 2004. This IDE study was ever published in a journal. A Medtronic-sponsored second “subanalysis” of the data from the same study [was just published in 2016](https://www.researchgate.net/profile/Karen_Anderson10/publication/301736804_Heterotopic_ossification_following_single-level_anterior_cervical_discectomy_and_fusion_Results_from_the_prospective_multicenter_historically_controlled_trial_comparing_allograft_to_an_optimized_dose_/links/57684b0808ae8ec97a4243f7.pdf).

**May 2013** -- **Recall** -- Medtronic initiates a worldwide recall of all sponges for Infuse because of “elevated endotoxin levels resulting from a process deviation.” About 40,000 Infuse packages are affected. FDA issues [Class 2 recall notice](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=118497).

**August 2013** - Medtronic initiates talks with the FDA about the unreported study.

**September 2013** - Kirwin’s immediate boss, Brian Barry, leaves Medtronic for a job at Covidien. The day after he leaves, Kirwin says he is called to human resources and told his performance has not been satisfactory. Kirwin resigns and tells compliance officer he is being forced out for calling attention to the unreported study.

**February 2014** - Medtronic files a single adverse event report with the FDA for an injured Infuse patient it was told about in 2007. Within that report is reference to a previously unreported “post market study” conducted from 2006-2008 of patients implanted with Infuse from 2002-2006. Medtronic redacts the number of patients and adverse events from the public database.

**December 2014** -- The North American Spine Society [publishes new guidelines](https://www.spine.org/Documents/PolicyPractice/CoverageRecommendations/rhBMP.pdf) for when insurers should cover Infuse, based on a sweeping analysis of all the available clinical data on Infuse. The guidelines concludes Infuse should NOT be used in: spinal-fusion patients who are likely to fuse without the bioactive chemical; most kids; healthy patients undergoing a one-level lumbar procedure; and routine anterior and posterior cervical fusion patients.

**May 2015** - FDA tells Star Tribune it must file Freedom Of Information Act request to get details of the 2006-2008 study. FDA declines to make staff available for interviews.

**August 2015** - FDA confirms to Star Tribune that post approval study of Infuse legally required in 2002 approval is not in the FDA post approval study database. Agency does not respond when asked if it has ever been filed.

**January 21, 2015** - [FDA issues safety alert](http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm430868.htm) about use of Infuse in children under 18, saying “FDA is aware of healthcare providers using bone graft substitutes containing recombinant proteins or synthetic peptides in patients under age 18. Reports of serious injuries, such as excess bone growth, fluid accumulation, inhibited bone healing, and swelling, have increased the FDA’s concern.”

**April 29, 2016 -- IDE data published** -- A decade after beginning its FDA-approved pivotal trial of Infuse in the anterior cervical spine, and 12 years after identifying cervical swelling as the No. 1 complaint about BMP, [Medtronic publishes a small slice of data](https://www.researchgate.net/profile/Karen_Anderson10/publication/301736804_Heterotopic_ossification_following_single-level_anterior_cervical_discectomy_and_fusion_Results_from_the_prospective_multicenter_historically_controlled_trial_comparing_allograft_to_an_optimized_dose_/links/57684b0808ae8ec97a4243f7.pdf) from its big BMP cervical-fusion study in a journal. Although the journal article focuses on the high rate of loss of range-of-motion from heterotopic ossification in ACDF cases compared to controls, it also cites “**unpublished data**” to conclude that the surgical implantation of Infuse at a concentration of 1.5 mg/ml with PEEK interbody spacer “is a safe and effective replacement for allograft bone” to induce fusion and “improve” pain and function in patients getting PEEK-BMP-ACDF from C3 to C7.