

Post-market surveillance of safety and efficacy of Silimed® breast implants with textured surface and polyurethane foam-coated surface

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## Sponsor's Approval Page

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Protocol

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Study Title

Post-market surveillance of safety and efficacy of Silimed® breast implants with textured surface and polyurethane foam-coated surface

Signatory Sponsor

Sergio Carlos Assis

Clinical Research Coordination

## Summary

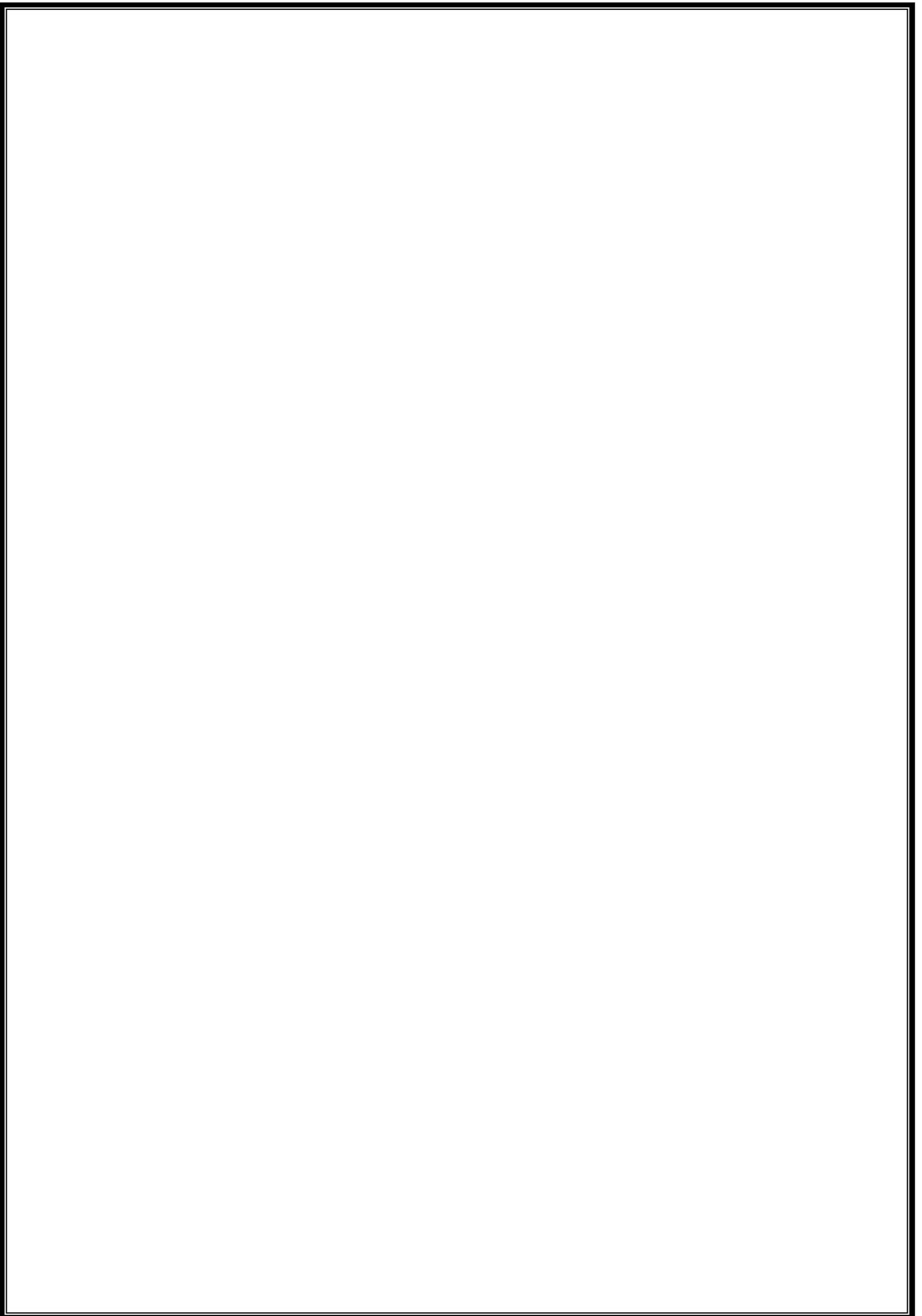
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## Executive Summary

Objective	Estimate the safety and performance of mammary implants with a textured surface and mammary implants with a polyurethane foam-coated surface of the brand Silimed® already available in the market
Primary Objective	Estimate the risk / rate of known and unexpected adverse events of short and long term for each type of implant Silimed®.
Secondary Objective	Estimate the performance of implants through satisfaction and quality of life after placement of the Silimed® breast implant.
Design	Phase IV clinical trial, open, non-randomized (or quasi-experimental) prospective trial.
Location	Brazil
Participants, inclusion and exclusion criteria	Consecutive inclusion within the recruitment period up to the estimated minimum sample size. Inclusion criteria: (1) provide written free and informed consent, (2) female at birth, (3) aged 18 years or older, (4) have received breast implant (s) up to 14 days prior who sought primary breast augmentation, (5) have received breast implants with textured surface or breast implants with polyurethane foam-coated surface of the brand Silimed®, (6) ability to comply with the protocol for the entire follow-up time. Exclusion criteria: (1) secondary breast augmentation (2) gestation or breastfeeding, (3) advanced fibrocystic disease at the time of implantation, (4) neoplasia of any type not yet treated or being treated at the time of implantation, (5) infection in activity not yet treated or in treatment at any site at the time of implantation, (6) reporting or recording of adverse reactions or intolerance to polyurethane or silicone prior to implantation, (7) immune diseases that affect connective tissue in activity or in treatment (e.g., lupus erythematosus, discoid lupus, scleroderma, etc.) at implantation, (8) signs of inflammation of the breast or implant site at implantation, (9) high surgical risk or complications in the immediate postoperative period prior to implantation, (10) drug use prior to implantation that increase the risk of immediate postoperative complications (e.g., medicines that interfere with coagulation), (11) may not have participated in another clinical trial up to 6 months prior to implantation, (12) any other condition that, based on the investigator or designee, may prevent the provision of informed consent, renders study participation unsafe, compromises adherence to the protocol, complicates the interpretation of data from the study outcome, or otherwise interferes with the achievement of study objectives.
Exposure / intervention of major interest	Silicone breast implant of the brand Silimed® (breast implants with textured surface and breast implants with polyurethane foam-coated surface of the brand Silimed®).

Primary outcomes	Expected or unexpected adverse events during the follow-up period. Examples of expected adverse events (but not restricted): asymmetry, breast pain, tissue atrophy, calcification, capsular contracture, rupture, delay in wound healing, extrusion, hematoma, infection, inflammation or irritation, lymphedema or lymphadenopathy, displacement, necrosis, anesthesia, hypoesthesia, paraesthesia or hyperesthesia of the breast or nipples, palpability, ptosis, ecchymosis, seroma, skin rash, visibility, wrinkling and undulation, cysts and nodules. The events of greatest interest initially are the events that cause the need for any reoperation, removal of the implant, removal of the implant with replacement or removal of the implant without replacement, events directly related to the presence of the implant (capsular contraction grade III / IV, implant, etc.).
Secondary outcomes	Breast self-assessment questionnaire (BEQ-Brazil), Rosenberg global self-esteem scale, patient satisfaction, researcher satisfaction.
Duration of the study	Each participant will be followed up to 10 years.
Allocation of treatment	As the participants will be invited to participate after the implants, the research protocol does not foresee any interference of the research procedures in the choice of the type or size of the implants as well as in the surgical technique used.
Masking / Blinding	There will be no masking / blinding.
Statistical analysis plan	For the primary endpoint, the risk / rate of groups of adverse events and specific events and their respective confidence intervals. These estimates will be made taking into account both the implant and the patient as unit of observation. There is also the intention to explore the heterogeneity between the participating centers and to adjust the rate estimates if the heterogeneity is present and for baseline elements that could change the prognosis of the volunteers. For the secondary objectives changes in scores over time will be used to construct gross and adjusted correlation trajectories.
Minimum Sample	700 participants divided into 2 groups formed by the type of implant. There will be 350 volunteers with implants with textured surfaces and another 350 with implants with polyurethane surface.
Intermediate analysis	They will always occur once a year for the duration of the study. Interim analyzes shall consist of the same analyzes provided for in the analysis plan for the final report, unless there is sufficient sample size. Security alarms will occur if one or more centers show differences in event rates (heterogeneity) between participating centers. The centers that stand out from the others in the rates of adverse events will be evaluated regarding the need for additional analysis of specific rates, and possible need for corrective measures.



