Universitat de Girona
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Efficacy of the Delay Procedure prior to Nipple-Sparing Mastectomy

A randomized, controlled, open-label clinical trial

FINAL DEGREE PROJECT

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1. ABBREVATIONS

BSE: Breast-Self-Examination

BPM: Bilateral prophylactic mastectomy

DBR: Delayed-Breast Reconstruction

DIBR: Delayed-Immediate-Breast Reconstruction

DIEP: Deep Inferior Epigastric Perforator

EMA: External Mammary Artery

GCU: Genetic Counselling Unit

HBOC: Hereditary Breast and Ovarian Cancer Syndrome

HRQoL: Health-Related Quality of Life

IBR: Immediate-Breast Reconstruction

ICO: Institut Català d'Oncologia

IGAP: Inferior Gluteal Artery Perforator

IMA: Internal Mammary Artery

MRI: Magnetic Resonance Imaging

MSFN: Mastectomy Skin Flap Necrosis

NAC: Nipple-Areola Complex

NAP: Nipple-Areola preserving

NSM: Nipple-Sparing Mastectomy

NSH: National Health System

OR: Odds ratio

RR: Relative Risk

RRM: Risk-Reduction Mastectomy

SCM: Subcutaneous Mastectomy

SM: Simple Mastectomy

SSM: skin-sparing mastectomy

TRAM: Transverse Rectus Abdominis Myocutaneous

TSSM: Total-skin-sparing Mastectomy

WMA: World Medical Association

YTQ: Years-To-Quitting (smoking)

2. ABSTRACT

Background Breast cancer represents the most recurrent tumor diagnosed and the first cause of death for cancer amongst Spanish women. Within those cases, 10% have a hereditary etiology.

BRCA 1 and BRCA 2 mutations represent the most frequent breast-cancer susceptibility genes, displaying an accumulative risk of presenting breast cancer around 72% and 69% at 80 years old respectively.

Therefore, rigorous screening and primary prevention to this vulnerable population is compulsory in order to reduce its breast cancer incidence. Mastectomy has shown to reduce the risk of breast cancer by at least 90% in women with BRCA 1 and/or BRCA 2 mutations. Nowadays there is a wide range of different mastectomies, standing out increasingly to more conservative procedures such as the skin-sparing mastectomy (SSM) or the nipple-sparing mastectomy (NSM).

Purpose The main purpose of this study is to compare the effectiveness of the Delay procedure prior to the Nipple-Sparing Mastectomy versus the Nipple-Sparing Mastectomy itself in **decreasing rates of necrosis** as a postoperative complication in women with a BRCA mutation who are candidates of Risk-Reduction Mastectomy.

Design A multicenter randomized controlled open-label clinical trial will be carried out in 20 hospitals through different autonomous communities in Spain.

Participants Female carriers of deleterious mutations in either the BRCA1 or BRCA2 gene who wish to undergo a Risk-Reduction Mastectomy in the hospitals included in our study and who do not have an actual or previous breast and/or ovarian cancer.

Interventions Delay Procedure prior to completion Nipple-Sparing Mastectomy versus the Nipple-Sparing Mastectomy itself.

Outcomes Primary outcome will be Skin Ischemia and Necrosis of the NAC and flap mastectomy assessed with *Skin Score from the Mayo Clinic*; secondary outcomes will be Grade of Satisfaction and Aesthetic Outcome with the surgical procedure, Sexual impact, Skin and Nipple Sensation and Quality of Life, assessed with *Breast-Q Questionnaire, Semmes Weinstein Monofilaments test, CSFQ-14-F Questionnaire* and *SF-36 Questionnaire* respectively.

Key words Nipple-Sparing Mastectomy, Delay Procedure, BRCA 1 and BRCA 2 mutation, necrosis rate.

3. INTRODUCTION

3.1: BACKGROUND: BRCA Mutations

3.1.1: Epidemiology of breast cancer in patients with BRCA mutations (Hereditary Breast and Ovarian cancer syndrome)

Breast cancer is considered by far the leading malignant tumor in women worldwide(1,2); it represents 26% of all cancers and is the first and second cause of death in developing and developed countries respectively amongst the female population.

In Spain, according to REDECAN2015(3), breast cancer is the most frequent tumor diagnosed and is placed in an intermediate situation at European level. The highest incidence registered is in Navarra, Tarragona and Girona (2003-2007). Although its mortality has decreased in the last years, it continues to be the first cause of death for cancer in spanish female population.

The incidence of breast cancer increases with age; this factor is the main non-modifiable risk factor, taking an increase in the age of 35 and a stabilization in age 55, which co-occurs with menopause (Table 1). Other modifiable and non-modifiable risk factors to take into account are: hormonal status (estrogen, progesterone, duration of active menstrual cycles), alcoholism and smoking, previous pathology in breast, precocious menarche, late menopause, nulliparity and age older than 30 at first birth, and of course family history of breast cancer.

Table 1. Annual average number of incident cases by age group in Girona. Women, period 2010 – 2012 (CanGir. El cancer a Girona 2010-12. Projeccions de la incidència 2017)(4)

Age	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	Total
Breast Cancer	0	0	0	0	0	2	8	20	36	46	50	41	40	34	28	39	30	32	405

In relation to **breast hereditary cancers**, they represent between 5-10% of all breast tumors. They are attributed to highly penetrant mutation in breast cancer-susceptibility genes; the most common genes affected are **BRCA 1** and **BRCA 2**, two tumor- suppressor genes.

According to Kuchenbaecker et Al. (5), for BRCA 1 and 2 carriers the accumulative risk of presenting breast cancer is situated around 72% and 69% at 80 years old respectively, while

in general population is around 10%. They are also diagnosed of breast cancer earlier and the high risk of developing a second tumor on the contralateral breast is around 5% annually.

- BRCA 1 gene: it consists of 22 coding exons on chromosome 17q21. It represents 45% of hereditary breast cancers and 80-90% of hereditary ovarian cancer. It can also affect other organs such as fallopian tubes or peritoneum, amongst others.
- BRCA 2 gene: it consists of 26 coding exons on chromosome 13q12-13. It represents 35% of hereditary breasts cancer (but has additional risk of breast cancer in men) and has a lower risk of ovarian cancer compared with BRCA 1. Other organs affected can be fallopian tubes, pancreas and occasionally gall bladder or skin (melanoma).

Table 2. Percentage of incidence in sporadic, familiar and hereditary breast cancer (31)

Sporadic breast cancer	65-75%
Familiar breast cancer	20-30%
Hereditary breast cancer ·BRCA1 ·BRCA2 ·p53 ·STK11/LKB1, PTEN, MSH2, ATM	5-10% 45% 35% 1% <1%

A comparative table with its common and different characteristics has been featured as it shows below:

Table 3. Comparative table of characteristics between BRCA1 and BRCA2 mutations.

	BRCA 1 Mutation	**BRCA 2 mutation**
Chromosome affected	22 coding exons on cr 17q21	26 coding exons on cr 13q12
% of all hereditary breast cancers -Breast cancer -Ovarian cancer	45% 80-90%	35% 20%
Risk of cancer carrying the BRCA mutation at 80 y/o -Breast cancer -Ovarian cancer	72% >40%	69% 20%
Risk male gender breast	Low	6%

cancer		
Type of breast tumor	-Ductal carcinoma (75%): Basal subtype, poorly-differentiated high-grade types -Atypical medullar carcinoma (10%)	-Ductal / lobulillar carcinoma: Luminal subtype, well-differentiated
Expression of hormonal receptors	ER/EP – (20%+), HER2-	ER/EP+, HER2-
Clinical characteristics	Early onset age (40-50 y/o) More prevalence on bilateral breast tumors Other cancers in affected subjects: ovarian, colon, prostatic, pancreas tumors. Higher rate of pregnancy-associated breast cancer < 50 y/o.	

3.1.2: Identification of BRCA-mutation carriers

There are several models which provide a woman's risk of breast cancer; the most common used in Spain is the Gail Model; however, in familial-type hereditary cases it underestimates the risk of breast cancer (the onset age is considered late; it also overlooks bilateral cancer on family members and breast cancer in non-first-degree relatives).

Therefore, according to *SEOM (Sociedad Española de Oncología Médica),* there are some clinical-pathological criteria for high risk of hereditary breast and ovarian cancer syndrome based on personal familiar history that medical specialists (particularly in primary care) should keep in mind:

Table 4: Clinical and pathological criteria for high risk of hereditary breast and ovarian cancer syndrome (6).

Number of cases in the family	**Clinical and pathological features**
1	• Breast cancer and Synchronous or Metachronous Ovarian cancer in the same person • Breast cancer diagnosed < age 35 • Bilateral breast cancer, when 1st was diagnosed < age 40 • Triple-negative breast cancer diagnosed before age 50 • High grade of serous-papillary ovarian carcinoma
2	• Bilateral breast cancer + Breast cancer diagnosed < age 50

	• 1 male breast cancer • Breast Cancer + Ovarian Cancer • 2 Breast cancer diagnosed < age 50
>=3	• ≥3 cases of breast cancer and/or ovarian cancer (regardless of age)

Once any family member has been considered to be in a high-risk of carrying a BRCA mutation, derivation to a Genetic Counselling Unit (GCU) has to be provided in order to reaffirm its surmise and assess the patient with educational information of the mutation. It is very important to explain them carefully the aim of their derivation and to provide basic notions of what genetic counselling and test means. Genetic study is then offered if there is a previous informed consent signed by the member affected.

In Catalonia, GCU programs for counselling follow Oncoguia del Consell i Assessorament genetics en el cancer hereditary protocol, which is (7):

1. FIRST VISIT - **Collection of Information**: Explanation of the main objectives of the visit, elaboration of a genealogical tree, explanation of inheritance's role in hereditary predisposition, evaluation of risk perception. It is very important to recommend advising other family members of the possible hereditary predisposition and to encourage them to make a genetic test.
2. SECOND VISIT - **Counselling visit** + **Informed Consent Form**: Health information and education on prevention and screening measures, definition of a care plan according to the risk situation, indication of a genetic test. Information about the possibility of consulting a Psychologist as many times as it is needed.
3. GENETIC TEST - **Blood extraction** by the nurse.
4. THIRD VISIT - **Results**: - Evaluation of the understanding of the results and implications to individual and family members, assessment of psychological impact, definition of a monitoring plan.

3.1.3: Risk-reduction Strategies on patients with BRCA-mutations: PRIMARY PREVENTION

Personalized medicine in a multidisciplinary scene (where patient plays as well a key role in her decision) is indispensable for achieving not only the best result in the prevention scheme but also in her psychosocial background.

Amongst early detection measures and prevention of breast and ovarian cancer in patients with BRCA mutations is included (8,9)

- **Surveillance:**
  - Annually a MRI and a mammography from 25-30 years old. An annual echography can be considered to patients <30 years old if MRI is not available.
  - Transvaginal echography and tumoral marker CA125 every 6-12 months from 35 years.
  - Other studies(10) suggest that bi-annual clinical examination from 25-35 years old and breast self-examination (BSE) from 18 years old are beneficial(11) an can be part of BRCA surveillance, although the effectiveness of BSE is open to debate(12). Nevertheless, *Sociedad Española de Oncología Médica (SEOM)* and the *National Comprehensive Cancer Network (NCCC),* amongst many others, include this practice to the recommended preventive strategies.
- **Prophylactic Surgery**
  - Prophylactic bilateral salpingo-oophorectomy
  - Bilateral prophylactic mastectomy (BPM) or Risk-Reduction Mastectomy (RRM)
- **Prophylactic Chemotherapy with Tamoxifen** (Chemoprevention): there is a controversy with the results published(10); most of them coincide with a reduction of cancer incidence on BRCA2 (ER+), but not BRCA1 (triple-negative)(13). It is important to mention that neither the *European Medicines Agency (EMA)* nor the *Agencia Española del Medicamento y Productos Sanitarios (AEMPS)* collects on the data sheet of tamoxifen or raloxifen the indication for prophylactic chemotherapy on BRCA-mutation carriers.

In this research project we will focus on the different types of **Risk-Reduction Mastectomy** (especially the Nipple-Sparing Mastectomy) that has been used for breast-cancer primary prevention on patients carrying a BRCA-mutation. This risk-reduction surgery has shown(14) a decrease of 90-95% in breast cancer risk; it is considered the most effective risk-reduction strategy in BRCA-mutation patients.

3.1.4: Risk-Reduction Mastectomy (RRM)

Types of Risk-Reduction Mastectomy in BRCA-mutation carriers:

- **Simple Mastectomy (SM):** Also known as radical mastectomy, which the entire breast is removed (>95%, including breast tissue, skin, nipple and areola). It is the surgery recommended on patients with large ptotic breast (D cup +) or those who have more risks of mastectomy flap necrosis.
- **Subcutaneous mastectomy (SCM):** The nipple-areola complex (NAC) is preserved, leaving a risk of residual breast tissue beneath its complex, the axillar tissue and in the skin-flap. Nowadays this procedure is controversial.
- **Nipple-Sparing Mastectomy (NSM) or Total-skin-sparing Mastectomy (TSSM):** Breast tissue is excised while the entire breast skin envelope and NAC are spared, dissecting this NAC as thin as possible while preserving vascularization and removing all breast glandular tissue. It gives a highly aesthetical result although the nipple becomes dysfunctional and sensation is altered.
    - **Delay procedure prior to NSM**: Also known as vascular delay, it consists of creating a surgical wound (separating skin and breast parenchyma) 7-21 days prior to NSM to stimulate vascular hypertrophy, augmentation of collateral flow and opening of choke vessels on breast skin, improving mastectomy flap perfusion and reducing risk of partial or total nipple-flap necrosis when NSM is done in a two-time approach(15–19). It has been used different terms through literature to refer to this procedure, such as Nipple Delay, Surgical Delay of the Nipple-Areolar Complex and Delay Phenomenon; nonetheless, we will only use Delay Procedure in our study to facilitate comprehension and reading.

- **Skin-Sparing Mastectomy (SSM):** NAC is removed along with breast tissue, but no skin is removed. Skin envelope is created by excessing all breast tissue while a thin subcutaneous layer is preserved in order to maintain skin vascularization.

Complications related to Mastectomy(20)

Table 5. Complications related to Mastectomy, separated into immediate side effects and long-term side effects.

Immediate side effects	Long-term side effects
- Hardness (due to scar tissue) formed at the site of incision - Wound infection - Hemorrhage or hematoma - Seroma / drainage of lymphatic fluid (swelling) - Breast pain/tenderness - Linear scar at the site of mastectomy - "Pulling" sensation - Ischemia and necrosis - Disruption of wound, dehiscence - Dermatitis - Post-operative complications: urinary retention, backache, shock (due to anesthesia).	- Phantom breast pain (post-mastectomy breast syndrome) - Aesthetic defects - Psychological effects (See Section 3.1.5: Psychological implications)

If we specify to **NSM**, we find nipple-related complications such as **ISCHEMIA AND NECROSIS OF THE NAC**. Definition and classification of this concept is explained in Section 7.5 Variables: Dependent Variable.

In order to understand why necrosis of the NAC is the major and most feared complication on NSM, we must first comprehend its vascularization. Venous congestion and arterial ingurgitation can be prevented if we study and obtain knowledge of which networks/vessels should be or should be not removed in our intervention, thus reducing significantly this

harmful complication (but we must as well always take into consideration other external factors a part from vascularization that can provoke necrosis).

Vascularization of the NAC:(21–23)

There are 3 levels of breast arterial irrigation which are interconnected between them:

1. Subdermical plexus: composed by cutaneous branches from thoracoacromial, supraescapular and inferior scapular arteries. They irrigate dermis and epidermis. Anastomosis with preglandular plexus is possible thanks to arterioles that follow Cooper's ligaments.
2. Preglandular plexus: Mostly composed by branches from internal mammary artery (IMA) but also branches from external mammary artery (EMA) and communicant arterioles from subdermical plexus that surround the areola comprising a circular network of 5 cm diameter approximately. It is the main responsible of NAC's irrigation, and it is removed in mastectomy surgeries.
3. Retroglandular plexus: Composed by perforant arterioles from III, IV, V and VI intercostal arteries. They irrigate mostly inferior quadrants of the breast.

