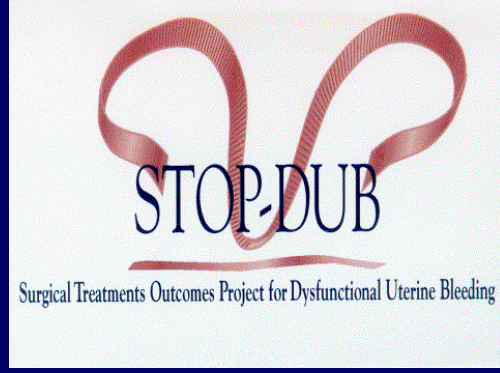


Clinical Trial Design & Small Studies
A Coordinating Center Perspective

Clinical Trials and Tribulations

Kay Dickersin, PhD

February 25, 2005

Bethesda, Md

AHCPR says more research is needed on hysterectomy - 1996

- Hysterectomy overused
- Alternative treatments for dysfunctional uterine bleeding (DUB) needed
- Applications requested for randomized clinical trials (RCTs)

How find out about current best evidence?

- Systematic reviews
  - *The Cochrane Library*
    - Database of systematic reviews
    - DARE
- RCTs
  - The Cochrane Library
    - Central Register of Controlled Trials (>350K trials at that time)

Comparison of the effectiveness of endometrial resection and ablation to reduce heavy menstrual bleeding versus hysterectomy [protocol]

Cooke I, Shepperd S.

Date of most recent substantive amendment : 29 May 1996

Date review expected : 31 July 1997

Background

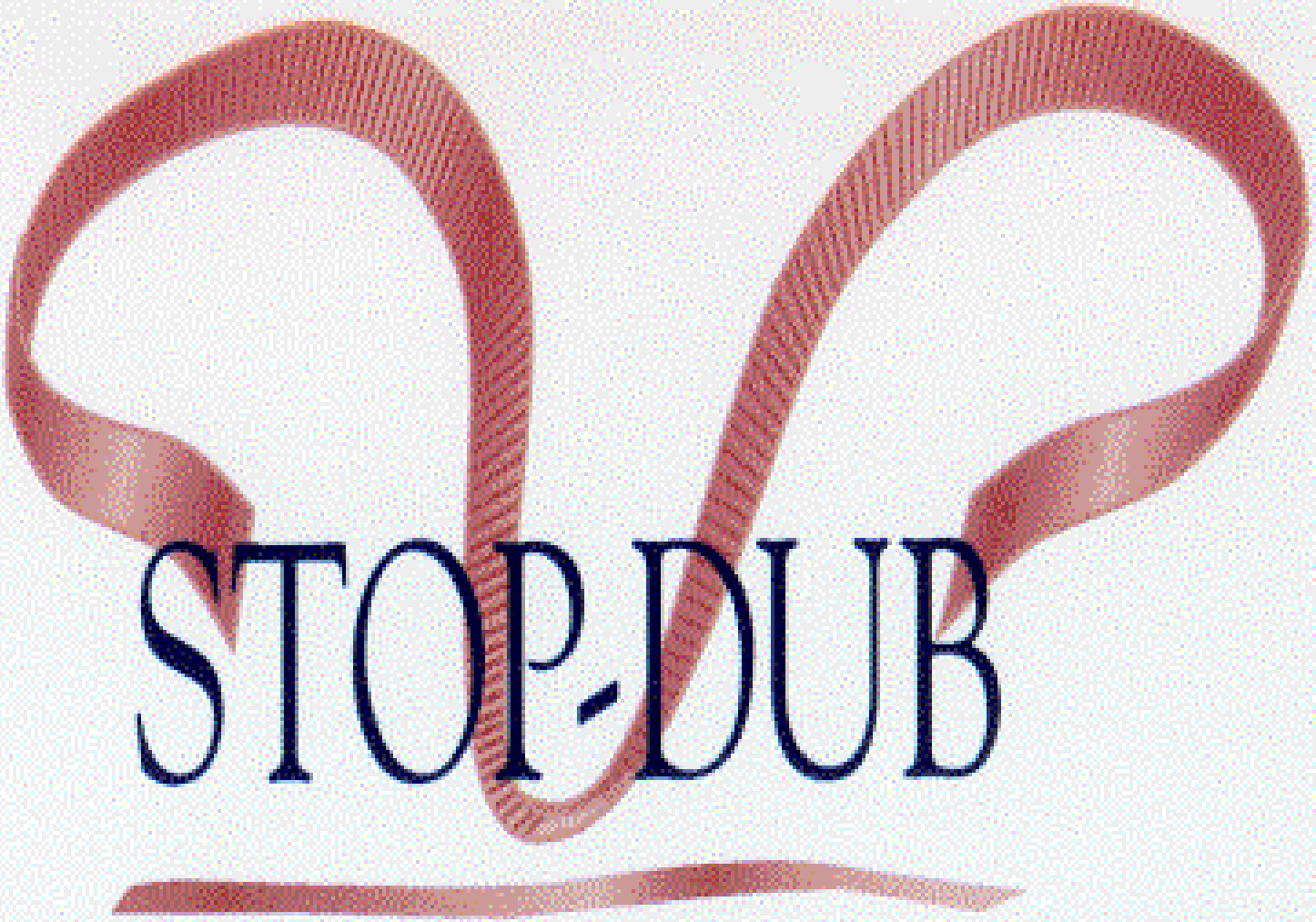
Heavy menstrual bleeding (HMB) is an important cause of ill health in women. One in 20 women aged 30-49 consult their General Practitioner (GP) each year with HMB (Vessey 1992) and it accounts for 12% of all gynaecology referrals (Bradlow 1992). Menorrhagia is clinically defined as greater then, or equal to 80 mls blood loss per menstrual cycle (Cole 1971; Hallberg 1966) but it is the woman's perception of her own menstrual loss which is the key determinant in their referral and indeed subsequent treatment.

