Evaluating the Morality of the FDA in its Regulation of Infuse™

STS Research Paper
Presented to the Faculty of the
School of Engineering and Applied Science
University of Virginia

By

Timothy L. Boyer

April 23, 2021

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

Signed: _____Timothy L. Boyer_____

Approved: _____ Date _____
Benjamin J. Laugelli, Assistant Professor, Department of Engineering and Society

Introduction

In 2011, the largest medical device company in the world, Medtronic, exceeded $750 million in sales with their spinal fusion product, Infuse™ (Mauney, 2020). However, since being approved by the FDA in 2002, the internal component of Infuse™ that uses recombinant human bone morphogenetic protein-2 (rhBMP-2) has caused a myriad of surgical complications, was researched for its safety under a serious conflict of interest, and led to multiple whistle-blower lawsuits against Medtronic. While a majority of the liability, appropriately, has been put on Medtronic as well as spinal surgeons for biased research, instances of bribery, and inappropriate off-label uses, it would be flawed to overlook how the FDA failed to repress the progression of complications associated with Infuse™. By assessing the FDA's actions toward Infuse™, engineers and policymakers can better understand the flaws associated with the regulatory agency that evaluates medical device safety. Herein, I suggest that while Medtronic and spinal surgeons rightfully bear most of the blame, the FDA acted immorally by delivering a late warning, insufficiently testing the device, and enforcing unjust labelling rules. I evaluate the morality of the FDA's involvement using three of William David Ross' prima facie duties (Reparations, Non-Maleficence, and Promote a Maximum of Aggregate Good) with attention given to the FDA's own Code of Ethics. To support my argument, I use various scientific articles and FDA reports that uncover the sequence of events regarding Infuse™ and rhBMP-2 that occurred mostly between 1998 to 2012.

Scientific Background & Timeline of Events

Bone morphogenetic protein-2 (BMP-2) is a naturally-occurring growth factor that stimulates bone and cartilage growth in joints around the body (Riley et al., 1996). Dr. Marshall Urist discovered BMP-2 and its osteoinductive effects to turn mesenchymal stem cells into bone cells in 1965 (Riley et al., 1996). In the late 1990s, BMP-2 proteins began to be cloned for their potential therapeutic usage to fuse bones together, adding "recombinant human" (rh) to BMP-2 (Riley et al., 1996). In the late 1990s and early 2000s, Medtronic sponsored pre-clinical and clinical trials of Infuse™, a medical device that combines a rhBMP-2 matrix on the inside and a metal cage on the outside. It was approved by the FDA in 2002 for anterior lumbar interbody fusion (lower back) only (United States Food and Drug Administration, 2002). From 2002 onwards, however, thousands of people have been injured due to the adverse effects of rhBMP-2 such as unwanted immune responses, compression of nerve root, uncontrolled and abnormal bone growth, sex organ failure, swallowing difficulties, and bone loss (Tannoury & An, 2014; Zimmerman, 2016) as well as reports of enhanced tumor stimulation (Skovrlj et al., 2014). Doctors began using Infuse™ off-label in an estimated 85% of cases (Ong et al., 2010) in areas such as between vertebrae in the neck, and it was not until 2008 that the FDA released a warning about the dangers of rhBMP-2 usage in the upper spine (Poeran et al., 2016). After nationwide contention regarding previous research, safety, and efficacy of their product, Medtronic sponsored the Yale Open Data Access (YODA) project in 2011 to independently review all literature surrounding Infuse™. The YODA project determined there was massive underreporting of adverse effects in initial studies and that Infuse™, compared to previous fusion methods, did not provide a benefit and resulted in more complications when used in certain areas of the spine (Le & Kurd, 2014).

Literature Review

Scholarly articles almost entirely blame the problems associated with Infuse™ on Medtronic and spinal surgeons. The review by Carragee et al., 2011 heavily emphasizes the underreporting of adverse side effects and how heavy financial conflict of interest impacted safety evaluations of Infuse™. Ong et al., 2010 points out that the usage of Infuse™ by spinal surgeons in off-label, unapproved areas was excessive, despite limited data, controversy, and uncertainty regarding safety in those regions. However, scholars have yet to hold the FDA significantly accountable for the risks they imposed towards patients who received Infuse™.