## 1. Team

### Scientific Team:

- Marcelo Vitoriano Oliven
- Pedro Emmanuel Alvarenga Americano do Brasil
- Sergio Carlos Assis de Jesus Junior
- Tonia Lourenço Cunha

### Scientific Consultant

- Marcelo Vitoriano Oliven
- Pedro Emmanuel Alvarenga Americano do Brasil

### Responsible for the elaboration of the research protocol:

- Pedro Emmanuel Alvarenga Americano do Brasil
- Sergio Carlos Assis de Jesus Junior
- Tonia Lourenço Cunha

### Representatives:

- *Industrial Director:* Fernando Zaia
- *Research and Development Manager:* Ana Cristina Soares Taveira
- *Regulatory Affairs and Quality Manager:* Ana Carolina da Cunha Paz
- *Research and Development / Clinical Research Coordinator:* Sergio Carlos Assis

### Epidemiologist

- Pedro Emmanuel Alvarenga Americano do Brasil

### Statistics and Data Management

- Pedro Emmanuel Alvarenga Americano do Brasil (Supervision)
- Sergio Carlos Assis (Supervision)
- Coreware (Execution)

### Study Coordination Committee:

- Sergio Carlos Assis
- Tonia Lourenço Cunha

### Monitoring Team:

- Sergio Carlos Assis
- Tonia Lourenço Cunha
- Amanda Trajano Baptista

## **2. Introduction**

### **2.1. State of the Art**

Saline and silicone breast implants have become available in the market for breast reconstruction and aesthetic indications since the 1960s. Since then, due to regulatory discussions, implants have been restricted to indications for breast reconstruction only and released after evidence accumulation at Respect for its effect and safety. [1] Even with the concerns of academia and regulatory agencies regarding safety and evidence regarding the risk of different complications, it is estimated that in the United States alone, more than one million two hundred thousand implantations occurred between the 1970s and 1980s [2] with an increasing trend since then. [3]

Over time, different types, contents, contours, shapes and size of implants appeared, always with the purpose of increasing the aesthetic result and reducing the risks of complications attributable to the implant and the related surgical act. There were also a number of surgical techniques for the same purpose, such as different accesses, reduction of the incision, addition of the patient's own tissues in the implant shop, change of store location, etc. Even so, implants need to be revised, since they generally have an estimated useful life of approximately 10 years, and may require periodic replacement. Still, once having used an implant, even without complications, the breasts are unlikely to return to satisfactory aesthetic appearance if the implant is removed for any reason.

In addition to primary reconstruction and primary augmentation, other indications and special situations unfolded and evidence with these situations also accumulated over time. Examples of such situations are reconstruction and secondary augmentation implants, gestation and breastfeeding in women with implants, radiotherapy in women with implants, recrudescence or recurrence of neoplasia in women with implants, multiple aesthetic interventions performed at the same time as implantation, etc. All these conditions could at first modify the safety and efficacy of implants when compared to primary increase.

The major concerns surrounding the use of breast implants have always been their safety. [4] Already in the 1990s, the Food and Drug Administration (FDA) has classified the complications attributable to breast implants in local and systemic. The local complications would be implant rupture (with or without gel migration), breast or thoracic pain, capsular contracture, changes in nipple sensitivity, delay in surgical wound healing, hematoma, galactocele or galactorrhea,

displacement or extrusion, interference in performance or interpretation of mammograms and seroma. The systemic complications potentially involved would be autoimmune diseases (connective tissue diseases) and neoplasms (not necessarily breast). [1,4]

## **2.2. Expectation of beneficial effects**

There is evidence showing that reduction in mortality of women who received implants after mastectomy [5-7] or after primary enlargement, [5,8] even when adjusted for prognostic factors such as age, social conditions, type, site, size and stage of neoplasia . However, other possible ways to measure the beneficial effect of breast implants for both primary mammary enlargement and reconstruction after mastectomy have emerged. Traditional outcomes focusing on morbidity and mortality are important but are no longer sufficient for a more comprehensive understanding of the effect of the implant.

The immediate and long-term beneficial effect expected is the satisfaction of the woman, which is in some way related to self-esteem, preoccupation with the image itself, which in turn has a relevant impact, although difficult to measure, in the style and in the quality of life. Therefore, numerous instruments for measuring these dimensions were applied, developed for this purpose. [9] Even so, hardly a single instrument could capture all the dimensions in the life of a person where implantation could have some effect. In the Allergan Pivotal study over 7 years, approximately 9 out of 10 women underwent primary augmentation or revision review with NATRELLE 410 Breast implants that answered the satisfaction question were definitely or a little satisfied with their breast implants.

## **2.3. Expectation of expected adverse events**

Technical reports provided by the FDA used for silicone breast implant registries from different manufacturers indicate a variety of risks from implant or surgery-related events. The most frequent event in all reports, consistent with the literature in general, is capsular contracture. Capsular contracture, when intense, is also the most frequent indication of implant removal. Below is a comparison of risks of events of interest by major interest groups and by different manufacturers. However, it is not possible, through the data from these reports to verify if there are differences between the different types of implants, nor what prognostic elements determine the events in the different interest groups.

*Cumulative incidence by type of event, implantation indication and implant brand (data retrieved from technical registration reports).*

Event	<i>Natrelle</i> (Textured Surface - in 7 years)		<i>Natrelle</i> (Textured Surface - in 3 years)		<i>Sientra</i> (any surface - in 3 years)		<i>Mentor</i> (any surface - in 3 years)	
	Augmentation	Reconstruction	Augmentation	Reconstruction	Augmentation	Reconstruction	Augmentation	Reconstruction
Any Complication	31,0%	53,0%	-	-	-	-	-	-
Any Reoperation	22,4%	45,2%	12,7%	21,0%	12,6%	34,9%	15,4%	27,0%
Removal of the implant with or without replacement	12,6%	29,3%	-	-	-	-	-	-
Removal of the implant without replacement	1,2%	5,3%	0,5%	2,9%	1,2%	7,0%	2,3%	5,7%
Removing the Implant with Replacement	11,5%	25,2%	5,0%	14,9%	4,6%	19,1%	2,8%	7,4%
Capsular contracture grade III / IV	6,1%	10,7%	2,1%	7,3%	6,0%	8,8%	8,1%	8,3%
Implant rupture	6,9%	8,9%	1,3%	0,0%	3,0%	0,0%	0,0%	0,0%

Although there is a perception that polyurethane coated implants present a lower risk of various complications (e.g. capsular contracture), lack of evidence with a direct comparison and differences in methods and follow-up times in textured surface implant studies and studies with Polyurethane surface, as well as the difference in the quality of the evidence for this comparison hinders a conclusion regarding the safety of these two types of implant.[10] However, there is evidence that some types of implants may present minor risks (particularly when compared to first generation smooth surface implants) of certain events (e.g., capsular contracture) in certain populations. [11-15]

Regarding the most common expected adverse event, capsular contracture, several questions can be posed as: it is an event that can be progressive with compromised aesthetic outcome, which is surgical treatment with removal of the implant in advanced progressions and

frequently occurs in the first 3 years after implantation. There is sufficient evidence showing different strategies that may reduce capsular contracture in the short term, such as: use of textured implants (compared to smooth implants), [14,15] capsule irrigation with antibiotics prior to implant placement, [16,17] ] Use of preferred surgical techniques, [18] use of non-talc gloves for manipulation of the implant, prophylaxis of surgical infection with antibiotics. The advantage of implants with textured surface compared to smooth surface implants is however evident only for capsular contracture [15] and short / medium term. [14]

Regarding possible systemic events in the use of implants, the academy and regulatory authorities worry or worry about specific conditions that have arisen over time. Among them, connective tissue diseases, neoplasias (especially anaplastic giant cell lymphoma - ALCL), and suicide.

Between the 1980s and 1990s, connective tissue diseases were a major concern due to the diversity of case reports and even judicialisation. [19] However, after several studies and initiatives to clarify this issue related to implants, several investigations have pointed to an absence of evidence of a causal relationship between breast implants and classic diseases of the connective tissue.

In addition, suicide has been and seems to be currently a recurring issue. There is evidence of epidemiological studies indicating an excess risk of suicide among women receiving breast implants. [21,22] There is also evidence that this population differs in some characteristics of the general population or of women who do breast reduction [ 24] including psychiatric conditions prior to implantation, use of alcohol and drugs. [23,24] Although there is a strong and consistent connection between breast implant and suicide, the causal connection is quite controversial [4] and there are recommendations for evaluations Psychological aspects prior to implantation to better address previous problems. [25]

The ALCL associated with the breast implant is a distinct type of T cell lymphoma that appears in the periphery of breast implants and apparently always involved with the presence of implants with textured surface. [26] Morphological investigations indicate that a chronic inflammatory process at the periphery of the implant, even if imperceptible to clinical examination, is the main phenomenon. ALCL is generally defined as a T-cell lymphoma that has continuity with the implant or a capsule scar, composed of pleomorphic cells that express CD30 uniformly and unpublished genetic anaplastic knockout or 2q23 chromosome of anaplastic kinase. [3,26] Despite being considered a serious condition with high morbidity, ALCL is a curable disease in the vast majority of cases, with a median survival of 93% and 89% at 3 and 5 years, respectively. The ALCL presentation is variable but is commonly associated with a peri-implant late seroma, is diagnosed on

average 10 years after implantation and apparently has no preference for indication group (reconstruction or increase). [3,26] The number Of cases identified each year is increasing since 1986. [26] The incidence of ALCL related to the implant from population data is higher than the incidence of ALCL in breast in the general population, and is higher than was believed until 2005. [3] However, this data is controversial when compared to the incidence in very long follow-up studies (30 years or more) of women who received an implant, where the incidence is similar to the incidence of the general population. Even so, the incidence is very low and was estimated as 1 case for every 30,000 textured surface implants. [3]

The evidence in the literature regarding the safety of silicone implants is vast and comes from a number of long-term retrospective and prospective studies. In most of the events considered, there is a consistent demonstration that the incidence of events is low, both for short and long term events after implantation, which does not lead to removal or re-surgery for correction. [4]

### **3. Justification**

Medical device manufacturers are routinely audited and requested to ensure the best current quality standards, to update the device's research plan and to provide updated efficacy and safety related documentation when requested by the competent authorities. When new events possibly related to devices are recorded or events already known concern the authorities and the scientific community as to their severity or the increase in their incidence, new clinical research may be necessary to specifically elucidate if these unwanted events are in fact related With the medical device. These studies are termed post marketing or phase 4 safety studies. For example, in the 1990s, silicone breast implants were suspected to be related to connective tissue diseases, and several investigations were conducted in an attempt to find this relationship [29], and more recently concern has arisen that breast implants may be related to anaplastic giant cell lymphoma (ALCL). [30] Other situations in which new clinical research is justified occur when the product is indicated for new conditions, or for a population with different characteristics of the original, or as a post-marketing strategy to verify the safety of the product.

