Journal of the History of Medicine and Allied Sciences, Vol. 72, No. 2, pp. 117–141
doi: 10.1093/jhmas/jrw027
Advance Access Publication: September 30, 2016

OXFORD

Surgical Innovation and the Multiple Meanings of Randomized Controlled Trials: The First RCT on Minimally Invasive Cholecystectomy (1980–2000)

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ABSTRACT

This article uses the case of the first randomized controlled trial (RCT) evaluating laparoscopic cholecystectomy to investigate the introduction of minimally invasive surgery in the 1990s and explore the meaning of RCTs within the context of the introduction of a new surgical technology. It thus brings together the history of the use of laparoscopic cholecystectomy to remove the gallbladder, and the history of the RCT, shedding light on particular aspects of both. We first situate the RCT in the context of the history of the various treatment options for gallstones, or cholelithiasis, then characterize the specific situation of the rapid, patient-driven spread of laparoscopic cholecystectomy, and in a next step describe how the local context of laparoscopic cholecystectomy as a new technology made it possible and desirable to conduct an RCT, despite numerous obstacles. This article then shows that in order to capture and understand the rationale of an RCT it is worth it to explore the various levels and dimensions of its context, demonstrating how even the RCT as an ostensibly universal tool draws its meaning from its contexts and that this meaning goes beyond the simple determination of efficiency and safety, including, maybe most importantly, the control and management of new technologies.

KEYWORDS: minimally invasive surgery, laparoscopic cholecystectomy, cholelithiasis, gallstones, gallbladder, randomized controlled trials, surgical innovation

The introduction and spread of laparoscopic cholecystectomy is a particularly important example of the rise in the 1980s and 1990s of minimally invasive surgery (MIS). Cholecystectomy, the surgical removal of the gallbladder in cases of symptomatic gallstones, has been considered one of the "bread-and-butter" interventions of general

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surgeons over the twentieth century.[1] Along with appendectomy and hernia repair, all three operations are considered paradigmatic for routine elective surgery and thus important markers of a new domain of surgery emerging in the late nineteenth century.[2] Beginning in the latter half of the 1980s many open operations in surgery, such as cholecystectomy, started to be replaced by this new minimally invasive technology in which surgical procedures are performed through small incisions in the skin. In MIS, a long thin tube with a camera at its end is passed through one of the incisions, along with specialized instruments allowing the operator to perform the procedure within the patient's body in the absence of a large open incision. The substitution of laparoscopic techniques for the methods of classic surgery is probably the most far-reaching change to surgical practice since the nineteenth century and has transformed the face of modern surgery. MIS is a technology that came with a novel set of instruments and visualization devices and required a radically different skill-set from traditional open surgery. As a novelty, often described as "disruptive,"[3] it brought with it uncertainty about risks and benefits, compared to the tried and tested open methods, which in many cases had been introduced more than a century earlier. The rapid spread of this new and relatively untested technology is a particular example of technical innovation, which has been a research topic in the history of medicine[4] and surgery[5] for quite a

1 James R. Zetka, *Surgeons and the Scope* (Ithaca: Cornell University Press, 2003), 121. Laparoscopic hernia repair and laparoscopic appendectomy also appeared about this same time, but this article will focus specifically on developments surrounding the adoption of the laparoscopic cholecystectomy.

2 See in particular on appendectomy: Dale C. Smith, "Appendicitis, Appendectomy, and the Surgeon," *Bull. Hist. Med.*, 1996, *70*, 414–44; the definition of "elective surgery" varies over time and among authors. A good example of this variability is ovariotomy, see Sally Frampton, *'The Most Startling Innovation': Ovarian Surgery in Britain, c. 1740–1939* (Ph.D. thesis: University College London, 2013); Cholecystectomy, appendectomy, and hernia repair are usually considered typical examples for this kind of operation. There are others, such as tonsillectomy, see Gerald N. Grob, "The Rise and Decline of Tonsillectomy in Twentieth-Century America," *J. Hist. Med. Allied Sci.*, 2007, *62*, 383–421.

3 Zetka, *Surgeons and the Scope,* speaks of "disruptive technology" from the perspective of the sociology of occupations. Lawrence Rosenberg and Thomas Schlich, "Surgery: Down for the Count?" *CMAJ*, 2012, *184*, 496, use a different conception of disruption, introduced by in Clayton M. Christensen, *The Innovator's Dilemma: When New Technologies Cause Great Firms to Fail* (Boston: Harvard Business School Press, 1997). The term "Minimally Invasive Surgery" was coined by the British urologist John Wickham in "Introduction," *British Medical Bulletin,* 1986, *42*, 221–22, see Roger Kneebone and Sally Frampton, "John Wickham's New Surgery: 'Minimally Invasive Therapy', Innovation, and Approaches to Medical Practice in Britain," (forthcoming manuscript, thanks to the authors for making this information available to us).

4 John V. Pickstone, "Introduction," in *Medical Innovations in Historical Perspective,* ed. John V. Pickstone (Houndmills, Basingstoke: Palgrave, 1992), 1–16; Ilana Löwy, "Medicine and Change," in *Medicine and Change: Historical and Sociological Studies of Medical Innovation,* ed. Ilana Löwy (Paris: Les Éditions INSERM, 1993), 1–19; Jennifer Stanton, "Introduction," in *Innovations in Health and Medicine: Diffusion and Resistance in the Twentieth Century,* ed. Jennifer Stanton (London: Routledge, 2002), 1–15; Thomas Schlich, "Risk and Medical Innovation: A Historical Perspective," in *The Risks of Medical Innovation: Risk Perception and Assessment in Historical Context,* ed. Thomas Schlich and Ulrich Tröhler (London: Routledge, 2006), 1–19.

5 Frampton, *The Most Startling Innovation*; Thomas Schlich, *Surgery, Science and Industry: A Revolution in Fracture Care, 1950s–1990s* (Basingstoke: Palgrave Macmillan, 2002); J. Anderson, F. Neary and J.V. Pickstone, *Surgeons, Manufacturers and Patients: A Transatlantic History of Total Hip Replacement* (Basingstoke: Palgrave Macmillan, 2007).

while. One of the most interesting themes in this research has been examination of the changing means for evaluating new technologies in different historical contexts. Of particular interest have been the methods of the clinical trial, and especially the randomized controlled trial (RCT), with the use of randomization to exclude bias, and the creation of prospective control groups for comparative analysis against another treatment or placebo.[6]

The emergence and the use of clinical trials have been topics of recent historical investigation. Harry Marks, for example, has shown how clinical trials originated in the specific context of pharmaceutical testing, motivated by wariness about the methods of drug manufacturers, and often complicated by the scarcity of the drug being tested.[7] He also identified control of the use of pharmaceuticals and the desire to manage the introduction of novel treatments as key components in the rise of the RCT. In the surgical realm the use of RCTs met with a more cautious reception, but concern to control new therapeutic interventions was a common theme here too. Thomas Schlich has investigated the construction of a particular culture of evidence associated with the development and spread of novel operative fracture care in the second half of the twentieth century.[8] His study on osteosynthesis has shown that the successful development of this new and potentially risky technology linked control over access with the collection of clinical data on use.[9] David Jones examined the use of different kinds of evidence in surgery and internal medicine in the controversies surrounding the treatment of coronary heart disease. His work is remarkable for situating the introduction of new treatments within the context of a landscape of other treatments and their comparative evaluation in RCTs.[10] Such an exploration of various therapeutic options and the relationship to the use of clinical trials at a particular time is a valuable approach to the history of medical innovation.[11] This is certainly true in the case of MIS, where, as we will see, the examination of other available technologies changes the way we understand the significance of the evaluative mechanism of the RCT.

6 On the history of the RCT, see e.g., Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990* (Cambridge: Cambridge University Press, 1997); Stefan Timmermans and Marc Berg, *The Gold Standard. The Challenge of Evidence-Based Medicine and Standardization in Health Care* (Philadelphia: Temple University Press, 2003); Marcia Lynn Meldrum, *'Departures from the Design': The Randomized Clinical Trial in Historical Context, 1946-1970* (Ph.D. thesis: State University of New York at Stony Brook, 1994); Jeanne Daly, *Evidence-Based Medicine and the Search for a Science of Clinical Care* (Berkeley and London: University of California Press, 2005).

7 Harry M. Marks, "Trust and Mistrust in the Marketplace: Statistics and Clinical Research, 1946-1960," *History Sci.*, 2000, *38*, 343–55.

8 Schlich, *Surgery*.

9 Thomas Schlich, "Degrees of Control: The Spread of Operative Fracture Care with Metal Implants. A Comparative Perspective on Switzerland, East Germany and the USA, 1950s-1990s," in *Innovations in Health and Medicine: Diffusion and Resistance in the Twentieth Century*, ed. Jennifer Stanton (London: Routledge, 2002).

10 David S. Jones, *Broken Hearts: The Tangled History of Cardiac Care* (Baltimore: Johns Hopkins University Press, 2013).

11 As argued, for example, by Thomas Schlich, "Why Were Surgical Gloves Not Used Earlier? History of Medicine and Alternative Paths of Innovation," *Lancet*, 2015, *386*, 1234–35.

Historical investigations of MIS are as yet scarce. They often come from the surgeons who were involved in pioneering the technology and thus have a specific perspective.[12] James Zetka has investigated the development of MIS from the perspective of occupational sociology and looked at the turf wars between the various occupational groups involved.[13] Rachel Prentice's ethnographic study focuses on aspects of the surgeon's acquisition of the new skills required by MIS.[14] This article brings together the history of MIS with the history of the surgical RCT by investigating how clinical trials were applied in evaluating this new technology. It thus situates the RCT in the context of its use within the controversies over a particular treatment modality, conducted within a local context that shaped its planning and its performance. In order to explore the relevant contexts sufficiently, we take a narrow focus and look specifically at one of the most spectacular examples of the rapid triumph of the new technology, laparoscopic gallbladder removal and the first successfully completed RCT that was conducted to evaluate this method. For understanding the origins and performance of this first RCT, it is necessary to contextualize laparoscopic cholecystectomy within the history of the various competing treatment options, pharmacological and surgical, for cholelithiasis, and thus identify the stakes associated with this particular RCT. After characterizing the more general context of the method at an international level and the purported need to control the spread of laparoscopic cholecystectomy through clinical trials, we then explore the local context and conditions of the successful RCT, which not only made it possible but also shaped it. An investigation along these lines opens up an additional dimension to the history of RCTs, characterizing it as a locally-rooted and context-dependent phenomenon that is not solely about evaluating a new treatment.

