

**SILICONE-FILLED BREAST IMPLANT
CORE CLINICAL STUDY**

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I. INTRODUCTION

A. Regulatory Background

Silicone devices for augmentation and reconstruction mammoplasty were introduced for clinical use in the early 1960s. Silicone-filled and saline-filled breast implants and other Class III devices marketed prior to the enactment of the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act (the Act) were granted "grandfather" status. The Food and Drug Administration (FDA) allowed certain pre-1976 devices, including silicone-filled breast implants, to remain in use with the understanding that manufacturers would later be required to submit scientific evidence of safety and effectiveness. In June 1988, the FDA identified both types of silicone breast implants, saline-filled and silicone-filled, as Class III devices, establishing its intent to require silicone-filled breast implant manufacturers to submit Premarket Approval (PMA) applications showing scientific evidence of device safety and effectiveness. In April 1991, the FDA published a section 515(b) Final Rule requiring PMA submissions for silicone-filled breast implants. McGhan Medical Corporation (McGhan Medical) and other manufacturers submitted PMA applications for silicone-filled breast implants to the FDA in July 1991. On January 6, 1992, the FDA called for a moratorium on the use of silicone-filled breast implants until new information on their safety could be reviewed by an advisory panel. On February 20, 1992, the panel recommended that breast implants be made available only on a limited basis under carefully controlled clinical studies. After a careful evaluation of the public health need, the alternatives to silicone-filled breast implants, and the known, potential, and suspected risks, the FDA Commissioner adopted the panel's recommendation on April 16, 1992. Because of a public health need, silicone-filled breast implants would continue to be available for women seeking breast reconstruction, but could no longer be marketed for the purpose of breast augmentation in healthy women. In announcing this decision, the Commissioner stated that more studies were needed to answer basic questions about the safety of silicone-filled breast implants. The purpose of this study and other ongoing studies is to obtain the answers to some of these questions.

Public and regulatory focus identifies several specific areas of interest for clinical study. Among these is a description of the incidence of postoperative complications associated with breast implants and breast implant surgery. This issue is of concern because, although there is considerable literature on the occurrence and natural history of local surgical complications, variability in measured incidence rates exists from study to study. The FDA, as a regulatory agency, needs accurate data to evaluate the devices in order to properly inform consumers about the products and the surgical procedure. Additional questions

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have arisen concerning an association between breast implants and rheumatic diseases, interference of breast implants with radiologic detection of cancer, the effect of breast implants on reproductive outcomes, and the potential excess risk of human cancers as a result of implantation.

B. Previous Research

Substantial literature exists describing the occurrence and treatment of known surgical complications, capsular contracture, and prosthesis failure. Data from major case series and clinical trials show both historical and cross sectional variability in the reported incidence of these complications. An aim of further studies is to improve estimates of incidence rates with respect to implant type, surgical technique and patient characteristics. Additionally, especially with respect to the phenomenon of "excess capsular contracture," observer variation in definition of outcomes and their measurement may contribute to variation in reported complication incidence rates. From a regulatory standpoint, improved descriptive data on the incidence of postoperative complications are desirable both to assess further implant efficacy and to provide consumers with information on the nature of the procedure and products.

Questions have been raised about whether silicone-filled breast implants are linked to autoimmune disorders such as lupus, scleroderma, and rheumatoid arthritis. Several human studies have been completed recently that provide substantial--but not complete--information about any possible link between breast implants and immune-related disorders.^{1,2,3,4} Taken together, these studies indicate that the vast majority of women will not develop immune-related disorders from their implants. A recent large human study by Hennekens and colleagues found a small but statistically significant increase in the risk of connective tissue disease as self-reported by women with breast implants when all connective tissue diseases were taken together, but not when each disease was analyzed individually.⁵ Thus, as in previous studies, this study found that the substantial majority of women with breast implants do not develop typical

¹ Gabriel SE, O'Fallon WM, Kurkland LT, Beard CM, Woods JE, Mellon LJ. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994; 330:1697-1702.

² Englert HJ, Brooks P. Scleroderma and augmentation mammoplasty--a casual relationship? *Aust NZ J ME* 1994;24:74-80.

³ Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunder DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *New Engl J Med* 1995;322:1666-1670.

⁴ Friis S, Mellekjaer L, McLaughlin JK, Breiting V, Kjaer SK, Blot W, Olsen JH. Connective tissue disease and other rheumatic conditions following breast implants in Denmark. *Annals of Plastic Surgery* 1997;39:1-8.

⁵ Hennekens CH, Lee I-M, Cook NR, Hebert PR, Karlson EW, LaMotte F, Manson JE, Buring JE. Self-reported breast implants and connective-tissue diseases in female health professionals. *JAMA* 1996;275:616-621.

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connective tissue disease. It is important to note that the Hennekens study has certain limitations in its design. For example, self-reported disease was not confirmed by medical records, the questionnaire was returned by only 25 percent of the potential participants, and no distinction was made between silicone-filled and saline-filled implants. In view of these limitations, the true risk of connective tissue disease may be different than that reported in the Hennekens study.

While no reports exist to date of adverse effects on human reproduction from breast implants, the ability to breastfeed after implantation is a stated concern of patients. Accurate background data on reproductive characteristics of women choosing mammoplasty with silicone-filled implants are desirable to assess the feasibility of any future studies on human reproductive outcomes, such as the possibility of birth defects or spontaneous abortions.

Increasing attention is placed on early detection of breast cancer, with promotion of periodic mammography as a primary screening tool. Some researchers⁶ question whether the presence of a breast implant impedes the early diagnosis of naturally occurring breast cancers. Others⁷ have asked whether implants themselves may alter the detection of naturally occurring breast tumors. Many published studies^{8,9,10,11} have shown no increased incidence of breast cancer in breast implant recipients.

II. OBJECTIVES

This prospective clinical study is designed to document the safety and effectiveness of McGhan Medical Silicone-Filled Breast Implants as indicated for breast augmentation, breast reconstruction, or breast implant revision. The safety of McGhan Medical Silicone-Filled Breast Implants will be assessed based on the incidence of local and implant-related complications, capsular contracture, and device failure. Effectiveness will be assessed based on changes in anatomical

⁶ Silverstein MJ, Handel N, et al. Breast cancer in women after augmentation mammoplasty. *Archives of Surgery* 1988;123:681-685.

⁷ Morganstern L, Gleischman SH, et al. Relation of free silicone to human breast carcinoma. *Archives of Surgery* 1985;120:573-577.

⁸ Berkel H, Birdsell D, and Jenkins H. Breast Augmentation: A Risk Factor for Breast Cancer? *New Engl J Med*, 326:25, June 1992.

⁹ Deapen DM, Bernstein L, Brody GS. Are breast implants anticarcinogenic? A 14-year follow-up of the Los Angeles Study. *Plast Reconstr Surg*, 1997;99:1346-53.

¹⁰ Malone KE, Stanford JL, Daling JR, Voigt LF. Implants and breast cancer. *The Lancet* 1992;339:1365.

¹¹ Brinton LA, Malone KE, Coates RJ, Schoenberg JB, Swanson CA, Daling JR, Stanford JL. Breast enlargement and reduction: Results from a breast cancer case-control study. *Plastic and Reconstructive Surgery* 1996;97:269-275.

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configuration (i.e., changes in bra size from pre- to post-surgery), patient and investigator satisfaction with the outcome of the procedure, and patient quality of life measures.

This study will provide data in support of a PMA application to the FDA and address post-market surveillance required by the FDA.

III. DEVICE DESCRIPTION

McGhan Medical Silicone-Filled Breast Implants to be evaluated in this study are listed in Appendix A. These implants are designed for use in augmentation, reconstruction, and revision. The principal features that distinguish the different styles are surface type, device shape, number of lumens, and size. To aid in the insertion of the textured products, a sterile polyethylene Delivery Assistance Sleeve is available separately.

"CAUTION- Investigational device. Limited by Federal (or United States) law to investigational use."