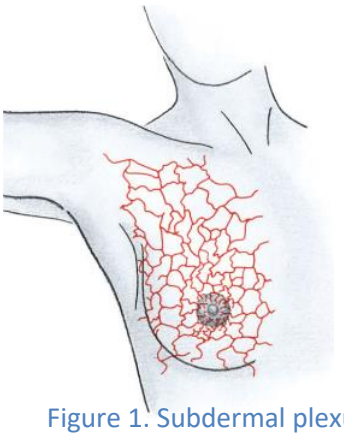

Figure 1. Subdermal plexus ((22)

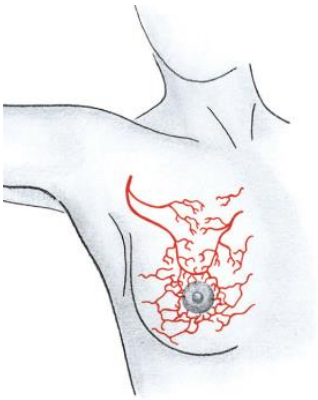

Figure 2. Preglandular plexus (22)

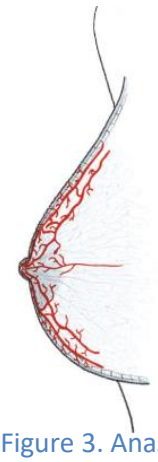

Figure 3. Anastomoses between subdermal and preglandular plexus (22)

In relation to **venous drainage**, there are two levels: superficial and deep systems.

1. The superficial vein system runs as a network through the skin constituting the circle of Haller around the areola. It converges to the subcutaneous plexus of Haller (very visible in lactancy period) under the NAC. This plexus drains to superficial veins (superficial cervical plexus and cephalic vein, amongst others). It is essential to preserve when possible the superficial system in surgeries so that complication rates decrease.
2. The deep vein system travels together with the arterial system through connective tissue tracts and septa on glandular lobes. It drains to the lateral thoracic vein (lateral) and internal thoracic vein (medial).

These systems anastomose between them by perforator veins (following Cooper's ligaments trajectory) and at the borders of the glands.

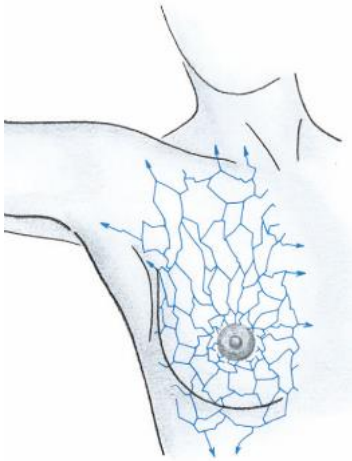

Figure 4. Superficial venous drainage (22)

Timing on Risk-Reduction Surgery

- **Immediate-Breast Reconstruction (IBR):** Breast reconstruction is done at the same time as mastectomy (1-stage approach). IBR protects patients from a period of psychosocial distress and sexual impact of amputated breasts (24), giving as well better aesthetic outcomes than the DBR; skin envelope can be preserved so more conservative-techniques such as NSM or SSM can be applied. It is not recommended on patients who are selected to undergo radiotherapy or on hospitals where there is not a multidisciplinary team (small territorial hospitals) because coordination of both breast surgeon and plastic surgeon is needed at the same operation.
- **Delayed-Breast Reconstruction (DBR):** Breast reconstruction is done in a 2-stage approach. Firstly, mastectomy is done. After breast cancer treatment is completed (RT, chemotherapy) then the reconstruction is performed. Additionally, DBR is used when patients are not convinced of undergoing breast reconstruction as well as

those who have great comorbidities that can give more complexity or complications in the procedure. Because skin preservation results are not as desirable as IBR, DBR is usually performed with autologous tissue.

- **Delayed-Immediate-Breast Reconstruction (DIBR):** A temporary tissue expander filled with saline is placed when the mastectomy is performed to preserve shape and dimensions of skin envelope till the breast reconstruction is done in a 2-stage approach. The expander can be deflated if radiotherapy is needed and then it is expanded again to undergo skin-preserving delayed reconstruction.

Breast-Reconstruction Techniques

- **Implant-Base Reconstruction:** Expander tissue is optional in this procedure, which is replaced for an implant in a 2-stage approach.

  Implant-Base Reconstruction is the best option on bilateral reconstructions because it gives an optimal chance to obtain a desirable symmetry between the two breasts (25).

  Nowadays, implants are usually placed in the submuscular level, under the major pectoral muscle.
- **Autologous tissue breast reconstruction:** We will only explain the most common ones on breast reconstruction, although other types of reconstruction are well-documented (25,26)
  - **TRAM (transverse rectus abdominis myocutaneous) flap:** there are three subtypes:
    - **1. Pedicled TRAM flap**: It takes skin, fat, abdominal muscle and overlying fascia and it is tunneled under the upper abdominal skin to the breast.
    - **2. Free TRAM flap:** The Flap is not tunneled to the chest; in this case, it is disconnected (free) and transplanted to the chest. Discomfort is lower but microsurgery is required in order to reconnect vessels.
    - **3. Muscle-sparing free TRAM flap**: It is similar to the free TRAM flap but muscle's proportion is smaller with or without the overlying fascia. Microsurgery is required in order to reinsert blood flow.

- **DIEP (deep inferior epigastric perforator flap)**: It uses the same lower abdominal skin and fat as a TRAM flap, but the underlying abdominal muscle is preserved. Blood supply from deep inferior epigastric artery and vein is disconnected and reconnected with microsurgery in the chest vessels.
- **IGAP (inferior gluteal artery perforator) / SGAP (superior gluteal artery perforator) flap:** These are flaps containing skin, fat and their blood vessels associated respectively that are taken from the buttocks.
- **Latissimus dorsi flap:** This flap contains skin, fat and latissimus dorsi muscle. It is tunneled from the back to the chest, preserving its thoracodorsal vessels. No microsurgery is needed.

➢ **Combination of implant and autologous tissue reconstruction:** for instance, latissimus dorsi flap plus a breast implant.

3.1.5: Psychological implications

Most common psychological consequences experienced by women after becoming aware of their BRCA-mutation condition are worry, anxiety and distress(27). Other psychosocial implications include: impact on family planning decisions, loss of social role and life insurance or employment discrimination.

It is crucial that BRCA-mutation carrier's decision to perform a RRM is made on the basis of her own wishes without external pressures, there is a correct knowledge of what this mutation implies and this decision is done under a realistic expectation of results.

RRM is a radical surgery that also hurts patient's psychosocial health; nowadays, surgeons tend to perform a more conservative surgery while oncological safety is maintained, preserving the skin-envelope of the breast.

Many studies (28,29) have highlighted that the NAC is the most important structure on a women's breast and NAC reconstruction after SSM has shown to enhance woman's health-related quality of life in addition to her body image. Notwithstanding this, results of NAC reconstruction are variable. Patient's dissatisfaction can be due to different factors, such as nipple projection, shape, color match and sensitivity(28).

NSM can be a solution to patients' dissatisfaction of NAC reconstruction, because their own NACs are preserved. We would like to study in this research project how their sensation is affected after NSM.

It is important to mention that RRM brings also psychological benefits: a reduction in worry and anxiety, no distress with false positive mammography results and no longer dependence on self-examination and screening. Also women who have performed this intervention tend to declare a high grade of satisfaction with their decision (30).

3.2: JUSTIFICATION

Patients with BRCA mutations represent between 35-45% (31) of all hereditary breast cancer; therefore, Bilateral Prophylactic Mastectomy (BPM) has been introduced as a treatment for preventing future breast cancers in those patients. Indeed, this surgery has a reduction on breast cancer by 90-95%, and it consists of the most valid or competent risk-reduction strategy.

Due to the fact that this type of surgery is considered as an aggressive mutilation of the female body, it can result with psychosocial consequences such as feelings of depression and impact on their sexuality (10); consequently, patient satisfaction must be taken into consideration to our procedure.

It is also relevant that the NAC consists the main element of breast identity (more than volume or shape of the breast)(29). Nahabedian and Tsangaris(32) announce that up to 80% of women that have had a traditional or non-sparing mastectomy, they are followed by a delayed or immediate nipple reconstruction; even though reconstruction of the NAC can be performed after mastectomy to satisfy patient's psychological impact, repeated surgical interventions are required and there is a low level on reconstruction's satisfaction(33). The NSM could lead to more women undergoing mastectomy, who would not choose it if only the radical mastectomy option were proposed, thus decreasing the total incidence of breast cancer in high-risk population.

The idea of preserving the NAC has been carried out for many decades, named as Subcutaneous Mastectomy (SCM). Research of this technique has led to different conclusions without achieving a significant contrast with the simple mastectomy results (14,33–36) .

Nowadays, thanks to the advancement of modern surgical techniques, the intention of NAC's preservation has been included inside the skin envelope while all breast tissue is removed (there is only between 3-5mm tissue left under the NAC, in comparison with 1-2cm on the SCM). Recent studies(14,29,37–39) support the NSM safety in oncological terms and it is thought to be a new growing technique which brings as well better aesthetic outcomes.

What are NSM disadvantages in comparison with SSM? Mostly it's ischemia of the NAC flap, although its frequency is low (it can vary from 0-40%, but most studies say from 5-15%); this is affected by risk factors such as smoking, pre-existing scars, or large ptotic breasts(19). A solution to that can easily be the Delay Procedure prior to the NSM, a technique that improves NAC's perfusion when performing the NSM in a second approach.

The aim of this study is to prove that adding the Delay Procedure prior to completion Nipple-Sparing-Mastectomy for oncoplastic surgery (which provides more supply to the distal segment of the NAC) can improve and diminish its complications rates in **necrosis skin and NAC flap** and as a result it can be used as a Risk-Reduction Mastectomy on BRCA mutation carriers leaving better aesthetic results and being oncologically as save as NSM.

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5. HYPOTHESES

5.1: MAIN HYPOTHESYS

Women with a BRCA mutation who are candidates of Risk-Reduction Mastectomy will achieve fewer post-operative complications related to necrosis with the Delay Procedure prior to completion Nipple-Sparing Mastectomy compared to the Nipple-Sparing Mastectomy itself.

5.2: SECONDARY HYPOTHESES

Women with a BRCA mutation who are candidates of Risk-Reduction Mastectomy will achieve with the Delay Procedure prior to completion Nipple-Sparing Mastectomy compared to the Nipple-Sparing Mastectomy itself:

a) Higher satisfaction rates and aesthetics outcomes.
b) Higher Skin and Nipple-Areola Sensation.
c) Lower impact on their sexuality life.
d) Higher Health-related quality of life.

6. OBJECTIVES

6.1: MAIN OBJECTIVE

To compare in women with a BRCA mutation who are candidates of Risk-Reduction Mastectomy the effectiveness of the Delay procedure prior to completion Nipple-Sparing Mastectomy versus the Nipple-Sparing Mastectomy itself in decreasing complication rates of necrosis.

6.2: SECONDARY OBJECTIVES

To compare in women with a BRCA mutation who are candidates of Risk-Reduction Mastectomy the effectiveness of the Delay procedure prior to completion Nipple-Sparing Mastectomy versus the Nipple Mastectomy itself in:

a) Increasing satisfaction rates.
b) Increasing sensitivity of skin and nipple-areola complex.
c) Decreasing sexual impact.
d) Increasing health-related quality of life.

7. SUBJECTS AND METHODS

7.1 STUDY DESIGN

We will carry out a multicenter preventive experimental study, which will be a randomized controlled open-label clinical trial. 20 hospitals through different autonomous communities will take part in a period of 3 years.

7.1.1 Randomization

Randomization will be done by a statistical specialist after assessment of eligibility and once the patient has signed the Informed Consent Form (See ANNEX 4), in order to avoid selection bias. The purpose of randomization is to guarantee that the only difference between the two groups is the intervention which is being compared *(ceteris paribus)*. The investigator or General Coordinator (GC) will not have access to randomization sequence nor knowledge of which intervention is done to any patient.

All participants will have the same probabilities of being assigned to one or the other group of the study. Patients of each hospital will be randomly assigned to an approach with the software SPSS.

Once randomization is done, information will be transmitted to the surgeon before the patient's operation in a closed envelope. Patient's name will be substituted for an identification number which will be used through all the study.

7.2 POPULATION OF INTEREST

Our population will be composed by female carriers of deleterious mutations in either the BRCA1 or BRCA2 gene who wish to undergo a Risk-Reduction Mastectomy in the 20 hospitals chosen previously through Spain. These female participants have been previously assessed for genetic risk in the Hereditary Cancer Program at Genetic Counseling Unit in their centers respectively. Informed consent for genetic testing is provided to all participants beforehand. If their results are positive in carrying a BRCA1 or BRCA2 mutation, information and assessment of the different risk-reduction strategies available is provided, and those who wish to have a RRM are stimulated to participate.

As **inclusion criteria** we define:

- Women diagnosed as carriers in either BRCA1 or BRCA2 gene.
- Women between 18 and 65 years old.
- Women who have read the Information Sheet for participants (See ANNEX 3) and have signed the Informed consent Form (See ANNEX 4)
- Women who are visited at hospitals included in our study.

As **exclusion criteria** we define:

- Women diagnosed for breast and/or ovarian cancer.
- Patients with >10 pack-year smoking history or < 5 YTQ prior to surgery (40).
- Patients with Body Mass Index (BMI) greater than 30.
- History of breast irradiation, previous breast surgery or scar.
- Breast ptosis grade C in reference to inframmamary fold and/or grade 3 in reference to breast contour (See ANNEX 2).
- Fictitious family history / Munchausen's syndrome.
- Psychiatric disorder that contraindicates surgery: major depression, carcinophobia, body dysmorphic syndrome.
- Pregnancy.
- Paget's disease.
- High non-beneficial anesthetic risk for performing major surgery.

As **withdrawal criteria** we define:

- No collaboration of the patient (not willing to attend appointments or answer questionnaires)
- Participant does no longer want to continue in the study and signs the revocation of information consent (See ANNEX 4).
- It is found a tumor on breast previously not detected when performing the pre-operative breast MRI exam (See Section 7.4.1: Description of the approaches).

All patients withdrawn from the trial or patients with missing outcomes will be included in the statistical analysis and will not be replaced by other subjects.

7.3 SAMPLE SIZE AND SAMPLING

We will use a non-probabilistic and consecutive sampling in a period of two years. All patients visited in hospitals that are included in our study or referred to them from other centers that fulfill inclusion's criteria and do not have any exclusion criteria will be encouraged to participate in our clinical trial. Each patient's scheme will take six months; therefore, as we will use a consecutive sampling, we will accept patients to participate in our research for one year and a half.

We estimate that the incidence of necrosis rate in Delay Procedure for NSM is 1%, according to clinical studies (15,17,19) and clinical experience of plastic surgeons from different hospitals incorporated in our research trial. In contrast, there is evidence of a necrosis rate in NSM technique without the Delay Procedure ranging from 5% up to 30%, although most research results tend to delimit to 15%.

Therefore, assuming an alpha risk (α) of 0.05 and a beta risk (β) of 0.2 and having a value or statistical power (1- β) of 0.8 in a bilateral contrast, we need 47 patients in each group (total = 94 patients) to detect as statistically significant the difference between the two necrosis rates, which for intervention A is expected to be 0.15 and intervention B 0.01. A tracking loss rate of 5% was estimated. It has been used an ARCSINUS through the "Calculadora de Grandària Mostral GRANMO"(41).

7.4 INTERVENTIONS

7.4.1: Description of the approaches

The first appointment will include explanation of the project, Information Sheet for Participants (See ANNEX 3) and, if the patients agree to participate in this project, Informed Consent Form (See ANNEX 4 and 5). Randomization will be done after first appointment.

On the following days, patients will receive a letter or text message (depending on patient's preference) with next appointment's citations with the oncologic/general surgeon and plastic surgeon; If everything is correct, before undergoing the intervention assigned, patient's overall health will be assessed (appointment 2)

- A **pre-operative breast MRI exam** will be done by a radiologist in order to see:
    - NAC's perfusion, using the NACsomes classification system of blood supply to the NAC[1].
    - Confirmation of non-breast tumor (BI-RADS category 1-Negative assessment and 2- Benign assessment).

The RMI protocol will be: T1-T2, dynamic with contrast (6 acquisitions – basal and every minute) and diffusion. The dynamic contrast-enhanced subtraction facilitates the perspective of an anatomic map of NAC vascularization with maximum intensity projection (MIP) images. Optimum visualization is thought to be at 60-120 seconds.

