
Evolution of a Clinical Trial: The STOP-DUB Experience

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Whether the goal is to design a clinical trial or to optimize individual patient care, finding, evaluating and staying current with reliable research findings can be difficult. The process by which systematic reviews and new information have been incorporated into the design of an ongoing clinical trial serves as an example of one means of accomplishing this task.

In 1996 our group at the University of Maryland initiated a multicenter, randomized clinical trial, the Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding (STOP-DUB),¹ in conjunction with the Gynecologic Studies Group, which is affiliated with the American College of Obstetricians and Gynecologists. The process by which we investigated the need for and, subsequently, designed and revised this study serves as an example of the close interaction between medical practice and research. This relationship is increasingly recognized as critical to the practice of evidence-based health care, the conscientious use of current best evidence in making decisions about the care of individual patients and the delivery of health services.² It should be noted that evidence-based health care does not exclude other elements of health-related decision making, such as patient preferences and clinician experience.

In this article I will describe the steps taken by our research group to obtain reliable summaries of current knowledge, frame appropriate research questions, keep abreast of the most recent data and reframe questions over time as new data emerged. In addition, I will highlight our use of specific resources currently employed by clinicians and researchers seeking efficient systems for obtaining and evaluating up-to-date, reliable information about the results of research. The general process we used is critical to those seeking to optimize individual patient care, and to those seeking to conduct relevant, well-designed research. These methods can be used not only to design clinical trials, but also to evaluate existing data for the purposes of routine patient care.

The well-designed, randomized clinical trial (RCT) remains the most rigorous study design and the gold standard for testing healthcare interventions. While RCTs form the basis of evidence-based decision making, until recently it has been largely up to individual clinicians and investigators to access and in-

formally synthesize reports of trials describing results in their interest areas. In some cases traditional literature reviews have been available, but these are often out of date and/or subjective, and follow no standardized format.

Systematic reviews, a fairly new concept in medicine, are reviews of existing knowledge that use explicit, scientific methods to assemble and update research on the topic in question. In a systematic review, the typical structure for a research report is used; the review methodology is described in detail (i.e., how the evidence is sought and synthesized), results are presented, usually in tabular form, and the findings are discussed in the context of current medical practice and other information. A systematic review can be accomplished whether or not the data from individual studies are combined quantitatively (meta-analysis).

High-quality systematic reviews based on RCTs are considered by many to be the highest level of evidence. In certain instances there are legitimate arguments about the appropriateness of combining data in a meta-analysis, but quality systematic reviews, which use scientific methods transparent to the reader, are always superior to *ad hoc* methods of reviewing the literature.

The process described below is an example of one way in which systematic reviews and recent updates have been incorporated into the design of an ongoing clinical trial.

STOP-DUB

In 1996 the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality [AHRQ]) issued a request for applications (RFA) for randomized trials to address research issues related to hysterectomy. The request was prompted by concern over appropriate utilization of hysterectomy and possible alternatives to the procedure for a number of conditions, including dysfunctional uterine bleeding (DUB).

Background. While the hysterectomy rate in the United States has decreased

somewhat in recent years, the incidence remains fairly high, and it is the most common nonobstetric surgery performed on women of reproductive age in the United States. In 1995 the incidence of hysterectomy was 5.5 per 1,000 women age 15 years and older (583,000 cases), according to data from the National Center for Health Statistics, National Hospital Discharge Survey.³ The United States has the highest rate of hysterectomy worldwide—more than twice that of Sweden, for example, where the rate was approximately 2 per 1,000 women 18 years and older in 1991.⁴ In 1995 in the United States, nearly half (42.8%) of women 55 years and older had undergone hysterectomy (data from the Behavioral Risk Factor Surveillance System).³

The rate of hysterectomy does not differ meaningfully across ethnic groups, but the procedure tends to be performed more often in women from lower income groups and with lower education levels; it is also associated with single marital status and with having medical insurance.³ Women in the southern United States are at the highest risk of hysterectomy, compared to women elsewhere in the country, especially those in the Northeast. Mortality rates associated with hysterectomy are fairly high; according to estimates of mortality from the 1950s forward, provided in a report from Rand,^{5,6} the mortality rate was approximately 1 per 1,000 women undergoing hysterectomy for nonmalignant indications. Studies have shown higher mortality post-hysterectomy in African-American women, compared to Caucasian women; in one study⁷ a mortality rate of 2.1 per 1,000 was reported for African-American women having hysterectomy for any indication, compared to a rate of 1.1 per 1,000 for Caucasian women. Morbidity rates associated with hysterectomy are also high and vary with the surgical approach taken, the use of antibiotics and other factors.^{5,6} Hysterectomy remains relatively expensive, despite decreasing duration of hospitalization.