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IV. RISKS AND BENEFITS

A. Risks

Risks associated with breast implants may be categorized as those associated with the surgical procedure and immediate postoperative period, capsular contracture, and device failure. Additionally, possible long-term risks associated with silicone include late complications, systemic events (e.g., connective tissue disease), and implant interference in detection of breast cancer. (See Package Inserts and Information for Women Considering Silicone-Filled Breast Implants in Appendix B.) Specific known risks of mammoplasty include the following:

| | |
|---|---|
| Surgical Risks | During surgery or immediate postoperative period: pain, infection, Toxic Shock Syndrome (TSS), hematoma, seroma, delayed wound healing, fluid accumulation, tissue or skin necrosis, risks associated with anesthesia, hypertrophic scarring, pneumothorax, loss of nipple sensation, nipple hypersensitivity, operative rupture of the implant. |
| Implant Failures and other Complications | Breakage, rupture, or leakage of the implant from weeks to years after surgery and risks associated with reoperation. Other complications include exposure or extrusion of the implant, implant movement or displacement, implant-related breast distortion, wrinkling, palpability or visibility, asymmetry, ptosis, calcification, tissue atrophy/chest wall deformity. |
| Fibrous Capsular Contracture | Unilateral or bilateral fibrous capsular contracture weeks to years after implantation that may cause pain, disfigurement, resurgery, or other conditions requiring clinical intervention. |
| Other Potential Effects | Possible systemic effects (e.g., tumorigenicity, carcinogenicity, teratogenicity, or Connective Tissue Disorder), silicone diffusion (e.g., possible local migration of silicone or migration of silicone to the lymph nodes), interference with radiologic detection of cancer, and interference with breast feeding. |

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B. Minimization of Risks

In order to minimize patient risks, numerous guidelines will be followed:

- Study will be conducted according to Investigational Device Exemption Regulations;
- McGhan Medical will carefully review all investigator credentials;
- Investigators must sign an Investigator's Agreement and Certification (Appendix C) agreeing to follow the protocol without deviation;
- Prior to patient enrollment, the protocol must be approved by all Institutional Review Boards (IRBs) governing facilities where study patients will have surgery;
- The protocol defines specific patient eligibility criteria that must be stringently followed and will be strictly enforced by McGhan Medical;
- The protocol specifically refers the investigator to the Warnings, Precautions, and Adverse Reactions sections of the Package Insert (Appendix B). The Package Insert furnishes the investigator with extensive information on a variety of factors that may affect the surgical outcome, and provides patient counseling information that the investigator must include as part of the informed consent process;
- Patients will be rendered informed consent prior to surgery, a process involving several elements. As part of this process, patients will be fully apprised of the known and suspected risks associated with breast implants prior to enrollment so that they may make an informed choice about participation in the study. The Informed Consent (Appendix D) completely describes these risks. Each patient and either the investigator or his/her designee (person rendering the consent) will concurrently sign and date the Informed Consent prior to surgery. Additionally, patients will be provided with a separate brochure explaining the risks (Appendix B, Information for Women Considering Silicone-Filled Breast Implants);
- All adverse events will be reported on the Case Report Forms (Appendix E);

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- Unanticipated adverse events must be reported to McGhan Medical within 10 working days of occurrence so that they may be promptly investigated;
- As sponsor and clinical monitor, McGhan Medical will conduct periodic audits of patient screening/enrollment logs, device accountability records, source documentation, and case report forms to ensure that the protocol is strictly followed.

C. Benefits

The major effect of breast implants is to enhance or restore the appearance of a woman's breast(s). Breast implant surgery may benefit women by providing a successful surgical breast reconstruction or augmentation procedure. Each individual woman has her own private sense of how she wishes to look and whether she wishes to go through surgery to achieve this appearance. There may be quality of life benefits to having breast implant surgery. Ongoing studies, including this study, will help determine to what extent breast implants improve a woman's quality of life. This study also may benefit women in the future by providing scientific information about the benefits and risks of breast implants. This study will evaluate risks and benefits according to the different indications of augmentation, reconstruction, and revision.

D. Warnings, Precautions, and Adverse Reactions

See "Possible Warnings, Precautions, and Adverse Reactions" section of Package Inserts, in Appendix B.

V. ALTERNATIVE PROCEDURES

There are several alternatives to augmentation or reconstruction with silicone-filled breast implants. Alternative procedures include: undergoing no treatment, wearing an external prosthesis inside the woman's brassiere, transferring tissue from other parts of the body (autologous tissue transfer procedure or flap procedure), or placement of saline-filled breast implants.

VI. STUDY DESIGN

A. Overall Design of the Study

This study is designed as a prospective clinical study intended to document the safety and effectiveness of McGhan Medical Silicone-Filled Breast Implants.

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Patients will be screened for eligibility and informed consent will be obtained from all patients prior to enrollment in the study. Patients will be evaluated pre-operatively, intraoperatively, and post-operatively at 0 – 4 weeks, 6 months, and annually for 10 years following implant surgery. In addition, an evaluation will be obtained at any unscheduled visit at which an adverse event/complication is noted.

All patients will be required to complete both the Quality of Life Questionnaire and the Activities and Lifestyle Index at baseline (pre-implant surgery) and at post-operative visits at 1, 2, 4, 6, 8, and 10 years. The Activities and Lifestyle Index will be reviewed by the investigator for indications of connective tissue disease to determine whether the patient should be referred to a rheumatologist. In addition, pre-operative and 1 year photographs will be required of all study participants.

In order to evaluate the occurrence of asymptomatic rupture, a subset of investigators will participate in the MRI portion of the study. Approximately 50% of the patients participating at these sites will be designated to undergo MRI at 1, 3, 5, 7, and 9 years post-implantation. Refer to the table below for specific data collected:

For specific requirements of data collection, refer to section VII. Study Procedures, F. Data Collection Requirements.

B. Study Duration

Patients will be followed for a minimum of ten (10) years following implantation. The data obtained through the year 2 visit will be submitted to the FDA in support of the PMA. The data obtained from year 3 through year 10 will be reported to the FDA as part of the post-market surveillance requested by the FDA.

C. Investigator Selection

Investigators will be selected by McGhan Medical based on but not limited to the following criteria:

- valid medical license in good standing
- certified by the American Board of Plastic Surgery (ABPS)
- experience in breast implant surgery with silicone-filled implants

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- evidence that their facility has the ability to provide the required support personnel to meet the study's documentation objectives in full compliance with FDA regulations
- evidence that their site can meet the required patient enrollment in the target enrollment period

Investigators will be notified by McGhan Medical of their patient enrollment assignments and enrollment limits (see section F. Investigator Assignments).

D. Study Population

Patients will be admitted into the study based upon the following eligibility criteria:

1. Inclusion Criteria

All patients at all study sites must meet the following requirements:

- a. Female, age 18 years or older.
- b. Patient presents with one or more of the following conditions:
 - i. **Primary breast augmentation** (i.e., no previous breast implant surgery) indicated for the following:
 - Patient dissatisfaction with size or shape of breast (e.g., mammary hypoplasia)
 - Asymmetry
 - Ptosis
 - Aplasia
 - ii. **Primary breast reconstruction** (i.e., no previous breast implant surgery other than implantation of tissue expanders or contralateral augmentation for asymmetry) indicated for the following:

For affected breast(s):

 - Mastectomy for cancer
 - Prophylactic mastectomy
 - Breast trauma (resulting in mastectomy)

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For the unaffected (contralateral) breast:

- Contralateral asymmetry (may be performed on the date of the mastectomy or the date when permanent implants are placed in the reconstruction breast).

iii. **Breast Implant Revision surgery** (i.e., removal and replacement of breast implants) indicated for the following:

- Previous augmentation or reconstruction with silicone-filled or saline-filled breast implants.

- c. Adequate tissue available to cover implants.
- d. At least 50% of patients at designated MRI sites must be willing to undergo MRI at 1, 3, 5, 7, and 9-year follow-up visits. The patient must be eligible for MRI (for example, no implanted metal or metal devices and no history of severe claustrophobia that may make her ineligible for MRI).
- e. Patient is willing to follow all study requirements, including agreeing to attend all required follow-up visits, and accepts the risks involved as indicated by signing and dating the study Patient Informed Consent prior to surgery.

2. Exclusion Criteria

Patients with any of the following characteristics will be excluded from the study:

- a. Advanced fibrocystic disease considered to be premalignant without accompanying subcutaneous mastectomy.
- b. Existing carcinoma of the breast, without mastectomy.
- c. Abscess or infection in the body at the time of enrollment.
- d. Pregnant or nursing.
- e. Have any disease, including uncontrolled diabetes (e.g., Hb A_{1c} > 8%), that is clinically known to impact wound healing ability.

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- f. Show tissue characteristics that are clinically incompatible with mammoplasty, such as tissue damage resulting from radiation, inadequate tissue, compromised vascularity or ulceration.
- g. Have, or under treatment for, any condition that may constitute an unwarranted surgical risk (e.g., unstable cardiac or pulmonary problems).
- h. Show psychological characteristics that may be incompatible with the surgical procedure and the prosthesis, such as inappropriate attitude or motivation (e.g., body dysmorphic disorder).
- i. Are not willing to undergo further surgery for revision, if medically required.

E. Sample Size

1. Overview

A total of 940 patients will participate in this study. Of these, approximately half will be enrolled for the augmentation indication (N = 500), one fourth for reconstruction (N = 220), and one fourth for revision (N = 220). The smaller sample sizes for the reconstruction and revision groups are based on the fact that these populations provide a much smaller available pool of women from which to draw compared with the augmentation indication. As such, an extremely lengthy enrollment period would be required to obtain 500 reconstruction and 500 revision patients. Further increasing enrollment difficulties for the reconstruction and revision cohorts is the fact that women undergoing these procedures can obtain the same silicone-filled devices through McGhan Medical's concurrent Adjunct Clinical Study, that involves half the time commitment and fewer follow-up requirements than does the present core study.