- A **pre-operative anesthetic evaluation**: assessment of patient's overall health status, uncovering hidden conditions that could cause problems with the intervention, perioperative risk determination (ASA's grading system (42))

The two approaches are described in detail below:

INTERVENTION A: NIPPLE-SPARING MASTECTOMY

This intervention consists of removal of all glandular breast tissue while skin-envelope and NAC is preserved. This will be done by an oncologist or general surgeon.

Before removal, a sterile marker will be used by a plastic surgeon to indicate the skin incision desired to be made for the oncologist/general surgeon in order to facilitate subsequently the NAC procedure.

Approach to the nipple: The plastic surgeon cores out the nipple leaving dermis and epidermis of NAC but major ducts are removed, remaining a NAC flap of 3-5mm in thickness. To obtain better results and minimize risk of thermal injury, it is recommended to invert the nipple and dissect with scissors the NAC from underlying tissue to facilitate the excision desired ("inverted sock" technique).

[1] **NACsomes classification**: Blood supply is classified into 5 anatomic zones: medial (type I), lateral (type II), central (Type III), inferior (Type IV) and superior (type V). There is a further subclassification with the source vessel for medial and lateral zones: (a) superomedial or superolateral, (b) medial or lateral, (c) inferiomedial or inferolateral. *For further information see:* (51)

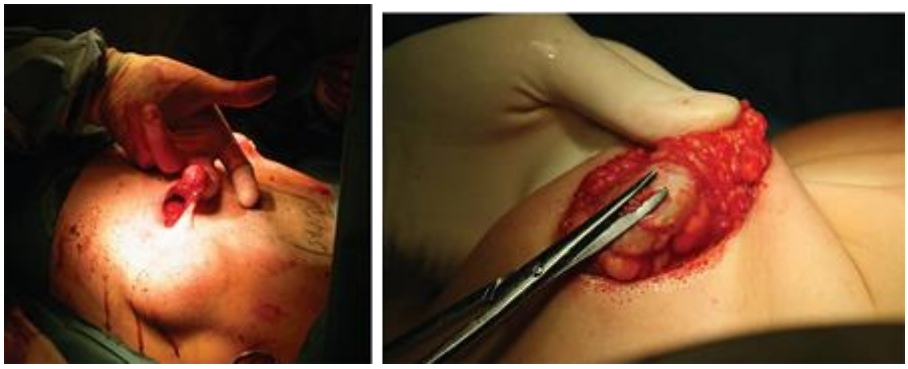


Figure 5. "Inverted-sock" technique. (43)

Ductal tissue will be sent to pathologic examination, where they will reveal if an invasive carcinoma or in situ is present (NAC must be removed if positive and will proceed to a SSM).

In relation to incision's technique, none has definitely shown superiority in NSM, although authors recommend mostly peri-areolar, inframmamary and lateral incisions. Others that can be used are: trans-areolar, radial, vertical, italic S. In any case it is very important not to transverse more than one half of the areola complex. In our study it will be used the 3 most common incisions techniques mentioned before.

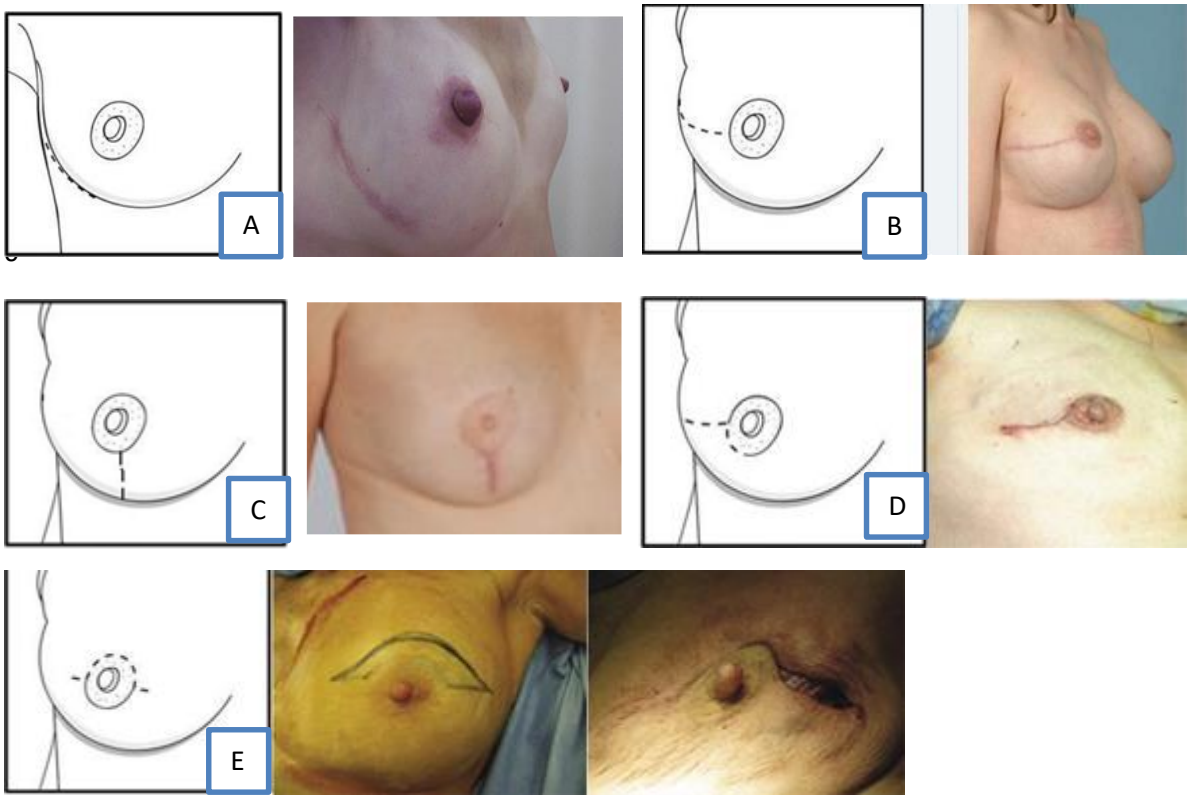


Figure 6. Types of skin incisions. A) Inframmamary crease incision, B) Lateral Radial incision, c) Vertical incision, D) Circumareolar with lateral incision, E) Omega (mastopexy) incision. *Images from* (43).

Breast reconstruction: NSM is in most cases completed with IBR with definite implant, expander or musculo-cutaneous flaps.

INTERVENTION B: DELAY PROCEDURE FOR NIPPLE-SPARING MASTECTOMY

This intervention will be made in two-times approaches.

1. **1st time approach**: Delay procedure. It will be done by the plastic surgeon 15 days prior to 2nd-time approach of the NSM. Local anesthesia with or without sedation or general anesthesia can be used to this approach and the anesthesiologist will decide which fits best for the patient.

Jensen et Al. (19) Delay procedure will be used with some modifications. The incision will be performed as planned for the subsequent mastectomy if possible. The intervention consists of radially undermining 3-5mm from the nipple (using as well inverted-sock technique) in a circumferential fashion using cold scalpel and sharp dissection scissors (Metzenbaum straight or curved blunt) to dissect the skin and subdermal plexus vasculature from the subcutaneous fat and underlying breast parenchyma. The plane of dissection is extended between 3 to 5 cm lateral, medial, superior and inferior to the areolar border respectively. The flap will be carefully elevated in order to diminish flap damage. Cautery with an electric scalpel can be used to stop bleeding from blood vessels, but it is not recommended to use it to dissect the planes because it can cause thermal injury to the skin and NAC flap.

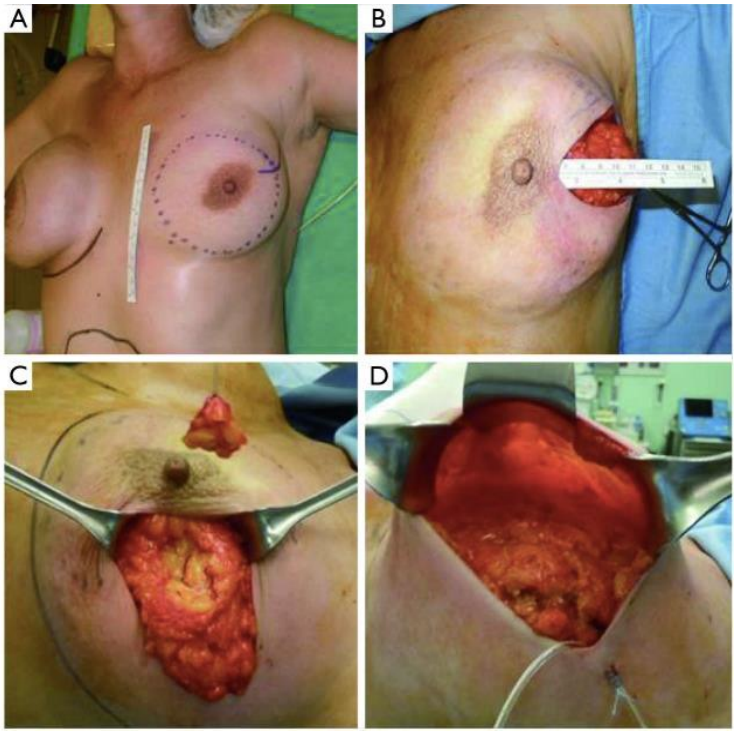


Figure 7. Surgical delay procedure. (A) Preoperative drawing: area of dissection; (B) preparation of the retroareolar and periareolar skin flap; (C) retroareolar biopsy; (D) skin flap. *Images from* (52)

Subareolar nipple biopsy will be sent to Anatomical Pathology Department for examination. If there is a pathologic result, the 2nd time approach will be substituted for a SSM.

2. 2nd time approach: Nipple-Sparing Mastectomy

The oncologic or general surgeon will remove all breast parenchyma as what we have seen in Intervention A, trying to use the incision already made in the 1st time approach.

Plastic surgeon will continue with breast reconstruction (if an IBR is considered) and will proceed to disclosure of the NAC and skin flap.

After interventions, there will be post-operative controls and further appointments (3, 4 and 5) to collect outcomes of the primary variable but also secondary dependent variables studied in this research project.

7.5 VARIABLES

All the variables studied in this research trial will be collected in the Case Report Form (CRF, See ANNEX 6).

- **Independent Variable**

The independent variable of our study is the allotment of the two surgical procedures: **Nipple-Sparing Mastectomy with or without Delay Procedure** (See 7.4: Study Interventions). It is a nominal qualitative dichotomous variable, which will be represented in proportions or percentages.

- **Dependent Variable**

The dependent variable of our study is the **Skin Ischemia and Necrosis of the NAC and flap mastectomy**. We understand ischemia as a decrease in blood supply and glucose necessary for the metabolism of the cells for their survival; if this deprivation of perfusion becomes significant it can lead to the death of these cells, which is then called necrosis.

It is a qualitative nominal dichotomous variable (YES/NO). To assess the severity and extension of the Mastectomy Skin Flap Necrosis (MSFN), we used the SKIN Score from the Mayo Clinic (See ANNEX 1 and 7.6 Measure Instruments), which correlates with the need for reoperation. We will measure this variable in 24h, 72h, 5 days, 15 days and 1 month after the intervention.

- **Secondary dependent variables**
  - **Grade of satisfaction and aesthetic outcome with the surgical procedure**: It is a quantitative discrete variable, which will be measured with BREAST-Q Questionnaire (See ANNEX 7).
  - **Skin and Nipple-Areola Sensation**: We will use Semmes Weinstein Monofilaments to measure the NAC and Skin sensation. We will convert filament sizes with categorical values, so it will be an ordinal qualitative variable (See 7.6 Measurement Instruments)
  - **Sexual impact**: We will measure sexual impact with the CSFQ-14-F Questionnaire (See ANNEX 8). It is a quantitative discrete variable.
  - **Quality of life (QoL)**: It is defined as the overall assessment of a person's well-being, which may include physical, emotional, and social dimensions, as well as stress level, sexual function and self-perceived health status[2] .The SF-36 questionnaire (See ANNEX 9) is the tool used to measure this quantitative discrete variable. It will be administered to patients from both procedures.
  - **Reoperation rate**: It is a quantitative discrete variable.
  - **Success of the flap**: It is a qualitative dichotomous variable, which will be collected in a table with "flap success" or "flap failure".
  - **Extirpation of the NAC**: It is a qualitative dichotomous variable (YES/NO).
  - **Delayed involvement of the NAC with cancer**: It is a qualitative dichotomous variable (YES/NO).
- **Co-Variables**:
  - **Non-genetic Risk Factors of Breast Cancer:** It is a qualitative nominal variable. The following terms will be included: Ethnicity, previous pathology

[2] Definition from *Medical Dictionary for the Health Professions and Nursing © Farlex 2012*

in breast, precocious menarche, late menopause, nulliparity, age older than 30 at first birth, breastfeeding history and alcoholism history.

- **Medical comorbidities**: It is a dichotomous nominal qualitative variable (YES/NO).
- **Marital status**: In a relationship/married, divorced, widowed, single. It is a categorical nominal variable.
- **Age**: It is a discrete quantitative variable.
- **Skin flap thickness:** It is a continuous quantitative variable that will be measured with millimeters.
- **Intraoperative biopsy results**: Malignant, Normal and Other. It is a nominal qualitative variable.
- **Type of reconstruction**: direct-to-implant, tissue expander/implant, autologous tissue or a combination. It is a categorical nominal variable.
- **Timing of the reconstruction**: immediate, deferred or delayed-immediate reconstruction. It is a categorical nominal variable.
- **Degree of breast ptosis**: It will be turned into a ordinal categorical variable to facilitate the analysis, following the classification from Hammond, Dennis.(44) (See ANNEX 2). We will include A-B (in reference to inframmamary fold) and 1-2 (in reference to breast contour). It is an ordinal qualitative variable.
- **Cigarrette smoking:** We will classify in non-smoker, ex-smoker and smoker with <10 PYS or >5YTQ prior to surgery. It is a categorical nominal variable.
- **Incision orientation**: Periareolar, trans-areolar, radial, lateral, inframmamary and vertical. It is a categorical nominal variable. Periareolar, lateral and inframmamary will be the types of incisions included in our study.
- **Body Mass Index (BMI)**: It is a quantitative continuous variable. Patients with >30 BMI will not be included in our study. IMC will be calculated with the following equation: $x = \frac{\text{Weight (Kg)}}{Height\ (m)^2}$.
- **Other postoperative complications (in the 7 days after surgery)**: Hemorrhage, Seromas, Infection, Hematoma, Aesthetics defects

[malposition, asymmetry (of shape, position, size, nipple color)], nerve lesion, lymphedema. It is a nominal qualitative variable.

7.6 MEASURE INSTRUMENTS

The study will be measured with the following instruments:

- **SKIN Score**: A scoring system that evaluates both depth (4-point letter score, from A as "no evidence of MSFN" to D as "full-thickness skin flap necrosis") and area involved (4 –point numerical score 1 as "0% surface" to 4 ">30% of breast or NAC") of the Skin Ischemia and Necrosis of the NAC and flap mastectomy (45–47). (See ANNEX 1).
- **BREAST-Q**: We choose only those scales pertinent to our research, which are satisfaction domains: Satisfaction with breast, Satisfaction with Outcome and Satisfaction with Care. These scales are formed in a clinically relevant hierarchy and they consist of 4-point likert-like scales from 1 "Very dissatisfied" to 4 "Very satisfied". Each scale has a series of items that are evaluated and then transformed through the Q-Score scoring software(48) or conversing tables (49) to a total scale score ranging from 0-100. The higher score, the greatest satisfaction. (See ANNEX 7).
- **Semmes Weinstein Monofilament test**: This test will use filaments with different diameters to evaluate degrees of fine touch following Dosset et Al. criteria (2.83, 3.61, 4.31, 4.56, 6.65) (50). Nipple and areola will be divided respectively into four quadrants (N1-4 and A1-4: upper inner, upper outer, lower outer, lower inner respectively) and sensation will be recorded, first individually and then both breast simultaneously to make a comparison. This test will be done once before the procedure and twice after the operation, in the 3rd and 6th month.

  Results will be collected following these categorical values: 0= no sensation, 1= 6,65, 2= 4,5, 3= 4,3, 4= 3,8 and 5= 2,8. Maximum number (5) represents higher fine touch discrimination.