Dr. Eugene Carragee, a spine surgeon at Stanford Medical School, has played a prominent role in exposing Medtronic for fraud. His 2011 review assessed the ten preclinical Medtronic-sponsored studies of rhBMP-2 and compiled the authors' comments on the adverse events (Carragee et al., 2011). The data showed that of the 780 participants that received a medical device containing rhBMP-2, 0 were reported to have post-treatment adverse effects. Based on these trials, he points out that the risk of rhBMP-2 is less than 0.5% with 99% certainty. However, given that thousands of people that have experienced adverse effects because of rhBMP-2 (Zimmerman, Brian, 2016), Carragee et al. suggests obvious fraudulent data by the authors who had strong ties to Medtronic. They calculated that of the studies that disclosed financial information (12 of 13), the median financial compensation the authors received from Medtronic was estimated to be between $12 million and $16 million per study. His review exposes Medtronic for its outrageous conflict of interest and unethical disregard for patient safety further by revealing one doctor falsified data regarding rhBMP-2 for nearly one million dollars (Carragee et al., 2011).

While Carragee et al. additionally notes that it was ultimately the doctors' decision to use rhBMP-2 off-label (which caused a majority of the adverse effects), his review mainly implicates Medtronic as the culprit. On the other hand, Ong et al. 2010's article suggests a major safety concern was the improper use of rhBMP-2 by spinal surgeons. Assessing data between 2003 and 2007 from the Nationwide Inpatient Sample, they showed the number of procedures involving rhBMP-2 increased 4.3 fold (Ong et al., 2010). Moreover, despite the FDA only approving Infuse™ for anterior lumbar interbody fusion procedures, they estimate that at least 85% of Infuse™ products that were implanted were for unapproved regions of the spine. For this reason mostly, Ong et al. blame rhBMP-2 failures on doctors who have used it off-label. Notoriously, untested high doses of rhBMP-2 used in the cervical spine have caused life-threatening swallowing and breathing issues (Ong et al., 2010).

While scholarly research primarily attributes the problems associated with rhBMP-2 with Medtronic and surgeons, they fail to consider how the FDA's involvement, or lack thereof, contributed to the disregard of patient safety. This science, technology, and society paper adds new insight by questioning the morality of the FDA's actions with regards to rhBMP-2 regulation using an evolved from of duty ethics in combination with the FDA's own code of ethics. In effect, the ways in which regulators play an essential role towards public health is elucidated.

Conceptual Framework

The FDA's involvement towards the safety of Infuse™ will be evaluated using a form of duty ethics developed by William David Ross. Ross' ethical theory is an evolved from of

Kantian theory whereby actions are governed by moral laws (do no harm, be just, etc.) that humans out of duty to their society should obey by (Skelton, 2012).

However, Ross argues that Kant's rules are too ridged and that morality is pluralistic in nature, meaning many principles that govern morality are interconnected and conflicting in given circumstances. In his books, *The Right and the Good*, 1930, and *Foundations of Ethics*, 1939, Ross establishes that there are five to seven *prima face* (Latin - "at first face") duties that humans should abide by to be morally good. However, *prima face* norms may conflict, and the context determines which norm supersedes and is "self-evident" norm. While Ross' ethical theory provides an advantage over Kantian duty ethics that emphasizes strict adherence to deontological morals rules, some flaws still exist such as the hierarchy of norms can be ambiguous (Skelton, 2012).

While Ross originally had seven distinct *prima facie* norms, in the *Foundations of Ethics*, he revises by suggesting three norms can be embodied one, giving rise to five distinct norms (Table 1) Moreover, he intentionally does not rank the norms as each is context dependent, but adds that likely most would agree that non-maleficence (do no harm) is superior in most contexts.