The source material used for our investigation consists of published material, such as research papers, editorials and review articles, as well as archival material made available by the historical actors and, finally, oral history interviews. For the interviews we identified, through our primary readings, the local leaders in using RCTs for the evaluation of laparoscopic cholecystectomy.[15] Additional witnesses were identified from suggestions by interviewees through "snowball" sampling, a method that is uniquely valuable for tracing the flow of technology and skills outward from the lead user group into wider populations.[16]

12 Grzegorz S. Litynski, *Highlights in the History of Laparoscopy: The Development of Laparoscopic Techniques - a Cumulative Effort of Internists, Gynecologists, and Surgeons* (Frankfurt on Main: Barbara Bernert, 1996); Othmar Schoeb and Dieter Hahnloser, "Die Entwicklung der minimalinvasiven Chirurgie in der Schweiz, 1990–2020," in *Schnitte, Knoten und Netze. 100 Jahre Schweizerische Gesellschaft für Chirurgie*, ed. Hubert Steinke, Eberhard Wolff, and Ralph Alexander Schmid (Zürich: Chronos, 2013), 187–94.

13 Zetka, *Surgeons.*

14 Rachel Prentice, *Bodies in Formation: An Ethnography of Anatomy and Surgery Education* (Durham: Duke University Press, 2013).

15 G. Guest, A. Bunce, and L. Johnson, "How Many Interviews Are Enough? An Experiment with Data Saturation and Variability," *Field Methods*, 2006, *18*, 59–82; Eric von Hippel, "Lead Users: A Source of Novel Product Concepts," *Manag. Sci.*, 1986, *32*, 791–805.

16 J. Faugier and M. Sargeant, "Sampling Hard to Reach Populations," *J. Adv. Nurs.*, 2008, *26*, 790-97; S. Berg, "Snowball Sampling," *Encyclopedia of Statistical Sciences*, vol. 8, ed. S. Kotz and N.L Johnson (New York: Wiley, 1988), 529–32.

In keeping with the methods of oral history,[17] we used an open-ended format to maximize the potential for unanticipated data, and to collect facts and opinions that may usefully complicate and/or enrich our hypotheses.

CHOLELITHIASIS

Cholelithiasis, or the condition of having gallstones, was originally managed through internal medications such as belladonna and opiates but became a surgical disease with the gradual adoption of cholecystectomy.[18] Carl Langenbuch in Berlin, in particular, advocated successfully for the removal of the gallbladder as a definitive cure for cholelithiasis, having first performed the procedure in 1882.[19] Despite some criticism from the eminent British pioneer of abdominal surgery Lawson Tait,[20] as well as from non-surgical colleagues,[21] the intervention would become one of the most common procedures performed by general surgeons. For most of the twentieth century, Langenbuch's procedure was considered the gold standard for the treatment of symptomatic gallstones and has remained largely unchanged.[22]

Despite the low morbidity and mortality of open cholecystectomy, there was some interest in developing less invasive treatments for cholelithiasis. In particular, the postoperative convalescence period of three to six weeks constituted an incentive for the development of nonsurgical methods to treat the disease.[23] The 1950s brought major investments in biomedical research that resulted in a rapid pace of therapeutic innovation and what has been referred to as an unanticipated "drug explosion."[24] Much of this research and development occurred in the hope of the discovery of pharmaceutical

17 Paul Thompson, *Voice from the Past: Oral History* (London: Opus, 2000); Thomas Schlich, "Zeitgeschichte der Medizin: Herangehensweisen und Probleme," *Medizinhistorisches J.*, 2007, *42*, 269–98.

18 John M. Beal, "Historical Perspective of Gallstone Disease," *Surg. Gynecol. Obstet.*, 1984, *138*, 181–89.

19 Kenneth J. Hardy, "Carl Langenbuch and the Lazarus Hospital: Events and Circumstances Surrounding the First Cholecystectomy," *Aust. N. Z. J. Surg.*, 1993, *63*, 56–64; L. William Traverso, "Carl Langenbuch and the First Cholecystectomy," *Am. J. Surg.*, 1976, *132*, 81–82.

20 Lawson Tait, "Note on Cholecystostomy," *BMJ*, 1884, *1218*, 853; Lawson Tait, "Cholecystostomy v. Cholecystectomy," *BMJ*, 1885, *1276*, 1224.

21 See, e.g., Justus Ohage, "The Surgical Treatment of Diseases of the Gall-Bladder," *Med. News*, 1887, *50*, 202–6.

22 Béla Halpert, "Fiftieth Anniversary of the Removal of the Gallbladder: Carl Langenbuch – 'Master Surgeon of the Biliary System' 1846-1901," *Arch. Surg.*, [1932]1982, *117*, 1526–30; Uptal De, "Evolution of cholecystectomy: A Tribute to Carl August Langenbuch," *Indian J. Surg.*, 2003, *66*, 97–100; A.J. Harding Rains, "A Thought for Carl Langenbuch (1846-1901): A Centenary," *Ann. R. Coll. Surg. Engl.*, 1982, *64*, 268–69; Charles K. McSherry, "Cholecystectomy: The Gold Standard," *Am. J. Surg.*, 1989, *158*, 174–78; Nathaniel J. Soper, "Laparoscopic Cholecystectomy," *Curr. Probl. Surg.*, 1991, *28*, 587–655.

23 R. Hermon Dowling, "The Goose that Laid the Golden Bile: Gallstone Dissolution in Man with Chenodeoxycholic Acid," *Ir. J. Med. Sci.*, 1974, 0, 115–27. See in retrospect: F. Dubois, G. Berthelot, and H. Levard, "Laparoscopic Cholecystectomy: Historic Perspective and Personal Experience," *Surg. Laparosc. Endosc.*, 1991, 1, 52–57.

24 Jeremy A. Greene, Prescribing by Numbers: Drugs and the Definition of Disease (Baltimore: The Johns Hopkins University Press, 2006), 22.

treatments for conditions that were previously being treated surgically.[25] For cholelithiasis, the surge in biomedical research resulted in an improved understanding of the biological basis for the disease and the biochemical nature of gallstones. The observation that patients suffering from gallstones had decreased levels of bile acid[26] led researchers at the Gastroenterology Unit of the Mayo Clinic to hypothesize that cholesterol gallstones, which make up an estimated 75–85 percent of those suffered, were the result of insufficient levels of bile acid in the gallbladder to keep cholesterol in solution.[27] The unit consisting of Rudy G. Danzinger, Alan F. Hofmann, Leslie J. Schoenfield, and Jonathan L. Thistle believed that the condition could thus be remedied by the oral administration of bile acids, such as chenodeoxycholic acid (CDCA). It was thought that CDCA would increase the solubility of cholesterol thereby preventing the formation of gallstones as well as dissolving existing gallstones. The group published their findings in the January 6, 1972 issue of *The New England Journal of Medicine (NEJM)* and presented the paper a few months later at the spring meeting of the British Society of Gastroenterology (BSG) reporting that gallstones in six women were seen to either decrease in size or disappear completely after six to eighteen months of taking CDCA orally, with no observed toxicity.[28]

Physicians quickly became inspired by the oral administration of CDCA as a potential cure for gallstones referring to it as "a novel and exciting form of therapy."[29] In addition, according to some surgical authors, there was a rising hope from the public that a noninvasive, medical cure for cholelithiasis would soon replace surgery.[30] As early as August 1972, one editorial in the *Journal of the American Medical Association (JAMA)* wrote that "the false claim of quacks and faint hope of physicians – the dissolution of gallstones has now crossed the threshold of reality."[31] However, critics believed that a medical treatment of gallstones was likely to be an indefinite therapy and no match for the "gold standard" of the "acceptably safe, sure, rapid, and lasting remedy" that surgery

25 Zetka, *Surgeons*, 122.

26 "Gallstones," *N. Engl. J. Med.*, 1967, *277*, 932; Z.R. Vlahcevic et al., "Diminished Bile Acid Pool Size in Patients with Gallstones," *Gastroenterology*, 1970, *59*, 165–73.

27 John P. Geyman, "Medical Treatment of Cholelithiasis," *West. J. Med.*, 1975, 123, 299–300; Barry J. Pearlman and Leslie J. Schoenfield, "Gallstones: The Present and Future of Medical Dissolution," *Med. Clin. North Am.*, 1978, 62, 87–105; Rudy G. Danzinger et al., "Dissolution of Gallstones with Chenodeoxycholic Acid," *N. Engl. J. Med.*, 1972, *286*, 1–8.

28 Danzinger, "Dissolution," 1-7; R.G. Danzinger et al., "Expansion of Decreased Bile Acid Pool and Dissolution of Gallstones by Chenodeoxycholic Acid," *Gut*, 1972, *13*, 321. These were replicated by G. Duncan Bell, Brian Whitney, and R. Hermon Dowling, "Gallstone Dissolution in Chenodeoxycholic Acid," *Lancet*, 1972, *7789*, 1213–16.