Data on DUB itself are scarce; an estimated 9-14% women bleed 80 cc or more

per cycle,⁸ and an estimated 20% of the premenopausal population have DUB.⁹ The proportion of women undergoing hysterectomy for DUB has been estimated variously from a low of 4% in the United States¹⁰ to about 50% in the United Kingdom.¹¹

Medical therapy appears to be effective in most cases of DUB. For some women, however, medical therapy is not effective or is not well tolerated, and hysterectomy or an alternative surgery is recommended. In the United States in 1996, most women for whom medical DUB treatment was not satisfactory had hysterectomy.

Examining the evidence: The Cochrane Library. Because of our interest in women's health issues and clinical trials, we prepared to respond to AHRQ's RFA. We first investigated the best available evidence in this area and began by talking with our colleagues and experts in the field, asking them to share their knowledge about DUB and hysterectomy, medical and surgical alternatives, and current U.S. practice.

We then proceeded with a more formal search of the various sources of best clinical evidence, deciding to begin by looking at systematic reviews in *The Cochrane Library* (www.cochrane.org). *The Cochrane Library* (Figure) is a quarterly electronic publication, available by subscription to individuals and organizations by CD-ROM or via the Internet. It is a product of the Cochrane Collaboration,¹² an international, not-for-profit organization formed in 1993 to facilitate healthcare decision making by preparing, updating and promoting the accessibility of the effects of healthcare interventions. Reviews are prepared by "Review Groups," each of which covers a specific area of interest. Each of the approximately 50 groups recruits reviewers (primarily academicians) whose reviews are first submitted to the editorial group as protocols. Each protocol undergoes peer review and revision before being published by an independent software company in *The Cochrane Library*. The review



Figure. Opening page of *The Cochrane Library*.

is completed and undergoes a second round of peer review before full publication.

The Cochrane Library includes several databases useful to clinicians and researchers: The Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effectiveness (DARE), produced outside the Collaboration; and CENTRAL, the Cochrane Collaboration's database of approximately 350,000 reports of controlled trials.

Once inside the Library we performed a relatively simple search to find information. We typed our search terms—the root words hysterectom* and endometr*—and searched the Cochrane databases simultaneously. In 1996 there were not yet any completed reviews related to the search terms we entered, but we were able to identify a Cochrane "protocol" in progress, describing a systematic review comparing hysterectomy and endometrial ablation for abnormal bleeding.

Protocols and reviews follow a standard software-driven format that includes a methods section, detailed descriptions and tables of included studies and their findings and implications for practice and future research. The completed review is updated regularly, as often as quarterly

and at least every 2 years, as new data become available. The published review is subject to postpublication peer review by those accessing the Library via the "Comments and Criticism" option within *The Cochrane Library* software.

Since there were no completed reviews available at the time we were to begin our trial, we examined more closely The Cochrane database of controlled trials (CENTRAL) and identified three United Kingdom controlled trials related to our topic.¹⁴ We questioned whether the results of these trials, taken together, provided sufficient information on which to base practice, or whether an additional trial was needed. In addition to examining the evidence directly, we conferred with our gynecologist co-investigators, who felt that U.S. clinicians were not willing to generalize the results of these studies to their own patient populations. For one thing, the UK trials only included patients with ovulatory DUB. In addition, patients in other trials had undergone primarily abdominal hysterectomy and hysteroscopic endometrial resection techniques. These differences, in addition to others related to exclusion of obese patients and differences in payment systems, led our co-investigators to

favor initiation of a U.S.-based trial.

