Novel Approach for Higher Follow-up in Clinical Trials

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BACKGROUND

From 1992 until 2006, the FDA placed a moratorium on silicone implants in the U.S. Although the health concerns related to silicone implants have been largely unsubstantiated in the scientific literature, there remains a market for saline implants. Based on ASAPS survey data, 20% of breast implants used in 2014 for cosmetic procedures were saline. Saline implants are an ideal choice for women who are apprehensive about risks of silicone, who wish to avoid MRI screening, or who want to avoid the risk of silent rupture. Traditionally, saline implants have looked and felt less natural and have been associated with a higher risk of rippling. The Ideal Implant was designed to create a more natural-appearing saline implant. It is a round, smooth surface implant with two lumens created by nested shells and intervening perforated baffle shells designed to restrict saline movement.

FDA approval of breast implants requires pre-market approval (PMA) applications with clinical studies demonstrating safety and effectiveness. High follow-up rates are difficult to achieve, but imperative to produce complete clinical data. The ten-year follow up rates for core breast implant trials is as low as 55% for some study cohorts. The PMA study for Ideal Implant, an innovative saline-filled implant recently FDA-approved, incorporated a novel incentive strategy to achieve higher follow-up rates than in previous breast implant trials.

Ideal Implant Core Clinical Trial

The Ideal Implant Core Clinical Trial enrolled 502 patients between Feb 2009 and Feb 2010 across 35 investigational sites with 45 investigators, who are American Board of Plastic Surgery-certified. The study is a 10-year prospective, multi-center, open label study with two cohorts: adult women undergoing bilateral primary augmentation and adult women undergoing bilateral revision of existing saline or silicone breast implants. Follow up time-points for history and examination included visits at 2mo, 6mo, and annually for 10 years.

At enrollment, $3,500 was deposited into an independent, irrevocable trust for each of the 502 subjects and invested in a diversified portfolio. Subjects cover implant and operative costs and are not paid for the required follow-up visits. If a visit is missed, the subject is exited from the study, but her share of the funds stay in the trust. At the conclusion of the 10-year study, the trust will be divided among those subjects who completed all their required follow-up visits (currently, each subject's share is $5,533).

Materials and Methods

Follow-up data was obtained and compared from each SSED (Summary of Safety and Effectiveness Data) for the 5 silicone and 3 saline FDA-approved implants. These documents are made publically available upon approval of the PMA (premarket approval) application. Insufficient follow-up data for Allergan's and Mentor's Saline implants and insufficient explanation of follow-up rate calculation for Allergan Natrelle and Mentor MemoryGel prohibited their inclusion in comparison analysis. All studies for implants approved since 2012 use consistent, standard calculation for follow-up data. Follow-up comparisons were possible for Ideal Implant, Mentor MemoryShape, Allergan 410, and Sientra Silicone. Comparisons were performed for 4 years of annual data, the longest available follow-up for Ideal Implant, based on individual augmentation cohorts, compared augmentation cohorts, and total combined study follow-up. Statistical analysis was performed using Chi-squared test using Ideal Implant completed follow-up and lost-to-follow-up percentages as the expected outcome to test whether the follow-up for other implants was different.

RESULTS

Ideal Implant Design

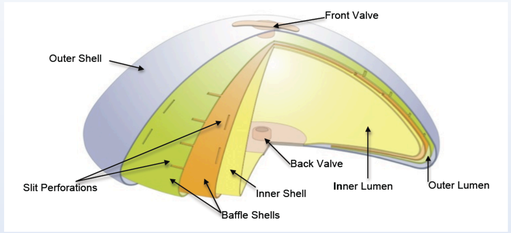

Fig 1. FDA-Approved Implants, used for SSED follow up comparison

Manufacturer & Implant Name	FDA Approval Date	Study Cohorts			
		Primary Aug	Revision Aug	Primary Recon	Revision Recon
Saline					
Ideal Saline-Filled Breast Implant	Nov 2014	X	X		
Allergan Medical RTV Saline	May 2000	X		X	
Mentor Saline-filled and Spectrum	May 2000	X		X	
Silicone					
Mentor MemoryShape	June 2013	X	X	X	X
Allergan 410 Highly Cohesive	Feb 2013	X	X	X	X
Sientra Silicone Gel	March 2012	X	X	X	X
Allergan Natrelle	Nov 2006	X	X	X	X
Mentor MemoryGel	Nov 2006	X	X	X	X