29 Kurt J. Isselbacher, "A Medical Treatment for Gallstones?" *N. Engl. J. Med.*, 1972, 286, 40–42; Ian A D. Bouchier, "Non-Surgical Treatment of Gall Stones: Many Contenders but Who Will Win the Crown?" *Gut*, 1988, *29*, 137–42; Hugh Gainsborough, "Gallstone Dissolution by Chenodeoxycholic Acid," *Lancet* 1973, *7793*, 42; Johnson L. Thistle, "Cholesterol Gallstone Dissolution," *Arch. Surg.*, 1973, 107, 831–32; Martin C. Carey, "Cheno and Urso: What the Goose and the Bear have in Common," *N. Engl. J. Med.*, 1975, *293*,1255–57; Geyman, "Medical," 299.

30 For example, Bouchier, "Crown," 137.

31 S.V., "Dissolution of Gallstones," *JAMA*, 1972, *221*, 600.

provided.[32] Thus whether surgeons might really be forced to "beat their gallstone scoops into medicine spoons,"[33] was controversial with many doctors demanding rigorous clinical trials to prove the efficacy and safety for the medical treatment of cholelithiasis.[34] In order to determine the safety and efficacy of CDCA in the treatment of the disorder, a national cooperative study was planned to begin in 1974, coordinated by Schoenfield and funded by the National Institute of Arthritis, Metabolism, and Digestive Disease.[35] Nonetheless, even before the study was concluded, by 1978, physicians in Britain were given the option of prescribing CDCA to their patients with gallstones.[36] In contrast, the Federal Drug Administration of the United States did not approve the use of CDCA in cholelithiasis treatment until 1983, after the conclusion of the study.[37]

In addition to possible liver toxicity,[38] the main issue was the recurrence of gallstones upon cessation of bile acid treatment.[39] It was predicted that 50 percent of patients for whom complete dissolution had been achieved would have a recurrence of gallstones within two years of ending their treatment[40] and as the *British Medical Journal* stated in a 1975 progress report, "at present the decision to place a patient on CDCA therapy is probably a life sentence."[41] Even though many physicians, such as Dowling's group, were unwilling to concede treatment of cholelithiasis to surgeons,[42] it looked like without a solution to the issue of gallstone recurrence, the treatment of cholelithiasis would "remain very much within the domain of the surgeons."[43]

32 William S. Haubrich, "Getting Rid of Gallstones without Surgery," *JAMA*, 1975, *231*, 747–48; "Abnormal Bile or Faulty Gall Bladder?" *BMJ*, 1970, *5735*, 571–72; K.W. Heaton, "Abnormal Bile or Faulty Gall Bladder?" *BMJ*, 1971, *5743*, 289.

33 S.V., "Dissolution," 600; Johnson L. Thistle and Alan F. Hofmann, "Efficacy and Specificity of Chenodeoxycholic Acid Therapy for Dissolving Gallstones," *N. Engl. J. Med.*, 1973, *289*, 655–59; Thistle, "Cholesterol," 832.

34 Danzinger, "Dissolution," 7; Isselbacher, "Medical," 41–42; Bell, "Gallstone," 1215; Thistle, "Cholesterol," 832; Leslie J. Schoenfield, "The Disappearing Gallstone and the National Cooperative Gallstone Study," *JAMA*, 1978, *239*, 1162.

35 Thistle, "Cholesterol," 832.

36 R. Hermon Dowling and Paul N. Maton, "Dose of Chenodeoxycholic Acid for Gallstone Dissolution," *Lancet*, 1978, *8085*, 378–79.

37 Alan F. Hofmann, "The Medical Treatment of Cholesterol Gallstones: A Major Advance in Preventive Gastroenterology," *Am. J. Med.*, 1980, 69, 4–7; Alan F. Hofmann, "Medical Treatment of Cholesterol Gallstones by Bile Desaturating Agents," *Hepatology*, 1984, *4*, 199–208, 200.

38 "More about Chenodeoxycholic Acid," *BMJ*, 1973, *5893*, 629; G.D. Bell et al., "Liver Structure and Function in Cholelithiasis – Effect of Chenodeoxycholic Acid," *Gut*, 1974, *15*, 165–72; R. Hermon Dowling, H.Y.I. Mok, and G.D. Bell, "Chenodeoxycholic Acid and the Liver," *Lancet*, 1974, *7862*, 875–76.

39 "Progress in Dissolving Gallstones," *BMJ*, 1975, *5960*, 699–700; H.Y.I. Mok, G.D. Bell, and R. Hermon Dowling, "The Effects of Different Doses of Chenodeoxycholic Acid and of Withdrawing Treatment on Bile Lipid Composition and Liver Function in Patients with Gallstones," *Gut*, 1974, *15*, 335–48.

40 Ian Forgacs, "Shock News for Gallstones," *BMJ*, 1987, *295*, 737–38.

41 "Progress," 699.

42 D.C. Ruppin et al., "Gall Stone Disease Without Gall Stones – Bile Acid and Bile Lipid Metabolism after Complete Gallstone Dissolution," *Gut*, 1986, *27*, 559–66, 565; David C. Ruppin and R. Hermon Dowling, "Is Recurrence Inevitable after Gallstone Dissolution?" *Lancet*, 1982, *8265*, 181–85.

43 Bouchier, "Crown," 140.

In 1981, the National Cooperative Gallstone Study was published. This was a multicenter, double-blind randomized controlled clinical trial based at the Cedars-Sinai Medical Center of the University of California at Los Angeles School of Medicine and funded by the National Institutes of Medicine.[44] The trial included 916 randomly assigned patients treated at ten clinical centers across the USA and ran from November 1976 to August 1980.[45] Each patient was treated with 750 mg/day, 375 mg/day or placebo capsules and followed for two years.[46] The study was published a year after its conclusion and reported that, at the higher dose, complete dissolution of gallstones confirmed by oral cholecystogram, occurred in a mere 13.5 percent of patients, while partial or complete dissolution occurred in 40.8 percent of patients.[47] This outcome was compared to the results of previous, mostly uncontrolled, studies that observed complete dissolution of gallstones in 20 percent of patients and partial or complete dissolution in 50 percent of patients treated for up to two years. The significant difference in dissolution rates between the previous studies and the national study was explained by the lack of validation of gallstone dissolution in the previous studies.[48] The results of the study were disappointing and according to gastroenterologist Lloyd Sutherland, "have saddened many internists and gladdened many surgeons."[49] In spite of the low rate of complete dissolution, the study concluded that CDCA is an "appropriate therapy for dissolution of gallstones in selected patients who are informed of the risks and benefits."[50]

Surgeons on the other hand, interpreted the data collected from the National Gallstone Study very differently. In the same issue of *Annals of Internal Medicine*, Charles K. McSherry published "A Surgeon's Perspective" on the report. Here, the efficacy of CDCA was recalculated as the total number of patients who had achieved complete dissolution in both the high- and low-dose groups bringing the success rate down to a measly 8 percent.[51] This may not have been a fair reassessment, but it does provide an indication of the surgical community's reservations about chemical dissolution as a therapy for cholelithiasis. Accordingly, McSherry believed that "[t]he importance of the Cooperative Study is in demonstrating that chemical dissolution of gallstones is possible and not that it provides a satisfactory alternative to surgery."[52] For surgeons, the National Gallstone Study strengthened their belief that medical gallstone treatments were no

44 Leslie J. Schoenfield et al., "Chenodiol (Chenodeoxycholic Acid) for Dissolution of Gallstones – The National Cooperative Gallstone Study," *Ann. Intern. Med.*, 1981, *95*, 257–82; Schoenfield, "Disappearing," 1162.

45 Schoenfield, "Chenodiol," 271; John M. Lachin et al., "Design and Methodological Considerations in the National Cooperative Gallstone Study: A Multicenter Clinical Trial," *Control. Clin. Trials*, 1981, *2*, 177–229.

46 Schoenfield, "Chenodiol," 271.

47 Ibid., 257; Ibid., 275.

48 Ibid., 257.

49 Lloyd R. Sutherland, "Medical Dissolution of Gallstones: An Illusion?" *CMAJ*, 1983, *129*, 232–33.

50 Schoenfield, "Chenodiol," 257.

51 Charles K. McSherry, "The National Cooperative Gallstone Study Report: A Surgeon's Perspective," *Ann. Intern. Med.*, 1981, *95*, 379–80.

52 McSherry, "National," 380.

match for surgery. The medical community seemed to be turning on the idea of a nonsurgical treatment of cholelithiasis with no resolution in sight.[53] Interestingly, none of the major American pharmaceutical companies seemed to show any interest in the development of medical treatments for gallstones suggesting that they had little confidence that cholelithiasis would be redefined from a surgical disease to a medical one.[54]

There were, however, others who believed in the medical treatment of gallstones but also thought that for chemical dissolution to be successful it would have to be enhanced by other means. Extracorporeal shockwave lithotripsy was a technology that had already been used successfully for the nonsurgical fragmentation of kidney stones and thus seemed like the next logical step for the noninvasive treatment of gallstones. In 1986, a German group led by Tilman Sauerbruch published a report of their successful treatment of gallstones with lithotripsy prior to the oral administration of a CDCA/UDCA mixture to allow for increased surface area contact with the acid.[55] The group reported two years later that this combined treatment achieved complete dissolution of gallstones in 91 percent of their first 175 cases.[56]

As with the initial reaction to chemical dissolution therapy, the response to the addition of lithotripsy was enthusiastic and full of hope.[57] According to the gastroenterologist Alan Barkun, toward the end of the 1980s, "There was a huge amount of enthusiasm for gallbladder stone lithotripsy . . . people jumped on the bandwagon at that time. It was like a one-way train going to the lithotripsy . . .."[58] However, the issue of a high recurrence rate remained, making it difficult to compete with cholecystectomy.[59] Patients would have to maintain lifelong bile acid treatment, similar to pharmaceutical treatment of other chronic conditions—a situation that was not ideal, but seemed to be acceptable.[60] Interestingly, although lithotripsy was introduced to enhance the medical treatment of gallstones, jurisdiction over the technology was claimed by the specialties of radiology, surgery, and gastroenterology.[61]

Nevertheless, cholecystectomy with its mortality and morbidity rates of 0.4 percent and 7 percent respectively, appeared to remain the most reliable option in the treatment of cholelithiasis.[62] Echoing the beliefs of their forefather Carl Langenbuch, the Nashville

53 Forgacs, "Shock," 737; Sutherland, "Illusion," 232; Schoenfield, "Chenodiol," 271; R. Hermon Dowling and Dermot Gleeson, "Medical Aspects of Gallstones – 1985: Sixty Years On," *Postgrad. Med. J.*, 1985, *61*, 875–86, 880–83.