### **4. Outcomes**

The main objective of this study is to estimate the safety and performance of breast implants with a textured surface, and of breast implants with polyurethane foam-coated surface of the brand

Silimed® already available in the market.

#### **4.1. Primary Outcomes**

- Estimate the known short-term and long-term risk / adverse event rate for each of the two types of implants of the brand Silimed®.
- Estimate the unexpected short-term and long-term risk / adverse event rate for each of the two types of implants of the brand Silimed®.

#### **4.2. Secondary Outcomes**

- Estimate the performance of the implants through the satisfaction and quality of life after breast implant of the brand Silimed®.

### **5. Methodology**

#### **5.1 Designing**

Phase IV clinical trial, open, non-randomized (or quasi-experimental) prospective trial.

#### **5.2 Location**

Brazil.

#### **5.3 Study Participants**

Participants will be selected consecutively from attendance at participating center, conducted within the recruitment period. The recruitment period will last until the planned minimum sample number is reached, unless the project is interrupted for security reasons. Study participants will be invited to participate in the first medical evaluation after they have performed the implantation procedure and the eligibility criteria described below should be applied.

##### **5.3.1 Inclusion Criteria**

Inclusion criteria: (1) provide free informed consent, (2) female at birth, (3) 18 years or older, (4) have received breast implant(s) for indication of primary augmentation up to 14 days prior,

(5) ability to comply with the protocol for the entire follow-up time, (6) have received breast implants with a textured surface or breast implant with a polyurethane foam-coated surface of the brand Silimed®

### **5.3.2 Exclusion Criteria**

Exclusion criteria: (1) secondary breast augmentation, (2) gestation or breastfeeding, medicines that increase the risk of immediate postoperative complications (e.g., medicines that interfere with coagulation), (3) advanced fibrocystic disease at the time of implantation, (4) neoplasia of any type not yet treated or being treated at the time of implantation, (5) infection in activity not yet treated or in treatment at any site at the time of implantation, (6) reporting or recording of adverse reactions or intolerance to polyurethane or silicone prior to implantation, (7) immune diseases that affect active or treating connective tissue (e.g., lupus erythematosus, discoid lupus, scleroderma, etc.) at the time of implantation, (8) signs of inflammation of the breast or implant site at the time of implantation, (9) high surgical risk or complications in the immediate postoperative period prior to implantation, (10) record or report of use of illicit drugs or medications that increase the risk of immediate postoperative complications (e.g., medicines that interfere with coagulation), (11) may not have participated in another clinical trial up to 6 months prior to implantation, (12) any other condition that, based on the opinion of the investigator or designee, may prevent the provision of informed consent, renders study participation unsafe, compromises the adherence to the protocol, complicate the interpretation of data from the study outcome, or otherwise interfere with the achievement of study objectives.

## **5.4 Exposures / interventions**

### **5.4.1 Interventions of major interest.**

#### **Silicone Gel Implant with Polyurethane Foam-Coated Surface**

Composed of a single silicone elastomer shell, mechanically resistant and coated with polyurethane foam. Contains a defined volume of high performance transparent silicone gel (HSC) developed so that its shape and consistency provide a natural breast appearance.

The shell with low bleed treatment are a contribution to the reduction of the transudation of silicone by osmosis, by the barrier of the elastomer shell, where part of the thickness of the shell is formed by an inner layer of elastomer especially impermeable to the silicone oils.

There is evidence that the implant with the polyurethane foam-coated surface presents a lower rate of capsular contracture when compared to a smooth surface. [11-13] The polyurethane coating allows a better interaction between the implant and the tissue around it.

The well-irregular surface of the polyurethane foam disadvantages the formation of the linear fibrotic capsule in favor of the multiplanar formation of the collagen fibrils. The formation of microcapsules around the polyurethane particles causes the contraction force to cease to have a single orientation, having multiple vectors, this force tends to cancel out, reducing the capsular contracture. [11]

It is up to the physician to select the appropriate size and type of fixation to meet the clinical and aesthetic requirements of each case. They are all supplied sterile and intended for single use. The package should only be opened inside the operating room and supplied with an auxiliary glove for implantation.

#### **Silicone Gel Implant with Textured Surface**

Composed of a single silicone elastomer shell, mechanically resistant, with a textured surface. Contains a defined volume of high performance transparent silicone gel (HSC) developed so that its shape and consistency provide a natural breast appearance.

The shell with low bleed treatment are a contribution to the reduction of the transudation of silicone by osmosis, by the barrier of the elastomer membrane, where part of the thickness of the membrane is formed by an inner layer of elastomer especially impermeable to the silicone oils. The textured surface is effective in reducing the occurrence of capsular contracture when compared to the smooth surface, [11-13] by allying with the low bleed shell in the greatest capacity to prevent this clinical condition.

It is up to the physician to select the appropriate size and type of fixation to meet the clinical and aesthetic requirements of each case. They are all supplied sterile and intended for single use. The package should only be opened inside the surgical center, also containing auxiliary glove for implantation.

#### **5.4.2 Descriptive characteristics or that could interfere in the prognosis.**

The rationale for conducting a randomized clinical trial is to create "comparable" groups (e.g. standard group / comparison vs. new intervention) such that the effects observed at the end of follow-up can be attributed to intervention. For this purpose, it is necessary to verify, at the

beginning of the follow-up, the characteristics that can lead to confounding. This procedure is also performed in non-randomized trials, and additionally these same characteristics may serve as elements to be adjusted, for example in group formation, where the estimation of event rates could be biased due to confounding (e.g. at some point the groups could be considered "non-comparable" given differences in initial characteristics requiring adjustments).

These characteristics will be grouped as follows: (a) clinical characteristics, (b) characteristics related to surgical procedures and wound care, and (c) characteristics related to the intervention / implants.

Examples of clinical characteristics (but not restricted to): age, weight, body mass index, marital status, ethnicity (skin color), instruction / education, comorbidities (e.g. Arterial hypertension, Diabetes Mellitus, Allergies, etc), use of medications, etc.

Elements related to surgery and surgical wound care (but not restricted to): implant placement technique (subglandular, submuscular, others), type of incision (periareolar, submammary, in previous procedure scar, others), size of the incision etc.

Examples of implant-related (but not restricted to) characteristics: texture, implant type, implant size, etc.

## **5.5 Primary Outcomes**

Primary outcomes will be the adverse events of the participants. Below is a section on the safety, monitoring, and classification of adverse events. The project foresees the classification of adverse events according to severity, intensity, causality, type (tissue-related, aesthetic or implant-related events) and according to the course of action for the solution of the event (e.g. unnecessary additional treatment, additional surgical treatment, surgical treatment without explantation and surgical treatment with explantation).

The events related to the tissue are the events that can occur following any breast surgery. Aesthetic events are primarily aesthetic and related to the presence of the implant (e.g., ripples, wrinkles, etc.). Events related to the implant are those that are specifically assigned to the presence of the implant (e.g., capsular contracture, implant rupture, etc.).

The adverse events can be defined as any medical event, yet the literature points to some

occurrences as more frequent or as expected, since they are events observed in previous studies and their incidence has already been estimated in these studies. Below is a list of events recorded in previous studies that are considered as expected adverse events:

- Anesthesia: loss of local sensitivity, both for pain and other sensations, usually reported by the patient during the medical evaluation.
- Asymmetry: after implantation, the breasts do not look identical or have a dissimilar appearance when both sides of a central line are compared for shape, size, level, or location.
- Tissue atrophy: thinning or shrinking of the skin, usually detected on inspection.
- Calcification of the capsule: deposits of calcium salts in the capsule or as a thin layer around the implant. Calcification may be local or diffuse and is usually asymptomatic, occasionally detected when an image of the chest (e.g. radiography or MRI) is performed for investigation of other health conditions.
- Cyst (requiring biopsy or removal): Cyst is a closed structure, such as a sac or bladder, formed in tissues, containing fluid or semi-fluid in its interior. May or may not have a calcified capsule. It can be identified by physical examination and medical evaluation if it is superficial, or by imaging tests (e.g. radiography or tomography)
- Capsular contracture (Baker's classification - check below): Capsular contracture occurs when the collagen fiber capsule shrinks, tightens and compresses the breast implant. Its identification and classification can be conducted during the medical evaluation by inspection and physical examination. [31,32]
- Wound dehiscence: opening of an incision that has been surgically closed. Identified during medical inspection and evaluation.
- Delay in surgical wound healing: Too long progression in wound healing; The surgical wound does not heal normally or takes longer than expected. Defined as requiring additional care (e.g. dressings or additional treatment) after 7 days of implantation.
- Displacement: movement of the implant from the original location or appropriate position, due to gravity, capsular contracture, muscle traction, healing forces or implant weight. It can be detected on inspection or physical examination.
- Breast pain: pain in the scar, in the breast or adjacent structures, and may be irradiation of a breast pain.
- Wrinkle: Unnatural nodular appearance that may occur on the side of the breast or underneath it. It can be identified by inspection and clinical evaluation.
- Extrusion: displacement of the implant through a rupture of the skin or through the surgical wound with the tendency of the original implant to exit the implant.