Figure 1. Currently 3 saline breast implants (Ideal Implant, Allergan, and Mentor) and 5 silicone implants (Mentor MemoryShape, Allergan 410, Sientra, Allergan Natrelle, and Mentor MemoryGel) are FDA-approved. The SSED's for all 8 implants were obtained for follow-up data. Four different cohort groups have been utilized amongst the implant core clinical trials. Insufficient follow up data was presented in the SSED for Allergan and Mentor saline implants. Insufficient explanation of follow-up rate calcuation for Mentor Memory Gel and Allergan Natrelle prevented their inclusion in the comparison

Fig 2. Ideal Implant Core Clinical Trial Follow-up

Cohort	Subject Status	Follow-up Time Interval					
		2 Month	6 Month	1 Year	2 Year	3 Year	4 Year
Ideal Implant Primary Augmentation	Theoretically due [A]	399	399	399	399	399	399
	Deaths	0	0	0	0	0	0
	All devices removed and replaced with other manufacturer's devices	0	3	7	7	8	8
	Voluntary withdrawal by subject	0	1	3	6	8	10
	Expected [B]	399	395	389	386	383	381
	Actual (Complete follow-up)	397	391	383	378	371	366
	Lost to follow-up	2	4	6	8	12	15
	Percent follow-up (Actual/Expected)	**99.5%**	**99.0%**	**98.5%**	**97.9%**	**96.9%**	**96.1%**
Ideal Implant Revision Augmentation	Theoretically due [A]	103	103	103	103	103	103
	Deaths	0	0	0	0	0	0
	All devices removed and replaced with other manufacturer's devices	0	2	5	7	7	8
	Voluntary withdrawal by subject	0	0	0	0	0	2
	Expected [B]	103	101	98	96	96	93
	Actual (Complete follow-up)	103	101	96	94	94	91
	Lost to follow-up	0	0	2	2	2	2
	Percent follow-up (Actual/Expected)	**100%**	**100%**	**98.0%**	**97.9%**	**97.9%**	**97.8%**

Figure 2. Detailed follow-up data for all time points collected to date for the Ideal Implant Core Clinical Trial. The same standard for reporting follow up rates has been utilized by the core trials for the last 4 FDA-approved implants. In this standard, the focus of follow-up rates is on those who are lost to follow-up for unknown reasons. Patients lost to follow-up are differentiated from those who voluntarily withdraw and those whose devices are prematurely removed or replaced.

[A] Subjects who would have been examined according to date of implantation and follow-up schedules.
[B] Subjects who are theoretically due minus the sum of the deaths, voluntary withdrawals and removals with replacement with different manufacturer's implants. Subjects with voluntary withdrawal or lost to follow-up date after a visit window in which they did not actually attend were counted as withdrawn in the relevant category at that missed visit.