Sixty percent of GP referrals for HMB in the UK are treated with hysterectomy within 5 years (Coulter 1991). HMB resulted over 25,000 hysterectomies in the UK in 1994 yet in at least a third of these cases a normal uterus was removed (Clarke 1995; Gath 1982).

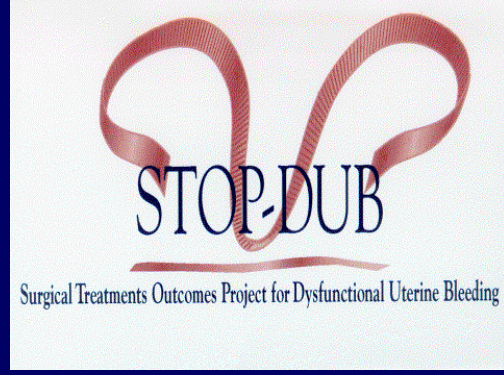
The surgical treatment of HMB include hysterectomy (vaginal, abdominal and laparoscopic approaches) and more recently less invasive techniques which aim to remove the entire thickness of the endometrium using electrocautery (80%), laser (18%)(and radiofrequency (2%) (RCOG 1995). The benefits claimed for such less invasive therapies are reduced trauma an

Existing evidence 1996: RCTS comparing hysterectomy to endometrial resection/ablation

- 3 U.K. RCTs
- Results generalizable to the US?
  - Ovulatory DUB only
  - Mainly abdominal hysterectomies
  - Hysteroscopic techniques only, mainly resection
  - "Cost" not resource-based



Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding



STOP-DUB
Randomized Trial
Objective

To assess the efficacy and effectiveness of hysterectomy compared to endometrial ablation for the treatment of dysfunctional uterine bleeding in women for whom medical management had not provided relief

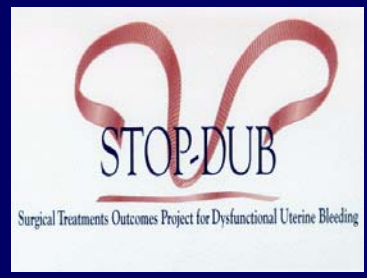
STOP-DUB Participating Sites

Arizona, U of
Boston U
Brown
Dartmouth U
East Carolina U
Florida, U of
Greenville Hosp Sys
Gynecol &Women's
Kansas, U of
Lelhigh Valley
Manitoba, U of
Mississippi, U of
Nevada (Los Vegas), U of