In the analysis section, I determine which of Ross' ethical norms apply to the FDA's Code of Ethics and subsequently evaluate the morality of the FDA's actions towards the regulation and development of Infuse™.

Table 1: Ross' ethical norms.

Ross' Norm	Meaning
Fidelity	Duty to keep promises/not lie
Reparation	Duty to act to amend wrongdoings
Gratitude	Duty to return services to those who have assisted us
Promote a Maximum of Aggregate Good	Duty to be just and distribute happiness to all, including self
Non-Maleficence	Duty to do no harm

Analysis

FDA's Code of Ethics

The Code of Federal Regulations (CFR) Title 21, applied to the Food and Drug Administration since 1958, lists the Code of Ethics for Government Service. Particularly apt towards Ross's ethical norms are codes 1, 2, 5, 9, and 10 (Table 2). Ross's ethical norm of gratitude does not apply to CFR Title 21.

Table 2: FDA Code of Ethics Applicable to Ross' Ethical Norms

FDA Code of Ethics	Applicable Ethical Norm(s)	Explanation
1. Put loyalty to the highest moral principles and to country above loyalty to persons, party, or Government department.	• Non-Maleficence • Fidelity • Promote Aggregate Good	The highest moral principles often are considered to be: do not harm, lie, be just, etc.
2. Uphold the Constitution, laws, and legal regulations of the United States and of all governments therein and never be a party to their evasion.	• Non-Maleficence • Promote Aggregate Good	Laws in the United States apply to do no harm and justice

5. Never discriminate unfairly by the dispensing of special favors or privileges to anyone, whether for remuneration or not	• Promote Aggregate Good	To non-discriminate implies to be just
9. Expose corruption wherever discovered	• Fidelity • Reparations	Exposing any corruption requires being honest Exposing internal corruption helps amend the affected party
10. Uphold these principles, ever conscious that public office is a public trust.	• Promote Aggregate Good	Government work is for the mass of people, not the few

With regards to Infuse™, the FDA has not directly lied, ignored a specific promise or otherwise broken Ross' fidelity duty, based on public knowledge. Thus, three out of five of Ross' duties directly apply to the FDA with respect to rhBMP-2 regulation and are discussed individually below.

Failure to Make Appropriate Reparations

The FDA failed to uphold Ross' ethical norm of reparations by sending out the warnings about the off-label use of rhBMP-2 way too late, omitting important scientific details, and neglecting to address serious conflicts of interest. While the original FDA approval of Infuse™ was intended to be for limited use in one area of the spine only, off-label use was frequent (Ong et al., 2010). It is important to note that this is not illegal as the FDA has no say in the regulation of the practice of medicine (David & Hyman, 2007). Instead physicians must review scientific literature to assess the safety of the device with their intended off-label use (Howard & Copland, 2013). Although it is out of their control, the FDA often protects the public health by indicating risks associated with off-label use (David & Hyman, 2007). It was not until six years after FDA

approval that the FDA issued a warning against the use of off-label rhBMP-2 products such as Infuse™. However, studies only three years after FDA approval demonstrated there was a significant increase in difficulty swallowing from patients who had Infuse™ as opposed to other anterior cervical treatments (Smucker et al., 2005). In the warning issue, they address complications with only cervical procedures (Cohort, 2008). Yet rhBMP-2 use was reported to cause inadvertent bone loss in multiple studies that evaluated posterior lumbar interbody fusion (PLIF) and lumbar interbody fusion (TLIF) (Ong et al., 2010). A 2006 study that imaged rhBMP-2 grafts for PLIF surgeries with CT scans reported, "Vertebral bone resorption and loss of endplate integrity occurs with the use of rhBMP-2. Bone resorption within the vertebral body led to graft subsidence and lack of radiographic evidence of progression toward fusion in multiple cases" (McClellan et al., 2006). While this study that shows lack of improvement and negative consequences was two years before the FDA warning, additional studies that questioned rhBMP-2's safety were as early as 2004 (Ong et al., 2010).