54 Hofmann, "Desaturating," 200.

55 Tilman Sauerbruch et al., "Fragmentation of Gallstones by Extracorporeal Shockwaves," *N. Engl. J. Med.*, 1986, *314*, 818–22.

56 Michael Sackmann et al., "Shock-wave Lithotripsy of Gallbladder Stones: The First 175 Patients," *N. Engl. J. Med.*, 1988, *318*, 393–97.

57 Jeffrey B. Raskin, "The Continuing Direct Assault on the Gallstone: Enlightening, Electrifying, and Shocking," *Gastrointest. Endosc.*, 1987, *33*, 262–63.

58 Alan Barkun, interview by Thomas Schlich and Cynthia Tang, Montreal, Quebec, January 12, 2015.

59 Raskin, "Assault," 263. Henk Vergunst et al., "Extracorporeal Shockwave Lithotripsy of Gallstones: Possibilities and Limitations," *Ann. Surg.*, 1989, *210*, 565–75.

60 Alan Barkun, interview.

61 Alan G. Johnson, "Extracorporeal Shockwave Lithotripsy for Gallstones," *J. R. Soc. Med.*, 1990, *83*, 66; Harvey Sigman, interview by Thomas Schlich and Cynthia Tang, Montreal, Quebec, June 18, 2015.

62 Forgacs, "Shock," 738.

surgeons Eddie Joe Reddick and Douglas Ole Olsen explained that "non-invasive methods of treating gallbladder disease have the major shortcoming of leaving a diseased organ in vivo, thereby predisposing the patient to recurrences of stones and gallbladder attacks."[63] However in spite of the low risk of surgery, the disappointing efficacy of CDCA, and the high recurrence rate after noninvasive treatment of cholelithiasis, physicians claimed that many patients preferred not to undergo surgery and were willing to endure long clinical trials of medical treatment in an attempt to avoid it.[64] As the pioneer of laparoscopic cholecystectomy François Dubois wrote in retrospect, both doctors and patients at this time were becoming increasingly apprehensive of the effects of general anesthesia as well as the inherent risks of open surgery. The cosmetic ramifications of the open procedure and the loss of wages due to recovery time were additional deterrents for patients.[65] In response, general surgeons attempted to minimize these disadvantageous aspects of open cholecystectomy by performing the surgery with an epidural anesthesia rather than subjecting the patient to general anesthesia. In addition, starting in 1982, surgeons began making progressively smaller incisions, developing what was called the "mini-cholecystectomy,"[66] allowing for shorter hospital stays and recovery times.[67] It was an indication, according to Olsen, "that surgeons are making an attempt to reduce [the] morbidity [of open surgery]."[68] Despite these adjustments, the medical treatment of gallstones was still considered to be "modern" and preferable to what was increasingly seen as the "old-fashioned" surgical method of open cholecystectomy.[69]

An "Explosion of Interest" in Laparoscopic Cholecystectomy

In the background of such sentiments was the fact that an even less invasive method was beginning to emerge. When, in 1987, the Paris surgeon François Dubois performed a mini-cholecystectomy and showed the new nurse on his surgical team what he claimed to be "the smallest scar in the world after gallbladder removal," the nurse was not impressed. She informed the surgeon that her previous employer, Phillipe Mouret, had successfully removed the gallbladder through a laparoscope just a few months earlier. Despite his immediate reaction of disbelief, the Parisian surgeon contacted Mouret to inquire about the technique. Mouret, a general surgeon with a private practice in Lyon, had been operating on a patient for a gynecological disorder when he opportunistically aimed the laparoscope upwards and removed the gallbladder to treat her gallstones, but had not published his results.[70] He agreed to meet Dubois at the

63 Eddie Joe Reddick and Douglas Ole Olsen, "Laparoscopic Laser Cholecystectomy: A Comparison with Mini-Lap Cholecystectomy," *Surg. Endosc.*, 1989, *3*, 131–33.
64 Sutherland, "Illusion," 232.
65 Dubois, "Historic," 53.
66 Douglas O. Olsen, "Mini-Lap Cholecystectomy," *Am. J. Surg.*, 1993, *165*, 440–43; Dubois, "Historic," 53.
67 Dubois, "Historic," 53; Olsen, "Mini-lap," 441.
68 Ibid., 440.
69 Dubois, "Historic," 53.
70 Grzegorz S. Litynski, "Mouret, Dubois, and Perissat: The Laparoscopic Breakthrough in Europe (1987-1988)," *J. Soc. Laparoend. Surg.*, 1999, *3*, 163–67.

Hilton Hotel in Paris and showed him the videos he had taken of two laparoscopic cholecystectomies. In reaction Dubois began to work with the technique as well.[71]

Eventually, Dubois published a report of his first 63 cases in *La Nouvelle Presse Medicale* in 1989,[72] followed by an English paper published in January 1990. By then the Paris surgeon had performed another 220 procedures with no complications in the last 180 patients.[73] Initially, as the pioneers of the method have noted in retrospect, many surgeons were skeptical about the new approach.[74] However, by the time Dubois' English-language report was printed in the *Annals of Surgery*, laparoscopic cholecystectomy had already spread from Europe to North America. Reddick and Olsen in Nashville had published their paper on laser laparoscopic cholecystectomy in September 1989.[75] Surgical groups from Cologne, Germany to Atlanta, Georgia to Omaha, Nebraska were taking up the revolutionary technique. Surgeons remember being impressed by the immediately visible and dramatic acceleration of postoperative recovery. According to one surgeon, it was "absolutely incredible . . . [patients] were usually able to go home the next morning and looked really quite good about a week or ten days after surgery."[76]

By 1991, only three years after Dubois performed his first cases in May 1988, laparoscopic cholecystectomy was already considered a routine procedure.[77] This phenomenon was often described as an "explosion of interest,"[78] thus emphasizing not only its speed but also the potential loss of control over the method's rapid spread. When in 1992 the National Institute of Health convened a Consensus Development Conference on Gallstones and Laparoscopic Cholecystectomy, it was estimated that the "demand for this form of surgery has escalated to the point where probably about 80 percent of cholecystectomies are being performed in this manner."[79] According to a group of British surgeons, the rapidity of the introduction of laparoscopic cholecystectomy into routine practice was "unprecedented in the history of surgical procedures."[80] The speed with which the surgical community adopted minimally invasive gallbladder removal is usually credited to the market demand for alternatives to open cholecystectomy.[81] Along these lines, the NIH Consensus Statement claimed that "laparoscopic cholecystectomy owes much of its rapid growth to market forces generated, not

71 Ibid., 164.
72 F. Dubois, G. Berthelot, and H. Levard, "Cholecystectomie par coelioscopie," *La Nouv. Presse Med.*, 1989, *18*, 980–82.
73 F. Dubois et al., "Coelioscopic Cholecystectomy: Preliminary Report of 36 Cases," *Ann. Surg.*, 1990, *211*, 59–62.
74 See, e.g., the recollections collected in Litynski, *Highlights.*
75 Reddick, "Laparoscopic laser," 131–33.
76 Gerald Fried, interview by Thomas Schlich and Cynthia Tang, Montreal, Quebec, June 13, 2014.
77 Dubois, "Coelioscopic," 60; Dubois, "Historic," 52–57;
78 Soper, "Laparoscopic," 591.
79 Sarah C. Kalser et al., "National Institutes of Health Consensus Development Conference Statement on Gallstones and Laparoscopic Cholecystectomy," *Am. J. Surg.*, 1993, *165*, 390–96.
80 Andrew J. McMahon et al., "Laparoscopic Versus Open Cholecystectomy and the Need for a Randomized Trial: A Survey of Surgeons and Ethical Committees in the British Isles," *J. Laparoendosc. Surg.*, 1992, *2*, 277.
81 Barkun, interview.

inappropriately, by patient demand."[82] Surgeons felt that if they did not offer the new technology they would lose patients: ". . . patients were driving the market" in a way that surgeons had not seen before.[83] The enthusiasm from patients for a less invasive treatment for cholelithiasis that was evident in their response to chemical dissolution therapy had clearly not wavered. In contrast, although laparoscopic techniques for appendectomy were also developed at this time, this procedure generated much less enthusiasm. Interestingly, surgeons explain this difference by a difference in market mechanisms: Whereas cholecystectomy is generally an elective procedure giving the patient time to consider his or her options, appendectomies are more often performed under emergency circumstances, so that the patients' choice played less of a role in the spread of MIS for this indication.[84]

There is further evidence of patient influence, where patient demand also pushed the frontiers of the method's indication.[85] For example, laparoscopic cholecystectomy was considered to be contraindicated during pregnancy when Harvey Sigman, a surgeon who was involved in the introduction of the technique in Montreal, was approached by a pregnant patient who asked specifically for the procedure.[86] When Sigman inquired into the reasons for its contraindication in pregnancy he was told, "Well you know, if the baby comes out with a problem, we may get sued . . . they'll say it was due to that. So we don't do it."[87] Sigman argued that laparoscopy, which originated in gynecology, was frequently performed in pregnant women by gynecologists for other purposes. So at the insistence of the patient, who was twenty weeks pregnant at the time of surgery, Sigman performed what he later found to be the second reported case of laparoscopic cholecystectomy in a pregnant patient.[88]