  To reduce modifications on different operation-dependent surgeons, only one plastic surgeon in every hospital will evaluate the patients of the study, and patients will be with eyes closed in order to reduce as well bias by the subject.
- **Short-Form of Changes in Sexual Functioning Questionnaire in Female (CSFQ-14-F)**: It consists of 14 questions of 5-point Likert scales that evaluate the sexual

functioning of the patients. Higher scores reflect higher sexual functioning for all items except number 10 (loss of interest after arousal) and 14 (painful orgasm), which aren't included in any scale score. The rest of items are included in 5 scales: (a) Desire / Frequency (It. 2 and 3), (b) Desire/Interest (It. 4, 5 and 6), (c) Arousal/Ejection (it 7, 8 and 9), (d) Orgasm/Ejaculation (It. 11, 12 and 13) and (e) Pleasure (item 1). (See ANNEX 8)

- **SF-36 Questionnaire:** It is an instrument that comprises 36 items measuring 8 dimensions of mental and physical health status. Each item is individually evaluated and then transformed into a scale from 0 to 100 score. The higher score, the better state of health; 0 means the worst state and 100 the best. (See ANNEX 9)

7.7 DATA COLLECTION

A **Case Report Form** (CRF, ANNEX 6) will be used in our study as data collection. All variables will be included (independent, dependent, secondary dependent and co-variables).

To check if the design of our CRF follows an optimal collection of data with our study protocol, we will first make a pilot experiment of our CRF. It will be controlled by a Clinical Research Associate (CRA). Modifications of the CRF will be made if needed, always based on the pilot study results.

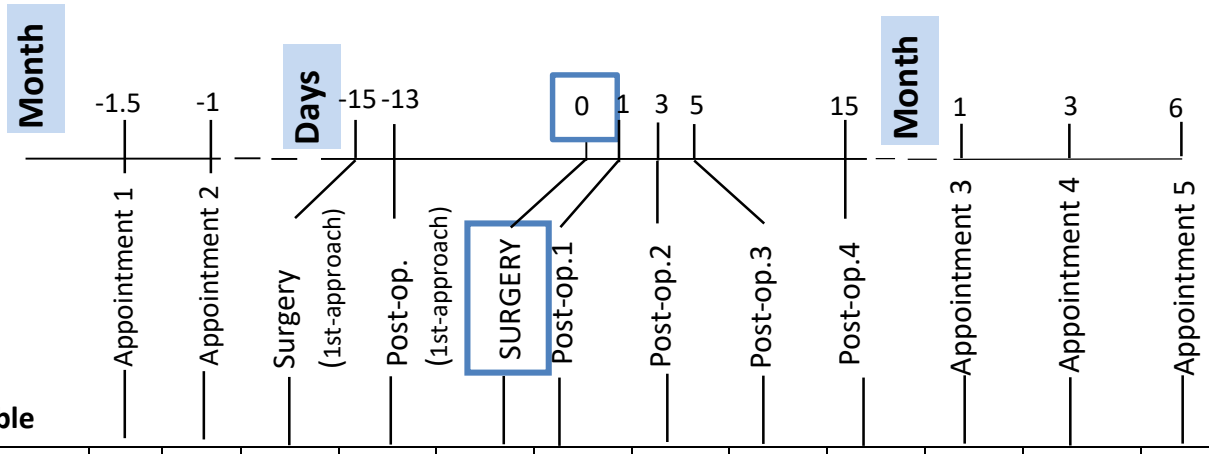
The CRF will include different parts on each appointment programmed. Names of the specialists that observe outcomes with the investigator must be written down. After that, it will be introduced to a computer database and the patient will receive a copy of the CRF.

Data collectors include oncologist surgeons and plastic surgeons on each hospital.

The medical team will be previously trained so that no intrapersonal subjective perspective can interfere to data collection and to patient's impressions or sensations.

The study scheme of each patient concludes as the following:

Figure 8. A lineal chronogram of the Data Collection, where each item is included simultaneously in columns in a table with variables disposed in rows.



Variable	Appointment 1	Appointment 2	Surgery (1st-approach)	Post-op. (1st-approach)	SURGERY	Post-op.1	Post-op.2	Post-op.3	Post-op.4	Appointment 3	Appointment 4	Appointment 5
Necrosis			✓	✓	✓	✓	✓	✓	✓	✓		
Grade of satisfaction		✓									✓	✓
Sexual impact		✓									✓	✓
Quality of Life											✓	✓
N-A Sensation		✓								✓		✓
Non-genetic Risk Factors		✓										
Medical comorbidities		✓										
Marital Status		✓										
Age		✓										
Degree breast ptosis		✓										
Smoking		✓										
BMI		✓										
Incision orientation			✓		✓							
Flap thickness			✓		✓							
Timing & type BR					✓							
Intraoperative biopsy results			✓		✓							

Also to summarize who, when and which data will be collected the following table has been made:

Table 6. This table makes a comparison between intervention A and B in each meeting scheduled; it is also included in columns the study member and the time (in months).

Month	Appointment	Collected data		Study Member
		INTERVENTION A	INTERVENTION B	
-1.5	Appointment 1	-Attendance to the appointment -Reading the Information Sheet Form -Reading and signing the Informed Consent Form		Plastic surgeon
-1	Appointment 2	-Attendance to the appointment -Demographic and general information, family genetic history, other risk factors. -Answering and punctuating the questionnaires: BREAST-Q™ preoperative, CSFQ-14-F -Semmes Weinstein Monofilament test -Reading and signing the Informed Consent Form to Surgical Procedures		Plastic surgeon
		Preoperative assessment: -Pre-operative MRI breast exam: NACsomes and BI-RADS classification		Radiologist
		Preoperative assessment: -Pre-operative anesthetic evaluation: ASA classification		Anesthesiologist
-0.5	SURGERY		1st-time approach -Attendance to the procedure - Skin flap thickness -Incision orientation Intra-operative biopsy results	Plastic surgeon
	Post-operation control		-Necrosis and ischemia outcomes	Plastic surgeon

0	SURGERY	2nd time approach -Attendance to the procedure -Surgeon number -BR -Timing of BR -Incision orientation -Intraoperative complications -Intra-operative biopsy results -Breast weight	Plastic surgeon Oncologist surgeon
0.03	Post-operation control 1	-Attendance to the appointment -Necrosis and ischemia outcomes	Plastic surgeon
0.1	Post-operation control 2	-Attendance to the appointment -Necrosis and ischemia outcomes	Plastic surgeon
0.16	Post-operation control 3	-Attendance to the appointment -Necrosis and ischemia outcomes	Plastic surgeon
0.5	Post-operation control 4	-Attendance to the appointment -Necrosis and ischemia outcomes -Flap success	Plastic surgeon
1	Appointment 3	-Attendance to the appointment -Necrosis and ischemia outcomes -Semmes Weinstein Monofilament test	Plastic surgeon
3	Appointment 4	-Attendance to the appointment -Answering and punctuation of the questionnaires: BREAST-Q™, CSFQ-14-F, SF-36	Plastic surgeon
6	Appointment 5	-Attendance to the appointment -Answering and punctuating the questionnaires: BREAST-Q™, CSFQ-14-F, SF-36 -Semmes Weinstein Monofilament test	Plastic surgeon

8. STATISTICAL ANALYSIS

We will describe symmetric quantitative variables with means (standard deviation +/- SD) and non-symmetric (discrete) quantitative variables with medians (interquartile range IQR). Qualitative variables will be described in proportions.

A contingency table will be made with the response variable in columns and the factors variable (Delay procedure and Non delay procedure) in rows.

We will contrast the null hypothesis of non-response between response and treatment in a bivariate analysis using Pearson's chi-square contrast as we are comparing categorical variables. Odds Ratio (OR) will be calculated with a confidence interval (CI) of 95% to measure the association between these variables.

Secondary quantitative variables will be measured by making a contrast between means with a T-student test.

In addition, stratification will be done to the following co-variables: Age, BMI and incision orientation. Those variables that are quantitative they will be categorized adequately to simplify analysis (e.g, age in quartiles and BMI in low-weight, normal-weight and over-weight).

We will proceed to a multivariate analysis only if we find that in the bivariate analysis co-variables have been distributed unequally between the two groups (but it is not expected to happen initially, as we are in a clinical trial where randomization has been properly done). Relation between dependent and independent variables will be adjusted in a logistic regression for the co-variables.

Sample size and sampling calculation has been described previously in Section 7.3: Sample Size and Sampling. Statistical analysis will be performed using an intention-to-treat approach. For missing data results of the last visit will be used.

Statistical analysis will be held with IBM SPSS software package. To manage computed data we will use Microsoft Excel.

9. WORK PLAN

9. 1 PERSONNEL OF THE RESEARCH TEAM

The research team will be composed by the general coordinator of the study (CG), oncologic or general surgeons (OS) and plastic surgeons (PS).

9.2 STUDY STAGES

Stage 0: Preparation [1 month]

November 17

- **Activity 1:** Protocol processing. It will be reviewed in order to identify possible misspellings, statistical errors or other mistakes. (CG) will be in charge.
- **Activity 2:** Presentation of the protocol to Clinical Research Ethics Commitee (CREC-R) for approval. (GC) will be the responsible for this activity.
- **Activity 3:** Presentation of the protocol to the director of each hospital . Their approval is required prior to starting the study. (GC) will be in charge.

Stage 1: Coordination [3 months]

December 17 – February 18

- **Activity 4:** Informative meeting. (CG) will contact throught e-mails or Skype ™ to the Heads of Services of Plastic & Reconstructive Department to the hospitals interested. A project manager (PM) will be hired to help together with the CG at coordinating between the different hospitals.
- **Activity 5**: Heads of Service, (PM) and (CG) will inform to the rest of the research team about the working plan, schedule and methods.
- **Activity 6**: Training session for the CRF. Clinical Research Associate (CRA) will be hired to train though Skype™ or e-mail how to collect data in the CRF and will make a revision to the pilot study.
- **Activity 7:** Database elaboration. This will be done by a computer engineer.

Stage 2: Field research [24 months]

March 18 – February 20

- **Activity 8**: Recruitment of patients. Patients will be randomly assigned to one of the intervention groups by the (SS) if they meet with inclusion and exclusion criteria. [March 2018 - August 2020, 18 months]
- **Activity 9**: Interventions. (OS) and (PS) will perform the intervention assigned. [April 2018 - February 2020, 23 months]

Stage 3: Data collection [24 months]

March 18 - February 20

- **Activity 10:** Data will be collected by (PS) or (OR) to the CRF and will be registered in the database. (CRA) will review it regularly to make sure there is a good quality of data collection and all information is correctly introduced.

Stage 4: Data analysis and interpretation [3 months]

March 20 - May 20

- **Activity 11:** (SS) will analyse data with the appropiate statistical test.
- **Activity 12:** Results will be discussed and interpretated by (GC), (OS), (PS), and (SS).
- **Activity 13:** Conclusions will be writen down and sketches of articles will be made.

Stage 5: Publication and dissemination of the research finding

June 20 - October 20

- **Activity 14:** Publication**.** Articles will be send to different journals for their publication by (GC).
- **Activity 15:** Dissemination of the findings. We will attempt to display our results in conferences or congresses related to Risk-Reduction Strategies for patients with a BRCA1 or BRCA 2 mutation.

9.2 CHRONOGRAM

		2017	2018						2019						2020				
Activity	PERS	XI-XII	I-II	III-IV	V-VI	VII-VIII	IX-X	XI-XII	I-II	III-IV	V-VI	VII-VIII	IX-X	XI-XII	I-II	III-IV	V-VI	VII-VIII	IX-X
STAGE 0. **Preparation**																			
1.Protocol	CG																		
2.CEIC	CG																		
3.Hospital	CG																		
STAGE 1. **Coordination**																			
4.Meeting	ALL																		
5.Informat.	ALL																		
6.CRF	DM, PS																		
7. Database	CE																		
STAGE 2. **Field Research**																			
8.Recruitm.	SS, PS																		
9.Intervent.	OS, PS																		
STAGE 3. **Data Collection**																			
10.Data Collection	PS, DM																		
STAGE 4. **Data Analysis and Interpretation**																			
11. Analysis	SS																		
12.Discussion	CG, OS, PS, SS																		
13. Sketch																			
STAGE 5. **Publication and dissemination of the research finding**																			
14.Publicat.	ALL																		
15.Dissemin.	CG																		

10. ETHICAL ANG LEGAL ASPECTS

In relation to general aspects, our study accepts and follows national and international rules related to them, which are:

- Medical international ethics defined in the WMA Declaration of Helsinki in 1964 that concerns the principles of human experimentation in medical terms.
- Law 14/2007 of 3rd July, of biomedical investigation that includes surgical interventions as "invasive procedures" and insists, amongst others, the necessity of prevailing health, interest and comfort of the human being that participates in a biomedical investigation over science and society interest.
- Principles of Good Clinical Practice and Quality Guarantee to ensure that clinical investigation is executed according to the highest standard of quality, according to the legislation of the state (R.D 561/1993) and the Community directive (91/507/CEE).
- Organic Law 15/1999 of 13 December on the Protection of Personal Data that guarantees and protects public liberties and fundamental rights and withholds in confidence personal data of the participants (we will use an identification code instead of the participant name to strengthen this principle). In relation to data collection process, all information will be treated homogenously and no exceptions to that will be made.

All participants will be informed in detail about this clinical trial in the Information Sheet Form (See ANNEX 3). They will be given as well an Informed Consent form of the study participation itself (See ANNEX 4) and the Surgical Intervention more specifically (See ANNEX 5). It is compulsory that patients have understood exhaustively the study procedure; they are aware of its advantages and possible complications and are in agreement with the method so that the principle of autonomy is respected. Health protection will be respected as article 43 of the Spanish Constitution of 1978 declares, and they will have the right to quit from the study without any medical or health care repercussions. An insurance will be provided to all patients which will offer compensation for damages if there is a loss or drop on their health induced by the investigation.

Approval by the Clinical Research Ethics Committee of Reference (CEIC-R) is required according to RD 223/2004, where it states that the CEIC-R is the responsible of making an assessment in multicenter clinical trials. This trial will be registered in ClinicalTrials.gov and EudraCT as a prevention of publication bias.

Another ethical consideration is that intervention B, which adds the Delay Procedure, is more likely to improve our outcomes researched; not only in diminishing necrosis rate but also in increasing patient's satisfaction, quality of life, nipple and areola sensation of mastectomized breasts and decreasing sexual impact. As our hypothesis is not yet proven, patients receiving the classical surgical intervention are not being predisposed to a worse intervention, so no ethical aspect is being violated in our study. To avoid producing a selection bias in the sample due to a possible paternalistic role of the surgeon assigned respectively, randomization will be done to each patient.

11. STRENGHTS AND LIMITATIONS

The main limitation of the study consists of being an open-label trial. Therefore, ascertainment or detection bias is present because there is lack of blindness. Double blind experimental design to surgeons and patients is certainly not possible because it is a surgical trial and interventions differ in time-approaches, so differences between them are present and perceptible to both patients and surgeons. To try to reduce it, an envelope with the patient's operation will be given to the surgeon on the same day of intervention and they will not know the patient's name (they will have only an identification number which will be used through all the study). Also we have measured as objective as possible our variable dependent in order to avoid systematic failure and to increase internal validity in our study. Necrosis outcomes will be classified dichotomously by YES/NO, and those answering YES will be further subclassified with the SKIN Score, a scientifically international score (See ANNEX 1).

A solution to minimize the bias produced by an open-label trial, the main investigator will not know the technique used in each patient till data analysis. Nonetheless, we cannot confirm that any patient or surgeon will not inform which intervention has been carried out to the investigator.

The research team will be trained to collect in an objective and homogenous way all outcomes from patients to the CRF (See ANNEX 6). This will reduce variability between different surgeons and evaluation bias. Also surgeons will meet in a coordination phase and discuss in detail the surgical interventions described above (See 7.4.1: Description of the approaches) in order to avoid procedure bias.

Regarding patients withdrawn from the trial or patients with missing outcomes, they are expected to be minimal as most of the appointments take part in the standard post-operation control care. If a patient does not attend to the appointment, the hospital will attempt to contact her via phone or e-mail; if an answer is still not received, intention-to-treat analysis will be proceed. This type of analysis minimizes type I error due to cautious approach and allows for the greatest generalizability.

Finally, it is important to highlight that although a multicenter study implies more coordination, training sessions and stronger efforts for quality assurance referring to

recruitment, treatment and follow-up, its sample's representation is higher than in an unicenter study, which gives more external validity. Nevertheless, we must take into account that the reduced number of patients that will be included in each center is an important limitation because each surgeon will have in total between 1-3 interventions, so variability between surgical experts is evident; that is the reason why we must emphasize the importance of making the procedures as homogenous as possible describing extensively each step of interventions and data collection must be made as well in an uniform way between the different hospitals with the CRF, as we have mentioned before.

