MemoryGel™ Implant PAS*

(*MemoryGel™ Postapproval Study)

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1.0 INTRODUCTION

The U.S. Food and Drug Administration (FDA) recently approved Mentor's MemoryGel™ silicone gel-filled breast implants for use in women who are undergoing primary or revisional breast augmentation and primary or revisional breast reconstruction surgery. The approval is conditional on Mentor conducting a 10-year study designed to collect long-term experience in U.S. women with MemoryGel implants. The postapproval study described in this protocol is intended to satisfy one element of FDA's postapproval monitoring requirements.

As a condition to gaining access to MemoryGel products, surgeons will be required to sign up for the MemoryGel™ Silicone Gel-filled Breast Implants Post Approval Study (PAS), and will be asked to actively encourage 41,900 women to participate in the 10-year study. In addition, there will be a concurrent control group of 1,000 women who are undergoing breast implantation with saline breast implants to serve as concurrent controls for assessing rheumatologic and neurologic signs and symptoms.

2.0 OBJECTIVES

This postapproval study is designed to address the issues identified in Table 1:

Table 1
POSTAPPROVAL STUDY OBJECTIVES

Complication/ Condition/ Disease	Issues to be Addressed
Local Complications[1]	• What are the Kaplan-Meier (KM) complication rates over time, including removal and reoperation rates? • What are the reasons for reoperation over time?
Connective Tissue Disease (CTD)[2]	• What are the types and rates of CTD diseases reported for women receiving Mentor MemoryGel implants and controls?
Rheumatological Signs and Symptoms[3]	• What are the types and rates of rheumatological signs and symptoms reported for women receiving Mentor MemoryGel implants and controls?
Neurological Disease[4]	• What are the types and rates of neurological diseases reported for women receiving Mentor MemoryGel implants and controls?
Neurological Signs and Symptoms[5]	• What are the types and rates of neurological signs and symptoms reported for women receiving Mentor MemoryGel implants and control group?
Offspring	• What are the rates of birth defects/congenital malformations (such as cleft lip, cleft palate, neural tube defect, esophageal deformity, and pyloric stenosis), premature birth, low birth weight, neonatal intensive care, and chronic illnesses (such as autoimmune disorders, cancer, and neurological disease) in children born to women receiving Mentor MemoryGel implants and controls?
Reproductive	• Of those women who attempted to have children, what are the rates of miscarriage and stillbirths for women receiving Mentor MemoryGel implants and controls?
Lactation	• Of those women who attempted to breast feed, how many were able in each of the groups (women receiving Mentor MemoryGel implants and controls)? What are the types and rates of lactation problems for women receiving Mentor MemoryGel implants and controls?
Cancer[6]	• What are the types and rates of cancer reported for women receiving Mentor MemoryGel implants and controls?
Suicide[7]	• What are the rates of suicide for women receiving Mentor MemoryGel implants and controls?

Complication/ Condition/ Disease	Issues to be Addressed
Mammography	• What is the rate of rupture with mammography in women receiving Mentor MemoryGel implants? • Are there interference issues (i.e., is there an effect with respect to the timing of breast cancer diagnosis?)
MRI Compliance and Results	• How many women receiving Mentor MemoryGel implants obtained MRIs as described in the patient brochure (i.e., at year 3 and every 2 years, thereafter)? If not this schedule, how often did they get one? • What are the rupture rates based on the MRI findings?

[1] To include (patient-reported key local complications): infection; breast pain; capsular contracture (Baker Grades I-IV); rupture; removal; and reoperation. Physicians will report all local complications, including reasons for reoperation, with or without removal, and reasons for removal, during scheduled and unscheduled/interim visits (see complications form in Section 15).

[2] To include the following diseases diagnosed or reviewed and confirmed by a board-certified rheumatologist; scleroderma, lupus, rheumatoid arthritis, Sjögren's Disease, fibromyalgia, and other CTDs or autoimmune diseases [participant to specify in questionnaire]. Separately, a survey-based evaluation of fibromyalgia, determined through patient reports via a validated instrument that correlates to rheumatologist diagnosis, will be included (Katz, R.S., F. Wolfe and K. Michaud. 2006. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. *Arthritis Rheum.* 54(1):169-176).

[3] To include: persistent joint stiffness that lasts at least one hour, over a period of two weeks or longer; persistent non-traumatic joint pain (more than 3 months); persistent joint swelling (more than 1 week); persistent muscle pain (more than 3 months); pain in taking a deep breath for more than a few days (pleurisy); persistent sleep disorders at night; persistent fatigue; persistent cognitive problems; frequent muscle cramps; persistent skin redness on both cheeks; loss of weight without dieting; skin that persistently feels tight, stretched, or hidebound; skin that breaks out routinely after being in the sun, other than sunburn; fingers becoming unusually pale, numb, or uncomfortable in the cold; excessively dry eyes or mouth; persistent unexplained fevers; ulcers in mouth for more than 3 weeks; difficulty swallowing; and unusual hair loss.

[4] To include the following diseases diagnosed or reviewed and confirmed by a board-certified neurologist: multiple sclerosis (MS); myositis (polymyositis, dermatomyositis, inclusion body myositis); and other neurological diseases [participant to specify in questionnaire].

[5] To include: persistent or recurrent tingling or numbness with a duration of at least several weeks; episode of sudden visual loss or double vision; persistent or recurrent dizziness; persistent memory problems, difficulty concentrating on simple tasks, such as reading, television, etc., lasting at least 3 months; difficulty with balance; new difficulty walking that is not related to arthritis; persistent muscle weakness with a duration of at least several weeks; loss of control of bowel or bladder that happens suddenly or urine retention; jaw weakness leading to difficulty chewing; and seizure, convulsion, or fit.

[6] Cancers: breast, lung, brain, and other cancers [participant to specify in questionnaire].

[7] Suicide information will be obtained from relevant sources, including the Social Security Death Index and designated contacts.

3.0 DESIGN

MemoryGel™ PAS uses a current cohort design of 41,900 women receiving Mentor's MemoryGel implants, with 10 years of follow-up. It will include augmentation, reconstruction, and revision patients, each in their naturally occurring proportions at participating study sites.

For the purpose of assessing rheumatological and neurological signs and symptoms, there also will be 1,000 saline breast implant patients from the participating surgeons' practices who will serve as concurrent controls. Concurrent control participants will be obtained in the following manner. Among MemoryGel participants, a 10 percent random sample will be selected on an ongoing basis. This selection is only for the purpose of triggering selection of a concurrent control and has no effect whatsoever on the participant selected. For each randomly selected participant, the corresponding site will be notified that it needs to recruit a concurrent control participant. After receipt of such notification, the first eligible saline implant patient who presents at the site will be asked to participate in this postapproval study. If the first saline implant patient declines to participate, each subsequent eligible saline implant patient will be asked to participate until one patient is successfully recruited. This process will continue until 1,000 participants are recruited into this study. The 1,000 control participants will thus be concurrent with, approximately, the first 10,000 MemoryGel participants in MemoryGel™ PAS.

Women will be enrolled into the postapproval study consistent with the flow chart in Figure 1. Baseline data will be collected from the participant using survey methodology. Limited data on operative characteristics will be collected from the surgeon. Follow-up data will be collected from the participant by a combination of mail, Internet, and telephone survey methodologies annually from 1–10 years, and on an interim/unscheduled basis, as needed, for key local complications and results of MRI evaluations (MemoryGel patients only), and results from rheumatological or neurological referral evaluations (MemoryGel and saline patients). Additionally, the surgeon will see the MemoryGel participants at year 1, a second time during years 4–6, a third time during years 9–10, and at unscheduled/interim visits. All local complications, including reasons for reoperation, with or without removal, and reasons for removal, reported by the participant or diagnosed by the surgeon will be recorded during these visits.

Controls for the postapproval study, including the concurrent controls, are indicated in Table 2.

Mentor will employ third party study entities that will be responsible for: (1) tracking participants throughout the 10-year study period; (2) collecting the baseline and follow-up questionnaire data and interim local complication forms from participants; (3) collecting data from surgeons; (4) entering data into and administering the study database; (4) generating enrollment and follow-up reports as well as datasets; (5) meeting with Mentor on a regular basis; and (6) analyzing the study data. Mentor will be responsible for: (1) physician enrollment; (2) IRB approval; (3) monitoring the third party entities; (4) study initiation; and (5) periodic reporting to FDA.