Despite the popularity and success of the technique, to the academic surgical community this patient demand-driven "explosion" was a movement that was getting out of control and needed to be reined in. Surgeons describe it as "a patient-driven, non-academic physician and company-supported Wild West"[89] with a "real risk that the procedures will be performed by many surgeons without adequate and proper training."[90] Private providers in the USA advertised the method directly to patients in whole-page ads, saying, for example that "Gallbladder Surgery Now Comes in Two Sizes."[91] Many surgeons in academic centers were concerned that without a proper assessment of the safety and efficacy of the new technique compared to open cholecystectomy and

82 Kalser, "National," 393.
83 Fried, interview.
84 Fried, interview.
85 Alex Mold, 'Repositioning the Patient: Patient Organizations, Consumerism, and Autonomy in Britain during the 1960s and 1970s', *Bull. Hist. Med.*, 2013, *87*, 225–49.
86 Sigman, interview.
87 Ibid.
88 Ibid.; Steven J. Jackson and Harvey H. Sigman, "Laparoscopic Cholecystectomy in Pregnancy," *J. Laparoendosc. Surg.*, 1993, *3*, 387–91.
89 Jeffrey Barkun, interview by Thomas Schlich and Cynthia Tang, Montreal, Quebec, September 24, 2014.
90 Alfred Cuschieri, George Berci, and Charles K. McSherry, "Laparoscopic Cholecystectomy," *Am. J. Surg.*, 1990, *159*, 273.
91 *The Miami Herald*, September 29, 1991.

adequate regulations for the training and accreditation of surgeons in laparoscopic cholecystectomy, the uncontrolled spread of the new procedure to smaller community hospitals would cause irreparable damage to the new technique's reputation and potential.[92] The popular press took up the story and featured doctors' warnings against the premature spread of the technique by insufficiently trained surgeons.[93] In fact, complications resulting from the unfettered use of the laparoscopic technique led the government of the state of New York to impose regulations.[94] Additionally, there was a great deal of concern that the technique had not been properly evaluated for safety.[95] Other editorials on laparoscopic cholecystectomy convey a sense of urgency in the need to regain control of the technique[96] through comprehensive training, accreditation programs and regulations, as well as properly controlled prospective clinical trials.[97] By then, prevailing standards for the introduction of new pharmaceuticals were evoked in an editorial in *The Lancet* lamenting that, "amid all the optimism there is one cause for regret – that once again a surgical procedure is finding a niche in standard practice after uncontrolled evaluations that would never pass muster for a new drug."[98]

THE PUSH FOR AN RCT

The most commonly used method of surgical evaluation has long been the case study. Surgical innovations are often announced to the community in the form of a case report and are then evaluated through case studies chronicling use under various circumstances and importantly, in different hands.[99] In many ways, the case study reflects the surgical field's emphasis on individual judgment and responsibility, as well as on the skill and experience of the operating surgeon. Although by the 1980s, the RCT had become an important reference method for evaluating pharmaceutical treatment, in surgery, reports of case series were still considered sufficient evidence of therapeutic effect.[100] Along these lines, Dubois' 1990 report on laparoscopic cholecystectomy consisted of the results of his first 36 cases.[101] More case studies detailing the experiences of other surgeons trickled into the surgical literature over the following two years. Some were prospective analyses of the first cohort of cases treated by laparoscopic

92 Zetka, *Surgeons*, 140; Cuschieri, "Laparoscopic," 273.

93 See, e.g., Lawrence K. Altman, "Complicated Surgery Through Tiny Incisions," *The New York Times*, August 14, 1990; Fried, interview; Sigman, interview.

94 Lawrence K. Altman, "Surgical Injuries Lead to New Rule," *The New York Times*, June 14, 1992, available at http://www.nytimes.com/1992/06/14/nyregion/surgical-injuries-lead-to-new-rule.html (accessed January 10, 2016).

95 Herschel A. Graves et al., "Appraisal of Laparoscopic Cholecystectomy," *Ann. Surg.*, 1991, *213*, 665–62, 661; Jeffrey F. Smith et al., "Comparison of Laparoscopic Cholecystectomy Versus Elective Open Surgery," *J. Laparoendosc. Surg.*, 1992, *2*, 311–17.

96 Ronald K. Tompkins, "Laparoscopic Cholecystectomy: Threat or Opportunity," *Arch. Surg.*, 1990, *125*, 1245; Cuschieri, "Laparoscopic," 273.

97 Tompkins, "Laparoscopic," 1245; Cuschieri, "Laparoscopic," 273.

98 "Cholecystectomy Practice Transformed," *Lancet*, 1991, *338*, 789–90.

99 Schlich, *Surgery*, 110–37; David S. Jones, "Visions of a Cure. Visualization, Clinical Trials, and Controversies in Cardiac Therapeutics, 1968-1998," *Isis*, 2000, *91*, 504–41.

100 See, e.g., Schlich, *Surgery*, 129–37.

101 Dubois, "Coelioscopic," 59–62.

cholecystectomy in a single center.[102] There were also both prospective and retrospective reports describing laparoscopic cholecystectomy cases performed at multiple institutions.[103] Another type of report prospectively or retrospectively compared the outcomes of laparoscopic cholecystectomies to those of open cholecystectomies performed either during the same time interval or right before the introduction of the laparoscopic method at the center.[104] These studies unanimously concluded that laparoscopic cholecystectomy was a safe and effective treatment for cholelithiasis with minimal risk when performed by a properly trained surgeon. None of these evaluations of laparoscopic cholecystectomy, however, was a truly randomized controlled clinical trial comparing the new technique to the prevailing standard of the open procedure. Without randomization, blinding, and prospective, parallel controls, bias could influence the assessment of results, causing some observers to consider the question of whether the laparoscopic method was as safe and effective as the open surgery to be unresolved.[105]

In April 1992, a survey of a random sample of 200 British general surgeons was conducted to determine whether the surgical community felt that a clinical trial that randomly assigned patients to either laparoscopic or open cholecystectomy was ethical.[106] For those surgeons who believed that there was already sufficient evidence for the superiority of the laparoscopic procedure, such a trial was not only unnecessary but perhaps also unethical, since it would require some patients to be randomly assigned to an outmoded procedure. The survey found that 58 percent of surgeons surveyed believed that it was necessary to perform a trial randomizing patients to laparoscopic cholecystectomy against either mini-cholecystectomy or open cholecystectomy, while 31 percent responded that such a trial would be unethical. The survey also found that 62 percent of respondents judged the safety of laparoscopic cholecystectomy to be satisfactory, leaving 38 percent unsure or concerned. In addition, ethics committees of a random sample of twenty teaching and twenty general hospitals received for approval a hypothetical ethics application for an RCT comparing open cholecystectomy to laparoscopic cholecystectomy. Twelve of these committees refused to comment but twenty-

102 Y.M. Dion and J. Morin, "Laparoscopic Cholecystectomy: A Report of 60 cases," *Can. J. Surg.*, 1990, *6*, 483–86; Jeffrey H. Peters et al., "Safety and Efficacy of Laparoscopic Cholecystectomy: A Prospective Analysis of 100 Initial Patients," *Ann. Surg.*, 1991, *213*, 3–12; Karl A. Zucker et al., "Laparoscopic Guided Cholecystectomy," *Am. J. Surg.*, 1991, *161*, 36–44; Graves, "Appraisal," 655–62; Robert J. Fitzgibbons Jr. et al., "Open Laparoscopy for Laparoscopic Cholecystectomy," *Surg. Laparosc. Endosc.*, 1991, *1*, 216–22.

103 Alfred Cuschieri et al., "The European Experience with Laparoscopic Cholecystectomy," *Am. J. Surg.*, 1991, *161*, 385–87; The Southern Surgeons Club, "A Prospective Analysis of 1518 Laparoscopic Cholecystectomies," *N. Engl. J. Med.*, 1991, *324*, 1073–78.

104 E. Neugebauer et al., "Conventional *Versus* Laparoscopic Cholecystectomy and the Randomized Controlled Trial," *Br. J. Surg.* 1991, *78*, 150–54; Smith, "Comparison," 311–17; Mark E. Stoker et al., "Laparoscopic Cholecystectomy: A Clinical and Financial Analysis of 280 Operations," *Arch. Surg.*, 1992, *127*, 589–95; Lester F. Williams Jr. et al., "Comparison of Laparoscopic Cholecystectomy with Open Cholecystectomy in a Single Center," *Am. J. Surg.*, 1993, *165*, 459–65.

105 For example: Graves, "Appraisal," 655; Thomas V. Holohan, "Laparoscopic Cholecystectomy," *Lancet*, 1991, *338*, 802; Zucker, "Guided," 36–42; Soper, "Laparoscopic," 651.

106 McMahon, "Survey," 277–80.

five gave approval, while three believed that the proposed trial would be unethical. Unsurprisingly, the survey found that those surgeons with more experience with the laparoscopic technique were less convinced of the need for an RCT. Based on this survey, it is clear that although the slight majority of surgeons believed that an RCT was needed to assess further the safety of laparoscopic cholecystectomy, the ethics of such a trial were still debatable. The authors of this study were themselves proponents of an RCT and argued that there was a higher incidence of bile duct injuries associated with the laparoscopic method and therefore "it is all the more urgent that the postulated benefits of laparoscopic cholecystectomy are put to the test of a randomized trial."[107] As we shall see, however, the rate of bile duct injuries as a result of laparoscopic surgery was too small to be easily detected by an RCT of practical size.