A subset of 150 augmentation patients, 101 reconstruction patients, and 73 revision patients from designated sites will be co-enrolled in the serial MRI portion of this study. This sample size for the serial MRI provides sufficient precision in estimating the asymptomatic rupture rate for the study device, as described in section E.4 below.

Estimated drop-out rates for each indication are 20% at the conclusion of the pre-market interval (2 years) and 40% at the conclusion of the post-market interval (10 years). Drop-out rates among the subset of serial MRI patients are anticipated to be 15% at the 1-year MRI screening and 60% at the 9-year MRI screening. These

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drop-out rates include drop-outs due to revision, since only primary implants will be included in the serial MRI analysis.

Determination of the total sample size for each indication was based on several considerations in the evaluation of device safety and effectiveness.

2. Safety Assessment

Two aspects of device safety were considered: comparison to controls and sufficiency of precision. First, the proposed sample size will provide sufficient power to detect moderate differences in complication rates between the historical control and study populations. Table VI.2 reports the minimum population proportion above the historical complication rate that would be detectable as significantly different at 2 and 10 years for a range of possible historical control values. Minimum detectable differences are calculated using the sample size and power formulas for a binomial test of proportions described in Cohen, 1988 (pp. 208-209)¹² with two-tailed alpha = .05 and power = .80. Final reported complication rates will be evaluated against the complication rates reported in the literature (see Appendix F) via the 95% confidence limits obtained using the Kaplan-Meier product limit method.

| TABLE VI.2 Minimum Population Proportion Detectable as Different from Historical Controls | | | | |
|--|--------------|-------------------------------|--------------|-------------------------------|
| Historical Control Rate | 2 Years | | 10 Years | |
| | Augmentation | Reconstruction or Revision | Augmentation | Reconstruction or Revision |
| | N = 400 | N = 176 | N = 300 | N = 132 |
| 1% | 2.9% | 4.2% | 3.2% | 4.9% |
| 2% | 4.4% | 6.0% | 4.9% | 6.8% |
| 5% | 8.5% | 10.6% | 9.1% | 11.6% |
| 10% | 14.6% | 17.2% | 15.4% | 18.4% |
| 20% | 25.9% | 29.1% | 26.8% | 30.5% |
| 30% | 36.6% | 40.1% | 37.6% | 41.7% |
| 40% | 46.9% | 50.5% | 48.0% | 52.1% |
| 50% | 57.0% | 60.5% | 58.1% | 62.1% |

Second, the sample sizes to be used in the present study will provide sufficient precision in describing complication rates for each indication. McGhan Medical believes that the confidence limits for each observed complication rate will provide satisfactory precision for informing patients about the risks and benefits associated with breast implants. Table VI.3 reports the expected 95% confidence

¹² Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Lawrence Erlbaum Associates, Hillsdale, NJ, 1988.

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limits for a range of potential complication rates based on estimated sample sizes at the conclusion of the pre-market (2 years) and post-market (10 years) intervals. Expected 95% confidence limits are calculated as the exact binomial limits as described in Zar, 1996 (pp. 524-527).¹³ The final reported 95% confidence limits will be obtained using the Kaplan-Meier product limit method and will depend on the actual loss to follow-up rate observed.

**TABLE VI.3 95% Binomial Confidence Limits
for 2 and 10 Year Complication Rates**

| Observed Complication Rate | 2 Years | | 10 Years | |
|----------------------------------|--------------|-------------------------------|--------------|-------------------------------|
| | Augmentation | Reconstruction or Revision | Augmentation | Reconstruction or Revision |
| | N = 400 | N = 176 | N = 300 | N = 132 |
| 1% | 0.3 - 2.5% | 0.1 - 4.0% | 0.2 - 2.9% | 0.0 - 4.8% |
| 2% | 0.9 - 3.9% | 0.5 - 5.3% | 0.7 - 4.3% | 0.3 - 6.2% |
| 5% | 3.1 - 7.6% | 2.3 - 9.4% | 2.8 - 8.1% | 1.9 - 10.3% |
| 10% | 7.2 - 13.4% | 6.0 - 15.4% | 6.8 - 14.0% | 5.4 - 16.5% |
| 20% | 16.2 - 24.3% | 14.3 - 26.7% | 15.6 - 25.0% | 13.5 - 27.9% |
| 30% | 25.5 - 34.8% | 23.3 - 37.4% | 24.9 - 35.5% | 22.3 - 38.6% |
| 40% | 35.2 - 45.0% | 32.7 - 47.7% | 34.4 - 45.8% | 31.6 - 48.9% |
| 50% | 45.0 - 55.0% | 42.4 - 57.6% | 44.2 - 55.8% | 42.1 - 58.8% |

3. Effectiveness Assessment

Determination of sample size was also based on the evaluation of device effectiveness via quality of life measures. The proposed sample size will provide sufficient power to detect small changes between pre- and post-implant quality of life scores. Table VI.4 reports the minimum difference between pre- and post-implant quality-of-life scale scores that are detectable as significant at 2 and 10 years. The minimum detectable differences are reported for all quality of life scales/subscales for which published standard deviation values are available.^{14,15,16,17} The minimum detectable difference is calculated utilizing the sample size and power formulas for a paired t-test described in Cohen, 1988 (pp. 208-209)¹² with two-tailed alpha = .05, power = .80, population scale/subscale standard deviation values obtained from the literature,^{14,15,16,17} and an assumed

¹³ Zar JH. Biostatistical Analysis (3rd ed.). Prentice Hall, Upper Saddle River, NJ, 1996.

¹⁴ Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey Manual and Interpretation Guide. The Health Institute, New England Medical Center, 1993, Boston, Massachusetts, pp. 10-14.

¹⁵ Burk J, Zelen SL, Terino EO. More than skin deep: A self-consistency approach to the psychology of cosmetic surgery. *Psychology of Cosmetic Surgery* 1985;76:270-280.

¹⁶ Conn VS, Taylor SG, Abele PB. Myocardial infarction survivors: Age and gender differences in physical health, psychosocial state and regimen adherence. *Journal of Advanced Nursing*, 1991;16:1026-1034.

¹⁷ Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey: Reliability and validity in a patient population. *Medical Care* 1988;26:724-735.

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correlation between pre- and post-implant scale scores of $r = +0.6$. The final analysis of quality of life data will be conducted by comparing baseline with post-implant scale scores through a repeated-measures (e.g., paired t-test) approach.

TABLE VI.4 Minimum Change Between Pre- and Post-Implant Quality of Life Scores Detectable as Different

| Quality of Life Scale/Subscale | 2 Years | | 10 Years | |
|---|--------------|----------------------------|--------------|----------------------------|
| | Augmentation | Reconstruction or Revision | Augmentation | Reconstruction or Revision |
| | N = 400 | N = 176 | N = 300 | N = 132 |
| MOS-20 Physical Functioning (R = 0-100, $\sigma = 30.80$) | 3.87 | 5.84 | 4.47 | 6.75 |
| MOS-20 Role Functioning (R = 0-100, $\sigma = 38.30$) | 4.81 | 7.26 | 5.55 | 8.39 |
| MOS-20 Social Functioning (R = 0-100, $\sigma = 23.60$) | 2.96 | 4.47 | 3.42 | 5.17 |
| MOS-20 Mental Health (R = 0-100, $\sigma = 20.20$) | 2.54 | 3.83 | 2.93 | 4.42 |
| MOS-20 Health Perceptions (R = 0-100, $\sigma = 26.80$) | 3.36 | 5.08 | 3.89 | 5.87 |
| MOS-20 Pain (R = 0-100, $\sigma = 27.70$) | 3.48 | 5.25 | 4.02 | 6.07 |

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| TABLE VI.4 CONTINUED | | | | |
|--|--------------|----------------------------|--------------|----------------------------|
| Minimum Change Between Pre- and Post-Implant Quality of Life Scores Detectable as Different | | | | |
| Quality of Life Scale/Subscale | 2 Years | | 10 Years | |
| | Augmentation | Reconstruction or Revision | Augmentation | Reconstruction or Revision |
| | N = 400 | N = 176 | N = 300 | N = 132 |
| SF-36 Role Limitations due to Physical Health Problems (R = 0-100, σ = 36.20) | 4.54 | 6.86 | 5.25 | 7.93 |
| SF-36 Physical Functioning (R = 0-100, σ = 24.60) | 3.09 | 4.66 | 3.57 | 5.39 |
| SF-36 Bodily Pain (R = 0-100, σ = 24.25) | 3.04 | 4.60 | 3.52 | 5.31 |
| SF-36 General Health (R = 0-100, σ = 21.50) | 2.70 | 4.07 | 3.12 | 4.71 |
| SF-36 Vitality (Energy/Fatigue) (R = 0-100, σ = 21.47) | 2.69 | 4.07 | 3.11 | 4.70 |
| SF-36 Social Functioning (R = 0-100, σ = 23.74) | 2.98 | 4.50 | 3.44 | 5.20 |
| SF-36 Role Limitations due to Emotional Problems (R = 0-100, σ = 34.43) | 4.32 | 6.52 | 4.99 | 7.54 |
| SF-36 Mental Health (R = 0-100, σ = 18.68) | 2.34 | 3.54 | 2.71 | 4.09 |
| Tennessee Self-Concept Scale: Physical Self Subscale (R = 18-90, σ = 7.10) | 0.89 | 1.35 | 1.03 | 1.56 |
| Rosenberg Self-Esteem (R = 10-40, σ = 4.13) | 0.52 | 0.78 | 0.60 | 0.90 |