Table 2

CONTROLS

Complication/ Condition/ Disease	Control
Local Complications	None needed
CTD	National norms[1]
Rheumatological Signs and Symptoms	Concurrent control group (saline breast implant patients)
Neurological Disease	National norms[2]
Neurological Signs and Symptoms	Concurrent control group (saline breast implant patients)
Offspring	National norms[3]
Reproductive	National norms[4]
Lactation	National norms[5]
Cancer	National norms[6]
Suicide	National norms[7]
Mammography	None needed
MRI Compliance and Results	None needed

[1] The sources for the comparison data will include Mayes et al. (2003) (Mayes, M., et al. 2003. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis & Rheumatism 48(8):2246-55), and may also include, as appropriate, relevant historical controls such as Brinton et al. (2004) (Brinton, L.A., et al. 2004. Risk of connective tissue disorders among breast implant patients. Am. J. Epidemiol. 160(7):619-27) and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study. The sources for comparison data for fibromyalgia may include: Brinton et al. (2004), the saline implant concurrent controls, and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

[2] The sources for the comparison data may include, as appropriate, relevant historical controls for each disease, such as Brinton et al. (2004) and Hennekens et al. (1996) (Hennekens, C.H., et al. 1996. Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. JAMA. 275(8):616-21), and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

[3] The sources for the comparison data may include, as appropriate, relevant historical controls such as the Centers for Disease Control's Pregnancy Risk Assessment Monitoring System (PRAMS), Center for Disease Control's Vital and Health Statistics, National Birth Defects Prevention Network, the California Birth Defects Monitoring Registry, the National Institutes of Health's (NIH's) First and Second Trimester Evaluation of Risk for Aneuploidy (FASTER) Trial, National Health and Nutrition Examination Survey (NHANES), and /or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study, such as the National Children's Study.

[4] The sources for the comparison data may include, as appropriate, relevant historical controls such as Centers for Disease Control, National Survey of Family Growth, Centers for Disease Control Vital and Health Statistics, National Birth Defects Prevention Network, NIH's FASTER Trial, and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

[5] The sources for the comparison data may include, as appropriate, relevant historical controls such as the CDC's Pregnancy Risk Assessment Monitoring System (PRAMS) and /or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

[6] The sources for the comparison data may include, as appropriate, relevant historical controls such as Surveillance Epidemiology and End Results (SEER), Brinton et al. (2000, 2001) (Brinton, L.A., et al. 2000. Breast cancer following augmentation mammoplasty (United States). Cancer Causes Control. 11(9):819-27. J. Long Term Eff. Med. Implants. 12(4):271-9; Brinton, LA., et al. 2001. Cancer risk at sites other than the breast following augmentation mammoplasty. Ann. Epidemiol. 11:248-56), Deapen et al. 1997 (Deapen, D.M., et al. 1997. Are breast implants anticarcinogenic? A 14-year follow-up of the Los Angeles study. Plast. Reconstr. Surg. 99:1346-1353), and /or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

[7] The sources for the comparison data may include, as appropriate, relevant historical controls such as National Violent Death Reporting System, U.S. Census data (2002), Brinton et al. (2001, 2006) (Brinton, L.A., et al. 2001. Mortality among augmentation mammoplasty patients. Epidemiol. 12(3):321-6; Brinton, L.A., et al. 2006. Mortality rates among augmentation mammoplasty patients: an update. Epidemiol. 17(2):162-9) and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

4.0 PARTICIPANT POPULATION

4.1 Eligibility Criteria: MemoryGel Breast Implant Participants

4.1.1 Inclusion Criteria

To be included in the study, each MemoryGel participant must be a woman who:

1. Is a candidate for breast augmentation with Mentor MemoryGel breast implants and is at least 22 years old (primary or revision)[1] ***OR*** is a candidate for breast reconstruction (primary or revision)[2] with Mentor MemoryGel breast implants
2. Signs an Acknowledgement of Informed Decision from the patient brochure
3. Signs an Informed Consent Form and an Authorization to Disclose Health Information and Release Medical Records
4. Completes the baseline questionnaire (as evidenced by the participant's signature on the last page of the questionnaire).
5. Agrees to authorize return of the device(s) to Mentor if the device is explanted
6. Agrees via Informed Consent to comply with study follow-up, including full participation in all follow-up questionnaires and responding to questionnaires in their entirety
7. Is a U.S. or Canadian resident

4.1.2 Exclusion Criteria

Consistent with the labeling, a woman is not eligible to receive Mentor MemoryGel implants and enroll in the postapproval study if she meets any of the following exclusion criteria:

1. Has active infection anywhere in her body.
2. Has existing breast cancer or pre-cancer of the breast without adequate treatment for those conditions.
3. Is currently pregnant or nursing.

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[1] Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of a primary breast augmentation surgery.

[2] Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction includes revision surgery to correct or improve the result of a primary breast reconstruction surgery.

4.2 Eligibility Criteria: Saline Breast Implant Control Participants

4.2.1 Inclusion Criteria

To be included in the study, each saline control participant must be a woman who:

1. Is triggered as part of the selection process for concurrent controls
2. Is a candidate for breast augmentation and is at least 18 years old (primary or revision) ***OR*** is a candidate for breast reconstruction (primary or revision) with saline breast implants.
3. Signs an Informed Consent Form and an Authorization to Disclose Health Information and Release Medical Records
4. Completes the baseline questionnaire (as evidenced by the participant's signature on the last page of the questionnaire).
5. Agrees to authorize return of the device(s) to Mentor if they are Mentor devices.
6. Agrees via Informed Consent to comply with study follow-up, including full participation in all follow-up questionnaires and responding to questionnaires in their entirety
7. Is a U.S. resident

4.2.2 Exclusion Criteria

A woman is not eligible to enroll in the postapproval study as a saline control participant if she meets any of the following exclusion criteria:

1. Has current or past, unilateral or bilateral, silicone breast implants
2. Has active infection anywhere in her body
3. Has existing breast cancer or pre-cancer of the breast without adequate treatment for those conditions
4. Is currently pregnant or nursing

4.3 Documentation of Non-Enrollment or Non-Participation

There may be circumstances where a participant meets all of the eligibility criteria, but ends up not enrolling in the MemoryGel™ PAS. To understand why this may occur, there are two forms to documents these reasons.

1. Non-Enrollment Form
2. Non-Participation Form

<u>Non-Enrollment Form</u>
The Non-Enrollment form is used when a patient has ***begun the enrollment process*** and is either diagnosed with a CTD and decides not to enroll, or the physician believes that the patient should not be enrolled (e.g., due to an ongoing clinical diagnosis of depression or other mental health disorder).

Non-Participation Form

The Non-Participation Form should be used after a patient has been counseled and educated about their choices in seeking MemoryGel™ implants, has not begun the MGPAS enrollment process, and at the outset of this process declines to participate in MemoryGel™ PAS.

Both forms can be found in section 15 of the protocol.

5.0 POSTAPPROVAL STUDY EVALUATIONS

As a condition to receiving Mentor's MemoryGel Silicone Gel-filled Breast Implants, surgeons will be required to participate as a site in the postapproval study. Participating physicians will be required to sign a Physician Agreement (see Section 15.0) indicating that they will adhere to the MemoryGel™ PAS study protocol. As part of the Agreement, the physician will commit to:

- confirm that any necessary IRB approval (national or local) has been obtained;
- review and become thoroughly familiar with the study protocol;
- adhere to the study protocol;
- ensure that the surgeon's staff understands and will adhere to the study protocol;
- counsel and educate women seeking MemoryGel™ implants about their choices, and encourage them to enroll in the MemoryGel™ PAS to assist Mentor Corporation to comply with post-approval conditions, and explain how their participation will contribute to furthering the scientific data collected on silicone breast implants, and counsel them about their voluntary participation in MemoryGel™ PAS;
- identify saline implant control implant participants according to the study protocol and randomization schedule and counsel them about their voluntary participation in MemoryGel™ PAS;
- answer all the participant's questions about her role in MemoryGel™ PAS;
- ensure Informed Consent and Authorization to Disclose Health Information and Release Medical Records are completed prior to implantation of MemoryGel or saline implants;
- ensure that all enrollment documents as required by the protocol, are sent promptly to the third party study entity identified on the Business Return Envelopes provided to the surgeon;
- complete an Operative form for each study participant and return the form promptly to the third party study entity on the Business Return Envelopes provided to the surgeon (control participants will receive standard of care, not recorded as part of this protocol.);
- see each MemoryGel participant at Year 1, a second time during Years 4-6, a third time during Years 9-10, and also for unscheduled/interim visits to record all local complications and reasons for reoperation, with or without removal, and reasons for removal (control participants will receive standard of care, not recorded as part of the study.);
- assist MemoryGel™ PAS participants in identifying an MRI facility with a dedicated breast coil and sufficiently strong magnets (at least 1.5 Tesla);

- assist MemoryGel™ PAS participants in identifying a board-certified rheumatologist and/or neurologist as appropriate;

- provide ongoing encouragement and communication to participants regarding completion of annual questionnaires through 10 years; and

- comply with Mentor's procedures regarding return of explanted MemoryGel devices.