The FDA made an unforeseen error in approving rhBMP-2 for use in the clinic. With thousands of injuries across the nation, lawsuits, and warning statements, this regulation slipped by prematurely (Zimmerman, 2016). I believe Ross would suggest the FDA has an ethical responsibility to make reparations to prevent further injuries. One means of accomplishing this would be to issue warnings of "off-label" use immediately. However, reparations were extremely late, and there were 38 reports of complications that occurred before the FDA delivered its warning (Cohort, 2008). Additionally, the warning did not include complications associated with other surgeries such as PLIF and TLIF, despite studies detailing unintended biological consequences (McClellan et al., 2006).

Given the rampant history of adverse events after FDA approval, data was clearly falsified to suggest that 0 of 780 patients experienced any adverse events in rhBMP-2 clinical trials (Carragee et al., 2011). Moreover, the study by Baskin et al. 2003, that reported no adverse effects of rhBMP-2 use in off-label anterior cervical spine was not only substantially paid by Medtronic but also had a coauthor, Dr. Volker Sonntag who was a previous vice president of the American Association of Neurological Surgery (AANS). Instead of being impartial towards the decision on whether rhBMP-2 is safe and effective in the neck, he was a contributor to this paper that was the unfortunate catalyst for rhBMP-2 use in the upper spine. Ironically, the journal AANS was established in the late 1900s specifically to advise on adverse events with respect to the neurological products. Not only could his association with this organization influence the peer-review publication process, but mandatory financial disclosure shows he had been paid the third highest of any author reporting on rhBMP-2 at over $22 million since 1997 (Table 3) (United States District Court, 2013), demonstrating a significant conflict of interest.

Table 3: Medtronic's Financial Relationships to rhBMP-2 Studies (adapted from United States District Court, 2013).

Year	Volker Sonntag
1996	—
1997	$34,745.92
1998	$207,622.16
1999	$795,053.91
2000	$1,756,041.55
2001	$1,036,993.00
2002	$1,646,050.49
2003	$1,904,689.00
2004	$2,728,639.00
2005	$2,202,595.00
2006	$2,090,998.00
2007	$2,163,661.90
2008	$2,271,477.00
2009	$1,772,361.00
2010	$2,241,156.00
Total	$22,852,083.93

Given the FDA is an organization that is scrupulous on evaluating and ensuring the safety of approved medical devices, it seems unlikely that they were blindly unaware of this potential corruption before approving Infuse™. Regardless, cognizant of the conflicts of interest on publications and with many reports of adverse effects, by not pursuing to address obvious corruption immediately or avoiding to expose Medtronic until 2008, the FDA did not uphold their Code of Ethics Title 21 Rule 9, "Expose corruption whenever discovered," simultaneous breaking Ross' reparations, and arguably fidelity, ethical norms.

Using Ross' ethical theory to evaluate whether any norms supersede "reparations", it seems clear that the lack of reparations was the self-evident norm as the lack of appropriate reparations resulted in physical harm to patients. Thus by sending out a late warning message, omitting problems associated with other regions of the spine, and not exposing corruption immediately, the FDA ethically faltered to amend the problems associated with their premature approval of rhBMP-2 products such as Infuse™.

Failure to Uphold Non-Maleficence

The FDA failed to uphold Ross' ethical norm of Non-Maleficence or "do no harm" by requiring inadequate testing for cancer and not accurately testing the dose of rhBMP-2 that was approved. Consequently, because they approved Infuse™ for commercialization, thousands of people got injured (Zimmerman, 2016). The 2002 "Summary of Safety and Effectiveness Data" for Infuse™ is a document by the FDA that assesses the safety and efficacy of medical devices. It is part of the premarket approval (PMA) series of documents, which determine if a high-risk medical device is approved. The FDA dutifully performed and summarized a variety of toxicity,

immunology, carcinogenicity, pharmacokinetics, and other safety measures (United States Food and Drug Administration, 2002).