4. Asymptomatic Rupture Assessment (MRI)

Determination of the appropriate sample size for the serial MRI portion of this study was based on obtaining a precision of approximately $\pm 2.5\%$ for estimating a by-device rate of 5% at 9 years. To obtain the desired precision level, a total of 525 devices must be enrolled in the study (assuming a 60% 9-year drop-out rate). The overall study sample size ratio of approximately 50%/25%/25% was used to determine the number of augmentation devices (n = 263), reconstruction devices (n = 131), and revision devices (n = 131) that are required to be enrolled. With an average of 2.0 devices per augmentation patient, 1.3 devices per reconstruction patient, and 1.8 devices per revision patient (based on enrollment in the McGhan Medical Large Simple Trial), a final sample size of 132 augmentation patients, 101 reconstruction patients, and 73 revision patients was determined for the serial MRI portion of this study. An additional 18 augmentation patients will participate in the

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serial MRI portion of this study because the previously approved version of this protocol (8/10/99) enrolled 150 augmentation patients. These additional 18 patients (36 devices) will result in a greater degree of precision than needed.

This sample size will provide sufficient precision in describing the asymptomatic rupture rate when performing a by-implant analysis. Table VI.1 reports the expected 95% confidence limits for a range of potential asymptomatic rupture rates based on estimated sample sizes at the conclusion of the pre-market (1 year) and post-market (9 years) intervals. Expected 95% confidence limits are calculated as the exact binomial limits as described in Zar, 1996 (pp. 524-527)¹⁸. The final reported 95% confidence limits will be obtained using the Kaplan-Meier product limit method and will depend on the actual loss to follow-up rate observed.

| TABLE VI.1 95% Binomial Confidence Limits for 1- and 9 Year Asymptomatic Rupture Rates | | |
|---|------------|------------|
| Observed Asymptomatic Rupture Rate | 1 Year | 9 Years |
| | N = 446 | N = 210 |
| 1% | 0.3-2.5% | 0.1-3.5% |
| 2% | 0.9-3.8% | 0.5-5.0% |
| 5% | 3.2-7.5% | 2.5-8.9% |
| 10% | 7.4-13.2% | 6.3-14.9% |
| 20% | 16.4-24.0% | 14.8-26.1% |
| 30% | 25.8-34.5% | 23.9-36.7% |
| 40% | 35.4-44.7% | 33.3-47.0% |
| 50% | 45.3-54.7% | 43.0-57.0% |

Furthermore, the subset of 525 devices in the serial MRI portion of this study will provide sufficient power to detect moderate differences in asymptomatic rupture rates between a comparison group and the study population. Table VI.2 reports the minimum population proportion above the comparison asymptomatic rupture rate that would be detectable as significantly different at 1 and 9 years for a range of possible comparison group values. Minimum detectable differences are calculated utilizing the sample size and power formulas for a binomial test of proportions described in Cohen, 1988 (pp. 208-209)¹⁹ with two-tailed alpha = .05 and power = .80.

¹⁸ Zar JH. Biostatistical Analysis (3rd ed.). Prentice Hall, Upper Saddle River, NJ, 1996.

¹⁹ Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Lawrence Erlbaum Associates, Hillsdale, NJ, 1988.

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| TABLE VI.2 Minimum Population Proportion Detectable as Different from Comparison Group | | |
|---|-------------------|--------------------|
| Comparison Group Rate | 1 Year N = 446 | 9 Years N = 210 |
| 1% | 2.7% | 3.8% |
| 2% | 4.3% | 5.7% |
| 5% | 8.2% | 9.9% |
| 10% | 14.5% | 16.6% |
| 20% | 25.6% | 28.2% |
| 30% | 36.2% | 39.1% |
| 40% | 46.5% | 49.5% |
| 50% | 56.5% | 59.4% |

F. Investigator Assignments

Each investigator will be assigned to enroll a specific patient population(s) (i.e., augmentation, reconstruction, revision).

The general patient enrollment targets for each indication are:

- Augmentation = 500 patients (with the smooth to textured patient groups approximately equal)
- Reconstruction = 220 patients (no target by device type)
- Revision = 220 patients (no target by device type)

These general targets will be addressed by pre-assignment of specific targets to each investigator by indication.

For each patient group assigned, an investigator will be instructed to meet the minimum required patient enrollment during the target enrollment period of 6 months as outlined below.

- Augmentation = 25 patients
- Reconstruction = 10 patients
- Revision = 10 patients

Investigators must update McGhan Medical's Clinical Research Department with the status of enrollment and to obtain approval to enroll additional patients above the assigned indication's minimum requirements.

An investigator may be assigned to enroll patients from only one of the three enrollment groups, or to enroll patients from more than one of the target groups. For all groups assigned, the investigator must meet the minimum patient

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enrollment for that group. For instance, an investigator may be assigned to enroll both reconstruction patients and revision patients, provided the investigator can meet the minimum of 10 patients per group during the 6 month enrollment period. Similarly, an investigator may be assigned to enroll both augmentation patients and revision patients, assuming that the minimum of 25 and 10 patients in the respective groups can be obtained. Investigators also can be assigned to enroll all three groups as long as the minimum enrollment for each group can be achieved.

Device styles included in this study are:

| | | |
|--------------------|---|-------------------------------|
| Styles 40 and 45 | = | Smooth, round implants |
| Styles 110 and 120 | = | Textured, round implants |
| Style 153 | = | Anatomical, textured implants |

Many plastic surgeons have established convictions about the relative benefits of specific device shape and surface texture based upon their clinical judgement and experience as well as the patient populations presenting in their practice. Therefore, the selection of device style for each patient will be based upon careful consideration of all factors by both the physician and patient.

For augmentation patients, it is expected that 80-90% of devices implanted will be round (either smooth or textured), whereas for reconstruction it is expected that 90% or more of patients will receive textured, anatomical implants. Anatomical implants are preferred in this latter population as the implant contour provides a better match to the natural breast, which is of particular importance for achieving symmetry. Additionally, textured implants have become the predominant choice for reconstruction patients due to the ability of the textured surface to maintain position, an issue of particular importance with anatomically-shaped devices. The distribution of device styles for revision patients is expected to resemble that of the augmentation group. The clinical considerations regarding device shape and surface texture are generally similar in these two patient populations.

All device styles (round smooth, round textured, and anatomical textured) are available for use in all patient groups. Within each indication, the data will be pooled across type of device and investigator (site) for the primary analyses of device safety and effectiveness.

In order to allow for a secondary analysis comparing smooth and textured device styles, investigators enrolling augmentation patients will be selected to ensure that a target of approximately half of the 500 patients are implanted with smooth

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devices and half with textured devices. Suitability of specific implant styles for the limited number of reconstruction and revision patients in conjunction with the study goal of achieving target enrollment during the 6 month enrollment period preclude enrollment of equivalent numbers of patients with specific device styles for these two indications. As with the reconstruction and revision groups, however, use of specific device styles among augmentation patients is left to the discretion of the physician and patient. As such, certain investigators may enroll augmentation patients only with smooth devices whereas other doctors may enroll augmentation patients strictly with textured devices. Consequently, any differences observed between smooth and textured products cannot unambiguously be attributed to device surface properties since the investigator is a confounding factor in the analysis.

VII. STUDY PROCEDURES

A. Investigator Responsibilities, Records, and Reports

1. Investigator Responsibilities

Each investigator must follow the Investigator Agreement (Appendix C), the protocol, and all conditions of IRB approval. A signed Investigator Agreement and written confirmation of IRB approval must be provided to McGhan Medical by the investigator prior to patient enrollment and the start of the study. This study must be conducted under all applicable Food and Drug Administration regulations including 21 CFR Part 812 (Investigational Device Exemptions), Part 50 (Informed Consent), and Part 56 (Institutional Review Boards).

The investigator shall make known to all study patients the nature, expected duration, and purpose of the study, the administration and potential risks of treatment, and available alternative therapy. Patients will be informed that their medical records will be subject to review by McGhan Medical and its representatives, the Institutional Review Board(s), and the Food and Drug Administration. The patients shall be informed that they are free to refuse participation in this clinical investigation, and if they do choose to participate, that they may withdraw from the study at any time without prejudicing future medical care. The signed and dated Patient Informed Consent must be obtained prior to surgery. The original will be kept by the investigator and will be subject to review by McGhan Medical. (A copy of the Informed Consent will be given to the patient.)