The evaluations to be performed in the postapproval study are shown in Table 3, Postapproval Study Evaluation Schedule. The following evaluations are to be undertaken:

Evaluation	**Evaluator**
Baseline questionnaire (preoperative)	Participant
Operative procedure	Surgeon
Follow-up questionnaire annually, 1-10 years	Participant
Unscheduled/interim reporting of key local complications and results of MRI evaluations	Participant*
Unscheduled/interim reporting of results from rheumatological or neurological referral evaluations	Participant
1 visit in Year 1	Surgeon*
1 visit in Years 4-6	Surgeon*
1 visit in Years 9-10	Surgeon*
Unscheduled/Interim visits	Surgeon*
Questionnaire at time of any participant discontinuation (when possible)	Participant**

*MemoryGel participants only
**In addition, the third party study entity will complete a Discontinuation Form documenting the date and reasons for discontinuation

Surgeon evaluations are being done to record all local complications (including reasons for reoperation, with or without removal, and reasons for removal) for the MemoryGel participants only.

Because of the mobility and general good health of participants who will be receiving MemoryGel implants, Mentor will encourage the appropriate medical societies to host Internet-available listings of surgeons who are available to perform follow-up evaluations of any MemoryGel participant in the postapproval study.

A flow chart of the postapproval study process is depicted in Figures 1 and 2. All participant and surgeon data will be forwarded to a third party study entity that will be responsible for administering the study database and analyzing the study data.

Table 3
POSTAPPROVAL STUDY EVALUATION SCHEDULE

	BASELINE		FOLLOW-UP		
Source	**Participant**	**Surgeon**	**Participant**	**Surgeon[1]**	**Participant**
			1-10 Years (Annually, and Unscheduled/ Interim)	1-10 Years (Year 1, Once in Years 4-6, Once in Years 9-10, Unscheduled/ Interim Visits)	Discontinuation
Eligibility Criteria		X			
Informed Consent	X				
Medical Records Release	X				
Participant Contact Information	X		X		
Demographics	X		X		
Medical History	X		X		
Family History	X		X		
Current Medications and Other Risk Factors	X		X		X
Surgical Characteristics		X			
CTDs[3]	X		X		X
Neurological Diseases[3]	X		X		X
Rheumatological and Neurological Signs and Symptoms	X		X		X
Cancer	X[1]		X[1]		X[1]
Deaths			X[1,2]		X[1,2]
Reproductive	X[1]		X[1]		X[1]
Offspring	X[1]		X[1]		X[1]
Lactation	X[1]		X[1]		X[1]
Key Local Complications[3]			X[1]		X[1]
All Local Complications[3]				X[1]	
MRI Data[3]			X[1]		X[1]
Mammography Data			X[1]		X[1]

[1]MemoryGel participants only.
[2]Information on the occurrence and cause of death, including suicide, will be obtained from relevant sources, including the Social Security Death Index and designated contacts.
[3] Reports will be both annually and on an unscheduled/interim basis, as needed.

Figure 1
POSTAPPROVAL STUDY PROCESS FLOW CHART:
MEMORYGEL PARTICIPANTS

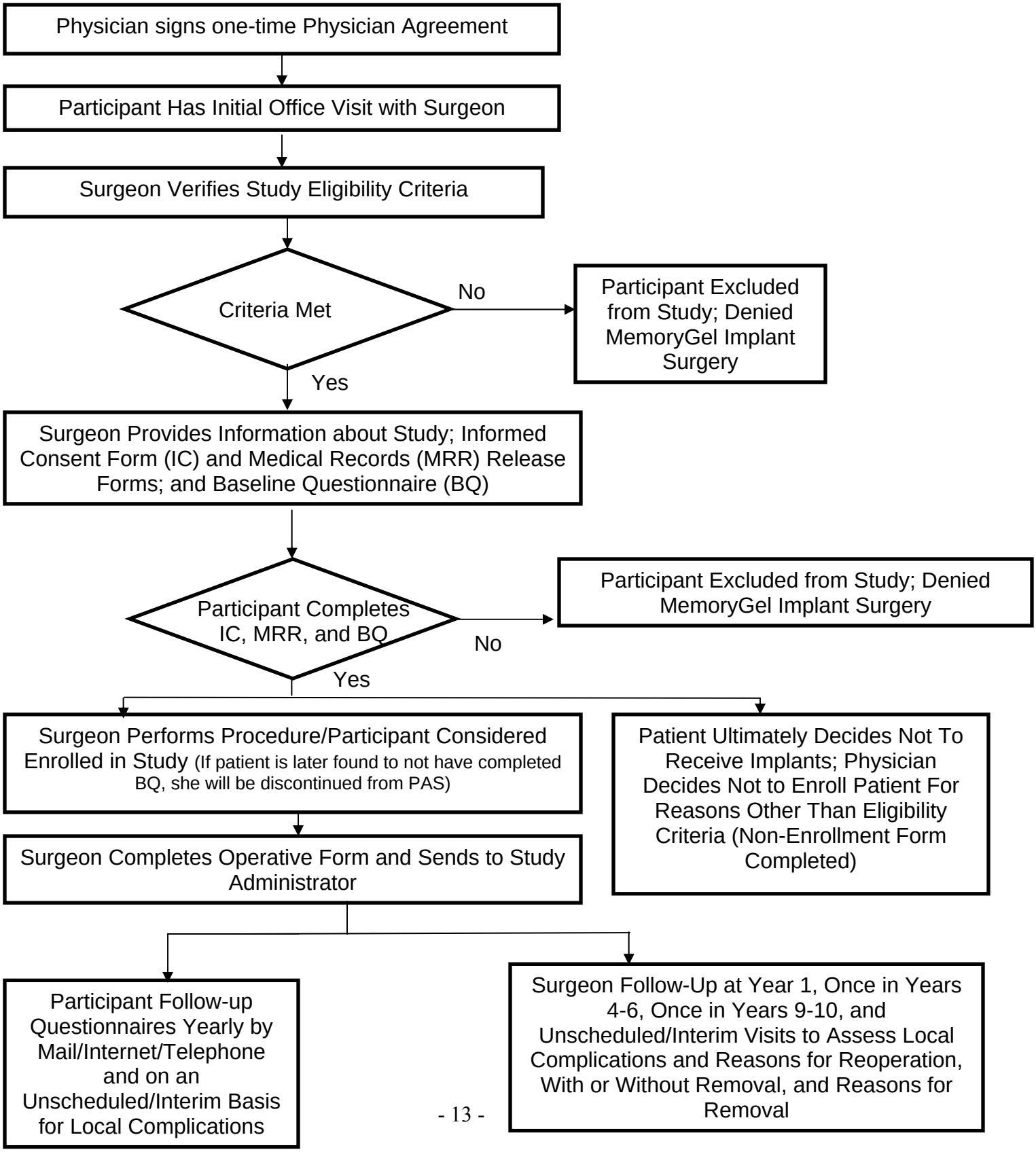
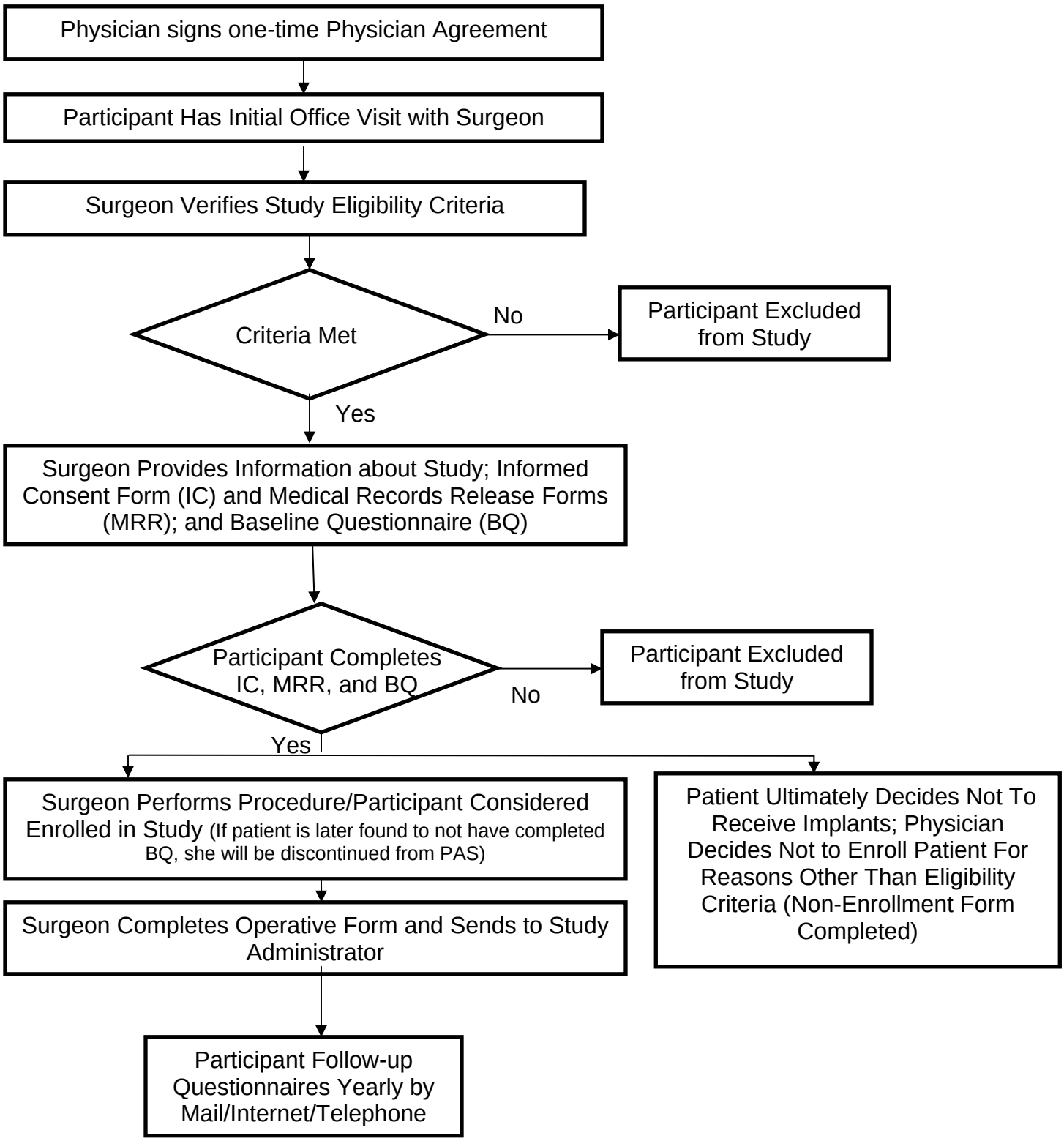