The PMA for Infuse™, which was approved in July of 2002 is lacking in critical tests about the adverse effects of Infuse™. This includes only using two *in vitro* tests to evaluate if rhBMP-2 affects cancer cells, as seen in Table 4.

Table 4: The two carcinogenicity tests listed in the PMA for Infuse™ (from United States Food and Drug Administration, 2002).

Study Type: Species/ Strain	Groups/ No. Animals/ Sex	rhBMP-2 (mg/kg)/Route	Relevant Findings
Growth potential on primary tumor isolates *in vitro* (Soda et al., *Anti-Cancer Drugs*, 1998)	n/a	10, 100, and 1000 ng/mL concentration *in vitro*	No tumor cell growth stimulation. Significant inhibition of colony forming units in 16 of 65 specimens at 1000 ng/kg
Inhibition of tumor growth *in vitro* with human tumor cell lines	n/a	10, 100, and 1000 ng/mL concentration *in vitro*	No effect on osteosarcoma cell line growth. Inhibitory effects on several soft tissue carcinoma cell lines.

One that was tested by the Medtronic used 10, 100, and 1000 ng/mL of rhBMP-2 study and the other that was referenced used the same concentrations against several cancer cell lines. (United States Food and Drug Administration, 2002). As a result, the study found that rhBMP-2 does not stimulate growth in cancer cells. (Soda et al., 1998). So then why does such a discrepancy exist between this Medtronic-sponsored preclinical data and that of Skovrlj, et al. 2014 which suggested that in 43% of reviewed studies on BMP-2, tumor function was enhanced? For one, the FDA used only two studies, one of which had a direct conflict of interest as it was sponsored by Medtronic, to assess the carcinogenicity of rhBMP-2, and it is likely that a limited small sample size may not be an accurate representation. Secondly, the carcinogenicity was specifically evaluated only in drug bolus form in *in vitro* models as to represent the

carcinogenicity of the medical device in a human. There were several non-human primate models that were tested, but cancer evaluation of those animal studies was not mentioned in the FDA "Summary of Safety and Effectiveness Data" document. Thirdly, the two tests only evaluated the effect of rhBMP-2 on cancer cell lines, not on whether non-cancerous cells become cancerous. Fourthly, Infuse™ was approved by the FDA with a concentration of rhBMP-2 of 1.5 mg/mL, which is 1500 times higher than the greatest dose tested in cell culture. Concentration, not mass, is consistent across different volumes, thus I believe at least 1.5mg/mL should also have been tested in cell culture. In an article titled, "Which concentrations are optimal for *in vitro* testing," the author states that a common strategy for *in vitro* testing is to test concentrations that are "20- or even 200-fold higher" than the maximum concentration intended for use *in vivo* (Albrecht, 2020) .

While this example is exclusive to cancer only, it raises the question that there might be other flaws in the FDA's evaluation of safety throughout the document, especially given that some of the tests were performed by Medtronic whose unreliability has already been addressed. The FDA's approach to evaluating carcinogenicity alone can be considered unethical as it infringes upon Ross's ethical norm of Non-Maleficence. By not carefully evaluating the carcinogenic effects of Infuse™, the FDA subsequently enhanced cancer in patients (Skovrlj et al., 2014; Tannoury & An, 2014).

With cursory evaluation of the carcinogenic effects of Infuse™, the FDA acted unethically. Some might argue, however, that the FDA can only test so much and it cannot be considered unethical if they find negative data regardless of the amount of studies performed. Besides, there were few studies that raised any concerns about BMP-2 in cancer before 2002. However, Infuse™ was approved after testing with inappropriately low doses and no animals

were tested for cancer at the approved 1.5mg/mL dose. For this FDA PMA, most animals tested for acute and chronic toxicity and fertility were not tested with a concentration of at least 1.5 mg/mL.

By evaluating carcinogenicity with few studies and testing at low doses, the FDA should be held ethically irresponsible for being reluctant to ensure non-malignancy. As non-maleficence is considered often the highest norm (Skelton, 2012), it can be considered the self-evident norm in this case.