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2. Investigator Records

Investigators will maintain complete, accurate, and current study records consisting of the following materials:

- a. Correspondence with McGhan Medical and its representatives, the Medical Monitor, the FDA, the IRB, and other investigators;
- b. Patient records, including Patient Case Histories (progress notes), Informed Consent documents, copies of Case Report Forms and any supporting documents (e.g., diagnostic reports), and registry/tracking documents;
- c. Patient Enrollment Log;
- d. Device Accountability Log (i.e., records of receipt, use, or disposition of a device);
- e. Study protocol with documentation of dates and reason for deviations (any protocol deviations require prior approval from McGhan Medical and the IRB);
- f. Copies of unanticipated adverse device effect reports;
- g. Retention of Records – The investigator must maintain study files and records after the completion or termination of this clinical study until McGhan Medical informs the investigator otherwise. If the records are transferred to the custody of another person, McGhan Medical and the FDA must be notified within 10 working days after the transfer occurs. McGhan Medical will assist the site in transferring the study records.

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3. Investigator Reports

Each investigator will be responsible for the reports listed in Table VII.1.

| TABLE VII.1 Reporting Requirements | | |
|---|--|---|
| Type of Report: | Time Frame: | Provided to: |
| a. Unanticipated Adverse Events | ASAP or within 10 working days after notification of event | McGhan Medical (Sponsor) & IRBs |
| b. Withdrawal of IRB approval | Within 5 working days | McGhan Medical (Sponsor) |
| c. Progress Report | At regular intervals but no less than yearly | McGhan Medical (Sponsor) & IRBs |
| d. Other Reports | Per Sponsor's, IRB's, or FDA's request | McGhan Medical (Sponsor), IRBs, & FDA |
| e. Final Report | Within 3 months after investigator's responsibilities cease | McGhan Medical (Sponsor) & IRBs |
| f. Emergency Protocol Deviations | As soon as possible but in no event later than 5 working days after the emergency occurred | McGhan Medical (Sponsor) & IRBs |
| g. Protocol Deviations | Prior approval from the sponsor; IRB approval (if applicable) | McGhan Medical (Sponsor) & IRBs (if applicable) |
| h. Failure to obtain Informed Consent (Note: Informed Consent must always be obtained prior to breast implant surgery.) | Within 5 working days after occurrence | McGhan Medical (Sponsor) & IRBs |

a. Unanticipated Adverse Events

All unanticipated adverse device events that occur during or immediately following the use of McGhan Medical Silicone-Filled Breast Implants must be documented by the investigator, including the time of onset, complete description of the event, severity, duration, actions taken, and outcome. An Unanticipated Adverse Event Form must be completed and submitted to McGhan Medical and the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the event.

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b. Withdrawal of IRB Approval

Investigators will report to McGhan Medical within five (5) working days if, for any reason, their IRB withdraws approval to conduct the investigation. The report will include a complete description of the reason approval was withdrawn.

c. Progress Reports

Investigators will provide accurate, complete, and current information to their IRB(s) whenever requested or necessary. The investigator is required to provide all active IRBs and McGhan Medical with updates on study participation at regular intervals but no less than yearly.

d. Other Reports

Upon request, investigators will provide accurate, complete, and current clinical study information as appropriate to McGhan Medical, the FDA, and their IRB(s).

e. Final Report

Study closure shall occur after all patients have either been discontinued from the study or seen at or missed the last study follow-up interval. A final report must be submitted to McGhan Medical and the reviewing IRB(s) within 3 months after termination or completion of the investigation.

f. & g. Protocol Deviations

Since breast implant surgery is an elective procedure, emergency deviations from the protocol cannot be justified. The regulations state, however, that in an emergency deviations from the protocol must be submitted to McGhan Medical and the reviewing IRB as soon as possible but no later than 5 working days after the emergency occurred.

In cases other than an emergency, prior approval from the sponsor is required. If the deviation or change may affect the scientific quality of the study or the rights, safety, or welfare of the patients, prior approval from the reviewing IRB is required. Documentation of dates and reason(s) for each deviation from the protocol must be provided.

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Unauthorized use of McGhan Medical Silicone-Filled Breast Implants will result in termination of participation of the investigator from this clinical study.

h. Informed Consent

Since breast implant surgery is an elective procedure, failure to obtain informed consent prior to surgery cannot be justified and will result in termination from the study. However, if failure to obtain informed consent prior to surgery occurs, the regulations state that the investigator must report any use of a device without a prior signed and dated Informed Consent to the sponsor and the reviewing IRB within 5 working days from the time the event occurred.

B. Institutional Review Board (IRB) Requirements

The clinical study of McGhan Medical Silicone-Filled Breast Implants may not begin at any site until approval is obtained from the Institutional Review Board (IRB) for the facility in which patients will have implant surgery. As previously stated, investigators will provide accurate, complete, and current information to their IRB(s) whenever requested or necessary. The investigator is required to provide all active IRBs updates on study participation on at least an annual basis, depending upon the IRB's requirements. Upon request, investigators will provide accurate, complete, and current clinical study information as appropriate to their IRB(s).

C. Informed Consent

Informed consent must be obtained from all study patients prior to surgery to permit their study participation. An Informed Consent is provided in Appendix D.

The following items must be completed:

- Patient must sign and concurrently date the Informed Consent prior to surgery;
- The investigator or his designee (person rendering consent) must sign and concurrently date the informed consent prior to surgery;
- If any patient or the patient's legally acceptable representative is unable to read, an impartial witness must be present during

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rendering of the Informed Consent and must sign and concurrently date the Informed Consent (on the same date as the patient) attesting that the information was explained to and apparently understood by the patient or the patient's representative and that consent was freely given;

- Case history (medical chart) documentation must verify that Informed Consent was rendered prior to surgery;
- The original signed and dated Informed Consent must be kept in the patient's study file/medical chart;
- A copy of the Informed Consent must be provided to the patient;
- A copy of the Informed Consent's signature pages must be provided to McGhan Medical prior to the patient's surgery. It is required that these pages be faxed to McGhan Medical for review prior to surgery.

Use of a study device prior to obtaining a complete Informed Consent for each patient is not acceptable under any circumstance. However, if failure to obtain informed consent prior to surgery occurs, the investigator must report to McGhan Medical and the reviewing IRB any use of a device without an Informed Consent within 5 working days from the time the event occurred. Any such occurrence will result in immediate termination from the study.

D. Device Accountability

Strict accountability of all study devices is required. A record of the receipt and disposition of all devices must be maintained. McGhan Medical will provide a Device Accountability Log for investigators to utilize in documenting device receipt and disposition (see Appendix G for a sample log). The implants will be shipped only to active investigators after documentation of IRB approval at the applicable surgical facility has been provided to McGhan Medical.

Any unauthorized use of McGhan Medical Silicone-Filled Breast Implants will result in termination of participation of the investigator in this clinical study.

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E. Patient Enrollment Log

A Patient Enrollment Log will be provided to identify and list all patients implanted with any silicone-filled breast implants by the investigator during the conduct of the study (see Appendix G for a sample log).

F. Data Collection Requirements

1. Case Report Form Completion

Case Report Forms will be completed for all study participants and must be reviewed and signed by the investigator. Copies of each of the Case Report Forms are provided in Appendix E.

All Case Report Forms should be completed within one week of the visit / treatment date and received at McGhan Medical within one month of the visit/procedure.

Using the postage paid envelopes provided, send forms directly to:

Clinical Research Department
McGhan Medical Corporation
700 Ward Drive
Santa Barbara, California 93111

Patients are considered enrolled when **Form 1** (Eligibility) and **Form 2** (Preoperative Medical & Breast Screening History) are completed.

Scheduled Follow-Up visits are based upon the date of the index surgery, which is defined as follows:

- For augmentation and revision patients, the date of implantation of the first study device
- For reconstruction patients, the date of implantation of the first study device in the affected breast (mastectomy)

Notes: Tissue expanders can be in place prior to or subsequent to enrollment.

Contralateral augmentation with a study device can take place any time after enrollment through the date of the index surgery.