Figure 2
POSTAPPROVAL STUDY PROCESS FLOW CHART:
SALINE CONTROL PARTICIPANTS



5.1 Baseline

Women who meet the eligibility criteria for the study will have the Informed Consent Form and Authorization to Release Medical Records explained to them. As part of the consultation process, women will be given a Baseline questionnaire, Informed Consent Form, and Authorization to Release Medical Records to complete prior to undergoing their implant surgery. The baseline questionnaire (see Section 15.0) will include the following:

- Participant contact information (including relatives' and/or friends' contact information)
- Demographic characteristics
- Medical history, including connective tissue (CTDs), neurological diseases, and cancer
- Family history
- Current medications and other risk factors
- Reproduction and offspring data (MemoryGel participants only; controls will only be asked if they are currently pregnant)
- Lactation history (MemoryGel participants only)
- Rheumatologic and neurologic signs and symptoms (with trigger points/algorithms for recommending participants consult a board certified rheumatologist or neurologist for a full work-up before receiving implants). These trigger points include the following:

o Presence of any of the following rheumatologic signs and symptoms (triggering referral to a board-certified rheumatologist):

  - Presence of two or more of the following signs/symptoms: persistent joint stiffness that lasts at least one hour, over a period of two weeks or longer; persistent non-traumatic joint pain; persistent joint swelling (more than 1 week); persistent muscle pain; pain in taking a deep breath for more than a few days (pleurisy); persistent sleep disorders at night, for example, waking up too early, not falling asleep for a long time, or awakening frequently; persistent fatigue that kept you from working inside or outside the home; frequent muscle cramps; persistent skin redness on both cheeks; loss of weight without dieting; skin that persistently feels tight or stretched on any part of the body; skin that breaks out routinely after being in the sun, other than sunburn; fingers becoming unusually pale, numb, or uncomfortable in the cold; excessively dry eyes or mouth; persistent unexplained fevers; ulcers in mouth for more than 3 weeks; difficulty swallowing; or unusual hair loss. ***OR***

  - VAS fatigue scale ≥6 ***AND***
    Regional pain scale (RPS)-derived body pain questionnaire ≥8 for any level of pain

o Presence of any of the following neurologic signs and symptoms (triggering referral to a board-certified neurologist): persistent or recurrent tingling or numbness with a duration of at least several weeks; episode of sudden visual loss or double vision; persistent or recurrent dizziness; persistent memory problems, difficulty concentrating

on simple tasks, such as reading, television, etc.; difficulty with balance; new difficulty walking that is not related to arthritis; persistent weakness in the muscles with a duration of at least several weeks; loss of control of bowel or bladder that happens suddenly (or urine retention); jaw weakness leading to difficulty chewing; or a seizure, convulsion or fit.

5.2 Operative Procedure

The surgeon will record selected characteristics of both the procedure and the implant(s), such as surgical approach and implant placement, and device style, size, and serial number(s), (see Section 15.0).

5.3 Participant Follow-up (Annually, 1 to 10 years)

At each follow-up contact, the following data will be collected from participants via self-reported questionnaires:

All participants:

- Updated participant contact information
- Updated family history
- Current medications and other risk factors
- Occurrence of CTDs and neurological disease
- Rheumatologic and neurologic signs and symptoms, with trigger points/algorithms for recommending participants consult a board certified rheumatologist or neurologist for a full work-up. These trigger points include the following:

  - Presence of any of the following rheumatologic signs and symptoms (triggering referral to a board-certified rheumatologist):

    - Presence of two or more of the following signs/symptoms: persistent joint stiffness that lasts at least one hour, over a period of two weeks or longer; persistent non-traumatic joint pain; persistent joint swelling (more than 1 week); persistent muscle pain; pain in taking a deep breath for more than a few days (pleurisy); persistent sleep disorders at night, for example, waking up too early, not falling asleep for a long time, or awakening frequently; persistent fatigue that kept you from working inside or outside the home; frequent muscle cramps; persistent skin redness on both cheeks; loss of weight without dieting; skin that persistently feels tight or stretched on any part of the body; skin that breaks out routinely after being in the sun, other than sunburn; fingers becoming unusually pale, numb, or uncomfortable in the cold; excessively dry eyes or mouth; persistent unexplained fevers; ulcers in mouth for more than 3 weeks; difficulty swallowing; or unusual hair loss. ***OR***

    - VAS fatigue scale ≥6 ***AND***
    - Regional pain scale (RPS)-derived body pain questionnaire ≥8 for any level of pain

- Presence of any of the following neurologic signs and symptoms (triggering referral to a board-certified neurologist): persistent or recurrent tingling or numbness with a duration of at least several weeks; episode of sudden visual loss or double vision; persistent or recurrent dizziness; persistent memory problems, difficulty concentrating on simple tasks, such as reading, television, etc.; difficulty with balance; new difficulty walking that is not related to arthritis; persistent weakness in the muscles with a duration of at least several weeks; loss of control of bowel or bladder that happens suddenly (or urine retention); jaw weakness leading to difficulty chewing; or a seizure, convulsion or fit.

MemoryGel Participants Only:

- Key local complications (breast pain, infection, rupture, capsular contracture (Baker grades I-IV), explantation, and reoperation, as well as reasons for reoperation, with or without removal, and reasons for removal) (annually, and on an unscheduled/interim basis as needed). If there are any discrepancies between the reasons for reoperation with or without removal, or reasons for removal, reported by the participant and those reported by the physician, the reasons reported by the physician will be entered into the PAS database.
- Occurrence of cancer
- Reproductive and offspring data
- Lactation data
- Mammography information
- MRI information[3]

The following records will also be collected for MemoryGel participants only:

- Records of rheumatologist diagnosed CTDs
- Records of neurologist diagnosed neurological diseases
- Records for diagnosed brain cancer
- Records of ruptures or suspected rupture based on MRI, as identified in both annual questionnaires and unscheduled/interim reports.