- Galactorrhea: spontaneous flow of milk from the breast, not associated with gestation and delivery, or breastfeeding. It can be both informed by the patient and visualized during inspection and medical evaluation.
- Hematoma: rupture of blood vessels followed by collection of blood and possibly clot formation may occur in structures adjacent to the implant, especially soon after implantation. Hematoma is spontaneously absorbed. They may require surgical drainage because of their size, location, severity or because of possible undesirable clinical consequences. The need for drainage will be assessed clinically on a case-by-case basis. Identified during medical evaluation and physical examination, occasionally identified through imaging tests such as ultrasound.
- Hypoesthesia: reduced local sensitivity, both for pain and other sensations, usually reported by the patient during the physical examination.
- Inflammation or irritation: response of the body to an external infection or aggression, which is characterized by redness, edema, heat or pain. Detected through inspection and physical examination.
- Lymphedema or lymphadenopathy: enlargement and engorgement of the lymph node (s), usually leading to edema resulting from lymph stasis. It can be identified on physical examination, especially if compared to a contralateral structure.
- Implant malposition: occurs when the implant is poorly positioned in the initial surgery. If implantation was considered adequate first and there was displacement, the event should be recorded as displacement (see above).
- Need for surgical removal of a capsule or scar (unacceptable scarring): The location of the incision or envelope may progress to an aesthetic result that does not look like healthy or expected skin.
- Need to remove the implant: removal of the implant will be considered a consequence, i.e. an additional therapy of a previous adverse event. It will not be considered an adverse event if it is performed only and exclusively at the request of the patient.
- Necrosis: cell death of tissues. Necrosis has several classifications according to the pathogenesis. It can usually be clinically identified by inspection because of the typical appearance or odor, or additional vascular findings.
- Ripple: The surface of the breast presents with ripples. It can be identified by physical examination.
- Palpability or visibility of the implant: the implant becomes visible or perceptible to the touch.
- Paresthesia or hyperesthesia of the breast or nipples: abnormal sensation (e.g. numbness or

itching) or acute sensations with no apparent cause such as pain, heat, cold or touch. Usually identified when informed by the patient during physical examination.

- Ptosis: Flaccidity and sagging of the breast, usually identifiable by inspection.
- Rash: a rash or efflorescence on the skin.
- Implant rupture: a hole or tear in the implant housing that allows the implant filling material, its contents, to escape from the housing. The ruptures may be intracapsular (within the capsule of the scar tissue surrounding the implant) or extracapsular (outside the scar tissue around the implant).
- Seroma: Similar to a hematoma, it occurs when the aqueous portion of blood is collected around a surgical incision or around a breast implant. Depending on its size and extent it may be identified on the physical examination, and additionally on the image (e.g. tomography, MR or US).

In case of reoperation, the frequencies of the reasons that led to reoperation within each initial indication will be studied, mainly if the reoperation was motivated by cosmetic / cosmetic reasons or not. In case of explantation, the following aspects will be investigated: (1) indication for explantation, (2) which adverse events were involved that culminated in the indication of explantation, (3) clinically relevant observations at the time of explantation (e.g. appearance of the capsule, gross defects, general conditions of the implants, etc), (5) discolouration and amount of extrusion content, (6) presence and extent of rupture, seroma, hematoma, inflammation or ALCL, (7) condition and appearance of the capsule. Silimed® will gather the information available from each explanation and will perform the procedures of analysis of removed implants.

For some selected adverse events (most frequent), the risk of recurrence of the same adjusted / stratified events by the type of treatment of the first event will be estimated. The most frequent events that need treatment are expected to be capsular contracture. The capsular contractures will be classified according to Baker's classification that considers whether the implant was for primary augmentation or for reconstruction. [31,32]

*Table. Baker's classification for capsular contracture after breast augmentation surgery.*

Class 1	Absolutely natural breasts. No one notices that there was an increase of the breasts.
Class 2	Minimal contraction. It is possible to note that surgery was performed, but

	patient does not present complaints.
Class 3	Moderate contracture: Patient notices hardening.
Class 4	Evident contracture. Apparent only by observation.

### **5.5.1 Monitoring of adverse events**

During the study (which begins when free and informed consent is signed), the investigator should monitor each participant for any occurrence of any adverse event (AE). An adverse event (AE) is defined as any unfavorable medical occurrence, unintentional harm, injury or undesirable clinical signs (including abnormal laboratory findings) in research participants, whether or not related to the medical device under investigation. Events related to the procedures involved (any procedure in the clinical investigation protocol) are also considered as AE. [33] All events that occur after the signing of the WICF must be registered in the proper AE form.

An AE may be a signal, a symptom, a complementary test with an abnormal or unexpected result for that participant. Any worsening of pre-existing conditions or new disease or syndrome should be recorded on an AE form. The nature of AE, starting date, duration, intensity, need for treatment, classification of causality, possible alternative etiologies, AE outcome, etc. along with the codifications of affected event and system are required information on the forms of AE for a better understanding and interpretation of the events.

The AEs should be actively investigated, i.e. the investigator should inquire into all AE assessments that have occurred in the period since the previous evaluation, and the investigator should not expect the participant to spontaneously report any such event. The active approach is particularly true for the expected AEs. For this purpose, a specific form for registration, follow-up and closure of each adverse event in this investigation will be developed. Each AE must be completed in the form. This means that a participant may have one or more AE forms completed in a same medical evaluation, corresponding to distinct events that may have different classifications, follow-ups, and behaviors. If the participant seeks medical assistance between scheduled visits due to an AE, the investigator must proceed with appropriate medical care, record the AE on a new form (in the case of a new AE) or complete data on an AE form in progress (in the case of one not yet closed). Therefore, clinical follow-up, registration on the AE forms should not be restricted to scheduled visits. When, during the visits scheduled for the period under evaluation, no AE has occurred, the non-occurrence of AE (negative notification) should be recorded.

Every new AE record or update of an AE in progress must be updated in the database within 72 hours (except those AEs classified as severe that should be reported / updated within 24 hours), even if the event still requires monitoring and the form still needs to be updated for later closure. The investigator will follow all AEs until clinical resolution. At the end of the follow-up, the form and database should be updated one last time for information on how EA has progressed and how it has been resolved.

Some codifications will be used in the AE record for regulatory and comparison purposes. The nomenclature of AE will be according to the MedDRA dictionary (<https://www.meddra.org/how-to-use/support-documentation/portuguese>).

All AEs should be classified according to intensity as described in the qualifying intensity gradation for health conditions (WHO) [33]:

<u>Grade 1 (Light):</u>	A problem is present less than 25% of the time, with an intensity that a person can tolerate and that rarely occurs in the last 30 days.
<u>Grade 2 (Moderate):</u>	It means that a problem that is present less than 50% of the time, with an intensity that interferes in the day to day of people and that happens occasionally in the last 30 days.
<u>Grade 3 (Severe):</u>	It means that a problem that is present in more than 50% of the time, with an intensity that partially alters the day-to-day of people and that happens frequently in the last 30 days.
<u>Grade 4 (Complete impairment):</u>	It means that a problem that is present in more than 95% of the time, with an intensity that completely changes the person's day-to-day life and that occurs every day in the last 30 days.
<u>Non-specified</u>	It means that there is not enough information to specify the intensity.
<u>Non-specified</u>	It means that it is inappropriate to use a gradation (e.g., menstrual functions).

The investigator will use the following WHO-UMC criteria to classify the AE for causality by always having breast implants as the cause of interest [33]:

<u>Certain / Definite:</u>	Event or alteration (abnormal) in a laboratory examination with a plausible temporal relation to the administration of the intervention; It cannot be explained by disease or other intervention or medication; Response to discontinuation or plausible withdrawal (pharmacologically, pathologically);
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	An event defined pharmacologically or phenomenologically (i.e., an objective and specific disorder or a pharmacologically recognized phenomenon); Satisfactory re-exposure, if necessary.
<u>Likely:</u>	Event or abnormal (abnormal) examination in a laboratory with a reasonable temporal relation to the administration of the intervention; Unlikely to be attributed to a disease or other intervention, medicine; Response to discontinuation or clinically reasonable withdrawal; Reexamination not required.
<u>Possible:</u>	Event or alteration (abnormal) in a laboratory examination with a reasonable temporal relation to the administration of the intervention; It can also be explained by illness or other interventions, medications; Information about withdrawal or discontinuation of treatment may be lacking or obscure.
<u>Unlikely:</u>	Event or alteration (abnormal) in laboratory examination that in relation to the moment of administration of the intervention makes an unlikely relationship (but not impossible); Sickness or other treatments subsidize plausible explanations.
<u>Conditional / Unclassified</u>	Event or alteration (abnormal) in laboratory examination; More data is needed for an appropriate assessment, or; Additional data under investigation.
<u>Not accessible or unclassifiable</u>	The narrative of the report suggests an adverse reaction; It cannot be classified because the information is insufficient or contradictory; Data cannot be supplemented or verified.

