

FIBROID Registry Protocol

Study Title:	Uterine Artery Embolization Fibroid Registry Outcomes Database
Working Title:	FIBROID Registry
Procedure Name:	Uterine Artery Embolization (UAE)
Sponsor:	Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF)
Objective:	To evaluate the safety and effectiveness data of UAE for treatment of symptomatic uterine leiomyomata
Study Design:	Prospective observational
Sample Size:	Estimated: 3,000 patients per year (2,600 patients per year from core sites); Longitudinal follow-up: 900 patients per year
Patient Selection Criteria:	<p>Patients undergoing UAE for uterine fibroids at participating sites</p> <p>Patients enrolled through a selected subset of approximately 25 high volume sites (core) will be consented for participation in a longitudinal follow-up sub-study.</p>
Primary Effectiveness Endpoints:	Symptom relief, subsequent procedure not required to treat recurrent symptoms of uterine fibroids
Safety Endpoints:	Adverse events
Study Procedures:	Baseline, procedural data and short term (30 day) follow-up data will be entered by site personnel onto web-based data forms. Participants enrolled into the longitudinal follow-up component will receive a follow up survey at 6 months, 12 months, and 24 months following the procedure.
Statistical analysis:	Descriptive analyses will include overall participant and procedure volume, patient characteristics, procedural variables, and outcomes. Core sites will be provided with site-specific processes and outcomes results.

Hypothesis

The primary hypothesis of the FIBROID Registry is that UAE is a safe and effective treatment for symptomatic uterine fibroids.

The corollary of this hypothesis is that patients are satisfied with the effect of the procedure.

Introduction

Between 177,000 and 366,000 hysterectomies and approximately 35,000 myomectomies are performed each year for the treatment of uterine fibroids. In addition, many women receive medical treatment for fibroids and many others suffer symptoms but never undergo treatment. Hence, there is an obvious potential for UAE to provide an important therapeutic alternative to hundreds of thousands of women each year.

Establishing UAE as a generally recognized option for the treatment of fibroids represents a considerable challenge. Additional scientific evidence is needed in order for UAE to be accepted as the standard of care. The Food and Drug Administration (FDA) and payers are looking for long-term data including evidence of safety, efficacy, durability, impact on uterine function, fertility, and quality-of-life (QOL).

In June 1999, in recognition of the research needed to advance UAE, CIRREF funded RAND Health to convene a multi-disciplinary panel to develop a consensus around a research strategy. The results of this panel, *Uterine Artery Embolization: A Systematic Review of the Literature and Proposal for Research* (Broder et al., 2000), identified four areas of research including the development of a prospective registry, a disease-specific quality-of-life instrument, randomized control trial, and a cost analysis. CIRREF awarded a grant to design, test, and validate a QOL instrument for uterine fibroids. The focus of this study is the development of a registry to collect high quality longitudinal data for this procedure in a cost-effective manner.

The data generated by the registry database, used in conjunction with data from randomized studies, will evaluate the use, safety and effectiveness of UAE for leiomyomata and will assess the potential advantages and disadvantages of the procedure (e.g., durability, fertility, surgical conversions, etc.). It will also be used to facilitate long-term surveillance of patients undergoing this procedure. In addition, the registry may be used as a Continuous Quality Improvement (CQI) tool on behalf of practicing interventional radiologists and will contribute to the development and refinement of standards of care.

Study Objectives

The primary objective of this study is to capture high quality patient safety and effectiveness data for UAE. This goal will be achieved by capturing a concise set of baseline, short and long-term functional and clinical outcome data for patients undergoing UAE.

Secondary objectives of this study include:

- To measure volume of patients undergoing UAE.
- To assess and benchmark clinical practice patterns (patient selection, technique, use of procedure across country).
- To collect and quantitate resource utilization of patients undergoing UAE.

These objectives will be achieved through the capture of selected process data for patients included in the registry.

Data collected in this study may also be used to support post-marketing surveillance, to develop and refine standards of care for use of UAE for leiomyomata and to facilitate the design of randomized clinical trials.

Study Design

Study Population

Consecutive patients undergoing UAE for uterine fibroids at participating sites will be approached for consent for inclusion into the registry by the treating interventional radiologist. An attempt should be made to solicit consent from all patients. Patients who refuse to have their data included in the registry will be counted for procedure volume but no patient specific data will be collected.