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Forms are completed at each interval as follows:

| TABLE VI.1 Data Collection | | | | | | | | | | | | | | |
|---|------------|---------------|---|------|------|------|------|------|------|------|------|------|------|-------|
| Data Collected | Enrollment | Index Surgery | 0 - 4 weeks | 6 mo | 1 yr | 2 yr | 3 yr | 4 yr | 5 yr | 6 yr | 7 yr | 8 yr | 9 yr | 10 yr |
| Form 1 - Eligibility | ✓ | | | | | | | | | | | | | |
| Form 2 - Medical/Breast Screening History | ✓ | | | | | | | | | | | | | |
| Form 3 - Quality of Life Questionnaire | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Form 4 - Activities & Lifestyle Index | ✓ | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Form 5 - Primary Surgery | | ✓ | | | | | | | | | | | | |
| Form 6 - Scheduled Visit | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Form 7 - Complication/Treatment | | | ANYTIME AS APPLICABLE | | | | | | | | | | | |
| Form 8 - Secondary Procedure | | | ANYTIME AS APPLICABLE | | | | | | | | | | | |
| Form 9 - Explant | | | ANYTIME AS APPLICABLE | | | | | | | | | | | |
| Form 10 - Breast Cancer | | | ANY PATIENT EVER DIAGNOSED WITH BREAST CANCER | | | | | | | | | | | |
| Form 11 - CTD | | | ANYTIME AS APPLICABLE | | | | | | | | | | | |
| Form 12 - MRI Central Reviewer (Designated Sites) | | | | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | |
| Form 13 - MRI Results (Designated Sites) | | | | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | |
| Form 14 - UAE | | | ANYTIME AS APPLICABLE | | | | | | | | | | | |
| Form 15 - Discontinuation | | | ANYTIME AS APPLICABLE | | | | | | | | | | | |
| Photographs | ✓ | | | | ✓ | | | | | | | | | |

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a. **Enrollment**

The following forms are completed for each study patient prior to surgery:

Form 1 (Enrollment)

Form 2 (Preoperative Medical & Breast Screening History)

Form 10, for all patients with prior or current breast cancer.

If information is not available prior to surgery, the **Form 10** should be completed as soon as possible.

Each patient must complete the following forms prior to surgery:

Patient Informed Consent

Form 3 (Quality of Life)

Form 4 (Activities & Lifestyle).

The investigator must review the completed **Form 4** and provide a determination of whether the patient should be referred to a rheumatologist for further evaluation.

b. **Primary Implant Surgery**

Form 5 (Primary Surgical Treatment) is completed at the time of the primary (study enrollment) surgery.

Form 9 (Explant) is completed as soon as possible after the primary surgery for all revision patients.

c. **Follow-up**

Form 6 (Scheduled Follow-Up) is completed at 0 – 4 weeks, 6 months and at the 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 year visits. All scheduled follow-up office visits must occur within a two-month window beginning on the anniversary of the primary surgery.

Form 7 (Complication / Treatment Log) is completed at any visit, scheduled or unscheduled, during which complications are reported, treated, or evaluated.

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Form 3 (Quality of Life) and

Form 4 (Activities & Lifestyle) are to be completed by each patient at the 1, 2, 4, 6, 8, and 10 year follow-up intervals at the same time as the patient's scheduled office visit.

The investigator must review the completed **Form 4** and provide a determination of whether the patient should be referred to a rheumatologist for further evaluation.

d. Secondary Treatment/Revisions

Form 8 (Secondary Procedure) is completed each time a secondary procedure is performed to the breast/chest area.

Form 9 (Explant) is completed whenever an implant is removed as part of a secondary treatment.

e. Unanticipated Adverse Event

Form 14 (Unanticipated Adverse Event) is completed each time an unanticipated adverse effect occurs during the study (see section 9. Adverse Event Reporting).

f. Patient Discontinuation

Form 15 (Discontinuation) is completed when a patient is discontinued or withdraws from the study.

g. Breast Cancer Information

Form 10 (Breast Cancer) is completed for all patients (reconstruction, augmentation, and revision) who have had breast cancer at any time prior to the implant surgery.

Form 10 also should be completed for any subsequent breast cancer diagnosis for all study patients.

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h. Connective Tissue Disease Confirmation

Form 11 (CTD Confirmation) is completed when a patient indicates either on the **Form 2** or **Form 6** that she has been diagnosed with a connective tissue disease.

Part A of this form is completed by the investigator based upon information reported by the patient. Part B can be completed either by the investigator (based upon verbal or written confirmation of the diagnosis from the diagnosing or attending physician) or sent to the attending / diagnosing physician for completion. The completed form should then be sent to McGhan Medical.

i. MRI Data (MRI Sites Only)

Form 12 (MRI Central Reviewer) is completed by the MRI Central Reviewer designated by McGhan Medical. Once completed, the MRI Central Reviewer will send the form to McGhan Medical.

Form 13 (MRI Results) is to be completed by the investigator after both the local MRI facility results and the MRI Central Reviewer's results (**Form 12**) are received (see section F. Data Collection Requirements, 5. Magnetic Resonance Imaging-MRI.)

2. Connective Tissue Disease Screening

In order to document and follow the signs and symptoms of Connective Tissue Disease (CTD), all study patients will be required to complete the Activities and Lifestyle Index (A&L Index) prior to surgery and at the 1, 2, 4, 6, 8, and 10 year follow-up visits. The A&L Index was originally designed to collect and follow potential CTD-related symptoms for patients diagnosed with CTD. After the patient completes the A&L Index, the questionnaire will be reviewed by the investigator to determine whether the patient should be referred to a rheumatologist for further evaluation. Referral will be based on the completed questionnaire in conjunction with the patient's current medical status and medical history. The investigator may consult with the Rheumatological Medical Monitor to assist with this determination (see Appendix H for Rheumatological Medical Monitor information). The role of the Rheumatological Medical Monitor is to serve as a source of specialized medical expertise for the investigator, if necessary, in assessing whether referral to a rheumatologist is required for a patient.

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A history of diagnosis of Connective Tissue Disease will be obtained prior to surgery (baseline) and at each follow-up visit. If the patient indicates that she has been diagnosed with a CTD, confirmation of the diagnosis must be obtained from the patient's diagnosing or attending physician.

3. Quality of Life Assessment

One measure of the effectiveness of McGhan Medical Silicone-Filled Breast Implants will be based on the patients' change in quality of life from pre- to post-implantation. Quality of life assessments elicit information directly from the patient and can provide substantial insight on the perceived outcome of breast implant surgery. Patients will be required to complete the Quality of Life questionnaire (Form 3) at baseline (pre-implant surgery) and at the 1, 2, 4, 6, 8, and 10 year follow-up visits. The patient must complete the Quality of Life questionnaire during the office visit. The patient should place the confidential questionnaire in the postage paid envelope provided and give the envelope to the study coordinator to be mailed directly to McGhan Medical. Since this questionnaire is confidential, a copy of the completed Quality of Life form should not be kept in the study/patient files. (See Appendix I. Quality of Life Information for additional discussion).

4. Photographs

Pre- and post-operative photographs will be taken by the investigator or his/her staff prior to surgery and at the 1 year follow-up visit. These photos, of the breast/chest area, may aid in evaluating the breast implant surgery. The photographs will remain at the investigator's site.

5. Magnetic Resonance Imaging-MRI (subset of sites)

Patients at designated sites will be co-enrolled in the serial MRI portion of the study and requested to undergo serial MRI in order to evaluate the occurrence of asymptomatic rupture. A subset of the investigators will participate in the MRI portion of the protocol. McGhan Medical will notify each investigator as to his/her participation in the MRI portion of the protocol. A total of 150 augmentation patients, 101 reconstruction patients, and 73 revision patients will be enrolled at this subset of sites. These patients will be required to undergo MRI at 1, 3, 5, 7, and 9 years post-implant surgery. The MRI should be performed within one month following the associated follow-up visit. The investigational site will assist the patient in scheduling the MRI.

Prior to participation in this portion of the study, patients will be evaluated for eligibility and willingness to undergo MRI. Patients will be excluded if they have any

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metal devices or metal implanted or past history of severe claustrophobia. Any questions regarding a patient's eligibility for MRI should be directed to McGhan Medical's MRI Central Reviewer (see Appendix H for MRI Central Reviewer information).

Patients will be required to attend an MRI clinic that can perform the appropriate MRI technique. McGhan Medical will consult with the investigator on the selection of a suitable MRI facility in which the appropriate MRI technique will be utilized. The MRI should be performed using a bilateral dedicated breast coil, with unilateral and bilateral switch positions, or a dual shoulder coil. The local MRI facility should be blind to the investigator's clinical judgment of whether the implant(s) may be ruptured. The local MRI facility will forward the results to the investigator. Additionally, the local MRI facility will send the MRI images on disk, without the report, to the MRI Central Reviewer (see Appendix H for MRI Central Reviewer's address).

The MRI Central Reviewer, who will be blind to the local facility's evaluation of the implant(s) and the investigator's clinical judgment of possible rupture, will perform an independent assessment of the MRI. The MRI Central Reviewer will complete the **Form 12** and provide a detailed report to both the investigator and McGhan Medical. The investigator will review the findings of both the local and the MRI Central Reviewer reports and consult with the patient as to the appropriate treatment, if necessary. The investigator will complete the **Form 13** and forward the completed form to McGhan Medical.

If, during the course of the study, an MRI participant has revision surgery and she no longer has any original study implant(s) placed or if other circumstances develop that make her ineligible for MRI, she will be discontinued from the MRI portion of the study. If a patient is pregnant at the time the MRI is due, she may skip this MRI and resume the MRI portion of the study following her pregnancy.