12. FEASIBILITY

Medical team

An interdisciplinary team composes the medical team in this clinical trial: The main investigator or general coordinator, plastic surgeons and oncologic/general surgeons from the 20 hospitals included, who all of them will be well-trained and will work coordinately to fulfill the marked objectives. These hospitals are:

1. Hospital Universitario Puerto del Mar, Cádiz (Andalusia)
2. Hospital Virgen de las Nieves, Granada (Andalusia)
3. Hospital Universitario Virgen del Rocío, Sevilla (Andalusia)
4. Hospital Universitario Miguel Servet, Zaragoza (Aragon)
5. Hospital Universitario Central de Asturias, Oviedo (Asturias)
6. Complejo Asistencial Universitario de Salamanca (Castilla y León)
7. Hospital Duran i Reynals, l' Hospitalet de Llobregat (Catalunya)
8. Hospital Germans Trias i Pujol, Badalona (Catalunya)
9. Hospital Universitari Dr. Josep Trueta, Girona (Catalunya)
10. Hospital Clínic de Barcelona (Catalunya)
11. Hospital Universitari Vall d'Hebron, Barcelona (Catalunya)
12. Hospital General Universitario de Albacete (Castilla La Mancha)
13. Hospital Universitari i Politècnic La Fe, Valencia (Comunitat Valenciana)
14. Hospital San Pedro de Alcántara de Cáceres, Cáceres (Extremadura)
15. Hospital Clínico Universitario de Santiago, Santiago (Galicia)
16. Hospital San Pedro, Logroño (La Rioja)
17. Hospital Universitario La Paz, Madrid (Madrid)
18. Hospital Clínico San Carlos de Madrid (Madrid)
19. Clínica Universidad de Navarra, Pamplona (Navarra)
20. Hospital de Cruces, Barakaldo (Basque Country)

Necessary means such as personnel salaries, operation rooms and follow-ups will be provided by the hospital respectively.

We will hire a Project Manager and a Clinical Research Associate to help the investigator at coordinating and data quality control and monitoring respectively, due to the fact that this multicenter study comprises many hospitals and there must be an extra effort or reinforcement on these aspects to avoid rectifiable errors than can reduce easily the value of the study.

We will hire a statistical analyzer as well to process the extensive statistical analysis implicated, and a computer engineer to create the database.

Available Resources

The operation room's availability depends on the hospital's characteristics. The hospitals included in the trial are hospitals of reference in the different autonomous communities, so it is given to the Department of Plastic and Reconstructive Surgery at least one operating room; sometimes they are being shared with other departments (such as Traumatology or Gynecology) but if it is being scheduled correctly and well-coordinated between departments this will not be an obstacle.

No hospitalization is needed for those having the Delay Procedure done on the first-approach; only on the second-time approach, like the standard mastectomy, will have to rest in hospital for 3-5 days approximately, so it is important to have available beds after the surgery.

The material required for this trial is the standard material used in a mastectomy intervention.

Patients

Taking as a reference women with BRCA 1/2 from ICO's in Girona, L'Hospitalet and Badalona who were carriers and wished to undergo to bilateral RRM as primary prevention and the incidence per year of breast cancer in Spain that are carriers of these deleterious mutations, we approximate that there is circa 103 cases per year of women with these characteristics in Spain (and possibly more because in Catalonia the percentage of performing RRM is lower than in other areas of Spain, which can reach up to 15-20%). Thus we will include 20 hospitals from different autonomous communities and recruitment will be made through 1 year and a half to approximate an inclusion in the study of 90-95 patients per year. The evaluation of the outcomes will be done in 6 months after the intervention, thus 2 years will be necessary to get the sample size and to evaluate the necrosis rate.

13. BUDGET

The development of this study does not include an increase of the costs of the surgical intervention because adding the Delay procedure prior to the standard technique does not involve more material for the surgery necessary than the standard technique itself; it is only required a cold scapel, sharp dissection scissors and an electric scalpel for cauterization, thus we will assume that CEIC will approve our petition to be covered by the hospitals.

After surgical procedure, patients will be hospitalized during few days, which are included in the postoperative plan.

We will hire a Project Manager (PM) to help the investigator to coordinate between the different 20 hospitals at the coordination stage; we will hire him for 20 hours/weekly for 3 months, which will cost 7.200€ (30€/h).

A skilled staff is required to be in charge with data monitoring and quality control data. The estimated costs for Clinical Research Associate is 11.340€ (35€/h, assuming 324 hours from 3h/week during 27 months).

We also require hiring a statistical specialist to randomize and code patients and to analysis statistically data collected, as well as hiring a computer engineer to create the database. The estimated salary will be 35€/hour with an estimated cost of 6.300€ (180 hours) and 700€ (20 hours) respectively. We will need to pay IMB SPSS Statistics license for the statistical analysis for one year which will cost 300€.

Skype™-Business will cost 4,20€/monthly per user. We will assume that we will need 22 users (the general coordinator and the analysis statistic + one user from each hospital respectively; this user will be created for the study exclusively and everyone from the research team will be able to enter, so they will know log-in names and passwords) in a period of 3 years, so we estimated a total cost of 3.326 ,40€.

A RMI of the breast will be made to each patient before intervention. Total cost is between 350-500€; the estimated budget will be 37.600€ (400€ per patient, total 94 patients).

We assume 250€ cost for printing information sheets for patients, informed consent forms, case reports forms and questionnaires.

We will buy through Amazon.com® 20 units of Semmes-Weinstein Monofilaments 5 piece Hand Kit, with a total cost of 2.120€ (106.00€/unit).

Once the study is finished, we will write a scientific article in order to be published and disseminated to scientific community, which will consist of 1.000€ for publication expenses to international scientific journals, and 1.100€ for broadcasting our outcomes in National and International Congresses: to the National Congress *de la Sociedad Española de Cirugía Plástica, Reparadora y Estética (SECPRE)* and to the International Congress *of the International Confederation of Plastic Reconstructive and Aesthetic Surgery (IPRAS)* in 2020, with a registration cost fee of 450€ and 650€ respectively. The costs of the trips, accommodation and food expenses are still unknown because localization of the congresses is not yet established, but we estimate approximately 300€ for the national and 600€ for the international one.

	Quantity	**Cost**	**Subtotal**
STAFF AND SERVICES			
Research team	Provided by the National Health System (NHS)		
Project Manager (coordinator)	240h	30€/h	7.200€
Clinical Research Associate (CRA)	324h	35€/h	11.340€
Statistical Expert	180h	35€/h	6.300€
Computer Engineer	20h	35€/h	700€
MATERIAL			
Surgical Material and Hospitalization	Provided by the NHS		
Magnetic Resonance Imaging for breasts	94	400€/patient	37.600€
IMB SPSS Statistics license	1y	300€/year	300€
Data storage (pen-drives, hard-drives)	20	10€/unit	200€
Skype™-Business	22	4,20€/mon/u	3.326,40€
Printing and other materials	X	X	250€
Semmes-Weinstein Monofilament 5-piece	20	106€/unit	2.120€
Box of 200 envelope	1	20€/unit	20€
Insurance policy	1	6.000€	6.000€
PUBLICATION AND PRESENTATION COSTS			
Publication expenses	1	1.000€	1.000€
Inscription to National Congress (SECPRE)	1	450€	450€
Inscription to International Congress (IPRAS)	1	650€	650€
Trips, accommodation and food expenses	2	350€+650€	900€
	TOTAL AMOUNT		**78.456,40€**

14. IMPACT ON THE NATIONAL HEALTH SYSTEM

As we exposed in Section 3.2 Justification, breast cancer is the leading malignant tumor in women worldwide and insight of the disease has nowadays incremented thanks to education and prevention; thus, it is understandable that is becoming more frequent to perform double prophylactic mastectomy on women who have predisposition at developing it due to hereditary factors.

Making a radical mastectomy to those women is inappropriate because they don't actually have the disease and more conservative procedures must be taken into consideration; here is where the Nipple-Sparing Mastectomy stands out from the other types of mastectomy, because the NAC is preserved leading to less impact on patients' self-esteem. A disadvantage of this technique is its necrosis flap rate: a solution to that can easily be adding the Delay Procedure to the NSM.

Although we are aware that the budget of this trial is quite high, we must not look now but on the future: If the **Delay Procedure** proves to be successful, we will reduce an enormous impact on the NHS because no nipple-areola reconstruction will be needed. This involves fewer second-time reconstruction operations, fewer post-operative hospitalizations (the Delay Procedure does not need to be hospitalized after surgery) and more women satisfied with their results. Also we can also expect less incidence of breast cancer in women with BRCA1/2 mutations if more people wish to perform this conservative surgery rather than surveillance.

15. ANNEXES

ANNEX 1: The Mastectomy SKIN Score for assessing severity and extent of mastectomy skin flap necrosis (MSFN)

Depth of MSFN		Surface area of MSFN	
Score	Definition	Score	Definition
A	No evidence of skin ischemia or necrosis	1	None
B	Color change of skin suggesting impaired perfusion or ischemia (may be cyanosis or erythema)	2	Change involving 1%-10% of breast skin or 1%-10% of NAC
C	Partial thickness skin necrosis resulting in at least epidermal sloughing	3	Change involving 11%-30% of breast skin or 11%-30% of NAC or total nipple involvement[a]
D	Full-Thickness skin necrosis [b]	4	Change involving >30% of breast skin or >30% of NAC

Abbreviation: NAC, nipple-areolar complex

[a]Because the nipple itself is considered a key to the aesthetics of the breast, If there is skin necrosis involving the entire nipple, the surface area score of the NAC is automatically upgraded to a score of at least 3, even if the nipple represents less than 10% of the surface are of the NAC

[b]Note: areas that are not definitely full thickness should be scored as partial thickness.

ANNEX 2: Classification combining Ptosis grade in reference to breast contour and to inframmamary fold (Atlas of Aesthetic Breast Surgery by Hammond, *Dennis C.*)

PTOSIS GRADE		IN REFERENCE TO BREAST CONTOUR		
		1	2	3
IN REFERENCE TO INFRAMMAMARY FOLD	A	Nipple at Apex Nipple above fold	Nipple below apex Nipple above fold	
	B	Nipple at apex Nipple at fold	Nipple below apex Nipple at fold	Nipple at lower border Nipple at fold
	C	Nipple at apex Nipple below fold	Nipple below apex Nipple below fold	Nipple at lower border Nipple below fold

ANNEX 3: Information Sheet for Participants

CATALAN VERSION

FULL D'INFORMACIÓ PER A LA PACIENT

Títol de l'estudi: Eficàcia de la tècnica *"Delay"* prèvia a la mastectomia preservadora del mugró i arèola en reduir la taxa de necrosis com a complicació post-operativa.

Investigadors: _____

Centre: _____

1. **INTRODUCCIÓ**

Ens dirigim a vostè per informar-la sobre un estudi d'investigació en el que se la convida a participar. Aquest estudi ha sigut aprovat pel Comitè Ètic d'Investigació Clínica corresponent i l'Agència Espanyola del Medicament i Productes Sanitaris, d'acord amb la legislació vigent, el Real Decret 223/2004, de 6 de Febrer, pel que es regulen els assajos clínics amb medicaments. La nostra intenció es tan sols que vostè rebi la informació correcta i suficient per a que pugui avaluar i jutjar si vol o no participar en aquest estudi. Per dur-ho a terme llegeixi aquest full d'informació amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir després de l'explicació. A més, pot consultar amb les persones que consideri oportú.

2. **PARTICIPACIÓ VOLUNTÀRIA**

Ha de saber que la seva participació en aquest estudi és VOLUNTÀRIA i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que per això s'alteri la relació amb el seu metge ni es produeixi perjudicis en el seu tractament.

3. **DESCRIPCIÓ GENERAL DE L'ESTUDI**

L'objectiu principal d'aquest estudi consisteix en comparar dues tècniques quirúrgiques preventives, ambdues conservadores de pell i mugró, per al càncer de mama en pacients portadores sanes de mutacions en els gens BRCA1 o BRCA2. Es compararà la tècnica actual amb una nova intervenció en el qual es pretén reduir el risc de complicacions i així augmentar el nombre de dones que opten per la cirurgia reductora de risc conservadora de pell i mugró com a part del tractament preventiu. Altres propòsits són esbrinar si aquesta nova intervenció augmenta la satisfacció, qualitat de vida i sensibilitat en el mugró-areola i si disminueix l'impacte sexual que pot causar una cirurgia major d'aquest caire.

En aquest estudi participaran aproximadament 94 dones portadores de BRCA 1 i/o 2 de diferents hospitals d'Espanya.

Totes les pacients seran assignades de forma aleatòria mitjançant un sistema informàtic a una de les dues intervencions quirúrgiques i no se li informarà de quina consisteix fins al post-operatori. Ambdues constaran de 5 visites programades amb el cirurgia plàstic (més les visites que vostè necessiti) a la consulta durant el transcurs de 6 mesos. Si vostè pertany al nou enfocament, la cirurgia constarà de dos temps – la primera 15 dies abans de la segona. Es realitzaran els controls post-operatoris pertinents (A les 24h, 72h, 5 dies, 15 dies i 1 mes) en ambdues tècniques.

En la primera visita programada a la consulta, se li sol·licitarà que ens faciliti informació personal i familiar que resulti d'interès per a concloure si vostè presenta els requisits per a participar en l'estudi. En cas afirmatiu, si firma el consentiment informat i aquest full d'informació afirmant que està conforme amb el procés, se li informarà en els dies posteriors de la segona visita preoperatòria amb el mateix metge, on se li explicarà un altre cop qualsevol dubte o qüestió en referència a la cirurgia, discutiran si vol optar o no per reconstrucció mamària i quina seria la més adequada segons les seves característiques o preferències, es farà una valoració pre-operatòria amb una ressonància magnètica de la mama i valoració anestèsica i es realitzarà el test de monofilament Semmes-Weinstein per a mirar quina sensibilitat té en el mugró-areola abans de sotmetre's a cirurgia.

La tercera, quarta i cinquena visites programades tindran lloc 1 mes, 3 mesos i 6 mesos després de la intervenció corresponent, i se li demanarà que complimenti una sèrie de qüestionaris (en la quarta i cinquena visita) sobre la seva opinió respecte diversos aspectes de la seva vida (grau de satisfacció, impacte sexual, estat anímic, entre d'altres). També es tornarà a realitzar el test amb monofilaments per avaluar la sensibilitat en la tercera i quarta visita.

A part de les visites programades, vostè pot rebre totes les visites de seguiment que consideri oportú o necessari.

Si vostè accepta participar en l'estudi implica que adquirirà les responsabilitats necessàries per assistir en els procediments de l'estudi, igual com seguir les instruccions del protocol i notificar qualsevol esdeveniment advers que li succeeixi als investigadors de l'estudi. També accepta emplenar els qüestionaris de forma veraç i amb el temps requerit per contestar-los durant les seves visites a consulta.

4. BENEFICIS I RISCS DERIVATS DE LA SEVA PARTICIPACIÓ EN L'ESTUDI

Vostè ha decidit realitzar-se una doble mastectomia profilàctica per tal de reduir els riscs de tenir càncer de mama en un futur. Si vostè rep la cirurgia convencional, rebrà el mateix tractament que si no participés en l'estudi i volgués conservar la pell, l'arèola i el mugró. Si està en el grup experimental es pot beneficiar de millors resultats estètics i possiblement funcionals (sensibilitat) amb menys riscs de complicacions, però haurà de fer-se la cirurgia en dos temps.

També és possible que vostè no obtingui cap benefici directe per participar en l'estudi; no obstant, es preveu que la informació que s'obtingui pugui beneficiar en un futur a altres pacients i pugui contribuir a un millor coneixement de l'efecte de la cirurgia reductora de risc amb preservació de pell i mugró en pacients portadores sanes genèticament predisposades a tenir càncer de mama.

No es preveuen riscs ni inconvenients per a participar en aquest estudi.

Els possibles esdeveniments adversos són els mateixos que qualsevol mastectomia, afegint complicacions amb la perfusió del mugró i l'arèola. Aquestes són les següents: Duresa o rigidesa al lloc de la incisió, infecció, hemorràgia o hematoma, seroma, dolor al pit, sensació de "tirament", dermatitis.