Information to be collected is depicted in Table 4.

Table 4
INFORMATION TO BE COLLECTED

	BASELINE		FOLLOW-UP	
Topic	**MemoryGel**	**Concurrent Controls**	**MemoryGel**	**Concurrent Controls**
PARTICIPANT REPORTED				
Demographics	X	X	X	X
Medical History	X	X	X	X
Family History	X	X	X	X

[3] If a participant does not know the results of her MRI examination, she will be encouraged to request the results from the referring physician. Her results would then be documented in another report or the subsequent follow-up questionnaire.

	BASELINE		FOLLOW-UP	
Topic	**MemoryGel**	**Concurrent Controls**	**MemoryGel**	**Concurrent Controls**
Medications and Other Risk Factors	X	X	X	X
Rheumatologic/Neurologic Signs & Sx	X	X	X	X
CTD and Neurological Diseases	X	X	X	X
Cancer	X	X	X	
Death (Including Suicide)*			X	
Lactation	X		X	
Reproductive	X		X	
Offspring	X		X	
Occurrence of Key Complications			X	
MRI			X	
Mammography			X	
PHYSICIAN REPORTED				
Surgical Characteristics	X	X		
All local Complications (including reasons for reoperation, with or without removal, and reasons for removal)			X	

* Information on the occurrence and cause of death will be obtained from relevant sources including the Social Security Death Index and designated contacts.

5.4 Physician Follow-Up Evaluations

The surgeon will see the MemoryGel participant at year 1, a second time during years 4–6, one final time during years 9–10, and at unscheduled/interim visits. All local complications (including reasons for reoperation, with or without removal, and reasons for removal) will be recorded during these visits. If there are any discrepancies between the reasons for reoperation with or without removal, or reasons for removal, reported by the participant and those reported by the physician, the reasons reported by the physician will be entered into the PAS database.

5.5 Explantation and Discontinuation

If a participant has been explanted, an attempt will be made to collect all of the data elements outlined in Section 5.3 above for the duration of the study.

In the event a participant indicates her intention to withdraw from the study, the reason for withdrawal will be recorded by the third party study entity**.** If this occurs before the operative procedure, the participant will simply be withdrawn from the study. If this occurs after the operative procedure, an attempt will be made to collect all of the data elements outlined in Section 5.3 above at the time of discontinuation, and the third party entity will complete the Discontinuation Form provided at Section 15.

6.0 RETURNED DEVICES

Pursuant to Mentor's policies and procedures, explanted MemoryGel and Mentor saline breast implants should be returned to Mentor Product Evaluation regardless of the reason for explant. Consistent with the patient's return authorization granted at the outset of her study participation, surgeons should return the explant to Mentor, using a product return kit. Mentor will use a good faith effort to obtain MemoryGel explanted devices if it becomes aware that explantation has occurred and the surgeon has not returned the devices. Mentor's saline breast implants, if explanted, will be handled in accordance with current standard operating procedures.

Upon receipt of the returned explant, Mentor Product Evaluation will examine the device by conducting a comprehensive investigation including visual and physical testing of the explanted device to try to determine the cause of a complaint, if any, or the condition of the device in accordance with established procedures and protocols. These analyses will be part of separate postapproval retrieval stud(ies) and/or product evaluation activities, and will not be considered part of this study.

7.0 MEDICAL DEVICE REPORTING

On a routine basis, the third party entity will report to Mentor pre-specified events (e.g., death of a participant) involving MemoryGel and Mentor saline breast implants consistent with Medical Device Reporting (MDR) standards. All data, including MDR-reported data, will be part of the annual reports for the MemoryGel™ PAS.

8.0 SURVEY METHODOLOGY

The methodology for collecting baseline and annual follow-up questionnaire data for MemoryGel™ PAS is described in this section. In addition to the collection of follow-up data annually, participant contact information will also be updated at each annual round of data collection. The baseline questionnaire will be designed for completion via hard copy. In order to achieve the highest possible follow-up rate, the 1–10-year follow-up participant questionnaire will be designed for completion via three modes: Internet, hard copy, and telephone administration.

8.1 Baseline Data Collection

Consent and Medical Records Release Authorization Forms

Consent forms will be filled out during the consultation visit and presented to the surgeon prior to the implant procedure. Surgeons will confirm that each participant has signed the Informed Consent form and the Medical Records Release Authorization forms prior to surgery.

Completed Informed Consent and Medical Records Release Authorization forms will be sent to the third party study entity via a Business Reply Envelope (BRE). The third party study entity will enter receipt of consent and release documents into the MemoryGel™ PAS database. All consent and release forms will be stored in a secure environment located within the third party study entity facility.

Baseline Questionnaire

A baseline questionnaire package will also be given to the participant during the preoperative evaluation by their surgeon. There will be separate baseline questionnaires for the MemoryGel and saline concurrent control participants. During the preoperative visit the participant will receive an Informed Consent Form, Informed Decision Brochure, Medical Records Release Authorization, and also a hard copy of the baseline questionnaire.

After reading and understanding the Informed Consent Form and Informed Decision Brochure, the participant must sign where indicated. The participant also must fully complete and sign the baseline questionnaire, which is available in hard copy form or online by logging onto: www. MGPAS.com.

The participant must return the signed Informed Consent Form, the signed signature page of the Informed Decision Brochure, and a signed hard copy baseline questionnaire to the surgeon, or present the surgeon with the online certificate of completion. The surgeon will forward a copy of the signed Informed Consent Form and Medical Records Release Authorization, along with the signed baseline questionnaire (or online certificate of completion), to the third party study entity in a BRE..

8.2 Follow-up Questionnaire

The MemoryGel™ PAS follow-up questionnaires (separate follow-up questionnaires for MemoryGel and saline concurrent control participants) will be completed annually by the participant, from 1 to 10 years following implant surgery. In order to achieve the highest possible response, the study will employ the Total Survey Design method (TSD).[4] As outlined below, the third party study entity will start by sending a follow-up questionnaire announcement. Soon after the follow-up announcement, the third party study entity will e-mail or mail an advance letter inviting women to complete the questionnaire via the Internet. Women who do not complete via the Internet will be mailed a hardcopy of the questionnaire approximately 6 weeks after the invitation to complete the questionnaire via the Internet. Women who do not complete via Internet or hardcopy will be contacted by telephone interviewing staff.

Mailed/E-mail Reminder

One month prior to follow-ups, the third party study entity will e-mail or mail a reminder to all study participants. This mailed/e-mail reminder will serve as an advance announcement to study participants for the annual follow-up questionnaires. The reminder will emphasize that the participant agreed to respond to the follow-up questionnaires at the time of implantation (both MemoryGel and control participants) and as a condition to getting MemoryGel implants (MemoryGel participants only). The reminder also will emphasize the importance of completing all applicable questions.

Advance Letter/E-mail Invitation to Internet Questionnaire

An advance mail/e-mail with an invitation to complete the questionnaire via the Internet will be sent out two weeks prior to their follow-up date.

Second Mailed/E-mail Reminder

A reminder mail/e-mail to study participants will be sent out one week after the invitation to the Internet questionnaire. This mailed/e-mail notice serves as a "top of the mind" reminder to complete the questionnaire.

Mailing of Hard Copy Questionnaire

A hardcopy of the questionnaire will be sent to study participants who have not completed the questionnaire via the Internet within 6 weeks after the invitation to the Internet questionnaire. Included in this questionnaire package will be the follow-up questionnaire and a BRE for participants to send back the completed questionnaire. In addition, the third party study entity will also include an invitation to the Internet questionnaire for those who may still choose to complete via this mode.

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[4] Dillman, D.A. 1978. Mail and Telephone Survey Design Method. NY: Wiley.

Second Mailed/E-mail Reminder

A reminder mail/e-mail to participants will be sent out 7-8 weeks after the invitation to the Internet questionnaire. This mailed/e-mail notice serves as a "top of the mind" reminder to complete the questionnaire.

Interactive Voice Response System (IVRS)

Participants who have not returned a paper questionnaire or web-based questionnaire will receive an automated phone call via the Outbound IVRS. The system will give the participant the option of requesting a paper questionnaire be mailed to them by pressing "1" or the option of speaking directly with a telephone interviewer to complete the questionnaire via phone.

Additional Methods for Increasing Questionnaire Response

Other methods to increase questionnaire response will include the re-mailing of the questionnaire, use of additional reminders, and reaching out to participant contacts, e.g., family or friends.