Failure to Promote a Maximum of Aggregate Good

Promoting a maximum of aggregate good is a general duty that encompasses beneficence (being kind to others), self-improvement (strive to improve our own well-being), and justice (distributing benefits and burdens evenly). The FDA did not promote a maximum amount of aggregate good by being unjust in their labelling of Infuse™. Howard and Copland, 2013 uncover an inherent flaw in the FDA's 50 year old system of drug and medical device approval. They suggest the FDA prevents doctors from understanding the consequences of off-label uses. This is because under the 1938 Food, Drug, and Cosmetic Act, the FDA prohibits any information regarded off-label uses to be on products (Howard & Copland, 2013). Instead, physicians rely on published academic papers for off-label use. In the case of Infuse™, an estimate 85% of the time, the product was used off-label (Ong et al., 2010). The lack of FDA off-label risks combined with questionable and fraudulent academic papers sponsored by Medtronic led to a myriad of unintended consequences and injuries. By restricting information about off-label uses, the FDA does not promote a maximum of aggregate good as it is unfair to patients who receive the product in an off-label scenario. Thus, the FDA's aged rule is unethical by being

discriminatory against the betterment of patient health, breaking FDA Code of Ethics rules 5 and 10 and subsequently Ross' norm of promoting aggregate good. Since this norm may affect the health and harm of individuals and there are no conflicting norms, it can be considered the self-evident norm.

Conclusion

Through William David Ross' ethical theory adaptation of duty ethics, I argue that the FDA acted unethically towards the regulation and development of Medtronic's Infuse™ by failing to make appropriate reparations, not avoiding maleficence, and by failing to promote a maximum of aggregate good. As a consequence, thousands of people suffered injuries. By sending out the warning notice about off-label uses way too late, avoiding to expose corruption of fraudulent data and conflicts of interest in a timely manner, the FDA breaks Ross' ethical norm of "reparations". Secondly, with inadequate testing of carcinogenicity and testing at inappropriate doses, the FDA fails to protect U.S. citizens from the adverse effects of Infuse™ and thus breaks Ross' "non-maleficence" norm. Lastly, by preventing products from containing information about off label adverse risks, the FDA inherently acted unjustly towards the 85% of patients from 2002-2007 who received rhBMP-2 in off-label fashion. Thus, the FDA breaks Ross' norm of "promoting a maximum aggregate good". In true Ross' ethical theory fashion I have considered and conclude these norms are self-evident and broken in each case. Through this ethical evaluation, I offer an overlooked perspective about the unintended consequences resulting from the FDA's actions in addressing the safety of Infuse™. Ross' ethical norms, which were broken, are ingrained in five of the FDA's Code of Ethics, underscoring the need for a critical

internal review and adjustment to how the FDA approaches professionalism and scientific analysis moving forward.

Word Count: 3738

References

Albrecht, W. (2020). Which concentrations are optimal for in vitro testing? *EXCLI Journal, 19*, 1172–1173. Retrieved from https://doi.org/10.17179/excli2020-2761.

Carragee, E. J., Hurwitz, E. L., & Weiner, B. K. (2011). A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: Emerging safety concerns and lessons learned. *The Spine Journal, 11*(6), 471–491. Retrieved from https://doi.org/10.1016/j.spinee.2011.04.023

Cohort, L.R., (2008) The FDA delivers a late warning. *The Back Letter*, *23*(10), 115. Retrieved from https://doi.org/10.1097/01.BACK.0000339096.22294.a9

David, Y., & Hyman, W. A. (2007). Issues associated with off label use of medical devices. *2007 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 3556–3558. Retrieved from https://doi.org/10.1109/IEMBS.2007.4353099

Howard, P., & Copland, J. (2013). Off-label, not off-limits: The FDA needs to create a safe harbor for off-label drug use. *Missouri Medicine*, *110*(2), 106–109. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6179680/

Le, M. E., & Kurd, M. F. (2014). A review and analysis of the YODA Trials: What can we glean clinically? *Current Reviews in Musculoskeletal Medicine*, *7*(3), 189–192. Retrieved from https://doi.org/10.1007/s12178-014-9220-4