Events should be considered serious adverse events (SAE) when they result in any of the following outcomes:

- a) Death;
- b) Potentially fatal adverse event (one which, in the notifier's opinion, puts the individual at immediate risk of death due to the happened adverse event);
- c) Disability / Persistent or significant disability;
- d) Requires hospitalization of the patient or prolongs hospitalization;
- e) Congenital anomaly or birth defect;
- f) Any suspicion of transmission of infectious agent by means of a medical device;
- g) Clinically significant event.

SAEs should also be considered to be deficiencies in devices that could have led to a serious adverse event if (a) appropriate measures had not been taken or (b) the intervention had not been done or (c) if circumstances had been less favorable. These are addressed under the system for reporting serious adverse events.

Finally, when a planned hospitalization occurs for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration, is not considered a serious adverse event.

All SAE events must be registered and notified to the sponsor within 24 hours. Unexpected SAEs classified as possible, probable or defined should be notified to the IRB/IEC and ANVISA by the sponsor. All events will be included in a periodic report for ANVISA and IRB/IEC system.

#### **5.5.2 Monitoring of Adverse Events with "diaries"**

As the visit plan has considerable time intervals between visits after the second half of the deployment, participants will be given a diary where they can briefly describe an event, with the dates and arrangements that were made for each event. Suppose there is an event in which the participant visits another health professional, or does not seek any health professional because it considers that the AE does not need medical attention, the event may be registered by the participant and later verified by the investigator (or his/her delegate) with greater reliability.

The diary will have a purpose of physical memory of the event for the participant. The investigator (or any member of the team delegated by him / her) shall properly investigate the AEs recorded in the diary, together with reports, records or medical prescriptions related to that event, and record them properly on the appropriate form and on the database within the stipulated timeframes from perception of the AE.

The requested data of the diary are in an easy and accessible language for better understanding and completion of the participants. The investigator must guide the participant that it should be filled out, regardless of whether or not there was any adverse event (negative notification). If the participants have any AE (sign, symptom or medical event), even if there is no potential relation to the surgery or implant, it should be recorded in the diary. In each visit, a new diary will be given to the participants and the participants will be guided as to the correct way to fill out. The completed diary must be delivered to the Study doctor on the subsequent visit. The journals should be reviewed to confirm that all fields are complete and filled out correctly. The recorded data needs to be legible and with clear and concise information. The journals will be archived at

participating centers and may be reviewed later by monitors.

If there is any AE in the diary, it should also be recorded in the respective medical record and additional information collected pertinent to its classification and resolution. Following the rationale of events ascertained in medical evaluations, events from the diary will also follow event nomenclature coding according to the MedDRA dictionary (<https://www.meddra.org/how-to-use/support-documentation/portuguese>). Participants should be oriented to immediately communicate to the study coordinators and / or investigators any and all SAE, as such events need to be reported to the Research Ethics Committee and ANVISA.

## **5.6 Secondary outcomes**

### **5.6.1 Rosenberg self-esteem scale**

In order to evaluate the overall self-esteem of the sample of this study, we will use the “Rosenberg Self-Esteem Scale” (RSES), translated and adapted to Portuguese.[34] This scale was initially developed by Rosenberg (1965) and results from a modification of Gutman's original scale (1953), in an attempt to achieve a one-dimensional measure of global self-esteem. This scale consists of ten items, of which five are positive and five are negative, however they are not presented consecutively to reduce the risk of targeted response and, in order not to induce the individual during filling. For each statement there are four possible answers: 1 - I agree completely; 2 - I agree; 3 - I disagree; 4 - I strongly disagree. For items 1, 2, 4, 6 and 7 (self-confidence) the score is as follows: I completely agree = 4, I agree = 3, I disagree = 2 and I strongly disagree = 1. Regarding items 3, 5, 9, and 10 (self-depreciation) the score is as follows: I completely agree = 1, I agree = 2, I disagree = 3 and I strongly disagree = 4. In order to obtain the total value relative to the global self-esteem, the sum of the values obtained in each of the items is added. The amplitude of the total scale value varies between 10 and 40 points. The higher the final result obtained, the higher the overall self-esteem of each individual and vice versa. The global self-esteem scale with values closer to 40 is a reflection of an individual who feels good, that is, he/she feels equal to others, not necessarily superior to others, reflecting a global assessment of the individual about himself own. Still, this scale adapts to the notion of multidimensionality of self-esteem and to the hierarchical structure defended in the present time.

1. De uma forma geral (apesar de tudo), estou satisfeito(a) comigo mesmo(a).
2. Às vezes, eu acho que eu não sirvo para nada (desqualificado(a) ou inferior em relação aos outros).
3. Eu sinto que eu tenho um tanto (um número) de boas qualidades.
4. Eu sou capaz de fazer coisas tão bem quanto a maioria das outras pessoas (desde que me ensinadas).
5. Não sinto satisfação nas coisas que realizei. Eu sinto que não tenho muito do que me orgulhar.
6. Às vezes, eu realmente me sinto inútil (incapaz de fazer as coisas).
7. Eu sinto que sou uma pessoa de valor, pelo menos num plano igual (num mesmo nível) às outras pessoas.
8. Não me dou o devido valor. Gostaria de ter mais respeito por mim mesmo(a).
9. Quase sempre eu estou inclinado(a) a achar que sou um(a) fracassado(a).
10. Eu tenho uma atitude positiva (pensamentos, atos e sentimentos positivos) em relação a mim mesmo(a).

**Opções de Respostas:**

- |                        |                        |
|------------------------|------------------------|
| a) Concordo plenamente | b) Concordo            |
| c) Discordo            | d) Discordo plenamente |

**Afirmativas 1, 3, 4, 7, 10**

- |   |                        |
|---|------------------------|
| 0 | a) Concordo plenamente |
| 1 | b) Concordo            |
| 2 | c) Discordo            |
| 3 | d) Discordo plenamente |

**Afirmativas 2, 5, 6, 8, 9**

- |   |                        |
|---|------------------------|
| 3 | a) Concordo plenamente |
| 2 | b) Concordo            |
| 1 | c) Discordo            |
| 0 | d) Discordo plenamente |

**5.6.2 Breast Evaluation Questionnaire (BEQ-Brazil)**

The Breast Evaluation Questionnaire (BEQ 55) was developed in 2006 in the English language and includes 55 questions related to satisfaction and comfort with the overall appearance of the breasts. In 2013, the BEQ was validated cross-culturally for use in the Portuguese language. [35]

BEQ 55 is a self-administered questionnaire of 55 questions developed to evaluate breast satisfaction and changes in quality of life in patients undergoing breast surgery. The answers are given in scales with five ranks, with 1 corresponding to very dissatisfied or very uncomfortable and 5, to very satisfied or very comfortable. It consists of three parts. The first part questions the satisfaction with size, shape and firmness of the breasts in different situations: sexual, social or professional activities. The second part checks for the degree of comfort with the overall appearance or appearance of the breasts when fully clothed, in bathing suits or naked, being alone, with intimate partner, with men in general, women in their relationship, not so intimate or professional women of health. The third part contains two questions, the first requesting to give the level of satisfaction with the appearance of the breasts to themselves, their partner, parents, siblings and friends. The final question asks to rate how important the size of your breasts are to yourself and the people in your relationship.

### QUESTIONÁRIO DE AVALIAÇÃO DAS MAMAS (BEQ 55)

À paciente: Anote o número mais adequado para sua resposta. Use uma única alternativa por resposta. Favor responder todas as perguntas. Não deixe nenhum item em branco.

#### 1. Qual é o seu grau de satisfação com cada um dos seguintes itens?

Por favor, avalie as questões preenchendo o número conforme a escala abaixo:

- 1 = Muito Insatisfeita
- 2 = Um Pouco Insatisfeita
- 3 = Nem Satisfeita Nem Insatisfeita
- 4 = Razoavelmente Satisfeita
- 5 = Muito Satisfeita

#### Com o tamanho das suas mamas?

Durante atividades íntimas ou sexuais \_\_\_\_\_  
Durante atividades sociais ou de lazer \_\_\_\_\_  
Durante atividades profissionais ou de trabalho \_\_\_\_\_

#### Com o formato das suas mamas?

Durante atividades íntimas ou sexuais \_\_\_\_\_  
Durante atividades sociais ou de lazer \_\_\_\_\_  
Durante atividades profissionais ou de trabalho \_\_\_\_\_

#### Com a firmeza das suas mamas?

Durante atividades íntimas ou sexuais \_\_\_\_\_  
Durante atividades sociais ou de lazer \_\_\_\_\_  
Durante atividades profissionais ou de trabalho \_\_\_\_\_

#### 2. Como você se sente quanto ao conforto ou desconforto em cada um dos seguintes itens, estando sozinha, com seu namorado ou parceiro íntimo, com outras mulheres de seu relacionamento (família ou amigas), com homens em geral, com mulheres menos íntimas (academia ou vestiário) ou com profissionais da saúde (médicos ou enfermeiras)?