8.3 Unscheduled/Interim Reporting of Key Local Complications, Results of MRI Evaluations, and Results of Rheumatological or Neurological Referral Evaluations

Accompanying the annual follow-up questionnaires will be a reminder to MemoryGel participants to report key local complications (reasons for reoperation with or without removal, reasons for removal), and the results of MRI evaluations on an unscheduled/interim basis as needed. All participants will be instructed to report the results of rheumatological or neurological referral evaluations on an unscheduled/interim basis as needed. The participants will be encouraged to use the Internet for purposes of interim reporting (as applicable) of key local complications, results of MRI evaluations, and results of rheumatological or neurological referral evaluations but, as a back-up, a hard copy of the unscheduled/interim reporting form (see Section 15) will be enclosed with the annual questionnaire, along with two Business Reply Envelopes.

8.4 Interim Tracking

The primary objective of interim tracking is to maintain information on as many baseline participants as possible. To maintain a high level of contact, the third party study entity will take steps both to minimize attrition and to maximize response rates.

Tracking methods must minimize intrusiveness for the study participants so that they will cooperate with the data collection over the long term. The third party study entity's tracking strategy contains both active methods (requiring interaction with the participant) and passive methods (requiring no contact with the participant).

Active Tracking
Active tracking activities will be conducted during each round of data collection. The third party study entity will mail letters to all participants. It will ask participants to update their current addresses and telephone numbers. It will also ask them to update names, addresses, and telephone numbers for one or two individuals who do not live with them but who always know how to reach them. The use of secondary contact data is crucial in a long-term study.

The updated active tracking information will be maintained in the MemoryGel™ PAS database. There will be multiple address records for each participant. Prior to the start of each wave of the questionnaire, a report listing the complete address history will be reviewed before mailings begin. By way of example, the third party study entity may provide participants with refrigerator magnets, or other forms of reminder, bearing the study name and a toll-free number to call and report address changes.

Passive Tracking
The third party study entity will submit all of the participants' address information to the National Change of Address (NCOA) data base two months prior to the collection of the annual follow-up questionnaires. The NCOA service is an electronic method for confirming or correcting address information. The NCOA update provides address changes within a two-year period (provided the individual filled out a US Postal Service change of address card); correctly formats addresses; indicates mismatches between city/state and Zip Code; and provides the most recent known telephone numbers for many addresses. In addition to the use of NCOA, the third party study entity will link participant social security numbers with a *Social Security Death Index database*.

Any participants who do not complete the questionnaire via Internet or hardcopy will be contacted by telephone. In order to have the most up-to-date phone numbers for participants and their contacts, the third party study entity will submit their address information to a *Telematch Service*. These data will be submitted to the Telematch Service one month prior to the beginning of the telephone data collection activity. Telematch will provide electronic confirmation of and/or new current phone numbers (and addresses) for households with listed phones.

If the methods described above do not yield new contact information, the third part entity will perform *Proprietary database searches.* Proprietary companies like Accurint and LexisNexis, maintain databases with updated addresses and telephone numbers. These types of searches will be performed once during each round of data collection after all other methods for obtaining updated information have been exhausted. Such database searches are useful for two reasons. First, if a participant is reported to be deceased during one of the data collection periods, the information can be confirmed. Second, such a tool may explain our inability to locate a participant.

9.0 SURVEY DATA COLLECTION

This section describes the proposed data collection strategy and management plan for MemoryGel™ PAS. It is expected that the bulk of completed questionnaires will be completed via Internet or hardcopy. Participants who do not respond via Internet or hard copy will be contacted by telephone interviewers who will conduct the interview and record the answers on a hard copy questionnaire.

9.1 The Survey System

The third party study entity will develop a survey system specifically for the MemoryGel™ PAS, including details on protocols for data collection, schedule of project activities, and procedures for validating questionnaire data. The system will address all functions and contingencies necessary for successful completion of the postapproval study. A description of key elements in the questionnaire system follows.

9.2 Codebook Development and Machine-Edit Software Generation (COED)

Questionnaires that are received via mail, and questionnaires administered through a telephone interview will be reviewed and coded by trained data managers familiar with the PAS protocol, and then validated using the third party entity's COED system.

The COED system (for codebook development and machine-edit software generation) is an integrated collection of software that operates interactively or in batch mode in a variety of hardware and operating system environments. The COED generated machine-edit software validates data values against the codebook. Continuous variables are range-checked, and categorical variables are compared with allowable code lists. The edit software also checks the data to ensure that skip patterns are followed. In addition to the automatically generated edits, COED allows the definition of cross-variable logic checks. The COED validation will produce summary statistics of the quality of the data received via paper or telephone interviews.

9.3 Hard Copy Questionnaire

The hard copy MemoryGel™ PAS questionnaire will be designed using the Total Survey Design (TSD) method. When designing the hard copy questionnaire, questions will be designed in a way that is most salient to the participants. The questionnaire will be designed in a manner that can be easily navigated, e.g., the use of visual aids like arrows, highlighting and user friendly formatting.

Receipt of Hard Copy Questionnaires

The hard copy MemoryGel™ PAS questionnaires will be received by the third party study entity. Receipt of these documents will be achieved through the use of barcode scanning technology. All questionnaires will have a barcode printed on the cover. This barcode will include the participant's unique identification number. This will serve as the only link to participant level study data. All participant contact information will be separated from all returned questionnaires

after they have been received via barcode scanning technology. The two sets of forms will be stored separately in secured filing cabinets within the third party study entity data entry department.

Security and Privacy of Hard Copy Questionnaires
The third party study entity will take the utmost precautions to ensure the privacy of individuals responding to MemoryGel™ PAS and to protect the confidentiality of all questionnaire data. Respondent names, address and contact information will be kept separate from completed questionnaires. All paper copies containing information that identifies individual respondents will be kept in locked file cabinets. Only project staff who need-to-know have access to these data so that few individuals will be allowed to open these locked cabinets. All staff sign general and project-specific pledges of confidentiality.

Physician Evaluation Data (MemoryGel Participants Only)
MemoryGel participants will be evaluated for all local complications (including reasons for reoperation, with or without removal, and reasons for removal) by their surgeons at Year 1, once during Years 4-6, once during Years 9-10, and at unscheduled/interim visits. The physician will submit the completed complications form via Internet or mail to the third party study entity for entry into the study database.

Because of the mobility and general good health of participants who will be receiving MemoryGel implants, Mentor will encourage the appropriate medical societies to host Internet-available listings of surgeons who are available to perform follow-up evaluations on any MemoryGel participant in the study.

Active involvement, support, and assistance of the relevant medical societies are essential to compliance with these follow-up visits. Meaningful follow-up compliance is entirely dependent on strong involvement, support, and assistance from the societies (e.g., free visits and society outreach to its members).

9.4 Quality Assurance

The proposed MemoryGel™ PAS modes of data collection will be subject to strict quality assurance procedures.

Internet Questionnaire Data Quality Assurance
The quality of the data for the Internet questionnaire is driven by the successful implementation/design of the questionnaire. The Internet system will be designed in order to minimize participant error. The design will include internal validity checks. The participant also will be prompted when information is missing.

Mail Questionnaire Data Quality Assurance
All mailings will be carefully checked by the third party study entity for accuracy prior to mailing. Completed questionnaires will be returned to the third party study entity where they will be reviewed for completeness and prepared for data entry.

Completeness of the questionnaire will be emphasized primarily through prospective instructions and reminders. For example, initial consents and subsequent cover letter notices will emphasize the participant's obligation to complete all questionnaires in their entirety. Also, at the end of each questionnaire, the participant is reminded that it is important to complete all applicable questions. In the follow-up questionnaires, for the web-based option, the participant will be prompted when information is missing.

Telephone Interview Quality Assurance

Telephone Centers will be equipped with separate monitoring rooms that allow for unobtrusive monitoring of interviewers. This system allows supervisors/monitors to select an individual interviewer for monitoring without the individual's knowledge and then to listen and observe the data collection process. Supervisors evaluate interviewers on several dimensions to ensure that the quality of the interviewer's voice and speech patterns are both interesting and well-modulated; the introductory material is properly read; the respondent's questions are properly answered; responses are appropriately probed; and interviewer recording is accurate.

9.5 Management

The third party study entity will develop systems and structures to effectively and efficiently manage the data collection for MemoryGel™ PAS. The third party study entity has experience in creating, maintaining, and management systems that ensure timely production of study data. Quality Assurance must be built into the management structure and into methods for collecting data and delivering data files with their documentation.