Related to these ethical questions, feasibility was another issue. To some, it appeared that the rapid emergence of laparoscopic cholecystectomy had made the performance of prospective trials comparing it to the old technique "all but impossible."[108] In fact, a group of surgeons led by Edmund Neugebauer in Cologne, Germany had attempted to perform an RCT comparing the two methods as early as October 1989.[109] While setting up the trial, the group was confronted with several practical problems that ultimately led them to convert their trial into an observational study. One of the biggest problems turned on the controversial issue of when to begin the trial. According to the Neugebauer group, on the one hand, "purists even state that it is scientifically and ethically inexcusable not to undertake RCTs as soon as possible."[110] However, surgery posed specific problems that complicated early RCTs, not only for laparascopic cholecystectomy, or even MIS, but for surgical procedures in general. Whereas drug therapy does not usually require special skills to administer new treatments, the results of a surgical treatment are highly dependent on the skill and experience of the operating surgeon. Therefore, participating surgeons must attain a certain level of skill with the new technique before the initiation of a trial. In surgery, skill has always been an important factor for the introduction of new techniques. However, the evaluation and appreciation of skill has been dependent on the contexts in which it was to be applied. Since the late nineteenth century the skill of following exact step-by-step instructions in a standardized way, thus enabling the replication of novel surgical procedures, has been considered a particularly important asset for surgeons.[111] In the context of clinical trials, surgical skill, however elusive it seemed to be, needed to be standardized to a certain degree. Thus, all surgeons in a trial had to reach a predetermined level of skill in order to be able to treat their operations as equivalent. In addition, investigators' experience with the technique was also necessary in order to determine appropriate endpoints and outcome indices.[112] But as historian David Jones notes in his study

107 Ibid., 280.
108 Smith, "Comparison," 312.
109 Neugebauer, "Conventional *Versus* Laparoscopic," 150–54.
110 Ibid., 150.
111 For this, see Thomas Schlich, "'The Days of Brilliancy Are Past': Skill, Styles and the Changing Rules of Surgical Performance, ca. 1820-1920," *Med. History*, 2015, 59, 379–403.
112 Neugebauer, "Conventional *Versus* Laparoscopic," 150.

on coronary artery bypass grafting, RCTs in surgery are further complicated by the experience of immediate success achieved by practitioners possessing the required skills, convincing surgeons of the efficacy of a new technique.[113] This makes it often seem unethical to conduct an RCT and randomize patients to another, inferior treatment. Sigman, for example, who was associated with the McGill Gallstone Group and contributed several patients to the trial, reported how his vast experience with laparoscopic cholecystectomy by the time the trial was organized made it ethically problematic for him to convince patients to join the study[114]—which fits in with the general observation by sociologist James Zetka on surgeons' concerns about the ethical admissibility of assigning patients to control groups "when they believed that the new technique could better help them."[115] This concern was reiterated by the Neugebauer group, insisting that it is "quite wrong for surgeons to engage in a RCT unless they are convinced that the answers to the questions being addressed are truly unknown."[116] This means that surgeons at the time doubted the existence of "clinical equipoise," a term coined in 1987 by bioethicist Benjamin Freedman who defined it as "a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial."[117]

THE MCGILL GALLSTONE STUDY

Interestingly, the McGill Gallstone Study, which included the first RCT on laparoscopic cholecystectomy, was not initially intended to test this therapy. In 1988, Alan Barkun, Chief Medical Resident at McGill University hospitals, went to France to train in lithotripsy only to return in 1990 to find "the most bizarre thing happened, that basically lithotripsies dropped off the map." Although enthusiasm for gallbladder stone lithotripsy was high prior to Barkun's departure for France, the high recurrence rate of gallstones after the therapy had begun to limit its use.[118] Barkun, who was at the time pursuing a master's degree in epidemiology and biostatistics at McGill University, set out to convince the *Fonds de Recherche Santé Québec* to fund a randomized trial comparing lithotripsy to open cholecystectomy. Barkun's twin brother Jeffrey Barkun was also in the program in epidemiology and biostatistics and decided to join his brother's trial on lithotripsy for his thesis work. At the time, however, Jeffrey was pursuing a biliary surgical fellowship in Toronto learning to do laparoscopic cholecystectomy.[119] The brothers realized that a third arm to the trial should be added to evaluate the emerging technique of laparoscopic cholecystectomy, which looked like a promising, and

113 Jones, "Visions," 531.
114 Sigman, interview.
115 Zetka, *Surgeons,* 105.
116 Neugebauer, "Conventional *Versus* Laparoscopic," 152. However, Neugebauer's group hoped that an RCT evaluating the minimally invasive technique would one day be successfully performed.
117 Benjamin Freedman, "Equipoise and the Ethics of Clinical Research," *N. Engl. J. Med.*, 1987, *317*, 141–45.
118 Alan Barkun, interview.
119 Jeffrey Barkun, interview.

popular, alternative.[120] The feeling at the time was that a rapid and uncontrolled spread of the technique was "just happening" without "formal, structured assessment,"—not an "ideal development," as Jeffrey Barkun later pointed out.[121] Barkun's concern built on the wide-spread expectation that new techniques ideally followed a linear development, with an innovative concept developed in medical research being first subjected to clinical trials and publication review, and only then diffusing out into community use. As the sociologist Zetka noted, for laparoscopic gallbladder removal, "this course was reversed," with an eager embrace of the procedure well in advance of complete testing.[122]

The Barkun brothers recognized that the developing use of laparoscopic cholecystectomy had strayed from the ideal path for an innovative therapy in medicine. Together the twins—a gastroenterologist and a gastrointestinal surgeon—spent a weekend in Montreal writing another grant proposal for a randomized trial comparing laparoscopic to the mini-open cholecystectomy using some of the same protocols from the first study, including the patient identification and triaging protocols resulting in "two randomized trials side-by-side, almost like the three-way randomization."[123] In order to meet the grant submission deadline of the Medical Research Council (now the Canadian Institute for Health Research), Alan Barkun made a two-hour trek to his parents' house in Ottawa where they were hosting a cocktail party. The Barkun family patriarch, Harvey Barkun, was the executive director of the Association of Canadian Medical Colleges as well as medical director of the Royal Victoria Hospital, Executive Director of the Montreal General Hospital, and Associate Dean of Professional Affairs of the McGill Faculty of Medicine. Fortunately for the Barkun twins, the Dean of Medicine at McGill was a guest at their parents' party and was willing to sign the proposal so that they could meet the deadline.[124]

This episode points to the many contingent circumstances in the origins of the first RCT on laparoscopic cholecystectomy—in this case the fortuitous family connections of the Barkun twins. Other such personal networks had significance for the initiation of related clinical trials, as, for example, the connection of Hans Troidl in Cologne, Germany, one of the few surgeons in the mid-1980s who was eager to use RCTs.[125] Troidl was a co-author on the paper by the Neugebauer group, mentioned above.[126] The German surgeon combined a skeptical attitude toward evidence in surgery with a strong interest in epistemic questions, based mainly on Karl Popper's critical epistemology, as was not unusual for the time.[127] In the McGill study, two of the surgeons who helped drive the RCT had trained with Troidl in Cologne. Jeffrey Barkun spent a year of his surgical residency training with him at the University of Cologne. By chance,

120 Alan Barkun, interview.
121 Jeffrey Barkun, interview.
122 Zetka, "Technological," 139.
123 Alan Barkun, interview.
124 Ibid.
125 Jeffrey Barkun, interview.
126 Neugebauer, "Conventional *Versus* Laparoscopic," 150–54.
127 Hans Troidl, interview by Nils Hannson, Starnberg, Germany, March 25, 2015.

the McGill surgeon Gerald Fried met Troidl in 1990 when the German surgeon was visiting Montreal to work on a book with David Mulder, then Chief of Surgery at the Montreal General Hospital.[128] Troidl had co-edited the textbook, *Principle and Practice of Research: Strategies for Surgical Investigators*, with Mulder and Walter Spitzer, Chairman of the Department of Epidemiology and Biostatistics and editor of the Journal of Clinical Epidemiology at the time.[129]

Passing by Mulder's office one Saturday morning, Fried was invited to join the two senior surgeons for lunch where Troidl told him about a new surgery he was doing in Cologne, the laparoscopic cholecystectomy. According to Fried, Troidl invited him to Germany to learn to do this operation, so that one day he would "be a famous surgeon." Because of this chance encounter on a Saturday morning, Fried had the opportunity to spend a week in Cologne learning the laparoscopic technique from Troidl.[130] It is conceivable that the encounters of both Fried and Jeffrey Barkun with Troidl contributed to their belief that an RCT evaluating laparoscopic cholecystectomy was necessary. It is also possible that during the year that Jeffrey Barkun spent in Germany, Troidl was able to impress upon him the importance of evidence-based medicine, motivating him and his brother to pursue graduate studies in epidemiology and biostatistics at a time when there was "no more than ten surgeons with epidemiology training in Canada."[131] We can see how this personal network of motivated researchers developed, forming a favorable environment for the RCT. This configuration helped to shape a specific local culture at McGill of heightened attention to evidence, which was another contingent factor in the background of the surgical RCT.