Patients enrolled through a selected subset of approximately 25 high volume (core) sites will be consented for participation in the longitudinal follow-up component of this study. A random sample of these consented patients (approximately 35% based on projected average enrollment at high volume sites of 2 patients/site/week) will be contacted at 6, 12 and 24 months for assessment of clinical outcomes, QOL and patient satisfaction. In addition, all consented patients intending subsequent pregnancy will be assessed for fertility and pregnancy history during these periodic contacts.

Study Procedures

Any center performing UAE and wishing to contribute patient data should submit the registry protocol for Institutional Review Board (IRB) review. A log-in ID for the web-based data-entry system and password authorization information will be provided by the UAE Registry Data Coordinating Center (Duke Clinical Research Institute [DCRI]) once documentation of IRB approval has been received. Sites selected for participation in the longitudinal follow-up study who have approval by their IRB will be permitted enrollment of patients into the longitudinal component.

DCRI will verify and document that sites have the appropriate regulatory documents in place to participate in the registry. This will include ensuring that all participating sites have received IRB approval and receive annual renewal of that approval. Informed consent to permit contact for follow-up purposes should be obtained prior to enrollment and copies will be collected by DCRI for those patients entered into the longitudinal follow-up component of the registry.

A participant (site) contact database will be developed and maintained by DCRI, including site information and a communications log. Core sites will be contacted by phone to evaluate/initiate participation in the longitudinal follow-up component and then on an ongoing basis to ensure that sites are enrolling patients and problems and/or issues are resolved. A notebook of data collection forms and instructions will be developed and provided to participating sites. This training will be augmented by web-based self-study/instruction, telephone inservices and training sessions at SCVIR conferences.

Patient characteristics, procedural data, in-hospital events, and post-discharge events (to 30-days) will be collected on all patients. Data will be entered by site personnel onto web-based data forms and submitted to the registry blinded as to patient identifying information. Site personnel will collect contact information for patients enrolled into the longitudinal follow-up component of the study. This contact information will be submitted along with a copy of the patient informed consent to the Follow-up Group at the Data Coordinating Center. Contact information will be maintained by the DCRI Follow-up Group and will not be accessible to other project personnel.

Participants enrolled in the longitudinal follow-up component will receive a follow up survey at 6 months, 12 months, and 24 months following the procedure. Surveys will be mailed by the Data Coordinating Center directly to the patient. Patients who do not return surveys will be contacted by phone to obtain follow-up information.

Data Collection and Statistical Analyses

The database specifications and corresponding data collection forms (approximately 50 data elements) will be developed by the DCRI in coordination with the Steering Committee and Industry Advisory Board.

A web-based data entry system will be provided for collection of registry data. The web application will be set up on DCRI servers for remote data entry. A database and data entry system for input of the follow-up data collection forms will also be developed in conjunction with a tracking application. Standard operating procedures for development and management of study databases will be developed and applied. Quality assurance procedures will be in place to ensure database security, protect patient and physician confidentiality, and enhance data management.

The site will be responsible for completion of baseline, procedural and 30-day follow-up data and sites will be alerted as to missing or late data for consented patients participating in the longitudinal follow-up studies. Follow-up data for those patients enrolled in the longitudinal component will be collected and entered into the study database by the Data Coordinating Center.

The primary hypothesis of the FIBROID Registry is that UAE is a safe and effective treatment for symptomatic uterine fibroids. Data will be analyzed descriptively to include overall participant and procedure volume, patient characteristics, procedural variables, and outcomes. Safety-related parameters, including adverse events, will be summarized and assessed for clinically significant abnormalities and shifts from historical data for surgical therapy.

The secondary hypothesis of interest, that patients are satisfied with the effect of the procedure, will be evaluated based on patient reported data collected on follow-up questionnaires.

Aggregate status and summary reports will also be posted on the web site for the sites to view. Core enrolling sites will receive copies of their site-specific data for comparison with the aggregate reports. All other reported data will be blinded as to provider and center.

Study Network and Coordination

Study Network

It is estimated that 50-100 sites will participate in the FIBROID registry. Approximately 25 of these sites will be invited to participate in the longitudinal follow-up study and will be designated core sites. (See Appendix 1 for list of proposed core sites.) Each participating site will designate a lead investigator to participate in Investigator Meetings. Lead investigators will ensure timely and accurate data contribution to the registry.