10.0 MEDICAL RECORDS

In certain circumstances, medical records of MemoryGel participants will be obtained to confirm information provided by the participant. Specifically, medical records will be obtained whenever the participant indicates any of the following:

- Pre-specified rheumatologist-diagnosed connective tissue diseases (including baseline records for saline controls.
- Pre-specified neurologist-diagnosed neurological diseases (including baseline records for saline controls).
- Diagnosed brain cancer.
- An implant that is ruptured or suspected of rupture based on MRI as identified in both annual questionnaires and unscheduled/interim reports.

For rheumatological and neurological records, the records will be reviewed to confirm that the diagnosis was made by a board-certified rheumatologist/neurologist; if a board-certified rheumatologist/neurologist did not make the diagnosis, a board-certified rheumatologist/neurologist will review the record to confirm the diagnosis, where possible.

The records listed above will be reviewed to confirm the information provided by the participant for these specific issues. If there is a discrepancy between the two, the findings recorded in the medical record will be utilized in the analyses.

11.0 STATISTICAL CONSIDERATIONS

11.1 Statistical Analyses

This section describes the analyses to be conducted to address each of the postapproval study's objectives, as identified in Table 1. It is important to recognize that this study is observational. As a result, data from this study can be used only to establish association, not causality, and data should be evaluated within the context of the broader composite of literature relating to these issues. All of the analyses, except for the analyses of rheumatological and neurological signs and symptoms, will be based on the MemoryGel participants only.

CTDs, Fibromyalgia, Cancer, Neurological Diseases and Suicide

The incidence of CTDs (by type), fibromyalgia, cancer (by type), neurological disease (by type), and suicide will each be estimated as the ratio of the number of new cases to the number of person-years of exposure (i.e., observed person-years with silicone breast implants) for MemoryGel participants only. Ninety-five percent confidence intervals will be computed. For CTDs, the incidences of scleroderma, lupus, rheumatoid arthritis, Sjögren's Disease, fibromyalgia, and other CTDs will each be estimated. For cancer, the incidences of breast, brain, lung, and other cancers will each be estimated. For neurological diseases, the incidences of MS, myositis, and other neurological diseases will each be estimated. In addition, Mentor will examine the prevalence of depression and anxiety. Ninety-five percent confidence intervals will be computed.

The relative risk for women with MemoryGel implants as compared to national norms will be estimated, standardizing for age, race, and other relevant characteristics, when appropriate. The relative risk will be tested for significance based on a one-sided test conducted at the 0.05 level of significance. Ninety-five percent confidence intervals will also be computed. The sources for the comparison data will include Mayes et al. (2003), and may also include, as appropriate, relevant historical controls such as Brinton et al. (2000, 2001a and b, 2004, and 2006), Hennekens et al. (1996), Deapen et al. 1997, Surveillance Epidemiology and End Results (SEER), National Violent Death Reporting System, U.S. Census data (2002), and/or other reliable and relevant sources, including new sources that may become available during the course of this study. The sources for the comparison data for fibromyalgia will include Brinton et al. 2004, the saline control participants, and/or other reliable and relevant sources, including new sources that may become available during the course of this study.

The baseline questionnaire, as well as the follow-up questionnaire, includes recommendations to all participants to see a rheumatologist or neurologist when the participant indicates she is experiencing certain combinations of signs and symptoms. At baseline, a participant will be advised to see a rheumatologist or neurologist if she identifies certain trigger signs and symptoms as specified in the questionnaire. If a participant does not choose to wait until her specialist evaluation before receiving implants, like all participants, she will be followed for the duration of the study, regardless of what the finding is.

Offspring

Through the course of the 10-year study, the incidence of birth defects/congenital malformations (total, and individual defects where appropriate national norms are, or will become, available), premature birth, low birth weight, and neonatal intensive care among women with MemoryGel implants will be estimated simply as the ratio of the number of offspring with these conditions to the total number of offspring of MemoryGel study participants. Ninety-five percent confidence intervals will be computed. The incidence of chronic illnesses (such as autoimmune disorders, cancer, and neurological disease), among children born to study participants after implantation of MemoryGel implants will be estimated as the ratio of number of new cases to the number of person-years. Ninety-five percent confidence intervals will be computed.

The relative risk for women with MemoryGel implants as compared to national norms will be estimated, standardizing for age, race, and other relevant characteristics of the mother, when appropriate. The relative risks will be tested for significance using one-sided tests conducted at the 0.05 level of significance. Ninety-five percent confidence intervals will be computed. The sources for the comparison data may include, as appropriate, relevant historical controls such as National Birth Defects Prevention Network, PRAMS, FASTER trial, the California Birth Defects Monitoring Registry, National Health and Nutrition Examination Survey (NHANES), and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study, such as the National Children's Study.

Complications/Reoperations

The cumulative incidence of key local complications (breast pain, infection, rupture, capsular contracture (Baker grades I-IV), explantation, and reoperation) for women with MemoryGel implants will be estimated based on the annual questionnaires as well as the three physician evaluations for the MemoryGel participants using Kaplan-Meier methodology to estimate the time to the first occurrence of the complication or reoperation. Ninety-five percent confidence intervals will be computed. In addition, the relative frequency of reasons for reoperation will be computed.

Reproductive

Incidence of reproductive outcomes (miscarriage and stillbirth) will be estimated as the ratio of the number of women with these outcomes to the total number of pregnancies among MemoryGel participants. The relative risks will be tested for significance using one-sided tests conducted at the 0.05 level of significance. Ninety-five percent confidence intervals will be computed.

The relative risk of reproductive difficulties for women with MemoryGel implants compared to national norms will be estimated, standardizing for age, race, and other relevant characteristics of the mother, when appropriate. The sources for the comparison data may include, as appropriate, relevant historical controls as Burkman et al. (2003), Centers for Disease Control National Survey of Family Growth, Centers for Disease Control Vital and Health Statistics, National Birth Defects Prevention Network, FASTER trial, and/or other reliable and relevant sources, including new sources that may become available during the course of this study.

Lactation

The rate at which women with MemoryGel breast implants are able to breast feed will be examined. For each MemoryGel participant who gives birth during the 10-year study period, the proportion of births for which she is able to breast feed successfully among all births for which she desires to breast feed will be calculated. This proportion will be averaged across MemoryGel participants.

The relative risk of lactation difficulties for women with MemoryGel implants as compared to national norms or other similar women without these implants (e.g., other plastic surgery controls, if available) will be estimated, standardizing for age, race, and other relevant characteristics of the mother, when appropriate. The sources for the comparison data may include, as appropriate, relevant historical controls such as PRAMS, and/or other reliable and relevant sources, including new sources that may become available during the course of this postapproval study.

In addition, the relative frequencies of various types of lactation difficulties will be calculated.

Mammography

The issue of mammography as a potential cause of ruptures will be analyzed using a Cox proportional hazards model of time to rupture with number of mammograms as a time varying covariate. In this model, all ruptures, both symptomatic and silent (identified by MRI), will be included. The number of mammograms will include mammography where a patient has been recalled for re-imaging. The coefficient of the time varying covariate will provide an estimate of the effect, if any, on risk of rupture of each mammogram. By collecting information on the timing of mammography and information concerning the stage of breast cancer upon first diagnosis, an analysis of any potential interference issues also will be performed.

MRIs

The frequency with which women with MemoryGel implants undergo MRI screening will be examined in three ways. First, the time to first MRI will be examined using the method of Kaplan-Meier. Similarly, the time to second MRI following the first MRI will be examined using the Kaplan-Meier method. Finally, the overall frequency of MRIs will be examined by computation of the ratio of the number of MRIs to the total number of person-years with MemoryGel implants.

MRI findings will be utilized in the analysis of overall rupture rates (including both symptomatic ruptures and "silent ruptures" detected by MRI) over time). These data will be analyzed using the method of Kaplan-Meier. In this analysis, both symptomatic ruptures and silent ruptures detected by MRI will be considered ruptures, except that implants with symptomatic and silent ruptures which are explanted and determined on physical examination by Mentor not to have been ruptured will be considered to be intact.

Rheumatological and Neurological Signs and Symptoms

In contrast to all of the above analyses, this analysis will be based on both the MemoryGel participants and the concurrent saline controls. The study will collect information on rheumatological and neurological signs and symptoms.