As discussed above, at this time, patient demand for the laparoscopic method was high, which made it difficult to include the older method of open surgery in clinical trials. According to surgeons' reports, patients knew that they wanted the MIS for cholelithiasis and many were not willing to be randomized in a trial where there was a chance that they would receive an open procedure. A surgical group in Nashville, Tennessee, published a retrospective study in April 1993 noting the same problem: "after the laparoscopic method of cholecystectomy was introduced in our community, it quickly became accepted and requested by the majority of patients, making it very difficult, if not impossible, to conduct such a trial."[132] A related problem in trying to evaluate laparoscopic cholecystectomy was that patients who were randomized to a nonlaparoscopic group could drop out and go elsewhere to have the operation. This is where Alan and Jeffrey Barkun believed they had an advantage in running their trial. According to the brothers and other authors of the study, the McGill Gallstone Treatment Clinic, which was created to run the cholelithiasis treatment study at multiple hospitals in Montreal, was the only clinic in the area that performed laparoscopic cholecystectomy, giving it a relative dominance over the treatment. However, as Fried, who became one of the other authors of the McGill Gallstone Study, noted, the situation was markedly

128 Jeffrey Barkun, interview; Fried, interview.
129 Samuel Shapiro, "In Memoriam Walter O. Spitzer (1937-2006)," *Am. J. Epidemiol., 2006, 164, 607.*
130 Fried, interview.
131 Jeffrey Barkun, interview; this was also discussed in Crenner, "Placebos," 12–14.
132 Williams, "Single Center," 462.

different from the conditions under the market-driven American health care system where the patients could easily switch to another doctor or hospital. In Canada, in contrast, doctors could make the treatment contingent on their patients' participation in a randomized trial in order to have a one in three chance of getting the MIS.[133] Even so, there were patients who were approached to join the trial but refused, citing reasons such as "I won't be a guinea pig" and "I came for the 'Laser' treatment," as Jeffrey Barkun later wrote to the editor of the *Lancet*.[134] As some patients resisted the trial, and the restrictive policy was no less controversial among some surgeons, for whom it reeked of "coercion."[135]

The Canadian context also allowed for other ways of exerting control over the technology. As Sigman reports, hospital privileges at the Montreal Jewish General Hospital for the use of the technique were only granted to surgeons who had been properly trained and deemed to be ready, in contrast to the situation described above in New York State. A whole list of conditions had to be fulfilled: the completion of a residency program that included laparoscopic surgery, other previous experience or instruction in the method, a written report by a "tutor" about the competency of the surgeon in diagnostic laparoscopy, participation in a "university-sponsored or academic society-recognized didactic course with clinical experience and hands-on live animal laboratory practice of two days duration," assistance in "at least ten laparoscopic cholecystectomies in humans," and performance of "at least five laparoscopic cholecystectomies under supervision." The surgeon must have "been proctored by an experienced surgeon in laparoscopic cholecystectomy (chosen by the head of the division of surgery at the JGH)." Furthermore, he or she "must provide notification to their patients of their experience with the procedure," "the results of laparoscopic surgery of each surgeon must be reviewed by a committee, designated by the head of the division, at six months intervals in order to renew laparoscopic privileges," and the surgeon had to attend one surgical meeting or course on laparoscopic surgery per year to keep updated.[136] As part of his training program, Sigman would have inexperienced surgeons work with his team and eventually give them access to the method once they had acquired the necessary skills.[137] This restriction was of course not popular with everybody and led to tension with some of his colleagues—it was "a big political battle going on at that time," as he put it.[138]

Another aspect of the Canadian situation was the relative scarcity of the equipment. Alan and Jeffrey Barkun and Jonathan Meakins wrote in the *American Journal of Surgery* that "The dissemination of [laparoscopic cholecystectomy] in Canada has been slower than in the USA, mostly because of the availability of equipment."[139] At that time, the

133 Fried, interview.

134 Jeffrey Barkun, Letter to Dr. Fox of *The Lancet* dated July 10, 1992. Archival material obtained from Jeffrey Barkun.

135 Sigman, interview.

136 "Jewish General Hospital Criteria for Granting Privileges in Laparoscopic Surgery," Fax copy of 1993, private archive, Harvey Sigman.

137 Sigman, interview.

138 Ibid.

139 Jeffrey S. Barkun, Alan N. Barkun, and Jonathan L. Meakins, "Laparoscopic Versus Open Cholecystectomy: The Canadian Experience," *Am. J. Surg.*, 1993, *165*, 455–58.

Canadian market was given low priority by the manufacturer and it took months before the equipment was delivered, "so that the Americans got first dibs on whatever's coming out." The Canadians were

> using borrowed equipment for about three months . . . [meaning] that, that equipment was crossing Canada. It would be in Burnaby three days ago, it would be in Toronto yesterday, Laval today, you could have it in two weeks. So you booked the patient ahead of time . . . then they would call you two days beforehand and would say [that] one piece is broken and needs to be repaired, so you would have to cancel.[140]

In history, scarcity of treatment material, of drugs or devices, has often been an important factor in controlling the spread of a new therapy.[141] Both the scarcity of instruments as well as the training requirements for surgeons to be given hospital privileges most likely contributed to the limited access to the minimally invasive treatment in Montreal, making it possible for the McGill Group to recruit enough patients to the RCT.

For the McGill study, patients were recruited from four university hospitals in Montreal and one in Toronto between September 1990 and September 1991.[142] Despite their relative control over the technique, the McGill group still had difficulty with patients dropping out after being randomized. Of the thirty-two patients randomized to the mini-cholecystectomy arm of the study, only twenty-five (78 percent) remained in the trial after randomization, albeit three of the patients that dropped out are known to have undergone non-mini open cholecystectomies by surgeons who were not participating in the trial. In comparison, only one patient withdrew from the laparoscopic group after randomization.[143] This, as the authors noted, reflected "the poor acceptance of surgical randomization by patients."[144]

As discussed earlier, one of the problems in conducting a surgical RCT stems from the dependence of the outcomes on the skill of the surgeon. Unlike pharmaceutical treatments, with a new surgical innovation there is a distinct learning curve for each surgeon. The RCT needed to be designed in a way that they started at the point in the learning curve of the group of surgeons involved where the skill levels were sufficiently similar. In addition, for clinical equipoise to exist, and thus for the study to remain ethical in randomly assigning treatments, the surgeons had to be equivalently skilled in applying both treatments. In order to calibrate this issue, Jonathan Meakins, one of the leading surgeons in the study, and the chair of the Department of Surgery at McGill at the time, instigated the establishment of a registry for the McGill Gallstone Group. In this registry, all laparoscopic cholecystectomies from the very beginning were diligently documented.[145] The resulting "McGill Laparoscopic Database" contained a standardized set of information

140 Sigman, interview.
141 See for surgery, e.g., Schlich, "Degrees of Control."
142 Barkun, "Laparoscopic," 1116.
143 Ibid., 1117.
144 Ibid., 1119.
145 Jonathan Meakins, interview by Thomas Schlich and Cynthia Tang, Montreal, Quebec, July 7, 2014.

on each patient, the operation done, the postoperative course, and the occurrence of complications.[146]

But clinical equipoise proved to be a slippery concept. According to Fried, RCTs are not usually of sufficient size to detect differences in the rare complications that might determine a slight superiority of one procedure over the other. Large case registries are better suited for judging the rates of infrequent but catastrophic complications such as bile duct injury.[147] Bile duct injuries occur at a rate of about 0.3 percent in open cholecystectomy. During the early days of laparoscopic cholecystectomy, the rate of bile duct injuries was estimated to be as high as 1 percent. A trial with thirty patients in each treatment group would not be able to detect such a low rate of complication, whereas a registry, such as the one published in 1991 in the *New England Journal of Medicine* by the Southern Surgeons Club which included over 1500 cases, could measure the risk of such relatively infrequent occurrences.[148] What looked like equipoise from one perspective might gradually disappear with the steady accumulation of data.

The McGill registry thus allowed the authors to track the outcomes of all laparoscopic surgeries done at the institution. Importantly, it also made it possible to determine when the learning curves of the surgeons began to plateau as well as which endpoints to measure in the study.[149] In order to standardize the surgical skill levels and make patients treated by different surgeons comparable, participating surgeons were required to have performed at least thirty laparoscopic procedures prior to the start of the trial as well as have the ability to do both the open and the minimally invasive procedures.[150] The endpoints that were chosen to be measured in the RCT were the duration of the operation, the rate of conversion to open cholecystectomy, the length of the hospital stay, postoperative days to full diet, duration of convalescence, postoperative pain, and quality of life.[151] Patients were followed up as outpatients for at least three months after the operation.[152] Postoperative pain was determined from the level of narcotics use during the hospital stay and the first postoperative week as well as by the McGill Pain Questionnaire. Quality of life was assessed preoperatively and at one and three months after the operation, using the Nottingham Health Profile Questionnaire, a German gastrointestinal surgery quality of life index which is based on patients rating their quality of life on a scale of 0 (poor) to 11 (excellent).[153]

However, the study had to be terminated before the sample size that had been calculated as being statistically significant at the start of the trial was reached, because patient recruitment became a major difficulty. According to Meakins, the trial was shut down because both the patients and the surgeons had lost "equipoise," believing that the superiority of the laparoscopic procedure in providing rapid, less painful recovery was too

146 The McGill Laparoscopic Database, form, undated, private archive, Harvey Sigman, Montreal.
147 Fried, interview.
148 Fried, interview; The Southern Surgeons Club, "1518 Laparoscopic," 1073–78.
149 Fried, interview.
150 Barkun, "Laparoscopic," 1116.
151 Ibid., 1117.
152 Ibid., 1116.
153 Ibid., 1117.

clear to continue to assign people randomly to open procedures.[154] And indeed, despite the early termination of the trial and the small sample size, the McGill Gallstone Group was able to show a statistically and clinically significant difference in the duration of convalescence between the mini-cholecystectomy and laparoscopic cholecystectomy groups. It was found that patients recovered from laparoscopic surgery 1.77 times faster than patients who had received the open surgery.[155] This optimistic view was not shared by everyone in the surgical public: Letters to the editor following the publication of the study in *The Lancet* show that other surgeons judged the statistical significance of the trial to be insufficient. The British group that had published the survey about the need for an RCT to evaluate laparoscopic cholecystectomy in 1992, now commented that "Dr. Barkun and colleagues' data hardly justify their conclusion that laparoscopic cholecystectomy is more effective than mini-cholecystectomy. The small sample size and difficulties with randomization limit the value of this trial."[156] In his author's reply in the journal, Jeffrey Barkun justified the limited size of the study on ethical grounds, since the "power of the study allowed" the researchers "to detect statistically and clinically significant differences. To have recruited more would not have altered the study conclusions and would have been ethically difficult to justify in the eyes of patients and surgeons."[157] Similarly, a later RCT also published in *The Lancet* by a group at the Prince of Wales Hospital in Hong Kong was likewise terminated due to loss of equipoise.[158]

The McGill Gallstone Group concluded that laparoscopic cholecystectomy produced superior results in terms of postoperative quality of life, as measured by duration of convalescence and time taken to return to a full diet[159] when compared to the mini-cholecystectomy. However, there were also limitations.[160] Among other things, the authors could not draw conclusions about comparative mortality and morbidity rates because of the small sample size, thus falling short on a more fundamental measure of clinical outcomes.[161] Nevertheless, similar RCTs on laparoscopic versus open cholecystectomy continued to be published analyzing other more proximate outcome measures such as, immune function, metabolic responses, pulmonary function, and the effects of surgical trauma, among others.[162]

154 Jeffrey Barkun, interview. Meakins, interview.

155 Barkun, "Laparoscopic," 1118.

156 Andrew J. McMahon et al., "Laparoscopic Cholecystectomy," *Lancet*, 1993, *341*, 249.

157 Jeffrey Barkun, "Laparoscopic Cholecystectomy - Author's Reply," *Lancet*, 1993, *341*, 249.

158 J.J.T. Tate et al., "Laparoscopic Versus Mini-Incision Cholecystectomy," *Lancet*, 1993, *341*, 1214.

159 Ibid.

160 Ibid.; The third arm of the study, which compared lithotripsy therapy to the mini-cholecystectomy, did not look at laparoscopic cholecystectomy and thus will not be discussed in this article.