Mauney, M. (2020). Infuse Bone Graft. *Drugwatch*. Retrieved from https://www.drugwatch.com/infuse/

McClellan, J. W., Mulconrey, D. S., Forbes, R. J., & Fullmer, N. (2006). Vertebral bone resorption after transforaminal lumbar interbody fusion with bone morphogenetic protein

(rhBMP-2). *Journal of Spinal Disorders & Techniques*, *19*(7), 483–486. Retrieved from https://doi.org/10.1097/01.bsd.0000211231.83716.4b

Ong, K. L., Villarraga, M. L., Lau, E., Carreon, L. Y., Kurtz, S. M., & Glassman, S. D. (2010). Off-label use of bone morphogenetic proteins in the United States using administrative data: *Spine*, *35*(19), 1794–1800. Retrieved from https://doi.org/10.1097/BRS.0b013e3181ecf6e4

Poeran, J., Opperer, M., Rasul, R., Mazumdar, M., Girardi, F. P., Hughes, A. P., Memtsoudis, S. G., & Vougioukas, V. (2016). Change in off-label use of bone morphogenetic protein in spine surgery and associations with adverse outcome. *Global Spine Journal*, *6*(7), 650–659. Retrieved from https://doi.org/10.1055/s-0036-1571284

Riley, E. H., Lane, J. M., Urist, M. R., Lyons, K. M., & Lieberman, J. R. (1996). Bone morphogenetic protein-2: Biology and applications. *Clinical Orthopaedics and Related Research*, *324*, 39–46. Retrieved from https://doi.org/10.1097/00003086-199603000-00006

Skovrlj, B., Marquez-Lara, A., Guzman, J. Z., & Qureshi, S. A. (2014). A review of the current published spinal literature regarding bone morphogenetic protein-2: An insight into potential bias. *Current Reviews in Musculoskeletal Medicine*, *7*(3), 182–188. Retrieved from https://doi.org/10.1007/s12178-014-9221-3

Smucker, J., Singh, K., Yoon, S., Heller, J., & Rhee, J. (2005). Postoperative airway or swallowing disturbance associated with use of rhBMP-2 in the anterior cervical spine. *The Spine Journal*, *5*(4), S43–S44. Retrieved from https://doi.org/10.1016/j.spinee.2005.05.083

Soda, H., Raymond, E., Sharma, S., Lawrence, R., Cerna, C., Gomez, L., … Izbicka, E. (1998). Antiproliferative effects of recombinant human bone morphogenetic protein-2 on human tumor colony-forming units: *Anti-Cancer Drugs*, *9*(4), 327–332. Retrieved from https://doi.org/10.1097/00001813-199804000-00006

Skelton, A. (2012). William David Ross. *Stanford Encyclopedia of Philosophy*. Retrieved from https://plato.stanford.edu/entries/william-david-ross/

Tannoury, C. A., & An, H. S. (2014). Complications with the use of bone morphogenetic protein 2 (BMP-2) in spine surgery. *The Spine Journal*, *14*(3), 552–559. Retrieved from https://doi.org/10.1016/j.spinee.2013.08.060

United States District Court (2013). Consolidated class action complaint for violation of the federal securities laws. Retrieved from https://www.zimmreed.com/wp-content/uploads/2015/01/MedtronicSecuritiesConsolidatedComplaintA-L.pdf

United States Food and Drug Administration. (2002). Infuse bone graft/LT-CAGE? lumbar tapered 15 fusion devices—P000058. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058B.pdf

Zimmerman, Brian. (2016). Medtronic: Failure to report adverse events in Infuse study was unintentional. *Becker's Clinical Review*. Retrieved from https://www.beckershospitalreview.com/quality/medtronic-failure-to-report-adverse events-in-infuse-study-was unintentional.html#:~:text=The%20study% 20in%20question %20 included,data%2C%20according%20to%20the%20Tribune.