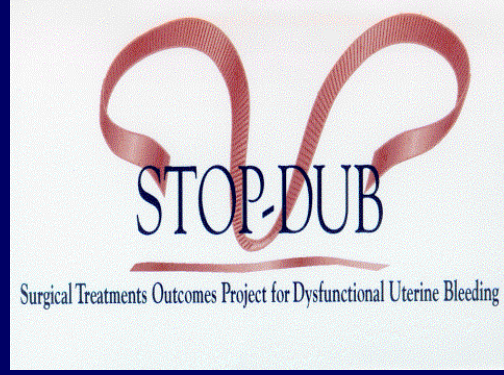
Oklahoma, U of
Pittsburgh (Magee) U of
South Carolina, MU
Stanford U
Texas (Galveston), U of
Texas (San Antonio), U of
Texas (Southwestern) U of
Medical Coll of Virginia
Western Ontario, U of
West Virginia U of
Women's Wellness
Women's Health USA (4)
York Hospital (PA)

STOP-DUB

Population



- Premenopausal women ≥ 18 years
- DUB ≥ 6 months
- Medical therapy had not worked
- No known polyps
- ≤3 leiomyomas
- Willing to consider loss of fertility and surgery



STOP-DUB

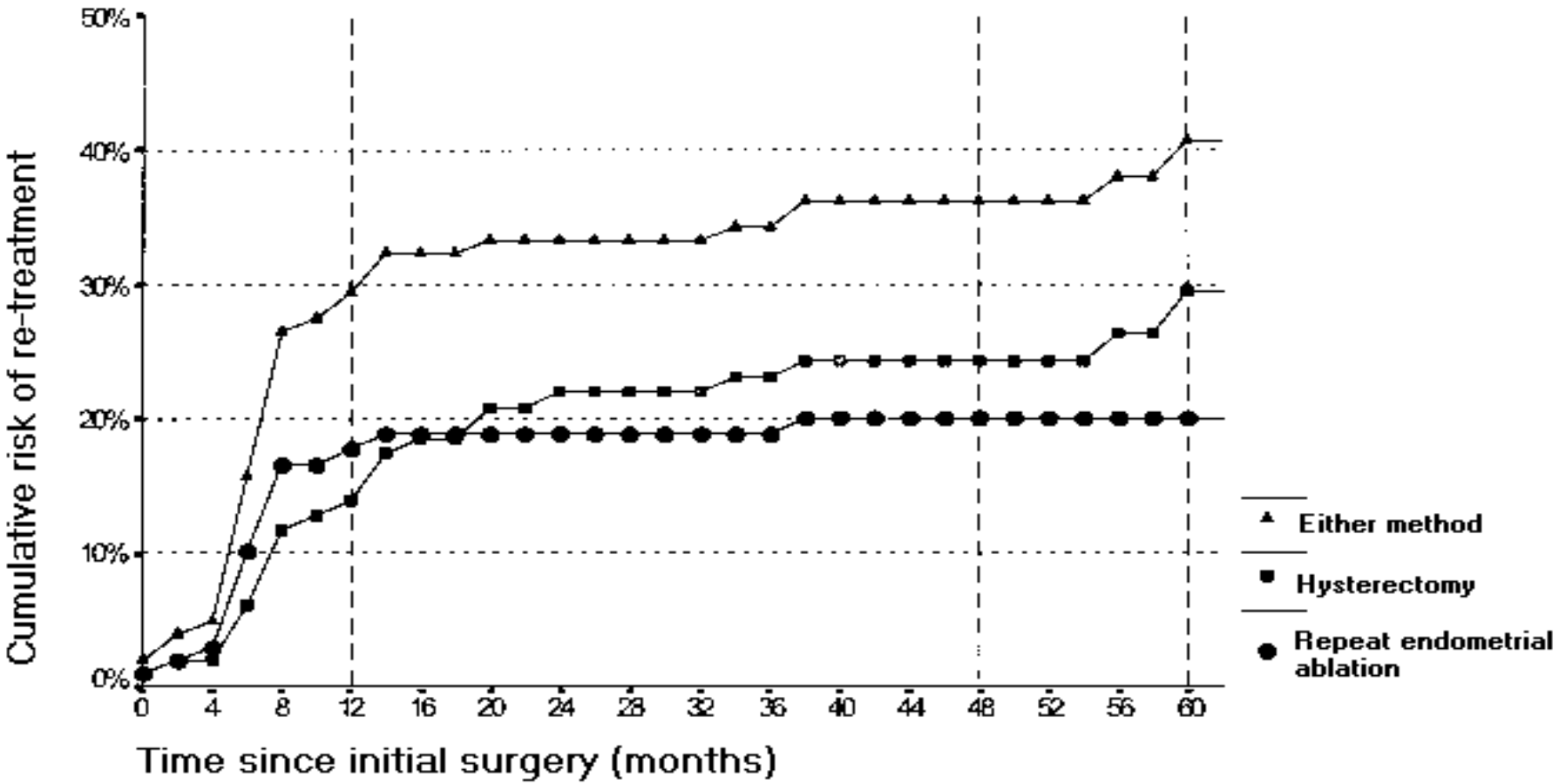
Outcomes

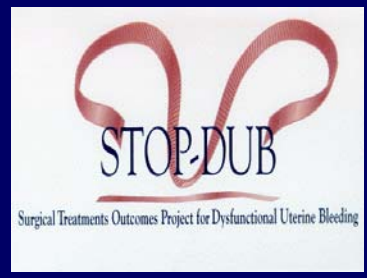
- Primary
  - Impact of the surgery on major symptom that led each woman to seek treatment, bleeding, pain, and fatigue.
- Re-treatment
- Surgical complications
- Activity limitation, sexual function, incontinence
- Costs
- Quality of life - SF-36, EuroQOL
- Women followed at least 2 years.

Stuff happens

- 1997
  - Randomization more difficult than predicted – DSMC membership change
  - Translation of study materials into Spanish – unexpected expense, few additional patients
  - Sample size re-estimated
  - FDA approval of ThermaChoice
- 1998 - Coordinating Center move
- 1999 - Aberdeen Study 4-year results published
- 2000 - Patient followup extended by DSMC and steering group
- 2002 – Additional followup not funded by AHRQ

Results of Aberdeen Study at 4 years:
Cumulative probability of retreatment





STOP-DUB

Coordinating Center Move

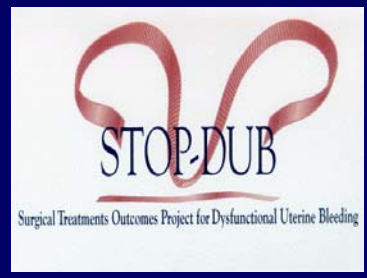
- Staffing – 4 staff moved with PI; hiring of high level staff difficult; building Coordinating Center team *de novo* difficult