Por favor, avalie as questões preenchendo o número conforme a escala abaixo:

- 1 = Muito Desconfortável
- 2 = Um Pouco Desconfortável
- 3 = Nem Confortável Nem Desconfortável
- 4 = Razoavelmente Confortável
- 5 = Muito Confortável

#### Quanto à sua aparência geral (corpo todo) quando está totalmente vestida?

Sozinha \_\_\_\_\_  
Com seu marido ou parceiro \_\_\_\_\_  
Com homens em geral \_\_\_\_\_  
Com mulheres do seu relacionamento \_\_\_\_\_  
Com mulheres menos íntimas \_\_\_\_\_  
Com profissionais da saúde \_\_\_\_\_

#### Quanto à sua aparência geral (corpo todo) de maiô ou biquíni?

Sozinha \_\_\_\_\_  
Com seu marido ou parceiro \_\_\_\_\_  
Com homens em geral \_\_\_\_\_  
Com mulheres do seu relacionamento \_\_\_\_\_  
Com mulheres menos íntimas \_\_\_\_\_  
Com profissionais da saúde \_\_\_\_\_

#### Quanto à sua aparência geral (corpo todo) despida (sem roupas)?

Sozinha \_\_\_\_\_  
Com seu marido ou parceiro \_\_\_\_\_

Com homens em geral \_\_\_\_\_  
Com mulheres do seu relacionamento \_\_\_\_\_  
Com mulheres menos íntimas \_\_\_\_\_  
Com profissionais da saúde \_\_\_\_\_

#### Quanto à aparência de suas mamas quando totalmente vestida?

Sozinha \_\_\_\_\_  
Com seu marido ou parceiro \_\_\_\_\_  
Com homens em geral \_\_\_\_\_  
Com mulheres do seu relacionamento \_\_\_\_\_  
Com mulheres menos íntimas \_\_\_\_\_  
Com profissionais da saúde \_\_\_\_\_

#### Quanto à aparência de suas mamas quando está de maiô ou biquíni?

Sozinha \_\_\_\_\_  
Com seu marido ou parceiro \_\_\_\_\_  
Com homens em geral \_\_\_\_\_  
Com mulheres do seu relacionamento \_\_\_\_\_  
Com mulheres menos íntimas \_\_\_\_\_  
Com profissionais da saúde \_\_\_\_\_

#### Quanto à aparência de suas mamas quando está despida (sem roupas)?

Sozinha \_\_\_\_\_  
Com seu marido ou parceiro \_\_\_\_\_  
Com homens em geral \_\_\_\_\_  
Com mulheres do seu relacionamento \_\_\_\_\_  
Com mulheres menos íntimas \_\_\_\_\_  
Com profissionais da saúde \_\_\_\_\_

#### 3. Você e as pessoas ligadas a você estão satisfeitas com a aparência (visual) das suas mamas?

Por favor, avalie as questões preenchendo o número conforme a escala abaixo:

- 1 = Muito Insatisfeito(a)
- 2 = Um Pouco Insatisfeito(a)
- 3 = Nem Satisfeito(a) Nem Insatisfeito(a)
- 4 = Razoavelmente Satisfeito(a)
- 5 = Muito Satisfeito(a)

Para você mesma \_\_\_\_\_  
Para seu marido ou parceiro sexual \_\_\_\_\_  
Mãe ou pai (aquele que você considera mais a opinião) \_\_\_\_\_  
Irmã(s, o, os) (aquele que você considera mais a opinião) \_\_\_\_\_  
Amigo(a, os, as) (aquele que você considera mais a opinião) \_\_\_\_\_

#### 4. Você e as pessoas ligadas a você dão importância ao tamanho das suas mamas (reparam)?

Por favor, avalie as questões preenchendo o número conforme a escala abaixo:

- 1 = Totalmente Sem Importância
- 2 = Pouco Importante
- 3 = Nem Importante Nem Sem Importância
- 4 = Razoavelmente Importante
- 5 = Muito Importante

Para você mesma \_\_\_\_\_  
Para seu marido ou parceiro sexual \_\_\_\_\_  
Mãe ou pai (aquele que você considera mais a opinião) \_\_\_\_\_  
Irmã(s, o, os) (aquele que você considera mais a opinião) \_\_\_\_\_  
Amigo(a, os, as) (aquele que você considera mais a opinião) \_\_\_\_\_

### 5.6.3 Satisfaction evaluation

Satisfaction regarding the aesthetic result of the surgery is evaluated by both the participant and the evaluating physician in all the on-site visits planned in the follow-up. To measure satisfaction, a Likert scale will be used where the following satisfaction options can be selected: 1 = definitely satisfied, 2 = satisfied, 3 = slightly satisfied, 4 = slightly dissatisfied and 5 = definitely unsatisfied.

### **5.7 Allocation for treatment**

As this study is being characterized as phase 4, and participants are being included after implantation, the allocation of the participant to a type of implant will be performed by the participant's attending physician according to his/her technical judgment considering the reasons for the implantation and clinical characteristics involved in each case, without sponsor interference. There will be no restriction on the shape or size of the implant.

### **5.8 Masking / Blinding**

There will be no masking / blinding

### **5.9 Statistical analysis plan**

The statistical analysis will be divided into two parts, one descriptive and one analytical. The descriptive part will consist of showing counts and fractions of categorical variables and central tendencies (mean + standard deviation or median + interquartile range) of continuous variables recorded at the beginning of the follow-up by the groups of major interest. The groups of major interest are formed by the indication of implantation and the type of implant (primary augmentation with textured surface implant, primary augmentation with polyurethane foam-coated surface implant). In addition, for the purpose of exploring heterogeneity this approach will also be done by participant center.

The initial statistical analysis for the analytical part is to estimate the risks (cumulative probabilities up to a follow-up time) and their respective confidence intervals of unwanted (expected and not expected) events in general and interest-specific ones (e.g. capsular contracture in the textured implants group, in the polyurethane implants group, mild events, serious events, events with probable causality, etc.), as well as events of different intensities (mild, moderate, severe, etc.). The accumulated risks up to the first events in the period of interest will be estimated through the Kaplan-Meier estimator. This analysis should consider the patient as an observation unit, and then the same approach will consider the breast as an observation unit.

The incidence density estimate (incidence rate = (number of events / person-year) x 100)

over a period of time, accumulated from the beginning of the follow-up and decomposed by the year of follow-up, will have the same rationale as the risk estimate, in the same patient groups and types of events, and will disregard the difference between incidence and recurrence of events as well as the period in which the participants were not at risk. This approach will allow estimating the incidence over a cumulative period (e.g. from the beginning of the follow-up) as well as decomposing the incidence into different periods (e.g. incidence in the second or third year of follow-up). In the same way as the previous approach, this analysis will consider a volunteer as an observation unit, then the same approach will consider a breast as the unit of observation.

The additional strategy for estimating the "hazard" for each of the most significant adverse events is to use a multiple model that allows the adjustment of each group's "hazard" for each event of major interest in the follow-up period by elements that could modify the prognosis of the volunteers or confuse the "hazard" estimate. These elements are described above in the section on "descriptive characteristics that could interfere with the prognosis".

Secondary outcomes, related to the desired effect of implants, that will be measured as continuous scales will be analyzed as trajectories over time. To this purpose, the individual crude trajectories of each participant will be verified, then the means / medians and their respective confidence intervals will be estimated at each follow-up time, and finally the marginal trajectories adjusted for correlation of each group (formed by each type of implant - textured and polyurethane) will be estimated, always having the follow - up time as a predictor.

#### **5.10 Minimum sample size**

The minimum sample size was estimated considering the variations of safety outcomes considered clinically relevant in the primary breast augmentation groups in different studies with a 3-year follow-up. It would be interesting to consider event risk estimates over 10 years because of the study follow-up plan. However, the risks available in the literature are rarely reported in 10 years or it is not possible to be sure that all volunteers have been followed for 10 years or more. It was possible to find only one study with a 9-year accumulated risk assessment with Silimed® products [36], which indicates that the risks of implant rupture are 4.3% and 1.2%, that the capsular contracture risks are 12,0% and 14.4%, that the risks of removal of the implant were 13.9% and 36.4%, and that the risks of any reoperation were 22.2% and 47.9%, always in the primary augmentation and primary reconstruction groups respectively. In this way, we also considered the

risk accumulated in 3 years of previous studies that were used to register similar products and that the risks between the implant types are equivalent.

The events considered relevant were: need for reoperation for any reason, removal of the implant without replacement, removal of the implant with replacement, capsular contraction grade III or IV and implant rupture initially having a study of 3 years of follow-up and as a measure of interest to be estimated at a given time event, in the example of 3 years of follow-up. We used the epiDisplay package of R-project software that has a function with a formula that indicates the probability of the event of interest in the population and the formula returns the minimum sample size (N). [37] In addition, we determined the additional arguments of the formula, which are the population size for which the results would be inferred as infinity, the significance as 5%, and the difference between the estimated probability and one of the limits of the confidence interval (accuracy) as follows: if the probability to be estimated between 0.30 and 0.70, the desired accuracy = 0.1; If the probability is between 0.10 and 0.30, or between 0.70 and 0.90, the desired accuracy would be = 0.05; If the probability to be estimated is less than 0.10 or greater than 0.90, the desired accuracy would be half the probability or half of the probability respectively.

With the reoperation as a result, it was decided that the probability to be estimated could vary between 10% and 18%, which would lead to a minimum sample N of 138 to 227 volunteers. Still in the same group having as an outcome the removal of the implant without replacement, it was decided that the probability to be estimated could vary between 0.5% and 3% which would take the minimum sample N between 3099 and 558. For the implant removal outcome with replacement, it was judged that the probability to be estimated could range from 5% to 25% by making the minimum sample N vary between 81 and 753 still in the primary augmentation group. As for the capsular contracture outcome, it was estimated that the probability to be estimated could vary between 2% and 10%, making the minimum sample N vary between 138 and 753.