Una vegada finalitzat l'estudi, vostè rebrà l'atenció mèdica necessària segons la seva condició independentment si ha participat o no en aquest.

Els participants no rebran una compensació econòmica per a participar en l'assaig clínic, doncs esbiaixaria la selecció de pacients.

5. TRACTAMENTS ALTERNATIUS

Les formes alternatives de tractament inclouen el no tractar aquesta situació per una conducta quirúrgica: mitjançant vigilància estreta (amb ressonàncies magnètiques o mamografies anuals i examinació bi-anual clínica) o quimioteràpia profilàctica amb tamoxifè. També és possible realitzar altres cirurgies més radicals amb extirpació de pell, mugró i arèola.

El metge li pot proporcionar més informació al respecte si ho desitja.

6. CONFIDENCIALITAT

El tractament, comunicació i cessió de dades de caràcter personal de tots els participants s'ajustarà segons la Llei Orgànica 15/1999 de 13 de desembre de protecció de dades de caràcter personal. D'acord amb el que estableix la legislació mencionada, vostè pot exercir els drets d'accés, modificació, oposició i cancel·lació de dades, pel qual haurà de dirigir-se al metge de l'estudi.

Les dades recollides per l'estudi estaran identificats mitjançant un codi i només el seu metge de l'estudi/col·laboradors podran relacionar aquestes dades amb vostè i la seva història clínica. Per tant, la seva identitat no serà revelada a cap persona sols en cas d'urgència mèdica o requeriment legal.

Només es transmetran a tercers i a altres països les dades recollides per l'estudi que en cap cas contindran informació que li pugui identificar directament, com nom i cognoms, inicials, direcció, nº de la seguretat social, etc. En el cas de que es produeixi aquesta cessió, serà pels

mateixos fins de l'estudi descrits i garantint la confidencialitat com a mínim amb el nivell de protecció de la legislació vigent en el nostre país.

L'accés a la seva informació personal quedarà registrat al metge de l'estudi/col·laboradors, autoritats sanitàries (Agència Espanyola del Medicament i Productes Sanitaris), al Comitè Ètic d'Investigació Clínica i personal autoritzat pel promotor, quan ho precisin per comprovar dades i procediments de l'estudi, però sempre mantenint la confidencialitat dels mateixos d'acord amb la legislació vigent.

7. ASSEGURANÇA I RESPONSABILITAT

El promotor de l'estudi disposa d'una pòlissa d'assegurances que s'ajusta a la legislació vigent i que li proporcionarà la compensació i indemnització en cas de menyscabament de la seva salut o de lesions que puguin produir-se en relació amb la seva participació en l'estudi.

8. ALTRA INFORMACIÓ RELLEVANT

Si vostè decideix retirar el consentiment per a participar en aquest estudi, cap dada nova serà afegida a la base de dades i pot exigir la destrucció de totes les mostres identificables prèviament retingudes per evitar la realització de nous anàlisis.

També ha de saber que pot ser exclòs de l'estudi si l'investigador ho considera oportú, ja sigui per motius de seguretat, per qualsevol esdeveniment advers que es produeixi per la intervenció en l'estudi o perquè consideri que no està complint amb els procediments establerts. En qualsevol dels casos, vostè rebrà una explicació adequada del motiu que ha ocasionat la retirada de l'estudi.

9. CONTACTE PER A MÉS INFORMACIÓ

Si desitja més informació, pot trucar a la investigadora Sra. Castellà al 685.529.805 o escriure un correu a a.castella.pujol@gmail.com.

Al firmar el full de consentiment adjunt, es compromet a complir amb els procediments de l'estudi que se li ha exposat.

SPANISH VERSION

HOJA DE INFORMACIÓN PARA EL PACIENTE

Título del estudio: Eficacia de la técnica "Delay" previa a la mastectomía preservadora del pezón y areola en reducir la tasa de necrosis como complicación post-operativa.

Investigadores: _____

Centro: _____

1. INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica correspondiente y la Agencia Española del Medicamento y Productos Sanitarios, de acuerdo con la legislación vigente, el Real Decreto 223/2004, de 6 de Febrero, por el que se regulan los ensayos clínicos con medicamentos. Nuestra intención es sólo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para llevarlo a cabo lea esta hoja de información con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

2. PARTICIPACIÓN VOLUNTARIA

Tiene que saber que su participación en este estudio es VOLUNTARIA y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que esto altere la relación con su médico ni se produzca prejuicios en su tratamiento.

3. DESCRIPCIÓ GENERAL DE L'ESTUDI

El objetivo principal de este estudio consiste en comparar dos técnicas quirúrgicas preventivas, ambas conservadoras de piel y pezón, para el cáncer de mama en pacientes portadoras sanas de mutaciones en los genes BRCA1 o BRCA2. Se comparará la técnica actual con una nueva intervención en la cual se pretende reducir el riesgo de complicaciones i así aumentar el número de mujeres que optan por la cirugía reductora de riesgo conservadora de piel y pezón como parte de tu tratamiento preventivo. Otros propósitos son averiguar si esta nueva intervención aumenta la satisfacción, calidad de vida y sensibilidad en el pezón-areola y si disminuye el impacto sexual que puede causar una cirugía mayor de este calibre.

En este estudio participarán aproximadamente 94 mujeres portadoras de BRCA 1 i/o 2 de distintos hospitales de España.

Todas las pacientes serán asignadas de forma aleatoria mediante un sistema informático a una de las dos intervenciones quirúrgicas y no se le informará de cuál consiste hasta el post-operatorio. Ambas constaran de 5 visitas programadas con el cirujano plástico (más las visitas que usted necesite) a la consulta durante el transcurso de 6 meses. Si usted pertenece al nuevo enfoque, la cirugía constará de dos tiempos – la primera 15 días antes de la segunda. Se realizarán los controles post-operatorios pertinentes (A las 24h, 72h, 5 días, 15 días y 1 mes) en ambas técnicas.

En la primera visita programada a la consulta, se le solicitará que nos facilite información personal y familiar que resulte de interés para concluir si usted presenta los requisitos para participar en el estudio. En caso afirmativo, si firma el consentimiento informado y lee bien esta hoja de información afirmando que está conforme con el proceso, se le informará en los días posteriores de la segunda visita preoperatoria con el mismo médico, donde se le explicará otra vez cualquier duda o cuestión en referencia a la cirugía, discutirán si quiere optar o no para la reconstrucción mamaria y cuál sería la más adecuada según sus características o preferencias, se hará una valoración preoperatoria con una resonancia magnética de la mama y valoración anestésica y se realizará el test de monofilamento Semmes-Weinstein para mirar qué sensibilidad tiene en el pezón-areola antes de someterse a la cirugía.

La tercera, cuarta y quinta visitas programadas tendrán lugar 1 mes, 3 meses y 6 meses después de la intervención correspondiente, y se le pedirá que completa una serie de cuestionarios (en la cuarta y quinta visita) sobre su opinión respecto distintos aspectos de su vida (grado de satisfacción, impacto sexual, estado anímico, entre otros). También se volverá a realizar el test con monofilamentos para evaluar la sensibilidad en la tercera y cuarta visita.

A parte de las visitas programadas, usted puede recibir todas las visitas de seguimiento que considere oportunas o necesarias.

Si usted acepta participar en el estudio implica que adquirirá las responsabilidades necesarias para asistir en los procedimientos del estudio, igual como seguir las instrucciones del protocolo y notificar cualquier evento adverso que le suceda a los investigadores del estudio. También acepta rellenar los cuestionarios de forma veraz y con el tiempo requerido para contestarlos durante sus visitas a consulta.

4. BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Usted ha decidido realizarse una doble mastectomía profiláctica para reducir los riesgos de tener cáncer de mama en un futuro. Si usted recibe la cirugía convencional, recibirá el mismo tratamiento que si no participase en el estudio y quisiera conservar la piel, areola i pezón. Si está en el grupo experimental se puede beneficiar de mejores resultados estéticos y posiblemente funcionales (sensibilidad) con menos riesgos de complicaciones, pero tendrá que hacerse la cirugía en dos tiempos.

También es posible que usted no obtenga ningún beneficio directo por participar en el estudio; no obstante, se prevé que la información que se obtenga pueda beneficiar en un futuro a otros pacientes y pueda contribuir a un mejor conocimiento del efecto de la cirugía reductora de riesgo con preservación de piel y pezón en pacientes portadoras sanas genéticamente predispuestas a tener cáncer de mama.

No se prevén riesgos ni inconvenientes por participar en este estudio.

Los posibles eventos adversos son los mismos que cualquier mastectomía, añadiendo complicaciones con la perfusión del pezón-areola. Éstas son las siguientes: Dureza o rigidez en el sitio de la incisión, infección, hemorragia o hematoma, seroma, dolor en el pecho, sensación de "tirantez", dermatitis.

Una vez finalizado el estudio, usted recibirá la atención médica necesaria según su condición independientemente de su participación o no en éste.

Los participantes no recibirán una compensación económica por participar en el ensayo clínico, pues sesgaría la selección de los pacientes.

5. TRACTAMIENTOS ALTERNATIVOS

Las formas alternativas de tratamiento incluyen el no tratar esta situación por una conducta quirúrgica: mediante vigilancia estrecha (con resonancias magnéticas o mamografías anuales y examinación bi-anual clínica) o quimioterapia profiláctica con tamoxifeno. También es posible realizar otras cirugías más radicales con extirpación de piel, pezón y areola.

El médico le puede proporcionar más información al respeto si así lo desea.

6. CONFIDENCIALIDAD

El tratamiento, comunicación y cesión de datos de carácter personal de todos los participantes se ajustará según la Ley Orgánica 15/1999 de 13 de diciembre de protección de datos de carácter personal. De acuerdo con lo que establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, por lo que tendrá que dirigir-se al médico del estudio.

Los datos recogidos en el estudio estarán identificados mediante un código y sólo su médico del estudio/colaboradores podrán relacionar estos datos con usted y su historia clínica. Por tanto, su identidad no será revelada a ninguna persona salvo en caso de emergencia médica o requerimiento legal.

Sólo se transmitirán a terceros y a otros países los datos recogidos del estudio que en ningún caso contendrán información que le pueda identificar directamente, como nombre y apellido, iniciales, dirección, núm. De la Seguridad social, etc. En caso que se produzca esta

cesión, será por los mismos fines del estudio descrito y garantizando la confidencialidad como mínimo con el nivel de protección de la legislación vigente en nuestro país.

El acceso a su información personal quedará registrado al médico del estudio/colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen para comprobar datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo con la legislación vigente.

7. SEGURO Y RESPONSABILIDAD

El promotor del estudio dispone de una póliza de seguro que se ajusta a la legislación vigente y que le proporcionará la compensación e indemnización en caso de menoscabo de su salud o de lesiones que puedan producirse en relación con su participación en el estudio

8. OTRA INFORMACIÓN RELLEVANTE

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a su base de datos y puede exigir la destrucción de todas las muestras identificables previamente retenidas para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el investigador lo considera oportuna, ya sea por motivos de seguridad, por cualquier evento adverso que se produzca por la intervención en el estudio o porque se considere que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado la retirada del estudio.

9. CONTACTO PARA MÁS INFORMACIÓN

Si desea más información, puede llamar a la investigadora Sra. Castellà al 685.529.805 o escribir un correo a a.castella.pujol@gmail.com.

Al firmar la hoja de consentimiento adjunta, se comprometa a cumplir con los procedimientos del estudio que se le ha expuesto.

ANNEX 4: Informed Consent Form to Participate in the Clinical trial *named*: Efficacy of the delay procedure prior to nipple-sparing mastectomy in reducing its necrosis rates as a post-operative complication: a randomized control clinical trial

FORMULARI DE CONSENTIMENT INFORMAT

Títol de l'estudi: Eficàcia de la tècnica *"Delay"* prèvia a la mastectomia preservadora del mugró i areola en reduir la taxa de necrosis com a complicació post-operativa

Jo,

_____

- He llegit el Full d'informació pel pacient i el Formulari de consentiment informat que se m'ha entregat. Entenc que podré conservar una copia d'ambdós.
- He pogut fer preguntes sobre l'estudi.
- He rebut suficient informació sobre l'estudi.
- He parlat amb:

  _____ (nom de l'investigador)

- Comprenc que la meva participació és voluntària.
- Comprenc que puc retirar-me de l'estudi:
  - 1º Quan vulgui
  - 2º Sense haver de donar explicacions
  - 3º Sense que això repercuteixi en la meva assistència mèdica
- Presto lliurement la meva aprovació per a participar en l'estudi i dono el meu consentiment per a l'accés i utilització de les meves dades en les condicions detallades en el full d'informació, sempre en conformitat amb la Llei Orgànica 15/1999, de 13 de desembre, sobre protecció de dades de caràcter personal.
- Accedeixo a que les mostres de sang o teixits obtinguts per a l'estudi puguin ser utilitzats en el futur per a nous anàlisis, relacionats amb la malaltia o fàrmacs de l'estudi no prevists en el protocol actual (quedant exclosos els anàlisis genètics).

☐ SÍ ☐ NO

Firma del pacient:

Nom i cognoms: _____

DNI: _ _ _ _ _ _ _ _ - _

Data: __/__/_____

Firma de l'investigador:

Nom i cognoms:_____

DNI: _ _ _ _ _ _ _ _ - _

Data: __/__/____

SPANISH VERSION

FORMULARIO DE CONSENTIMIENTO INFORMADO

Título del estudio: Eficacia de la técnica "*Delay*" previa a la mastectomía preservadora del pezón y areola en reducir la tasa de necrosis como complicación postoperativa.

Yo,

_____

- He leído la hoja de información para el paciente y el formulario de consentimiento informado que se me ha entregado. Entiendo que podré conservar una copia de ambos.
- He podido hacer preguntas sobre el estudio
- He recibido suficiente información sobre el estudio.
- He hablado con:

  _____ (nombre del investigador)

- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio:
  - 1º Cuando quiera
  - 2º Sin tener que dar explicaciones
  - 3º Sin que esto repercuta en mis cuidados médicos
- Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información, siempre en conformidad con la Ley Orgánica 15/1999, de 13 de diciembre, sobre protección de datos de carácter personal.
- Accedo a que las muestras de sangre o tejidos obtenidas para el estudio puedan ser utilizadas en el futuro para nuevos análisis relacionados con la enfermedad o fármacos del estudio no previstos en el protocolo actual (quedando excluidos los análisis genéticos).

☐ SÍ ☐ NO

Firma del paciente:

Nombre y apellidos: _____

DNI: _ _ _ _ _ _ _ _ - _

Fecha: __/__/_____

Firma del investigador:

Nombre y apellidos:_____

DNI: _ _ _ _ _ _ _ _ - _

Fecha: __/__/____

ANNEX 5: Informed consent to surgical procedures

CATALAN VERSION

PACIENT

Jo, participant de l'estudi amb el número d'identificació | | | | | |

he llegit el full informatiu que m'ha entregat el/la Dr/a _____. He comprès les explicacions que m'ha facilitat, i el metge que m'ha atès m'ha permès totes les observacions i m'ha aclarit tots els dubtes que li he plantejat. També comprenc que, en qualsevol moment i sense necessitat de donar cap explicació, puc revocar el consentiment que ara presto. Per això, manifesto que em considero satisfet/a amb la informació rebuda i que comprenc la indicació i els **riscs més freqüents** que poden aparèixer a nivell general durant la realització d'aquest **procediment quirúrgic** així com els riscs concrets que poden aparèixer en el meu cas donada la meva situació clínica i les meves circumstàncies personals (riscs personalitzats) i que són:

_____

_____

_____

I en tals condicions dono el meu consentiment per que es practiqui el següent procediment

Mastectomia bilateral profilàctica conservadora de pell i areola-mugró.

_____

_____, __ de _____ de 20__

Signatura del pacient

DNI: _ _ _ _ _ _ _ _ - _

Signatura del metge

Noms i cognoms: _____

Nº col·legiat:_____

SPANISH VERSION

PACIENTE

Yo, participante del estudio con el número de identificación | | | | | |

he leído la hoja informativo que me ha entregado el/la Dr/a _____. He comprendido las explicaciones que me ha facilitado, y el médico que me ha atendido me ha permitido todas las observaciones y me ha aclarado todas las dudas que le he planteado. También comprendo que, en cualquier momento y sin necesidad de dar ninguna explicación, puedo revocar el consentimiento que ahora presto. Por eso, manifiesto que me considero satisfecho/a con la información recibida y que comprendo la indicación y los riesgos más frecuentes que pueden aparecer a nivel general durante la realización de este procedimiento quirúrgico así como los riesgos concretos que puedan aparecer en mi caso dada mi situación clínica y mis circunstancias personales (riesgos personales) y que son:

_____

_____

_____

Y en tales condiciones doy mi consentimiento para que se practique el siguiente procedimiento:

Mastectomía bilateral profiláctica conservadora de piel y areola-pezón.