Our randomized trial to compare hysterectomy and endometrial ablation for the treatment of DUB was funded by AHRQ in 1996 for 5 years¹. The study population includes premenopausal women aged 18 years or older who have had DUB for at least 6 months and who have undergone a failed course of medical therapy of at least 3 months' duration. Additional enrollment criteria include having no known polyps and a willingness to consider surgery and experience loss of fertility. Our four major outcomes are outcomes of importance to women: relief from the major symptom that led the woman to seek treatment, as well as relief from bleeding, pelvic pain and fatigue. We were also interested in outcomes related to surgical complications, retreatment, costs, activity limitations, sexual function and quality-of-life issues associated with each of the interventions. Our original proposal specified that randomized women be followed for at least 2 years. The study involves 32 participating sites in the United States and Canada, and aims to randomize 250 women.

Responding to change. STOP-DUB will complete its fifth year on September 30, 2001; as evidence becomes available and changes in medical practice occur, we continuously reevaluate the relevance, direction and design of our study. Any protocol changes are reviewed and approved by the Data and Safety Monitoring Committee, the Steering Committee and the AHRQ.

Recruitment to STOP-DUB was much more difficult than we originally anticipated, in part because many clinicians and patients have a preference for one type of surgery, even if the evidence is not yet conclusive. Thus, although recruitment was initially planned to take 2 years, the protocol was modified to allow it to continue until April 2001.

A significant protocol change occurred in 1997, when the FDA approved use of a specific type of nonhysteroscopic ablation using a thermal balloon. In response, we altered the STOP-DUB protocol to

allow this type of ablation, in accordance with our goal of conducting a trial relevant to current U.S. medical practice. Another change occurred in the fall of 1998, when our group, which serves as STOP-DUB's coordinating center, moved to Brown University, where it remains today.

In 1999, 4-year results from the Aberdeen Trial¹³ provided new information about retreatment rates for women who had undergone endometrial resection and ablation. At 4 years of follow-up, almost 40% of the Aberdeen women treated with resection or ablation had undergone retreatment. These findings had not been anticipated when we started the study, and we recognized that it would be important to increase the length of follow-up in STOP-DUB, to see whether the U.S. experience would be similar. Hence, in March 2000, STOP-DUB was modified to increase patient follow-up to a minimum of 4 years (pending funding for continuation).

During our ongoing study we have regularly returned to *The Cochrane Library* to learn of new developments. In 1999 our search yielded a completed Cochrane review and five randomized trials.¹⁴ Cochrane reviews include a detailed evidence table summarizing descriptive characteristics of the individual studies. Also included are summaries of meta-analyses for a range of outcomes, including morbidity, mortality and quality of life, all listed by duration of follow-up. We were especially interested in the review's outcomes for "need for further surgery," and analyses at 1, 2, 3 and 4 years of follow-up. The review showed that only the Aberdeen Trial had produced long-term follow-up information. The review also provided information about the proportion of women satisfied with treatment and reported that, overall, there was a high level of satisfaction with both hysterectomy and ablation at follow-up.

Implications for practice and research. At the end of a Cochrane review there are two important sections—"Implications for Practice" and "Implications for Re-

search." Implications for Research is particularly relevant to our concerns; this section recommended that additional trials are needed, especially those involving vaginal hysterectomy and newer methods of ablation. These recommendations are right on target with the ongoing STOP-DUB trial.

At this time [end of 2000] we are completing STOP-DUB recruitment and applying to AHRQ for funding to continue following this important cohort of women for at least 4 years. We strongly believe that DUB is an important health problem and remain uncertain of the relative efficacies of hysterectomy and endometrial ablation. In the case of DUB, the opinion of the patient will be extremely important in defining efficacy, and satisfaction with treatment might vary. Women with DUB are likely to be seeking surgical treatment for a number of outcomes in addition to relief from bleeding. For example, women might be variously concerned about retaining their uterus, receiving assurance that DUB will not return, sexual function, possible adverse effects of surgery, cost or the desire to resume normal activities as soon as possible. Through STOP-DUB we anticipate being able to provide women with the best evidence and choices appropriate to their needs and preferences.

Conclusions

Sound, reliable evidence is the basis of quality health care. Finding, evaluating and staying current with reliable research findings is not an easy task. The method we used to develop STOP-DUB, described above—specifically, use of *The Cochrane Library*—is only one approach. A few additional online resources that provide summaries of reviewed evidence are listed below. (It should be noted that the Web addresses and even the existence of such sites are constantly changing.)

- Clinical Evidence (www.evidence.org)
- ACP Journal Club (www.acponline.org)
- Best Evidence (www.bmj.com/data/ebm.htm)

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