Considering that the study will follow a larger follow-up than the example above, and that the risk of these events will accumulate, and that the highest and lowest risk of events observed in 9 years were respectively 1.2% and 47.9 % [36], the minimum sizes for desired accuracy in the primary augmentation groups would be 246 volunteers, that is, 246 volunteers in the textured implant group and other 246 in the polyurethane implant group. Finally, if we consider a loss of follow-up of 40% over 10 years, the total sample size should be increased from 492 to 700 (proportionally distributed between the 2 groups). In conclusion, a sample of 350 volunteers in the textured implant group and another 350 in the polyurethane implant group.

### **5.11 Intermediate analysis**

Intermediate analyzes with generation of progress reports should always occur once a year, throughout the duration of the study, in the month following the first recruitment. Interim reviews shall consist of the same analyzes provided for in the analysis plan for the final report unless the number of participants included up to the time specified in the report does not allow this. At first, as the study is not randomized and interventions are already recorded for routine clinical use, as well as there is a greater interest in long-term safety-related events, there is no intention of early interruption of the study as a whole for safety reasons or benefit evident between the different implants to be studied. However, there is a need to indicate in the interim reports whether or not there are differences in the rates of safety-related events between participating centers that merit greater attention from the sponsor and possible need for corrective measures.

### **5.12 Quality criteria for data management and periodic reports.**

Data quality should be verified in a stratified form, and the following indicators are considered as minimum elements, including quality indicators.

1. Total number of participants since the beginning of the recruitment, and number of participants in the previous 30 days.
2. Number (fractions) of visits made within the windows provided from the beginning and in the last 30 days.
3. Number (fractions) of fields with missing or inconsistent data.
4. Number (fraction) of CRFs finalized up to 3 business days after the end of the visit window from the beginning of the study and in the last 30 days.
5. Number (fractions) of adverse events not closed up to 6 months after initial event record.
6. Number (fraction) of adverse events, serious adverse events and grade 3, grade 4 or unclassifiable from the start of the study and the last 3 days.

## **6. Procedures of the study**

### **6.1 Instruments of data collection**

- ICF

- Participant information form
- Inclusion and exclusion criteria form
- Socio-demographic data form
- Vital signs form
- Surgical procedure form
- Rosenberg self-esteem scale and patient satisfaction
- Form of satisfaction of the evaluator as to the aesthetic result
- BEQ - Brazil
- Extra visit form
- Telephone contact form
- Medical history form
- Concomitant medication supplement
- Adverse event forms
- Diary of Adverse Events
- Protocol deviation form
- Study completion form

## **6.2 Selection of participants and strategies for recruitment**

Female adults will be approached and invited to participate in the study. Subsequently they will be included, respecting the eligibility criteria. There will be a host interview in which the objectives of the study, the necessary procedures (visits, possibilities of not meeting the eligibility criteria, etc.), the periodicity, duration, benefits and risks of the study will be presented. The Informed Consent Form (ICF) will also be read and discussed. Those who agree to participate must sign the ICF in two copies, one way will be filed at the institution and another copie will be delivered to the study participant. The interviewer, as representative of the team responsible for the Project, should also sign, at the same time, the two copies of the ICF.

All promotional material of the study for recruitment of participants must be approved by the Ethics Committee.

After signing the ICF, we will proceed to the clinical evaluation of all participants as part of the eligibility analysis process of the likely participants.





etc.)																				
Scheduling of the next visit	x	x	x	x		x		x		x		x		x		x		x		x

**6.4.2 Clinical files (CRF) per visit and visit windows.**

<p>Visit 1: up to 14 days after implantation</p>	<p>ICF          FORM 01 - Identification of participants          FORM 02 - Inclusion and Exclusion Criteria          FORM 03 - Date of Visit / Surgery          FORM 05 - Socio-demographic data          FORM 06 - Vital Signs          FORM 07 - Surgical Procedures          FORM 08 - Rosenberg self-esteem scale and patient satisfaction          FORM 09 - Evaluator's satisfaction regarding aesthetic outcome          FORM 10 - BEQ - Brazil          FORM 11 - Questions</p>
<p>Visit 2: 60 days after implantation (window of + or - 30 days )</p>	<p>FORM 04 - Date of visit          FORM 08 - Rosenberg self-esteem scale and patient satisfaction          FORM 09 - Evaluator's satisfaction rearding the aesthetic result          FORM 10 - BEQ - Brazil          FORM 11 - Questions</p>

Visit 3: 180 days after implantation (window of + or - 30 days)	FORM 04 - Date of visit FORM 08 - Rosemberg self-esteem scale and patient satisfaction FORM 09 - Evaluator's satisfaction rearding the aesthetic result FORM 10 - BEQ - Brazil FORM 11 - Questions
Visit 4: 365 days after implantation (window of + or - 30 days))	FORM 04 - Date of visit FORM 08 - Rosemberg self-esteem scale and patient satisfaction FORM 09 - Evaluator's satisfaction rearding the aesthetic result FORM 10 - BEQ - Brazil FORM 11 - Questions
Visits 4t, 5t, 6t, 7t, 8t, 9t, 10t, 11t, 12t: 1,5; 2.5; 3.5; 4,5; 5.5; 6.5; 7.5; 8.5; 9.5 years after inclusion (window of + or - 60 days)	FORM 13- Telephone Contact
Visits 5, 6, 7, 8, 9, 10, 11 and 12: 2, 3, 4, 5, 6, 7, 8, 9 years after inclusion (window of + or - 60 days)	FORM 04 - Date of visit FORM 08 - Rosemberg self-esteem scale and patient satisfaction FORM 09 - Evaluator's satisfaction rearding the aesthetic result FORM 10 - BEQ - Brazil FORM 11 - Questions
Visit 13 – Final Visit: 10 years after implantation (window of + or - 60 days) / Early withdrawal	FORM 04 - Date of visit FORM 08 - Rosemberg self-esteem scale and patient satisfaction FORM 09 - Evaluator's satisfaction rearding the aesthetic result FORM 10 - BEQ - Brazil FORM 11 - Questions FORM 17 - End of study
Extra Visit	FORM 11 - Extra visit

Conditional	FORM 14 - Medical History FORM 15 - Concomitant Medication FORM 16 - Adverse Event FORM 17 - End of study FORM 18 - Deviation
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The procedures for each data collection file can be performed on different dates as long as they are performed within the specified window of each visit.

**Visit 1:** The following procedures will be performed - 4 days after implantation (window of + or - 7 days):

- Identification of potential research participants
- Reception interview.
- Reading, acceptance and signature of the Informed Consent Form (ICF).
- Completion of the Research Inclusion Questionnaire (QIP).
- Completion of clinical history and complete physical examination.
- Completion of the adverse event form, referring to the period between surgery and inclusion.
- Application of patient's and evaluator's quality of life and satisfaction questionnaires.
- Delivery of the adverse event diary and guidance on its use and completion.
- Scheduling the return to the research center, 60 days after implantation.

**Visit 2:** The following procedures will be performed – 60 days after implantation (window of + or - 30 days)

- Return of adverse event diary and evaluation of completion.
- Complete physical examination by the physician.
- Assessment and guidance on possible adverse events and conduct.
- Application of patient's and evaluator's quality of life and satisfaction questionnaires.
- Delivery of the adverse event diary and guidance on its use and completion.
- Scheduling the return to the research center, 180 days after implantation.

**Visit 3:** The following procedures will be performed – 180 days after implantation (window of + or - 30 days)

- Return of adverse event diary and evaluation of completion.
- Complete physical examination by the physician.
- Evaluation and guidance on possible adverse events and conduct.
- Application of patient's and evaluator's quality of life and satisfaction questionnaires.
- Delivery of the adverse event diary and guidance on its use and completion.
- Scheduling the return to the research center, 365 days after deployment.

**Visit 4:** The following procedures will be performed – 365 days after implantation (window of + or - 30 days)

- Return of adverse event diary and evaluation of completion.
- Complete physical examination by the physician.
- Application of patient's and evaluator's quality of life and satisfaction questionnaires.
- Evaluation and guidance on possible adverse events and conduct.
- Delivery of the adverse event diary and guidance on its use and completion.
- Scheduling the return to the research center, 365 days after deployment.

**Visit 5, 6, 7, 8, 9, 10, 11, and 12:** The following procedures will be performed – 2, 3, 4, 5, 6, 7, 8, 9 years after implantation (window of + or - 60 days)

- Return of adverse event diary and evaluation of completion.
- Complete physical examination by the physician.
- Application of patient's and evaluator's quality of life and satisfaction questionnaires.
- Evaluation and guidance on possible adverse events and conduct.
- Delivery of the adverse event diary and guidance on its use and completion.
- Scheduling the return to the research center, 360 days after deployment.

**Visits 4t, 5t, 6t, 7t, 8t, 9t, 10t, 11t, 12t:** The following procedures will be performed (window of + or - 60 days)

- Guidance on possible adverse events and conduct.
- Guidance on using and completing the adverse event diary.
- Confirmation and reinforcement of the return to the research center on the scheduled dates.

**Final visit 13:** The following procedures will be performed – 3650 days after implantation (window of + or - 60 days) Final visit / Early withdrawal

- Return of adverse event diary and assessment of completion.
- Complete physical examination by the physician.
- Guidance on possible adverse events and conduct.
- Orientation regarding the procedures of ending of study.