_____

_____, __ de _____ de 20__

Signatura de la paciente

DNI: _ _ _ _ _ _ _ _ - _

Signatura del médico

Nombres y apellidos: _____

Nº colegiado:_____

ANNEX 6: Case Report Form (CRF)

CASE REPORT FORM (CRF)	**Hospital:** _____
Project title: *Efficacy of the delay procedure prior to nipple-sparing mastectomy in reducing its necrosis rates as a post-operative complication.*	Patient's identification number | | | | | |

INSTRUCTIONS FOR COMPLETION OF THE CRF

General

- Please print all entries in BLOCK CAPITAL LETTERS using a black ballpoint pen.
- All text and explanatory comments should be brief.
- Answer every question explicitly; do not use ditto marks.
- Do not leave any question unanswered. If the answer to a question is unknown, write "**NK**" (Not Known). If a requested test has not been done, write "**ND**" (Not Done). If a question is not applicable, write "**NA**" (Not Applicable)
- Where a choice is requested, **cross (X)** the appropriate response

Dates and Times

- All date entries must appear in the format DD-MMM-YYYY (e.g 09-Oct-2017). The Month abbreviations are the first three letters of each month respectively.
  In the absence of a precise date for an event or therapy that precedes the participant's inclusion into the study, a partial date may be recorded by recording "NK" in the fields that are unknown.
- All time entries must appear in **24-hour format**. Entries representing midnight should be recorded as 00:00 with the date of the new day that is starting at that time

Correction of Errors

- Do not overwrite erroneous entries, or use correction fluid or erasers
- Draw a straight line through the entire erroneous entry without obliterating it
- Clearly enter the correct value next to the original (erroneous) entry
- Date and initial the correction

APPOINTMENT 1 ☐	Doctor 'surname: _____ Date: D D M M M Y Y Y Y
- The patient has read the **Information Sheet** ☐ - The patient has signed the **Informed Consent** ☐	
APPOINTMENT 2 ☐	Doctor 'surname: _____ Date: D D M M M Y Y Y Y
INTERVENTION A ☐	INTERVENTION B ☐

PARTICIPANT INFORMATION

- Date of birth:
- Weight (kg): _ _ ,_ _.
- Height (m): _ _ , _ _
- Cigarrette Smoking:
  - Non Smoker ☐
  - Ex-Smoker ☐
  - Smoker with ☐

    <10 PYS or >5YTQ prior to surgery
- Grade of ptosis:

  A ☐ 1 ☐

  B ☐ 2 ☐

Marital status:

Single ☐

In a relationship/married ☐

Divorced ☐

Widowed ☐

Medical Comorbidities

Yes ☐ No ☐

Other non-genetic Risk Factors of Breast Cancer:

Previous pathology in breast ☐

Precocious menarche ☐

Late menopause ☐

Nulliparity ☐

Age >30 at first birth ☐

Breastfeeding history ☐

Alcoholism history ☐

Ethnicity:

Caucasian ☐

Hispanic ☐

Asian ☐

Indian ☐

American ☐

African ☐

- The patient has signed the **Information Consent to Surgical Procedures** ☐

Semmes Weinstein Monofilaments test:

	0	1	2	3	4	5		0	1	2	3	4	5
N1							A1						
N2							A2						
N3							A3						
N4							A4						

SURGERY ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

ONLY FOR **INTERVENTION B** (1st time approach) NOTE: *Please do not answer this section if your patient has been assigned to Intervention A and continue to the next step.*

- Skin Flap Thickness (mm) : _____
- Incision orientation
  - Periareolar ☐
  - Lateral ☐
  - Inframmamary fold ☐

Date:

D D M M M Y Y Y Y

Post-operation control:

- **Necrosis and ischemia outcomes**

Yes ☐ No ☐

If yes, please specify grade:

A	☐	1	☐
B	☐	2	☐
C	☐	3	☐
D	☐	4	☐

Post-operation control:

- **Post-operative complications**

Yes ☐ No ☐

If yes, please which:

Hemorrhage	☐	Seroma	☐	Infection	☐
Hematoma	☐	Aesthetic defects	☐	Nerve lesion	☐
Lymphedema	☐				

BOTH **INTERVENTION A** AND **INTERVENTION B** (2nd time approach)

- Skin Flap Thickness (mm): _____
- Incision orientation
  - Periareolar ☐
  - Lateral ☐
  - Inframammary fold ☐
- Intraoperative complications

  Yes ☐ No ☐

  If yes, please specify which: _____

Timing of the breast reconstruction:

IBR	☐
DBR	☐
DIBR	☐

- Intraoperative biopsy results:
  - Normal ☐
  - Malignant ☐
  - Other ☐
- Breast weight (kg): _ _,_ _

Type of breast reconstruction:

- Direct-to-implant ☐
- Expander/implant ☐
- Autologous tissue ☐
- Combination ☐

POST-OPERATION CONTROL 1 ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

- Necrosis and ischemia outcomes

Yes ☐ No ☐

If yes, please specify grade:

A ☐ B ☐ C ☐ D ☐

1 ☐ 2 ☐ 3 ☐ 4 ☐

- Post-operative complications

Yes ☐ No ☐

If yes, please which:

Hemorrhage ☐ Seroma ☐ Infection ☐

Hematoma ☐ Aesthetic defects ☐ Nerve lesion ☐

Lymphedema ☐

POST-OPERATION CONTROL 2 ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

- Necrosis and ischemia outcomes

Yes ☐ No ☐

If yes, please specify grade:

A ☐ B ☐ C ☐ D ☐

1 ☐ 2 ☐ 3 ☐ 4 ☐

POST-OPERATION CONTROL 3 ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

- Necrosis and ischemia outcomes

Yes ☐ No ☐

If yes, please specify grade:

A ☐ B ☐ C ☐ D ☐

1 ☐ 2 ☐ 3 ☐ 4 ☐

POST-OPERATION CONTROL 4 ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

- Necrosis and ischemia outcomes

Yes ☐ No ☐

If yes, please specify grade:

A ☐ B ☐ C ☐ D ☐

1 ☐ 2 ☐ 3 ☐ 4 ☐

- Flap success

Yes ☐ No ☐

- Post-operative complications

Yes ☐ No ☐

If yes, please which:

Hemorrhage ☐ Seroma ☐ Infection ☐

Hematoma ☐ Aesthetic defects ☐ Nerve lesion ☐

Lymphedema ☐

APPOINTMENT 3 ☐

Doctor's surname: _____

Date: D D M M M Y Y Y Y

- -Necrosis and ischemia outcomes

Yes ☐ No ☐

If yes, please specify grade:

A ☐ B ☐ C ☐ D ☐

1 ☐ 2 ☐ 3 ☐ 4 ☐

Semmes Weinstein Monofilaments test:

	0	1	2	3	4	5		0	1	2	3	4	5
N1							A1						
N2							A2						
N3							A3						
N4							A4						

APPOINTMENT 4 ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

	Answered	Punctuation
BREAST-Q	☐	☐
CSFQ-14-F	☐	☐
SF-36	☐	☐

APPOINTMENT 5 ☐

Doctor' surname: _____

Date: D D M M M Y Y Y Y

	Answered	Punctuation
BREAST-Q	☐	☐
CSFQ-14-F	☐	☐
SF-36	☐	☐

Semmes Weinstein Monofilaments test:

	0	1	2	3	4	5		0	1	2	3	4	5
N1							A1						
N2							A2						
N3							A3						
N4							A4						

ANNEX 7: BREAST-Q™ Questionnaire

CATALAN VERSION

BREAST-Q™ MÒDUL MASTECTOMIA (PREOPERATIVA) VERSIÓ 2.0 SATISFACCIÓ DELS PITS – Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Tenint en ment l'àrea del pit, al llarg de la setmana passada, quin grau de satisfacció o insatisfacció ha tingut amb:

	Molt insatisfeta	Una mica insatisfeta	Una mica satisfeta	Molt satisfeta
a. Com es veu al mirall vestida?	1	2	3	4
B. Quina confortabilitat troba respecte el seu sostenidor?	1	2	3	4
c. És capaç de fer servir roba més ajustada?	1	2	3	4
d. Com es veu al mirall sense roba?	1	2	3	4

BREAST-Q™ MÒDUL MASTECTOMIA (POSTOPERATIVA) VERSIÓ 2.0 SATISFACCIÓ AMB ELS PITS– Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Tenint en ment l'àrea del pit, al llarg de la setmana passada, quin grau de satisfacció o insatisfacció ha tingut amb:

	Molt insatisfeta	Una mica insatisfeta	Una mica satisfeta	Molt satisfeta
a. Com es veu al mirall vestida?	1	2	3	4
B. Quina confortabilitat troba respecte el seu sostenidor?	1	2	3	4
c. És capaç de fer servir roba més ajustada?	1	2	3	4
d. Com es veu al mirall sense roba?	1	2	3	4

BREAST-Q™ MÒDUL MASTECTOMIA (POST-OPERATIVA) VERSION 2.0 SATISFACCIÓ AMB EL CIRURGIÀ– Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Aquestes preguntes es dirigeixen sobre el cirurgià plàstic. Ha sentit que ell/ella:

	Definitivament en desacord	Una mica en desacord	Una mica d'acord	Definitivament d'acord
a. Va ser professional?	1	2	3	4
B Li va donar confiança?	1	2	3	4
c. La va involucrar en el procés de presa de decisions?	1	2	3	4
d. Va ser tranquil·litzador?	1	2	3	4
e. Va respondre totes les seves preguntes?	1	2	3	4
f. La va fer sentir còmode?	1	2	3	4
g. Estava allà des del principi fins al final?	1	2	3	4
h. Va ser fàcil parlar-li?	1	2	3	4
i. Va entendre el que vostè volia?	1	2	3	4
j. Era sensible?	1	2	3	4
k. Va fer temps per resoldre les vostres inquietuds?	1	2	3	4
l. Estava disponible quan tenia problemes?	1	2	3	4

BREAST-Q™ MÒDUL MASTECTOMIA (POST-OPERATIVA) VERSIÓ 2.0 SATISFACCIÓ AMB L'EQUIP DE METGES– Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Aquestes preguntes es dirigeixen sobre l'equip mèdic. Ha sentit que ell/ella:

	Definitivament en desacord	Una mica en desacord	Una mica d'acord	Definitivament d'acord
a. Van ser professionals?	1	2	3	4
b. La van tractar amb respecte?	1	2	3	4
c. Eren experts?	1	2	3	4
d. Van ser amables i atents?	1	2	3	4
e. La van fer sentir còmode?	1	2	3	4
f. Estàven allà des del principi fins al final?	1	2	3	4
g. Estaven disponibles quan tenia problemes?	1	2	3	4

SPANISH VERSION

BREAST-Q™ MÓDULO MASTECTOMIA (PREOPERATIVA) VERSIÓN 2.0 SATISFACCIÓN DE LOS PECHOS – Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Teniendo en mente el área del pecho, a lo largo de la semana pasada, qué grado de satisfacción o insatisfacción ha tenido con:

	Muy insatisfecha	Un poco insatisfecha	Una poco satisfecha	Muy satisfecha
a. ¿Cómo se ve al espejo vestida?	1	2	3	4
B. ¿Qué confortabilidad encuentra respecto su sujetador?	1	2	3	4
c. ¿Es capaz de utilizar ropa más ajustada?	1	2	3	4
d. ¿Cómo se ve al espejo sin ropa?	1	2	3	4

BREAST-Q™ MÓDULO MASTECTOMIA (POSTOPERATIVA) VERSIÓN 2.0 SATISFACCIÓN CON LOS PECHOS– Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Teniendo en mente el área del pecho, a lo largo de la semana pasada, qué grado de satisfacción o insatisfacción ha tenido con:

	Muy insatisfecha	Un poco insatisfecha	Una poco satisfecha	Muy satisfecha
a. ¿Cómo se ve al espejo vestida?	1	2	3	4
B. ¿Qué confortabilidad encuentra respecto su sujetador?	1	2	3	4
c. ¿Es capaz de utilizar ropa más ajustada?	1	2	3	4
d. ¿Cómo se ve al espejo sin ropa?	1	2	3	4

BREAST-Q™ MÓDULO MASTECTOMIA (POST-OPERATIVA) VERSIÓN 2.0 SATISFACCIÓN CON EL CIRURJANO– Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Estas preguntas se dirigen hacia el cirujano plástico. Ha notado que él/ella:

	Definitivamente en desacuerdo	Un poco en desacuerdo	Un poco de acuerdo	Definitivamente de acuerdo
a. ¿Fue profesional?	1	2	3	4
B ¿Le dio confianza?	1	2	3	4
c. ¿La involucró en el proceso de toma de decisiones?	1	2	3	4
d. ¿Fue tranquilizador?	1	2	3	4
e. ¿Respondió todas sus dudas?	1	2	3	4
f. ¿La hizo sentir cómoda?	1	2	3	4
g. ¿Estuvo allí des del principio hasta el final?	1	2	3	4
h. ¿Fue fácil hablarle?	1	2	3	4
i. ¿Entendió el que usted quería?	1	2	3	4
j. ¿Fue sensible?	1	2	3	4
k. ¿Hizo tiempo para resolver sus inquietudes?	1	2	3	4
l. ¿Estaba disponible cuando tenia problemas?	1	2	3	4

BREAST-Q™ MÓDULO MASTECTOMIA (POST-OPERATIVA) VERSIÓN 2.0 SATISFACCIÓN CON EL EQUIPO DE MÉDICOS– Memorial Sloan Kettering Cancer Center and The University of British Columba, 2017.

Estas preguntas se dirigen hacia el equipo médico. Ha notado que:

	Definitivamente en desacuerdo	Un poco en desacuerdo	Un poco de acuerdo	Definitivamente de acuerdo
a. ¿Fueron profesionales?	1	2	3	4
b. ¿La trataron con respecto?	1	2	3	4
c. ¿Eran expertos?	1	2	3	4
d. ¿Fueron amables y atentos?	1	2	3	4
e. ¿La hicieron sentir cómoda?	1	2	3	4
f. ¿Estuvieron allí des del principio hasta el final?	1	2	3	4
g. ¿Estuvieron disponibles cuando tenía problemas?	1	2	3	4

ANNEX 8: Short-Form of the Changes in Sexual Functioning Questionnaire for females - (CSFQ-14-F)

CATALAN VERSION

NOTA: Es tracta d'un qüestionari sobre l'activitat sexual i la funció sexual. Per activitat sexual, volem dir relacions sexuals, masturbacions, fantasies sexuals i altres activitats.