Fig 3. Comparison of Follow-up for Primary Augmentation Cohorts

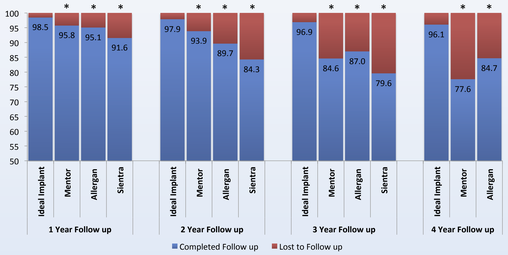

Fig 4. Comparison of Follow-up for Revision Augmentation Cohorts

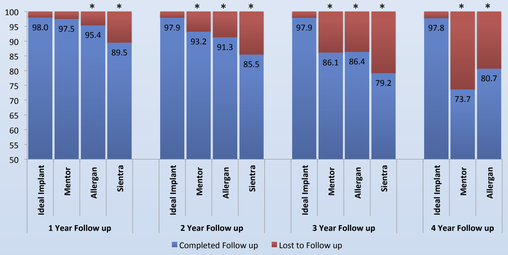

Fig 5. Comparison of Total Follow-up for All Cohorts

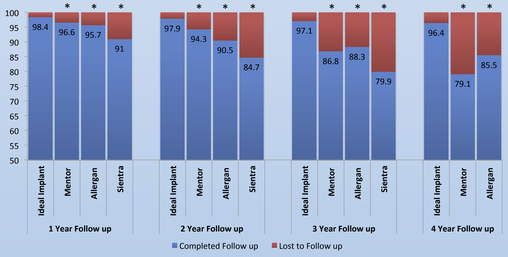

Figure 3-5. Comparison of Follow up for primary augmentation cohorts (Fig 3), revision augmentation cohorts (Fig 4), and all study cohorts combined (Fig 5). Asterisk (*) signifies p<0.05 for Chi square test comparisons to Ideal Implant as expected outcome. Data is represented at "Completed Follow up" and "Lost to Follow up" since these percentages and numbers were utilized to perform the chi square tests. Mentor is abbreviated for Mentor MemoryShape Implant. Allergan is abbreviated for Allergan 410 highly cohesive implant. Sientra only had 3 years of follow up at the time of PMA application submission so it not included in the 4 year comparison.

RESULTS

Amongst primary augmentation cohorts, Ideal implant has higher follow-up for all four annual time points (98.5%, 97.9%, 96.9%, 96.1%) compared to Mentor MenoryShape (95.8%, 93.9%, 84.6%, 77.6%), Allergan 410 (95.1%, 89.7%, 87.0%, 84.7%), and Sientra (91.6%, 84.3%, 79.6%, 4yr data not available) with p<0.05 for each comparison. Amongst revision augmentation cohorts, Ideal Implant has higher follow-up for all four annual time points (98.0%, 97.9%, 97.9%, 97.8%) compared to Mentor MemoryShape (97.5%, 93.2%, 86.1%, 73.7%), Allergan 410 (95.4%, 91.3%, 86.4%, 80.7%) and Sientra (89.5%, 85.5%, 79.2%, 4yr data not available) with p<0.05 for each comparison except for 1yr comparison with Mentor MemoryShape (p=0.7). Amongst total compiled study data, Ideal Implant has higher follow-up for all four annual time points (98.4%, 97.9%, 97.1%, 96.4%) compared to Mentor MemoryShape (96.6%, 94.3%, 86.8%, 79.1%), Allergan 410 (95.7%, 90.5%, 88.3%, 85.5%), and Sientra (91.0%, 84.7%, 79.9%, 4yr data not available) with p<0.05 for each comparison.

Traditionally, implant trials have incentivized study participation with payments per follow up appointment, with escalated amounts for later follow up appointments. For example, Mentor MemoryGel Core Study provided $500 after surgery, $300 at 6mo, $500 at 1yr, $700 at 2yr with $200 bonus if no missed visits, $150 for years 3 through 10, and $250 bonus if no missed visit at 10 yrs. The MemoryShape Core Study provided $100 at baseline, $50 at 10wks, $200 at 1yr and at 2yr, $200 bonus at 2yr for no missed appointments, $150 yearly for 3 yr through 10yr, and a $250 bonus for no missed appointments. A patient who attends all visits for 10 years would get paid $3650 and $2100 in the Mentor MemoryGel and MemoryShape trials, respectively. Ideal implant committed $3500 per patient to incentivize follow up, which is comparable to the potential financial commitment to a patient in the Mentor MemoryGel study. In the Ideal Implant, a patient could profit more depending on investment return and attrition. Neither Ideal Implant nor Mentor cover the cost of the implant or surgical fees. Financial incentive data was not available for Allergan or Sientra. Future work should evaluate the effect of total potential financial gain on follow-up rates.

CONCLUSIONS

Ideal Implant Core Clinical Trial demonstrates the utility of a novel approach to maximize study participation. Retention is promising based on the available 4 year participation data and high follow-up rates are anticipated as the Ideal Implant trial continues. This incentivized approach can benefit any prospective research by providing more complete data.

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