161 Ibid., 1118.

162 For example, H.P. Redmond et al., "Immune Function in Patients Undergoing Open vs Laparoscopic Cholecystectomy," *Arch. Surg.*, 1994, *129*, 1240–46; A. Milheiro et al., "Metabolic Responses to Cholecystectomy: Open vs. Laparoscopic Approach," *J. Laparoendosc. Surg.*, 1994, *4*, 311–17; A.J. McMahon et al., "Laparoscopic and Minilaparotomy Cholecystectomy: A Randomized Trial Comparing Postoperative Pain and Pulmonary Function," *Surgery*, 1994, *115*, 533–39; R. Dionigi et al., "Effects of Surgical Trauma of Laparoscopic vs. Open Cholecystectomy," *Hepatogastroenterology*, 1994, *41*, 471–76.

CONCLUSION: THE MULTIPLE MEANINGS OF RCTS

The instigation, performance, and meaning of RCTs can be investigated at different levels. We have seen how, at the local level, a clinical trial was facilitated through mechanisms for controlling the access to, and the use of, the treatment method. In the case of laparoscopic cholecystectomy in Montreal, this control was manifested through limits on the practitioners who offered the new treatment as well as on patients who sought it out. We have seen how, by comparison, other research groups were not able to complete clinical trials because patients could readily opt out of the study after randomization to seek care elsewhere. This finding also highlights the importance of patient agency and choice in the deployment of RCTs, a factor that should be investigated further in accounts of both the history of clinical trials and the history of surgical innovation. The value of control has been shown previously for other historical cases as well, as for example, famously, in the first RCT conducted by Austin Bradford Hill to evaluate the use of streptomycin in tuberculosis treatment;[163] or, as mentioned above, in the development of operative fracture care in communist East Germany in the 1970–1980s.[164] The McGill case also points to the importance of what one could call local cultures of evidence where RCTs could be initiated, conducted, and valued. Such cultures of evidence have local as well as more distributed elements. At McGill, this culture was in part institutionalized within the Department of Epidemiology and Biostatistics. In part it was a personal network that included clinicians such as Mulder, Fried and the Barkun brothers, and extended internationally to reach Troidl in Germany and the Cologne group. Within this network, the RCT as the standard of evidence was not controversial and warranted application to the rigorous testing of laparoscopic cholecystectomy. We can also see the importance of motivated researchers for this kind of project. For Fried as a young surgeon, for example, the new technology was an opportunity to build a reputation in a particular area of expertise. Similarly, for the Barkun brothers, the testing of treatment methods by RCTs represented an attractive opportunity to apply their research skills, and to build upon their personal connections. The project was relevant and timely enough to be able to be financed by a high-prestige funding agency and subsequently published in high profile journals such as *The Lancet*. The history of this RCT is a good example of the importance of the local dimensions of clinical trials generally. To be sure, the RCT as a method comes with a strong claim of universality and context-independence. Thus, data originating from RCTs are ranked as the most objective and valid form of evidence in weighing the value of treatment. However, the historical examination of clinical trials requires the opposite movement: historians need to focus on the local context of an individual RCT's design, use, and effect, and take this local dimension into account.[165]

163 Marks, *The Progress of Experiment*, 136–263, Peter Keating and Alberto Cambrosio, "Before There Were Trials," *Cancer on Trial: Oncology as a New Style of Practice* (Chicago: University of Chicago Press, 2012), 33–52, 52; Marcia L. Meldrum, "Brief History of the Randomized Controlled Trial: From Oranges and Lemons to the Gold Standard," *Hematol. Oncol. Clin. North Am.*, 2000, *14*, 745–60, 752.

164 Schlich, "Degrees of Control."

165 This is in line with other historical studies of clinical trials, e.g. Marks, *The Progress of Experiment*; and Jones, "Visions."

A further important historical context for the RCT relates to its position within the therapeutic landscape of its time. We can only fully understand the motivations for testing laparoscopic cholecystectomy if we look at the other treatment options for cholelithiasis that were available. The RCT drew its significance from the context of the different competing therapeutic approaches—open surgery with large or small access, pharmaceutical gallstone dissolution treatment with or without lithotripsy, and MIS. The history of the various therapeutic approaches shows why laparoscopic cholecystectomy was particularly attractive to doctors and patients at that point in time: It combined the advantage of the definitive surgical approach with a low level of invasiveness making it comparable to more conservative treatment. The enthusiasm for less invasive treatments for cholelithiasis generated by chemical dissolution therapy and lithotripsy may have been a contributing factor to the unprecedented speed with which patients accepted laparoscopic cholecystectomy. It is illuminating to see the dynamics of the mutual influence among these approaches, and how the advent of MIS re-positioned the elements of the therapeutic calculus of cholelithiasis. Thus, without MIS, lithotripsy might have become the standard treatment for the disorder,[166] diverting patients away from surgeons.

What was the function and the effect of the RCT in all of that? The general consensus of the researchers that were interviewed was that although an RCT evaluating laparoscopic cholecystectomy was highly anticipated and the McGill study was ultimately published in *The Lancet*, its impact on the technique's general acceptance for the treatment of cholelithiasis was insignificant.[167] By the time the study was published, Alan Barkun, pointed out, "people said, 'Oh, that's nice.' But everybody was already convinced that laparoscopic was the way to go." The high quality of evidence from the study was appreciated, but the change in practice had already taken place.[168] Still, the McGill group felt that the comparative evidence examining laparoscopic versus minicholecystectomy in terms of safety and short- and long-term outcomes was insufficient prior to their RCT. Since there were reports of a higher incidence of common bile duct injury as a result of the laparoscopic method, the authors believed that the advantages of laparoscopic surgery over open surgery needed to be proven and clearly defined in order to improve the analysis of risk and benefit.[169] Even surgeons who had ethical concerns about convincing patients to be part of the trial defended the trial because of its capacity to detect and objectify shortcomings that had not been appreciated before. One interviewee made the comparison to "procedures that have been around for a long time and all of a sudden they become discredited because one realizes there are things that are happening that you didn't know about or think about at the time."[170] Examples of procedures with such unanticipated consequences included gastric freezing for

166 Alan Barkun, interview.

167 Fried, interview; Meakins, interview; Jeffrey Barkun, interview; Alan Barkun, interview.

168 Alan Barkun, interview.

169 Jeffrey S. Barkun, *A Randomised Controlled Trial Comparing Laparoscopic to Mini Cholecystectomy* (MSc thesis: McGill University, 1993), 17.

170 Sigman, interview.

ulcers, mentioned by Barkun,[171] and internal mammary artery ligation for the treatment of angina, investigated by historians.[172] Surgeons had felt sure of the benefits of these treatments, and thus wanted to reject the clinical equipoise necessary for an ethical trial. Similarly, in the debate over clinical trials to evaluate radical versus simple mastectomy, surgeons felt it to be unethical to randomize patients to what seemed an inferior treatment.[173] The laparoscopic cholecystectomy trial won allies for its potential to expose some such shortcomings, although, as noted above, the sample size in the McGill study was too small to detect a difference in rare complications such as bile duct injury.

We have also seen that, apart from determining the benefits and risks of laparoscopic cholecystectomy, the idea of controlling a therapeutic enthusiasm that had gotten out of hand was another important appeal of the RCT. Thus RCTs are not only about objectively evaluating new therapies. They are also about managing and controlling the spread of new treatments, keeping them, or drawing them back into the hands of the medical centers that are seen as acting responsibly and in a disciplined way, thus regaining control and re-centering developments that come from the perceived margins of academic medicine. Thus RCTs have more than one meaning. Likewise, performing and completing RCTs depends on a whole range of conditions. The openness of the original question examining the safety and efficacy of a treatment method is just one such condition. Investigating this more general context of different treatment options alongside the RCT's local context makes it possible to see how these levels of context are linked up in the inception and implementation of such a trial. It shows how local actors try to create universal validity for their trial, how such claims can be contested, and to what degree the claim to universality may rely on the control of local conditions. Combining the examination of various levels of context in the historical study of clinical trials and their role in medical innovation thus helps to elucidate how even an experimental method with a strong claim to clarity and universality can have multiple meanings and functions.

ACKNOWLEDGEMENTS

The authors would like to extend many thanks to George Weisz for his comments on a previous version of this paper, as well as to Nicholas Whitfield, Ariel Zimmerman, the McGill History of Surgery Group, and our anonymous reviewers for their careful reading, encouragement, and helpful comments.

FUNDING

This work is funded by the Canadian Institutes of Health Research (MOP-130488).

171 Jeffrey Barkun, interview.
172 Jones, "Visions."
173 Lerner, "Reality," 124.