The Coordinating Center for the FIBROID study will be the DCRI at the Duke University Medical Center in Durham, North Carolina. A study coordinator at the Data Coordinating Center will coordinate all efforts of the FIBROID project. Access to the Coordinating Center is encouraged and facilitated via a telephone hotline.

Project Sponsor

The study sponsor CIRREF and its affiliate, the Society of Cardiovascular & Interventional Radiology (SCVIR) which represents over 3,700 interventional radiologists throughout the United States and abroad and is acutely aware of the issues regarding UAE facing providers, regulatory agencies, payers and the needs of patients.

Steering Committee and Industry Advisory Committee

The UAE Registry Steering Committee is responsible for defining and prioritizing the objectives and goals of the registry and providing input into the project processes, as well as overseeing access to and publication of registry data. The Steering Committee is comprised of interventional radiologists, obstetricians/gynecologists, and DCRI representatives. Steering committee members were selected based on clinical knowledge and experience with the procedure and other related research activities (e.g., disease-specific QOL instrument; proposed randomized control trial comparing UAE to myomectomy), and/or technical skills and expertise to develop and successfully carry out the registry.

An Industry Advisory Board, comprised of representatives of project sponsors, has been formed to represent industry needs and concerns. Regular updates on the status of the study will be provided by the project team to SCVIR/CIRREF and the Steering Committee and Industry Advisory Board. Input and recommendations on the project processes will be requested on a routine and as-needed basis.

Special advisors will be designated by the Steering Committee to provide specific expertise as needed throughout the project. For example, during Phase I representatives from the FDA have provided scientific input into the data elements to be collected and analyses to be performed. Potential advisors include representatives from: FDA, National Institutes of Health, Office of Women's Health, Society for Women's Health Research, industry, information technology, patient advocacy, and medical ethics.

Project Timeline

Consecutive patients meeting study entry criteria at participating sites will be evaluated for inclusion in the FIBROID study. The total enrollment across all sites is projected to be 3000 patients per year. The average enrollment for core sites is projected to be about 2 patients per site

per week. It is estimated that 2600 patients will be accrued from the core sites per year and that approximately 900 of these will be allocated to the longitudinal follow-up component. Enrollment is projected to start in January 2001 and to continue through June 2003.

Investigator and Sponsor Obligations

Institutional Review Board

The FIBROID protocol and informed consent (Appendix 2) must be reviewed and approved by an appropriate Institutional Review Board (IRB) at each center before subjects are enrolled in the study. It is the responsibility of the investigator to assure that all aspects of the institutional review are conducted in accordance with current Federal regulations.

Informed Consent

Before the UAE procedure, patients must sign the informed consent in order to be enrolled in the FIBROID Registry. The signed informed consent will be retained with the study records. A copy will be submitted with the patient contact information sheet for patients enrolled into the follow-up component of the study.

Data Reporting

A FIBROID Case Report Form (CRF) and 30-day follow-up report should be completed and signed (electronically) by the principal investigator for each patient enrolled. Results of patient questionnaires will be reported on a supplemental section of the CRF.

Retention of Data

Records should be maintained as specified by the FIBROID protocol and in accordance with Federal regulations.

Disclosure of Data and Publication

Presentation and/or publication of the results of the study is permitted under the terms of the Data Access and Publication Policy. Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers in the computer files. Subject medical information may be given to the subject's personal physician or the appropriate medical personnel responsible for the subject's welfare.

Data generated as a result of this study will also be available for inspection on request by FDA auditors (if applicable), the sponsor's monitors and by the IRB.