6. Explanted Devices/Revision Surgery

An Explant Disposition **Form 9 (Explant)** as well as an Explant Disposition Form (see Appendix J) must be completed and returned to McGhan Medical if explant surgery is indicated and an implant(s) is removed. McGhan Medical strongly recommends that explanted devices be returned. It is also recommended that a signed patient release form be obtained from each patient before the investigator returns the explanted implants to McGhan Medical.

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McGhan Medical requests that any explanted study devices be sterilized prior to returning them. Return the sterilized devices to:

Quality Assurance Department
McGhan Medical Corporation
700 Ward Drive
Santa Barbara, CA 93111

Attention: Sterile Clinical Study Product Enclosed

McGhan Medical will analyze and store any returned study devices, which may result in alteration or destruction of the device(s). The results of this analysis may be sent to the investigator. The FDA has indicated that important information may be gained from analyzing all explanted implants.

7. Patients Lost to Follow-Up

All patients meeting eligibility requirements who sign an Informed Consent and have an implant placement procedure with a McGhan Medical Silicone-Filled Breast Implant are considered study patients. Any study patient who misses a scheduled study appointment will be contacted as soon as possible and rescheduled by the investigator's office. McGhan Medical will assist the investigator in attempting to locate patients lost to follow-up.

8. Patient Discontinuation/Withdrawal

Patients will be considered discontinued from the study for the following reasons:

- a. Patient no longer has any study implants, as a result of explantation without replacement with a study device;
- b. Patient death;
- c. Patient choice;
- d. Other reason: Contact McGhan Medical Clinical Research Department to determine if any "other" reason may be applicable for a patient to discontinue or withdraw from the study.

9. Relocated Patients

If a patient relocates, a physician (active investigator) in the new area may see the patient for required follow-up visits and any treatments relating to the patient's breast implants. It is the responsibility of the patient to inform the investigator of the

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intended relocation. The investigator is responsible for assisting the patient in locating a physician in her new area. The investigator should notify McGhan Medical's Clinical Research Department regarding a patient's relocation. McGhan Medical may assist in locating and contacting an investigator or physician in the patient's new location.

10. Adverse Event Reporting

a. Adverse Events

The investigator must fully document all serious adverse events, life-threatening problems, or deaths that occur during or following the use of McGhan Medical Silicone-Filled Breast Implants, including the time of onset, a complete description of the event, severity, duration, actions taken, and outcome. The appropriate form (i.e., **Form 7 Complication & Treatment Log**, **Form 8 Secondary Procedure**, or **Form 15 Discontinuation**) must be completed and submitted to McGhan Medical.

b. Unanticipated Adverse Events

Unanticipated adverse events are defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by or associated with the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or package insert (including a supplementary plan), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of patients.

Investigators will report any unanticipated adverse events caused by or associated with use of McGhan Medical Silicone-Filled Breast Implants as soon as possible but no later than 10 working days of learning of the event to the Sponsor (noted below) and reviewing IRB. A **Form 14** (Unanticipated Adverse Event) must be completed and forwarded to the Sponsor:

Sponsor: Clinical Research Department
McGhan Medical Corporation
700 Ward Drive
Santa Barbara, CA 93111

Attention: Unanticipated Adverse Event Form Enclosed

Tel: (805) 862-4426

Fax: (800) 972-3278

G. Study Costs and Reimbursement

1. Incentive Program

McGhan Medical is offering an incentive program to all patients and sites participating in this important research study. The incentive program is designed to compensate patients and the investigational sites for the time spent in scheduling, conducting study-related visits, and completing case report forms (see Appendix K for more information).

2. Insurance

All costs incurred in this study are to be contracted between the patient and investigator unless otherwise specified in the Patient Informed Consent. This includes costs for any additional procedures or visits to other specialists that may be required for related secondary surgeries/treatments, should they become necessary. Operations and associated costs may or may not be reimbursed through insurance.

Elective cosmetic procedures, such as breast augmentation, are generally not covered under most insurance policies. It is the patient's responsibility to contact her insurance company and determine what coverage, if any, is available for her proposed surgery.

3. Patient Compensation for Injury

Through the McGhan Medical ConfidencePlus™ Program, McGhan Medical offers limited financial assistance to cover certain revision expenses in the event of an implant rupture and guarantees lifetime implant replacement. Compensation for physical injuries, complications, or medical treatment as a result of the patient's participation in this study is not available from McGhan Medical, unless otherwise noted. If a problem occurs, patients should see their surgeon (see Appendix L for the ConfidencePlus™ Program).

VIII. ADMINISTRATIVE

A. Sponsor and Clinical Monitor

McGhan Medical will serve as the Sponsor and Clinical Monitor for this study. Responsibilities for these roles will include selecting qualified investigators, ensuring that IRB approvals are obtained and that any reviewing IRBs and the

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FDA are promptly informed of significant new information about the study, conducting periodic audits of device accountability records, receiving the completed Case Report Forms, monitoring the study to ensure that the proper records are being maintained and that study procedures and all applicable FDA regulations are being followed, insuring that complete and accurate data are being collected, verifying quality assurance of data processing, and preparing clinical reports of the results of the study. Any questions regarding these matters should be addressed to McGhan Medical Clinical Research Department.

McGhan Medical Clinical Research management personnel and Clinical Research Associates (CRAs) are trained and qualified to act as Clinical Monitor.

Clinical Research Department
McGhan Medical Corporation
700 Ward Drive
Santa Barbara, California 93111

TEL: (800) 862-4426

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B. Monitoring Procedures

1. Pre-Study Visits

McGhan Medical Clinical Research personnel will conduct Pre-Study Visits prior to study start-up. At the Pre-Study Visit the Clinical Monitor will review with the investigator and study coordinator relevant FDA regulations and inspection procedures, the protocol, IRB review and approval, completion and submission of Case Report Forms, record keeping requirements, and administrative reports. The availability of the investigator, the potential number of study participants, the provisions for support staff, and the ability to perform the study requirements also will be addressed during the Pre-Study Site Visit.

2. Investigational Site Visits

To ensure that investigators and their staff understand, accept, and fulfill their defined responsibilities, the Clinical Monitor (or individuals contracted by McGhan Medical) will maintain regular correspondence with the site and perform periodic site visits during the course of the study. At the site visits, the monitor will verify the continued acceptability of the facilities, compliance with the protocol and relevant FDA regulations, and the maintenance of complete

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records. Clinical monitoring also will include review and resolution of missing or inconsistent data, as well as source document checks (i.e., comparison of submitted study data to original reports) to assure the accuracy of the reported data.

The Clinical Monitor will evaluate and summarize the results of each site visit in written reports, identifying any recurrent data problems with an investigator and specifying recommendations for resolution of noted deficiencies.

C. Medical Monitor

The Medical Monitor's responsibilities include review of the protocol, review of adverse reactions or unanticipated adverse device events, and interpretation of clinical results. The Medical Monitor is qualified by training and experience to perform these duties as described (see Appendix H for Medical Monitor information).

D. Clinical Quality Assurance

This clinical study protocol details procedures that are designed to ensure that complete, timely, and accurate data are submitted, that protocol requirements are followed, and that adverse events/complications or unanticipated adverse events are immediately identified.

McGhan Medical Clinical Research personnel will review all incoming data to identify inconsistent or missing information and adverse events. Data problems will be addressed in calls and/or in writing to the investigational sites and during site visits. To insure that all data remain confidential, McGhan Medical will maintain secure hard copy forms and data files.

E. Patient Registry & Device Tracking

McGhan Medical requires that all study patients participate in the Implant Registry program. All information required on the Medical Device Registration Form must be entered on the form and returned to McGhan Medical in a timely manner for entry into McGhan Medical's Implant Registry. Patients may not decline participation in the Implant Registry (see Appendix J).

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F. Patient Confidentiality

Patient confidentiality will be protected as much as possible throughout this study. Medical records may be reviewed by McGhan Medical Clinical Research personnel, the Institutional Review Board, and the FDA, as required. Results reported from this study will not include any personal identifiers.

For internal identification, tracking, and monitoring purposes, patient's initials and a pre-assigned unique patient identification number will be listed on all clinical study records including clinical study Case Report Forms. SSN is requested on the Informed Consent, however, disclosing SSN is optional.

The possibility exists that clinical records and information could be obtained by Congress or by a court order. Every effort will be taken by McGhan Medical to keep this information confidential. However, under certain circumstances public disclosure of patient information and subsequent loss of patient confidentiality is possible.

IX. DATA ANALYSIS

A. Overview

Analyses and reports of the safety and effectiveness data obtained in this study will be submitted to the FDA in two phases: the first phase will be submitted as part of a Pre-Market Approval application and will assess outcomes through the 2 year post-operative follow-up interval; the second phase is designed for post-marketing surveillance and will provide safety and effectiveness results over a longer period of implantation (3 to 10 years of post-surgical follow-up).

Primary analyses will involve separate assessment of safety and effectiveness for each of the three study populations (i.e., augmentation, reconstruction, and revision). Within each indication, patients from all investigational sites will be pooled together for analysis. A total of 20-25 investigational sites per indication are included in this study to insure a good representation of clinical practice and a representative sample of the study populations. Likewise, all device styles included in the study will be pooled together for primary analysis. Although there is no reason to expect outcome differences due to product style, augmentation patient enrollment is being structured to permit a comparison of smooth and textured implants.