1. En comparació amb l'activitat sexual més plaent que ha tingut mai, quant agradable és la teva vida sexual ara mateix?
    1. □ Cap gust o plaer
    2. □ Poc gust o plaer
    3. □ Algun gust o plaer
    4. □ Molt de gust o plaer
    5. □ Gran gust o plaer
2. Amb quina freqüència es dedica a l'activitat sexual ara? (coit, masturbació, etc.)
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al mes o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies
3. Amb quina freqüència desitja realitzar alguna activitat sexual ara?
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al més o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies
4. Amb quina freqüència duu a terme els pensaments sexuals (pensar sobre el coit, fantasies sexuals) actualment?
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al mes o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies
5. Gaudeix de llibres, pel·lícules, música o obres d'art amb contingut sexual?
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al mes o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies

6. Quant de plaer o gust obté de pensar i imaginar activitats sexuals?
    1. □ Cap gust o plaer
    2. □ Poc gust o plaer
    3. □ Algun gust o plaer
    4. □ Molt de gust o plaer
    5. □ Gran gust o plaer
7. Amb quina freqüència aconsegueix excitar-se sexualment?
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al mes o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies
8. S'excita fàcilment?
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al mes o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies
9. Té lubricació vaginal adequada durant l'activitat sexual?
    1. □ Mai
    2. □ Rarament (molt menys que la meitat de les vegades)
    3. □ De vegades (la meitat de les vegades)
    4. □ Sovint (molt més que la meitat de les vegades)
    5. □ Sempre
10. Quantes vegades s'excita i després perd interès?
    1. □ Mai
    2. □ Rarament (molt menys que la meitat de les vegades)
    3. □ De vegades (la meitat de les vegades)
    4. □ Sovint (molt més que la meitat de les vegades)
    5. □ Sempre
11. Amb quina freqüència experimenta un orgasme?
    1. □ Mai
    2. □ Rarament (molt menys que la meitat de les vegades)
    3. □ De vegades (la meitat de les vegades)
    4. □ Sovint (molt més que la meitat de les vegades)
    5. □ Sempre
12. És capaç de tenir un orgasme quan vol?
    1. □ Mai
    2. □ Rarament (molt menys que la meitat de les vegades)
    3. □ De vegades (la meitat de les vegades)
    4. □ Sovint (molt més que la meitat de les vegades)

5. □ Sempre

13. Quan de plaer o gust obté dels orgasmes?
    1. □ Cap gust o plaer
    2. □ Poc gust o plaer
    3. □ Algun gust o plaer
    4. □ Molt de gust o plaer
    5. □ Gran gust o plaer

14. Amb quina freqüència té orgasmes dolorosos?
    1. □ Mai
    2. □ Rarament (una vegada al mes o menys)
    3. □ De vegades (més d'una vegada al mes o fins a dos cops per setmana)
    4. □ Sovint (més de dues vegades per setmana)
    5. □ Tots els dies

SPANISH VERSION

NOTA: Se trata de un cuestionario sobre la actividad sexual y la función sexual. Por actividad sexual, queremos decir relaciones sexuales, masturbaciones, fantasías sexuales y otras actividades.

1. En comparación con la actividad sexual más placentera que haya tenido nunca, cómo de satisfactoria es su vida sexual ahora mismo?
    1. □ Nada satisfactoria
    2. □ Poco satisfactoria
    3. □ Más que un poco satisfactoria
    4. □ Mucho satisfactoria
    5. □ Gran satisfactoria
2. ¿Con qué frecuencia se dedica a la actividad sexual ahora? (coito, masturbación, etc.)
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días
3. ¿Con qué frecuencia desea realizar alguna actividad sexual ahora?
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días
4. ¿Con qué frecuencia lleva a cabo los pensamientos sexuales (pensar sobre el coito, fantasías sexuales) actualmente?
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días
5. ¿Disfruta de libros, películas, música o obras de arte con contenido sexual?
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días

6. ¿Qué grado de satisfacción obtiene de pensar y imaginar actividades sexuales?
    1. □ Nada satisfactorio
    2. □ Poco satisfactorio
    3. □ Más que un poco satisfactorio
    4. □ Mucho satisfactorio
    5. □ Gran satisfactorio
7. ¿Con qué frecuencia consigue excitarse sexualmente?
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días
8. ¿Se excita fácilmente?
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días
9. ¿Tiene lubricación vaginal adecuada durante la actividad sexual?
    1. □ Nunca
    2. □ Raramente (mucho menos que la mitad de las veces)
    3. □ A veces (la mitad de las veces)
    4. □ A menudo (mucho más que la mitad de las veces)
    5. □ Siempre
10. ¿Cuántas veces se excita y después pierde interés?
    1. □ Nunca
    2. □ Raramente (mucho menos que la mitad de las veces)
    3. □ A veces (la mitad de las veces)
    4. □ A menudo (mucho más que la mitad de las veces)
    5. □ Siempre
11. ¿Con qué frecuencia experimenta un orgasmo?
    1. □ Nunca
    2. □ Raramente (mucho menos que la mitad de las veces)
    3. □ A veces (la mitad de las veces)
    4. □ A menudo (mucho más que la mitad de las veces)
    5. □ Siempre
12. ¿Es capaz de tener un orgasmo cuando quiere?
    1. □ Nunca
    2. □ Raramente (mucho menos que la mitad de las veces)
    3. □ A veces (la mitad de las veces)
    4. □ A menudo (mucho más que la mitad de las veces)

5. □ Siempre

13. ¿Qué grado de satisfacción obtiene de los orgasmos?
    1. □ Nada satisfactorio
    2. □ Poco satisfactorio
    3. □ Más que un poco satisfactorio
    4. □ Mucho satisfactorio
    5. □ Gran satisfactorio
14. ¿Con qué frecuencia tiene orgasmos dolorosos?
    1. □ Nunca
    2. □ Raramente (una vez al mes o menos)
    3. □ A veces (más de una vez al mes o hasta dos veces por semana)
    4. □ A menudo (más de dos veces por semana)
    5. □ Todos los días

ANNEX 9: 36 Item Short Form Survey Instrument (SF-36)

CATALAN VERSION

Triï una opció per a cada ítem del qüestionari:

1. En general, vostè diria que la seva salut és:
    1. ☐ Excel·lent
    2. ☐ Molt bona
    3. ☐ Bona
    4. ☐ Justa
    5. ☐ Pobre

2. **En comparació a fa un any**, com qualificaria la seva salut en general **ara**?
    1. ☐ Molt millor ara que fa un any
    2. ☐ Una mica millor ara que fa un any
    3. ☐ Més o menys el mateix
    4. ☐ Una mica pitjor que fa un any
    5. ☐ Molt pitjor ara que fa un any

Els següents ítems parlen sobre activitats que podria fer en un dia quotidià. **La seva salut la limita ara** en aquestes activitats? En cas afirmatiu, quant?

	Sí, em limita molt	Sí, em limita una mica	No, no em limita gens
3. **Activitats vigoroses**, com córrer, aixecar objectes pesants, participant en esports extenuants	☐ 1	☐ 2	☐ 3
4. **Activitats moderades,** com moure una taula, utilitzar l'aspiradora, jugar als bitlles, jugar a golf	☐ 1	☐ 2	☐ 3
5. Aixecar o carregar comestibles	☐ 1	☐ 2	☐ 3
6. Pujar diversos trams d'escales	☐ 1	☐ 2	☐ 3
7. Pujar **un tram** d'escala	☐ 1	☐ 2	☐ 3
8. Flexionar, agenollar-se o ajupir-se	☐ 1	☐ 2	☐ 3
9. Caminar **més d'un quilòmetre**	☐ 1	☐ 2	☐ 3
10. Caminar **diverses illes urbanes**	☐ 1	☐ 2	☐ 3
11. Caminar **una illa urbana**	☐ 1	☐ 2	☐ 3
12. Dutxar-se o vestir-se	☐ 1	☐ 2	☐ 3

Al llarg de les **4 setmanes anteriors**, ha tingut algun d'aquests problemes amb la seva feina o altres activitats diàries regulars **com a resultat de la seva salut física**?

	Sí	No
13. Reduïa la **quantitat de temps** que dedicava en la feina o altres activitats	☐ 1	☐ 2
14. **Realitzava amb èxit menys coses** del que li agradaria	☐ 1	☐ 2
15. Estava limitada en el **tipus** de treball o altres activitats	☐ 1	☐ 2
16. Tenia **dificultats** per a realitzar la feina o altres activitats (per exemple, requeria esforços extres)	☐ 1	☐ 2

Al llarg de les **4 setmanes anteriors**, ha tingut algun d'aquests problemes amb la seva feina o altres activitats diàries regulars **com a resultat de problemes emocionals** (com ara sentir-se trista o angoixada)?

	Sí	No
17. Reduïa la **quantitat de temps** que dedicava en la feina o altres activitats	☐ 1	☐ 2
18. **Realitzava amb èxit menys coses** del que li agradaria	☐ 1	☐ 2
19. No feia la feina o altres activitats tan **curosament** com de costum.	☐ 1	☐ 2

20. Al llarg de les **4 setmanes anteriors**, fins a quin punt la seva salut física o problemes emocionals han interferit amb les seves activitats socials normals amb la família, amics, veïns o grups?
    1. ☐ Gens
    2. ☐ Molt poc
    3. ☐ Moderadament
    4. ☐ Una mica
    5. ☐ Extremadament
21. Quan de **dolor al cos** ha tingut durant **les quatre setmanes anteriors?**
    1. ☐ Cap
    2. ☐ Molt lleu
    3. ☐ Lleu
    4. ☐ Moderat
    5. ☐ Sever
    6. ☐ Molt sever
22. Al llarg de les **4 setmanes anteriors**, fins a quin punt el **seu dolor** ha interferit amb la seva feina?
    1. ☐ Gens
    2. ☐ Molt lleu
    3. ☐ Lleu

4. ☐ Moderat
5. ☐ Sever
6. ☐ Molt sever

Aquestes preguntes tenen relació amb els seus sentiments i com les coses han anat durant **les 4 setmanes anteriors**. Per a cada pregunta, respongui només una de les 5 opcions en cada fila que considera més pròxima a la forma com s'ha sentit.

Amb quina freqüència al llarg de les **4 anteriors setmanes...**	Quasi tot el temps	La majoria del temps	Una bona part del temps	Alguna part del temps	Poquet del temps	Gens del temps
23. S'ha sentit ple de vitalitat?	☐1	☐2	☐3	☐4	☐5	☐6
24. Ha estat nerviosa?	☐1	☐2	☐3	☐4	☐5	☐6
25. S'ha notat tan trista que res li aixecava els ànims?	☐1	☐2	☐3	☐4	☐5	☐6
26. S'ha sentit calmada i tranquil·la?	☐1	☐2	☐3	☐4	☐5	☐6
27. Tenia energia?	☐1	☐2	☐3	☐4	☐5	☐6
28. Es sentia desanimat i trist?	☐1	☐2	☐3	☐4	☐5	☐6
29. Es sentia esgotada?	☐1	☐2	☐3	☐4	☐5	☐6
30. Era feliç?	☐1	☐2	☐3	☐4	☐5	☐6
31. Es sentia cansada?	☐1	☐2	☐3	☐4	☐5	☐6

32. Al llarg de les **4 setmanes anteriors**, amb quina freqüència la seva salut física o problemes emocionals han interferit amb les seves activitats socials normals amb la família, amics, veïns o grups?

1. ☐ Tot el temps
2. ☐ Quasi tot el temps
3. ☐ Una part del temps
4. ☐ Poc temps
5. ☐ Gens del temps

Especifiqui en quin grau de VERTADER o FALS és **cadascuna** de les següents frases:

	Definitivament cert	Majoritàriament cert	No ho se	Majoritàriament fals	Definitivament fals
33. Crec que em poso malalta més fàcilment que les altres persones	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Sóc igual de sana que qualsevol altra persona	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Crec que la meva salut empitjorarà	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. La meva salut és excel·lent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SPANISH VERSION

Escoja una opción de los siguientes ítems del cuestionario:

1. En general, usted diría que su salud es:
    1. ☐ Excelente
    2. ☐ Muy buena
    3. ☐ Buena
    4. ☐ Justa
    5. ☐ Pobre

2. **En comparación a un año atrás**, ¿cómo cualificaría su salud en general **ahora**?
    1. ☐ Mucho mejor ahora que hace un año
    2. ☐ Algo mejor ahora que hace un año
    3. ☐ Más o menos igual que hace un año
    4. ☐ Un poquito peor ahora que hace un año
    5. ☐ Mucho peor ahora que hace un año

Los siguientes ítems hablan sobre actividades que podría hacer en un día cuotidiano. ¿**Su salud la limita ahora** en estas actividades? En caso afirmativo, ¿cuánto?

	Sí, me limita mucho	Sí, me limita un poco	No, no me limita nada
3. **Esfuerzos intensos**, tales como correr, levantar objetos pesados, o participar en deportes agotadores	☐ 1	☐ 2	☐ 3
4. **Esfuerzos moderados**, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de una hora	☐ 1	☐ 2	☐ 3
5. Coger o llevar la bolsa de la compra	☐ 1	☐ 2	☐ 3
6. Subir **varios pisos** por la escalera	☐ 1	☐ 2	☐ 3
7. Subir **un solo piso**	☐ 1	☐ 2	☐ 3
8. Agacharse o arrodillarse	☐ 1	☐ 2	☐ 3
9. Caminar **más de un kilómetro**	☐ 1	☐ 2	☐ 3
10. Caminar **varias manzanas**	☐ 1	☐ 2	☐ 3
11. Caminar **una manzana**	☐ 1	☐ 2	☐ 3
12. Ducharse o vestirse	☐ 1	☐ 2	☐ 3

Durante las **4 últimas semanas**, ¿ha tenido alguno de estos problemas con su trabajo o otras actividades diarias regulares **como resultado de su salud física?**

	Sí	No
13. **Reducía el tiempo** dedicado al trabajo o a sus actividades cotidianas	☐ 1	☐ 2
14. **Realizaba con éxito menos cosas** del que le gustaría	☐ 1	☐ 2
15. Estuvo limitada en el **tipo** de trabajo o otras actividades	☐ 1	☐ 2
16. Tenía **dificultades** para realizar el trabajo o otras actividades (por ejemplo, requería esfuerzo extras)	☐ 1	☐ 2

Durante las **4 últimas semanas**, ¿ha tenido alguno de estos problemas con su trabajo o otras actividades diarias regulares **como resultado de problemas emocionales** (como sentirse triste o angustiada)?

	Sí	No
17. **Reducía la cantidad de tiempo** que dedicaba en el trabajo o otras actividades	☐ 1	☐ 2
18. **Realizaba con éxito menos cosas** del que le gustaría	☐ 1	☐ 2
19. No hizo su trabajo o sus actividades cotidianas tan **cuidadosamente** como de costumbre	☐ 1	☐ 2

20. Durante las **4 últimas semanas,** ¿hasta qué punto su salud física o problemas emocionales han interferido con sus actividades sociales normales con la familia, amigos, vecinos o grupos?
    1. ☐ Nada
    2. ☐ Muy poco
    3. ☐ Moderadamente
    4. ☐ Bastante
    5. ☐ Extremadamente
21. Tuvo **dolor** en alguna parte del cuerpo durante las **4 últimas** semanas?
    1. ☐ No, ninguno
    2. ☐ Sí, muy poco
    3. ☐ Sí, un poco
    4. ☐ Sí, moderado
    5. ☐ Sí, mucho
    6. ☐ Si, muchísimo

22. Durante las **4 últimas semanas**, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?
    1. ☐ Nada
    2. ☐ Muy leve
    3. ☐ Leve
    4. ☐ Moderado
    5. ☐ Severo
    6. ☐ Muy severo

Estas preguntas tienen relación con sus sentimientos y cómo las cosas le han ido durante las **4 últimas semanas**. Para cada pregunta, reponga sólo una de las 5 opciones en cada hilera que considere más próxima a la forma cómo se ha sentido.

Con qué frecuencia a lo largo de las **4 semanas anteriores…**	Casi todo el tiempo	La mayoría del tiempo	Una bona parte del tiempo	Alguna parte del tiempo	Poco del tiempo	Nada del tiempo
23. ¿Se sintió llena de vitalidad?	☐1	☐2	☐3	☐4	☐5	☐6
24. ¿Ha estado nerviosa?	☐1	☐2	☐3	☐4	☐5	☐6
25. ¿Se sintió tan baja de moral que nada podía animarle?	☐1	☐2	☐3	☐4	☐5	☐6
26. ¿Se sintió calmada y tranquila?	☐1	☐2	☐3	☐4	☐5	☐6
27. ¿Tenía energía?	☐1	☐2	☐3	☐4	☐5	☐6
28. ¿Se sintió desanimada y triste?	☐1	☐2	☐3	☐4	☐5	☐6
29. ¿Se sintió agotada?	☐1	☐2	☐3	☐4	☐5	☐6
30. ¿Se sintió feliz?	☐1	☐2	☐3	☐4	☐5	☐6
31. ¿Se sentía cansada?	☐1	☐2	☐3	☐4	☐5	☐6

32. Durante las **4 semanas anteriores**, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos, familiares, vecinos o grupos)??
    1. ☐ Todo el tiempo
    2. ☐ Casi todo el tiempo

3. ☐ Una parte del tiempo
4. ☐ Poco tiempo
5. ☐ Nada del tiempo

Especifique en qué grado de VERDADERO o FALSO es **cada una** de las siguientes frases:

	Definitivamente cierto	Mayoritariamente cierto	No lo sé	Mayoritariamente falso	Definitivamente falso
33. Creo que me pongo enferma más fácilmente que otras personas	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Estoy tan sana como cualquiera.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Creo que mi salud va a empeorar	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Mi salud es excelente	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5