## **Discontinuation**

### **Discontinuation of participants**

Participation of the volunteer in the study may be discontinued at any time, at the discretion of the investigator/sponsor and by decision of the participant. If study participation is discontinued, all outcome data should be collected in accordance with the study procedures schedule. The sponsor will be notified of all cases of withdrawal or interruption of participant.

The reasons why the investigator or sponsor may withdraw a study participant include the following:

- AE, which according to the Principal Investigator's judgment, renders participation in the study unsafe for the participant.
- Severe protocol violation.
- Study closure by sponsor.
- Withdrawal of consent (option of participant).
- Removal or replacement of breast implants even if requested by the participant.
- Other aesthetic interventions in the breasts.
- Participation in another clinical investigation with experimental intervention.
- Events that compromise cognition or ability to understand in a persistently or permanently way, (e.g. Alzheimer's disease, stroke, or traumatic brain injury), in a way that impedes the provision of reliable data regarding follow-up.
- Loss of follow-up of the participant, defined as non-attendance in face-to-face evaluations for a period equal to or greater than two years, or two windows of face-to-face visits after the first year of follow-up.

Any participant (or his/her legal representative) may withdraw consent to participate in the study at any time, without prejudice to the participant. The investigator will need to withdraw any participant requesting withdrawal from the study. If a participant withdraws consent, all appropriate outcome and safety assessments at the time of withdrawal of the participant should be obtained if

possible. The evaluations listed in the Study Procedures Schedule for the early termination visit should be performed, as applicable.

Every effort should be made to keep volunteers as participants in the study. If a participant fails to return for scheduled visits, a documented effort must be made to determine the reason. If a participant withdraws before completing the study, the reason for withdrawal should be documented in the CRF.

### **Interruption of the study**

The sponsor reserves the right to discontinue the study at any time and for any reason.

## **7. Control and active search for defaulters**

The forms of contact with the research participants will be agreed during the host interview by the Principal Investigator team. It will be noted in detail the home address, with landmarks; home or contact phone; business address and telephone number; plus another alternate address (close relatives). Two weeks prior to the scheduled return date for visit, the participant will be contacted by telephone in order to remind her. If the participant does not attend the return, the field team will seek to contact through:

- Phone
- Electronic media (email, Whatsapp, and etc)
- Postcard

An allowance is foreseen for the transportation cost of the participant, in order to make attendance possible at the research center. In situations to be agreed upon, the transportation of the participant to the research center may be arranged. The home visits, aiming the search of the participant, will be carried out after the exhaustion of the attempts of telephone contact. A contact management bank will be used for permanent control of appropriate intervals between contacts since the beginning of the study. Each participant will have a personal identification card in the survey that will include the dates scheduled for return and the contact phones of the principal investigator and coordinator of the study. Participants will be asked to communicate, through the telephones indicated, any medical care performed outside the research center.

### **7.1. Strategies for retention of study participants**

At each visit to the study, the participant will have recorded the date and reason for the next visit on his research participation card. Phone calls will be made to confirm the date of the return visits in the study. If the participant misses a visit, the researchers will try to contact them by other possible means (phone contact, for example) using the contact information provided by the participant on the first visit. Such information will be updated at each meeting with the participant at the study site. The need for adherence to the study protocol will be reinforced at each visit. Participants will be entitled to a medical attendance certificate confirming the study visit. In all the visits there will be refund of the displacement of the participant with a predetermined amount.

## **8. Quality control and quality assurance of the study**

### **8.1 Study Coordination**

All members of the Study Coordination participated actively in the creation of this protocol and will be responsible, once the study is approved, for its implementation. The Coordination will meet whenever possible to discuss the progress of the research, listen to the Monitoring reports and make relevant decisions about the conduct of the study. In the event of any serious adverse event reported by the Principal Investigator as related to the medical device, it shall be the responsibility of the members of this coordination to evaluate the temporary suspension of the survey and to communicate, within a maximum of 24 hours, to the members of the IRB/IEC, on the occurrence.

### **8.2 Internal study monitoring group**

A Monitoring team will be set up to ensure that the protocol is followed without deviations, that the rights and well-being of the participants are guaranteed and that the data is generated and collected in a complete and accurate manner. The monitors should be familiar with the products used, the study protocol, the ICF, and any other written information that is provided to the participants.

The monitors should be the main link between the research center and the sponsor. It will be up to the monitor to check if the institutions involved remain in optimal working conditions throughout the study period. Among the functions that will be performed by the monitors, we can

mention, among others, to ensure that the personnel hired to perform the study are always updated in the procedures established in the protocol, ensure that the eligibility criteria are followed without deviations, ensure that the ICF is applied correctly and prior to the inclusion of the participant in the study, verify all data present in forms at the end of each day of study and make the corrections necessary to ensure the veracity of the data collected, ensure that any adverse reactions are reported in the correct way and have the follow-up determined in the protocol and ensure that the most severe or severe adverse reactions are reported to the Ethics Committee. It will also be up to the monitor to control missing data, avoiding to the maximum that this fact occurs due to collection defect. The monitor should report flaws and operational problems in the study, and propose solutions along with the study coordination team.

### **8.3. Quality assurance**

An initiation study visit will be carried out at the research center, viability at the research center. During the initiation visit, the monitor will visit all areas of the research center where study activities will be conducted. He/she will train the Principal Investigator and his/her team in the procedures and protocol requirements, investigator responsibilities, materials handling, logistic and any questions that may arise. The training of the research center staff will be documented so that a copy is kept in the investigator's files and the original must be archived in the study's central archives. The Principal Investigator shall make every effort to be present at the initiation visit. The monitor will generate a report to document the actions taken during the visit.

The Principal Investigator will supervise the activities of the research center staff to ensure compliance with good clinical practice, adherence to the clinical trial protocol, investigator file, handling of the product under investigation as requirement, strictly follow the study procedures, and any local regulations governing human research. The Principal Investigator shall also make any corrections required, as well as implement corrective and preventive actions in his/her research center as instructed by the monitor or auditor in the event of an audit.

To ensure adherence to good clinical practice, lost, unusable or spurious data, or deviations from the protocol or statistical plans, will be explained and analyzed as they are perceived by the research team or statisticians, implementing corrective measures.

## **9. Protecting study participants**

### **9.1 Confidentiality**

The Informed Consent Form ensures the confidentiality of the personal data to the participant.

### **9.2 Risks**

The Informed Consent Form explains to the participant the risks foreseen in the study, and guarantees the participant medical and quality assistance throughout the course of the study. Silimed® shall bear any expenses necessary for medical care of the participant, if they are related to the medical device during the study, if there is a proven causal relationship with the product under investigation.

### **9.3 Benefits.**

By participating in the study, the participant will receive regular medical follow-up from a qualified medical team. In addition, he/she will have the opportunity to contribute in a valuable way to the scientific advancement regarding the safety and efficacy of breast implants, thus helping others who undergo the breast implant procedure in the future

### **9.4 Research Ethics Committee**

The study will only be started at the research center, after its approval by the respective Ethics Committee.

### **9.5 ANVISA**

Likewise, the study will only be initiated after its approval by the National Sanitary Surveillance Agency (Anvisa).

## **10. Good Practices**

The study will follow the standards of Good Clinical Practice, according to ICH / GCP, Document of the Americas and specific legislation of the National Commission of Ethics in Research and

National Agency of Sanitary Surveillance. The medical device was produced following Good Manufacturing Practices and laboratory tests will be conducted according to Good Clinical Laboratory Practice standards.

#### **11. Publications**

The scientific team will write the conclusive report of the study that should be sent to the Ethics Committees and ANVISA. The scientific team will also designate the person responsible for writing a scientific paper for presentation at congresses and / or publication.

#### **12. Record and data management**

The data collection instruments of the study will be elaborated and processed in an electronic clinical record system that will allow the insertion of data in a database, simultaneously by all the participating centers in a hierarchical and organized way. The system is parameterizable by study, fully developed in Portuguese and follows the instructions of RDC 17/2010 of ANVISA and CRF 21 part 11 FDA. The data will be transcribed to the system from a source document, and then monitored by the monitors. Only the research team working on the present study will have access to the stored study data. Documents associating personal data with participant identifiers will be stored in a System protected by login and password management and will only be accessible to the principal investigator, study manager, and data manager.

The names and identities of the participants will be kept confidential by the Principal Investigator and his/her team and by the research monitor. No information will be provided outside the research center without the participant's consent. The data consistency work will be performed in part within the system itself.

#### **13. Expected outcomes**

It is expected from this investigation that Silimed® products are of similar safety or safer than literature data indicate, when compared to the results of the Silimed® products themselves prior to commercialization, or when compared to results of similar products from competing manufacturers. That could elucidate which groups of patients could be at greater risk of adverse events or that allow to discuss in what moments/conditions there could be additional interventions to reduce the known events. In addition, the beneficial effect of the implants is expected to be equivalent to or above a desired measure.

**14.Execution Schedule:**

Activities and indicators of progress	Time				
	2017	2018	2019	2020 to 2028	2029
- Submission of the project to the IRB	X	X			
- Patients Inclusion		X	X*		
- Presentation of the partial analysis of the data collected			X	X	
- Presentation of the final analysis of the data collected					X

\* If the total number of participants is not reached in the year 2018, the recruitment may be extended until the year 2019.

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