For each individual rheumatological and neurological sign and symptom, the rheumatological categories for persistent fatigue, combined pain, and fibromyalgia-like symptoms, and the combined neurological categories for central nervous system-related, peripheral nervous system-related, and muscle-related signs and symptoms, the post-baseline prevalence will be estimated for each participant as the proportion of post-baseline contacts in which the participant reports the sign or symptom to be present at the time of the contact. These proportions will be averaged across MemoryGel participants and averaged across the controls. For all of the above, except the individual signs and symptoms, the proportions for the control participants will be compared to the corresponding proportions for the approximately 10,000 MemoryGel participants with whom they are concurrent. Regression analyses will be used to adjust for differences in age, race, and other relevant patient characteristics. The significance of the difference between the two will be tested for significance using a one-sided test conducted at the 0.05 level of significance. These means will be compared using a test based on the normal approximation. In addition, 95% confidence intervals for the estimated prevalences will be computed.

These analyses will be performed for the following rheumatological signs and symptoms categories:

- Persistent fatigue
- Combined pain
  - persistent non-traumatic joint pain (more than 3 months), ***OR***
  - persistent muscle pain (more than 3 months), ***OR***
  - pain in taking a deep breath for more than a few days (pleurisy)
- Fibromyalgia-like symptoms[5]
  - VAS fatigue scale ≥6 ***AND***
  - Regional pain scale (RPS)-derived body pain questionnaire ≥8

Additionally, these analyses will be performed for the following combined neurological categories:

[5] Fibromyalgia-type symptoms will be assessed using a validated survey instrument employing a combination of a VAS fatigue scale and a regional pain scale (RPS)-derived body pain questionnaire. Details of the methodology are provided in Katz, Wolfe, and Michaud (2006) (Katz, R.S., F. Wolfe, and K. Michaud. 2006. Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria. *Arthritis Rheum.* 54(1):169-176), Wolfe (2003) (Wolfe, F. 1003. Pain extent and diagnosis: development and validation of the regional pain scale in 12,779 patients with rheumatic disease. *j. Rheumatol*. 30(2):369-378), and Wolfe (2003) (Wolfe, F. 2003. Fatigue assessments in rheumatoid arthirits: Comparative performance of Visual Analog Scales and longer fatigue questionnaires in 7760 patients. *J. Rheumatol.*31:1896-902). This protocol relies on the VAS fatigue scale and RPS-derived body pain questionnaire items that are used by Dr. Wolfe.

- Central nervous system (CNS)-related
  - persistent memory problems and difficulty concentrating on simple tasks, such as reading or television lasting at least 3 months, ***OR***
  - seizure, convulsion, or fit ***OR***
  - episode of sudden visual loss or double vision, ***OR***
  - persistent or recurrent dizziness, ***OR***
  - sudden onset loss of bowel or bladder or urine retention), ***OR***
  - difficulty with balance ***OR***
  - new difficulty walking not associated with arthritis, ***OR***
  - persistent or recurrent tingling or numbness lasting at least several weeks, ***OR***
  - persistent weakness in muscles lasting at least several weeks
- Peripheral nervous-system-related
  - difficulty with balance ***OR***
  - new difficulty walking not associated with arthritis, ***OR***
  - persistent or recurrent tingling or numbness, ***OR***
  - persistent weakness in muscles lasting at least several weeks
- Muscle-related
  - difficulty with balance ***OR***
  - new difficulty walking not associated with arthritis, ***OR***
  - persistent weakness in muscles lasting at least several weeks, ***OR***
  - jaw weakness leading to difficulty chewing, ***OR***
  - difficulty swallowing; frequent muscle cramps

11.2 Sample Size Determination

The required number of MemoryGel participants was determined in the following manner. It is assumed that it is required to have 80% power to be able to detect as statistically significant a relative risk of 2.0 for adverse events that occur, without implants, with a frequency of 2.85 per 100,000. This figure is based on the incidence of scleroderma as reported by Mayes et al. (2003). It is assumed this would be based on a one-sided test conducted at the $\alpha = 0.05$ level of significance. Based on these specifications, it was determined that approximately 338**,**000 person-years would be required.

Patients are to be followed for 10 years. For purposes of sample size calculation, assuming a follow-up rate of 65% at 10 years and a linear loss to follow-up, there would be an average of 8.075 person-years per participant. Thus, in order to obtain the 338**,**000 person-years, a total of 41,900 MemoryGel participants would be required.

The concurrent control sample size was selected in order to be able to detect a relative risk of 2.0 for MemoryGel participants as compared to control participants, for rheumatologic and neurologic signs and symptoms with a prevalence of approximately 2% among MemoryGel participants. It is assumed this would be based on a one-sided test conducted at the 0.05 level of significance with a power of 80%. Similar combined rheumatologic categories of signs and symptoms from Mentor's existing Core Study of these silicone gel implants all have estimated prevalence of at least 2% after year 2. These data will be analyzed by first computing, for each participant, the proportion of time points in which the participant reports the sign or symptom as being prevalent and then calculating the mean of these participant-level proportions across

participants within each group. For purposes of sample size calculation, it is assumed that these means will be compared using a simple test based on the normal approximation.

Given an expected 65% follow-up rate at 10 years, it is assumed participants will have reports, on average, at 8 time points. The correlation between different reporting time points for an individual participant is taken into account. From Mentor's existing Core Study of silicone gel-filled breast implants, for the three combined categories of signs and symptoms correlations between time points that are 1 year apart range from 0.47 to 0.59, and correlations between time points that are 2 years apart range from 0.35 to 0.41. As expected, the correlations decrease with distance between time points. On average, considering all pairs of time points and ignoring loss to follow-up, time points will be 3.7 years apart. (For example, years 1 and 3 are 2 years apart and years 1 and 10 are 9 years apart.) Thus, it is assumed that the correlation, on average, would not be higher than 0.30. Based on the above, it was determined that a sample size of 1,000 concurrent controls would be more than sufficient.

12.0 INSTITUTIONAL REVIEW BOARD APPROVAL

National or local IRB approval will be obtained for each site. If local IRB approval is needed, a copy of that approval will be forwarded to Mentor before any breast implants can be shipped.

13.0 INFORMED CONSENT AND AUTHORIZATION OF MEDICAL RECORDS RELEASE

Written informed consent must be obtained from each participant prior to the participant being enrolled into this postapproval study. The Informed Consent Form (see Section 15.0) will detail the participant's obligations and rights under the study protocol. Attached to this form will be an Authorization to Disclose Health Information and Release Medical Records form, also to be signed by the participant (see Section 15.0). Both the Informed Consent Form and the Disclosure and Release Authorization address applicable privacy requirements.

The Informed Consent and Release Authorization Forms must be signed and presented to the surgeon before the participant can be enrolled into the postapproval study. The forms will be in triplicate. The surgeon will mail the original signed forms in a Business Reply Envelope (BRE), along with the sealed envelope containing the first (baseline) questionnaire, to the third party study entity. The surgeon will keep the second copy of the informed consent and medical records release authorization for retention in the participant's records. The third copy will be kept by the participant.

Consents and releases will be broad enough to secure permission to: access medical records required to be collected by this protocol; contact individuals that the participant has designated as a means to locate the participant; use Social Security Numbers to search proprietary databases (e.g., the National Change of Address (NCOA) database, the Social Security Death Index database, and other proprietary databases) as needed. Consents and releases will also permit participant data and information to be provided to the Food and Drug Administration (FDA), Institutional Review Boards (IRBs), and/or courts as needed. Additionally, informed consents and releases will make reference to the agreement of the participant to cooperate in allowing the third party study entity to obtain medical records required by this protocol.

14.0 CONFIDENTIALITY

The identity of participants enrolled in the postapproval study and the information contained in their study records will be kept confidential in accordance with this protocol and the Informed Consent and Medical Release Authorization forms.

To ensure confidentiality, each participant will be tracked via a unique participant identifier. Participant names and contact information will be stored separately from participant data. Confidentiality will be protected throughout the 10-year study period.

Although the third party study entity will have complete access to all study data, the participant's name and data will not be disclosed, except to the FDA, IRBs, or courts of law as needed. In those events, Mentor will also receive access. Also, pursuant to consents and medical records release authorizations, the participant's name (but not data) will be disclosed to the participant's physicians, as part of medical record collection required by this protocol. Additionally, the participant's Social Security number may be used to search proprietary databases (e.g., the National Change of Address (NCOA) database, the Social Security Death Index database, and other proprietary databases) as needed.

Data analyses and reports made available for review as required by the FDA and IRBs, will be reported as confidential statistical information. If supporting documentation, such as medical records, is required to be collected, the third party study entity will send a request on behalf of the participant to the surgeon/physician or other parties from which medical records may be requested.

Any research, presentations, and/or publications of study findings by Mentor, medical societies, or other third parties will not disclose participant names or other participant identifying information.

15.0 FORMS