CIRREF UAE FIBROID REGISTRY CORE SITES

<u>Lead Investigator</u>	<u>Institution</u>	<u>City</u>	<u>State</u>
1. Scott Goodwin, MD	UCLA Medical Center	Los Angeles	CA
2. Jeffrey Dieden, MD	Kaiser Medical Center Oakland	Oakland	CA
3. Mahmood Razavi, MD	Stanford University Hospital	Palo Alto	CA
4. Anne Roberts, MD	UCSD Medical Center	San Diego	CA
5. Issac Kaplan, MD	Kaiser Hospital Vallejo	Vallejo	CA
6. James Spies, MD	Georgetown University Hospital	Washington	DC
7. Neal Joseph, MD	Memorial Regional	Hollywood	FL
8. Gerald Niedzwiecki, MD	Mease Countryside Hospital	Safety Harbor	FL
9. John Lipman, MD	Piedmont Hospital	Atlanta	GA
10. Robert Ryu, MD	Northwestern Memorial Hospital	Chicago	IL
11. Steven Smith, MD	LaGrange Memorial Hospital	LaGrange	IL
12. Karen Ehrman, MD	Methodist Hospital on Indiana	Indianapolis	IN
13. David Brophy, MD	Mount Auburn Hospital	Boston	MA
14. Joseph Gemmete, MD	University of Michigan	Ann Arbor	MI
15. Rajinder Sharma, MD	Henry Ford Hospital	Detroit	MI
16. William Romano, MD	William Beaumont Hospital	Royal Oak	MI
17. David Hovsepian, MD	Washington University at Saint Louis	Saint Louis	MO
18. Gary Siskin, MD	Albany Medical Center	Albany	NY
19. David Siegel, MD	Long Island Jewish Medical Center New Hyde Park		NY
20. Robert Min, MD	Cornell Vascular-NY Presbyterian Hospital	New York	NY
21. James Newman, MD, PhD	Cleveland Clinic Foundation	Cleveland	OH
22. Robert Worthington-Kirsch, MD	Delaware Valley Imaging	Philadelphia	PA
23. Richard Shlansky-Goldberg, MD	University of Pennsylvania	Philadelphia	PA
24. Joseph Bonn, MD	Thomas Jefferson University Hospital	Philadelphia	PA
25. Keith Sterling, MD	INOVA Alexandria Hospital	Alexandria	VA
26. George Fueredi, MD	Burlington Memorial Hospital	Milwaukee	WI

Sample Informed Consent for FIBROID Registry

The Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF) in collaboration with the Duke Clinical Research Institute (DCRI) is conducting a study to understand how effective uterine artery embolization (UAE) is in meeting the needs of patients with uterine fibroids. You are being asked to participate in this study because you have uterine fibroids and are scheduled to undergo uterine artery embolization. The UAE that you are scheduled to undergo is not a part of this study. This study is designed to study the impact of this procedure on fertility and quality of life.

Uterine fibroids are a condition that affect many women. From 20 to 40 percent of women age 35 and older have uterine fibroids of significant size. African-American women are at higher risk for fibroids: as many as 50 percent have fibroids of significant size. Fibroids are a common cause of symptoms such as abnormal menstrual bleeding, lower abdominal (pelvic) pain and discomfort, and frequent urination and constipation. This study will help physicians and researchers learn more about UAE's impact on fertility and quality-of-life.

Over 3000 patients per year will be involved with this research study. Dr. _____ is involved to gather information that will be used to improve the care of women with symptomatic uterine fibroids. We hope that you will agree to participate in this important project. Please note that:

- **Participation in this study is completely voluntary. You may decide not to take part in this study without altering your medical care. If you decide not to participate, treatment of your uterine fibroids will occur as you and your personal doctor have decided.**
- **If you choose to participate, you have the right to refuse to answer any questions you wish.**
- **There is no direct benefit to you as an individual from participating.**
- **Your current quality of care will not be effected in any way by your participation or by your refusal to participate in this study.**
- **All information that you provide will be kept confidential. Your name and any identifying information will be kept separate from your medical history and procedure information.**

The United States Food and Drug Administration (FDA) will have access to procedure information in order to help monitor and improve UAE safety. Aside from information necessary to contact you for follow-up, all identifying data will be kept anonymous. Nobody will be given your name or other identifying information.

If you choose to be a part of this study, you will need to read this form completely. After you have signed it, you and Dr. _____ will complete the first set of forms and go on with your treatment plan.

If you are among the group selected for longer study, the study center will mail to you a brief questionnaire about your health and quality of life at the following times. If you do not return the questionnaire, you will be contacted by telephone.

In six months from today's visit, on or about ____ / ____ / ____

And at 12 months from today's visit, on or about ____ / ____ / ____

And at 24 months from today's visit, on or about ____ / ____ / ____

You may also be contacted at yearly intervals until you reach menopause.

If there are any questions concerning this research study, please call Dr. _____ at _____, or _____ (the study coordinator) at _____.

Please keep a copy of this form for your files.

I have read the informed consent and Dr. _____ has answered any questions I may have about participation in the FIBROID Registry. I agree to participate in this study.

Signed: _____ Date: _____

Witness: _____ Date: _____