- Database move – Extra resources required; extended period to complete transfer of data management system because of competing computing demands while study recruiting
- Storage accessibility, and confidentiality of records – Steep learning curve for staff with no previous trial experience (documentation, attention to detail)

STOP-DUB

Coordinating Center Move

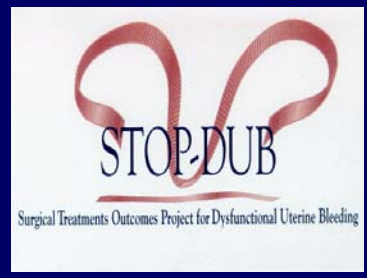
- Maintaining communication – Temporary staff confused clinical centers
- Finances – subcontracting to original institution required additional funds; unexpected costs
- IRB approvals – Multiple IRB issues at new institution due to lack of RCT experience
- Office space – Renovations not complete at time of move, unexpected costs, despite planning

STOP-DUB
Lessons learned



- Staffing is key to success – skills, teams, dedication
  - Trained, experienced, high level staff are a MUST
  - Teamwork key
- Role of Coordinating Center is challenging for staff – policemen vs scientists, never good enough
- Good documentation is boring and a pain, but absolutely necessary
- Clinical Centers chronically underfunded (we need to do better)

STOP-DUB
Lessons learned



- Clinical Centers have limited experience as full partners. Training and close monitoring needed
- RCTs are expensive! Plan for it!
- Never take anything for granted – IRB experience, costs for space and telephone, modern computing
- 5-year grant periods too short for adequate followup and reaping the harvest of hard work
- The study waits for nothing and no one!!!!