Primary analyses will be conducted using the number of patients and/or the number of implants as the unit of analysis, as appropriate. Analysis will be

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based on primary implants only (i.e., devices implanted at study enrollment). Data on these primary study implants will be collected from enrollment through the 10 year post-market follow-up interval or until explantation, whichever occurs first.

If a primary study implant is removed and replaced with a non-study device or not replaced at all, no further data will be collected on the explanted side. If a primary study implant is replaced with another study device ("secondary" study implant), data will continue to be gathered on the secondary study implant, adhering to the patient's same ongoing study schedule as for a primary study implant. However, data collected on these secondary study implants will not be included in the primary analysis for any of the three indications. Safety and effectiveness data on these secondary study implants will be monitored and evaluated on an ad-hoc basis.

B. Success/Failure Criteria

In addition to evaluating device safety by describing associated complication rates, a comparison with historical values also will be conducted. Previous complication rates will be obtained from the published literature. Historical control values are available for capsular contracture, rupture, asymptomatic rupture, and infection (see Appendix F). For each of these complications, the worst-case historical control value will be evaluated with respect to the calculated 95% confidence limits for the rate observed in the present study.

Comparisons to historical control values will be conducted only for those complications and indications for which methodologically comparable rates are available. For instance, published research has focused primarily on augmentation patients, with limited data available for reconstruction patients and almost no rates reported for a clearly identifiable cohort of revision patients (see Appendix F).

C. Evaluation of Safety Outcomes

Assessment of the safety of McGhan Medical Silicone-Filled Breast Implants will be based on the incidence of local complications (e.g., infection), implant-related complications (e.g., wrinkling, asymmetry), capsular contracture, and device failure (e.g., rupture, explantation). Additionally, a qualitative analysis will be performed on patients who experience a systemic condition (e.g., connective tissue disease), breast cancer, or other adverse event.

1. Medical History

Prior to implantation, a detailed medical history will be obtained from all patients, including reproduction/lactation history, medications taken, diagnoses of disease, and a detailed history of all breast-related disease, surgery, and cancer. Although no formal quantitative analysis is planned for these data, this information will be available for use in any retrospective evaluation of adverse events, such as breast cancer.

2. Local and Implant-Related Complications

The occurrence and degree (mild to very severe) of any local complications, including those due to surgery, and any implant-related complications will be assessed at each follow-up visit.

Local complications may include hematoma, delayed wound healing, tissue or skin necrosis, abnormal scarring, lymphadenopathy, or capsule calcification. Implant-related complications encompass rippling, implant malposition, asymmetry, implant palpability, implant visibility, implant extrusion, and suspected implant rupture.

Time to first occurrence of each complication will be assessed using the Kaplan-Meier product limit method. A descriptive analysis (e.g., frequency distribution) of the degree of occurrence of each complication also will be provided. Additionally, for suspected rupture, a frequency distribution of reasons for suspected rupture will be presented. The worst case historical infection rate from the implant-related (see Appendix F) or general surgery literature will be compared with the 95% confidence limits obtained from the Kaplan-Meier analysis.

3. Capsular Contracture

The incidence and degree of fibrous capsular contracture also will be assessed at each scheduled follow-up visit. Formation of a fibrous tissue capsule surrounding the implant is a normal physiological response to implantation of a foreign body. Contracture of the fibrous capsular tissue surrounding the implant may result in firmness, discomfort, or pain in the breast, distortion of the breast, palpability of the implant, and/or displacement of the implant. In this study, the occurrence and degree of clinical firmness of fibrous capsular contracture will be evaluated by the examining physician using the four-point Baker Classification Scale.

Time to first occurrence of significant capsular contracture, defined as a Baker Grade Classification of III or IV, will be reported via the Kaplan-Meier product limit method. A frequency distribution of each Baker Grade Classification also will be provided. Finally, the worst case historical rate of capsular contracture (see Appendix F) will be compared to the 95% confidence limits obtained from the Kaplan-Meier analysis.

4. Implant Rupture

Upon removal, each study product will be evaluated by the investigator for evidence of rupture, including gel bleed, visible holes, visible tears, intracapsular rupture, and extracapsular rupture. Time to first occurrence of device rupture will be reported via the Kaplan-Meier product limit method. A descriptive analysis of the evidence for rupture at removal also will be provided. Finally, the worst case historical rupture rate (see Appendix F) will be compared to the calculated Kaplan-Meier 95% confidence limits.

For those patients enrolled in the MRI portion of the study, all MRI screenings are required to be performed within one month after the patient's annual follow-up visit. At the follow-up visit immediately preceding the patient's MRI screening, the possible occurrence of and evidence for suspected rupture will be obtained from the investigator. If rupture is suspected, the patient will be classified as symptomatic for rupture; otherwise, she will be classified as asymptomatic for rupture. If the results of the MRI indicate evidence of rupture, a true implant rupture will be assumed to exist (i.e., the assumed sensitivity of the MRI is 100%). Among those patients who are asymptomatic for rupture, time to first occurrence of rupture, as indicated by the results of the MRI, will be reported using the Kaplan-Meier product limit method. The worst case historical asymptomatic rupture rate (see Appendix F) will be compared with the 95% confidence limits obtained from the Kaplan-Meier analysis.

5. Explant

On explantation, the reason for implant removal will be assessed. Reasons for explant include to increase or decrease size, rippling, asymmetry, implant malposition, capsular contracture, infection, pain, necrosis, extrusion, and suspected rupture. Time to first explantation will be reported using the Kaplan-Meier product limit method. A frequency distribution of reason for implant removal also will be presented.

6. Connective Tissue Disease

A number of well-designed studies, which include internal control groups and confirmed diagnosis of CTD through medical record review, have found no indication of a relationship between breast implants and connective tissue diseases.^{1,3,4} In order to document and follow signs and symptoms of autoimmune and rheumatological disorders, this study includes a connective tissue disease screening questionnaire administered before and after breast implant surgery. Upon a confirmed post-operative diagnosis of a connective tissue disease (**Form 11**), information from the CTD screening questionnaire will be examined. These data will be interpreted via a qualitative evaluation comparing pre- and post-implantation signs and symptoms of connective tissue disease.

7. Breast Cancer

Numerous studies examining the issue of a possible link between breast implants and breast cancer have provided no evidence that such an association exists.^{8,9,10,11} At enrollment, all patients will be asked for results of any mammogram done within the preceding year. Also at enrollment, patients with a prior or current diagnosis of breast cancer will be asked to provide information regarding tumor size and location, pathology, adjunctive therapy, and results of screening mammography.

During the course of the study, mammographic results will be obtained from any patients that undergo this procedure.

Upon a diagnosis of primary or recurring cancer, previous breast history and breast cancer information will be examined and the results from any screening mammographies will be submitted for review by a consulting oncologist for their relevance to the implant.

D. Evaluation of Effectiveness Outcomes

Assessment of the effectiveness of McGhan Medical Silicone-Filled Breast Implants will be based on changes in anatomical configuration, patient and investigator satisfaction with the outcome of the procedure, and quality of life measures.

1. Changes in Anatomical Configuration

To document that implantation with McGhan Medical Silicone-Filled Implants increases the size of the breast, each patient's breast/chest dimensions will be measured and recorded both prior to and six months following implant surgery. These measurements will be converted into bra sizes according to a matrix. A matrix or cross-tabulation comparing the frequency of each pre-implant bra size with the frequency of each post-implant bra size will be created. Additionally, the breast/chest measurements will be converted to a numerical scale to allow a more direct comparison of the change between pre- and post-implant bra sizes.²⁰

2. Satisfaction with Outcome

At each follow-up visit, both the physician and patient will be asked to indicate their satisfaction with the implant surgery (definitely satisfied to definitely dissatisfied), and to specify any reasons for dissatisfaction. A frequency distribution of the degree of satisfaction expressed by physicians and patients will be presented. Differences between physician and patient assessments also can be examined via a paired t-test. Finally, reasons for dissatisfaction will be described.

3. Quality of Life

Prior to breast implantation and at selected follow-up visits, patients will be asked to complete a quality of life questionnaire. This questionnaire includes validated scales that are widely used and assess both general and specific quality of life domains relevant to breast implant surgery (e.g., general health, body image, expectation and satisfaction with breasts). To evaluate the effects of breast implantation on patient quality of life, changes pre- to post-surgery in the various measures and scales on the questionnaire will be examined via paired t-tests. Appendix I provides more detailed information regarding McGhan Medical's measurement and analysis of patient quality of life in this study.

²⁰ Young VL, Nemecek JR, Nemecek DA. The efficacy of breast augmentation: Breast size increase, patient satisfaction, and psychological effects. *Plastic and Reconstructive Surgery* 1994;94:958-969.