BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009903
Article Type:	Protocol
Date Submitted by the Author:	10-Sep-2015
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Epidemiology
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY

Dead space closure with quilting suture versus conventional closure with drainage for the prevention of seroma after mastectomy for breast cancer (QUISERMAS): protocol for a multicentre randomised controlled trial

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Abstract

Introduction

Postoperative wound seromas is common after mastectomy. This complication is associated with significant impact on patient outcomes and healthcare costs. The optimal closure approach for seroma prevention remains unknown but some evidence suggests that quilting suture of the dead space could lower the incidence of seroma. The aim of this trial is to compare seroma formation using quilting suture versus conventional closure with drainage in patients undergoing mastectomy.

Methods and analysis

This is a multicentre, randomised controlled trial in women undergoing mastectomy with or without axillary involvement. Exclusion criteria include indication of bilateral mastectomy or immediate reconstruction and any physical or psychiatric condition that could impair patient's ability to cooperate with postoperative data collection or that do not allow an informed consent. Three hundred and twenty participants will be randomised in a 1:1 ratio to receive either quilting suture or conventional wound closure with drain. The primary outcome is seroma requiring either aspiration or surgical intervention within 21 days following mastectomy. Secondary outcomes include seroma regardless of whether or not it requires an intervention, surgical site infection, pain score, cosmetic result, patient's quality of life, costs and cost-effectiveness. The primary analysis will be an intention-to treat analysis performed with a χ^2 test (or Fisher's exact test).

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20,

16/12/2014). Study findings will be published in peer-reviewed journals and presented at relevant national and international breast cancer conferences.

Trial registration number:

The QUISERMAS trial is registered with clinicaltrials.gov (NCT02263651).

Strengths and limitations of this study

- QUISERMAS is the first multicentre randomised controlled trial to assess quilting suture of the dead space after mastectomy on seroma prevention
- Cosmetic result will be assessed by an independent adjudication committee.
- An economic evaluation will be conducted alongside the trial.
- Surgeons and patients cannot be blinded to the surgical arms, there is a risk of bias in the assessment of outcomes and decisions to perform seroma aspiration.

Introduction

Breast cancer is the most common cancer worldwide. Surgical treatment is the preferred option and about 14.000 mastectomies are performed each year in France. [1] Postoperative seroma is a common complication after mastectomy. [2-9] This complication is secondary to the disruption of lymphatic channels that inevitably complicates extensive surgical dissection and disruption of tissue planes creating a "dead space". Excessive fluid accumulation in a seroma stretches the skin, resulting in patient discomfort, impaired homolateral shoulder function and higher risk of surgical site infection (SSI). In rare cases, a fibrous encapsulated seroma forms that is resistant to conservative treatment and requires subsequent surgical resection. Thus, this complication may also impact healthcare costs requiring prolongation of hospital stay or unplanned outpatient visits and may delay adjuvant therapy.

Conventional wound closure commonly uses suction drain after mastectomy to prevent seroma despite seroma frequently occurs after drain removal. [10] Studies on seroma prevention have focused on the obliteration of the dead space through, fibrinogen, thrombin sealants and glues or Tetracyclin with poor results. [11-20] Some recent evidence suggests that quilting suture reduces the incidence of seroma. [21-23] Quilting suture consists in suturing the skin flaps to the underlying musculature to reduce "dead space"[24]. It aims to restore the integrity of tissue planes. Ten Wolde et al, retrospectively analysed 176 consecutive patients who underwent mastectomy and/or axillary lymph node dissection (ALND), this included patients undergoing an ALND with lumpectomy in whom only the axilla was quilted. All patients had a drain in the quilted area that was removed on the day of discharge, at least within 36 h following surgery. The incidence of seroma decreased significantly from 80.5% to 22.5 % in the quilted group (n=89), $p<0.01$ and the volume of aspirations from 1660 ml to 611ml ($p=0.05$). [22] Quilting closure technique was also assessed in an observational study based on 119 consecutive patients in our tertiary breast cancer unit whose fifty-nine received quilting suture (without drain) and 60 received conventional closure with drainage. The results showed a

significant reduction in seroma for patients with quilting suture as compared to patients with conventional closure with drain (odds ratio [OR] = 0.26, 95% Confidence Interval = 0.08-0.86; p=0.03) The hypothesis around quilting efficacy is that dead space is the major contributor to seroma formation, and that this surgical technique applied to obliterate the dead space might reduce the incidence of this complication. [23]

As recommended in the IDEAL framework describing the stages for development of innovation in surgery, quilting suture now needs to be assessed in a controlled randomised trial. [25] Thus, the aim of our project is to assess, in a randomised controlled trial, quilting suture of the "dead space" without drainage at the pectoral area as compared to conventional closure with drainage on seroma prevention within 21 days following mastectomy for breast cancer.

Study objectives

Our primary objective is to assess the impact of quilting on rates of wound seroma requiring ponction or surgical intervention within 21 days following mastectomy.

Secondary objectives are to compare quilting suture of the "dead space" without drainage of the pectoral area to conventional closure with drainage after mastectomy for breast cancer regarding wound-related complications, surgical morbidity, pain, shoulder movement, cosmesis results, health related quality of life, costs and cost-effectiveness.

Methods and analysis

Study design

QUISERMAS is a multicentre randomised controlled trial with parallel groups comparing quilting suture with conventional closure with drain in the prevention of seroma in patients undergoing mastectomy with or without axillary surgery.

Setting

The trial will be conducted in four French university hospitals (Tours, Nantes, Poitiers, Rennes). The study will be conducted in the Breast surgery Departments of these academic centres.

Participants

Inclusion criteria

The inclusion criteria are: (1) Patients with operable breast cancer (invasive carcinoma and/or ductal carcinoma in situ) for whom mastectomy is recommended or preferred by the patient either alone or in association with axillary clearance either sentinel lymph node biopsy or standard level I/II axillary node dissection, (2) Aged ≥18 years and ≤ 85 years,

Exclusion criteria

The exclusion criteria are: (1) Patients with an indication of bilateral mastectomy or immediate reconstruction, (2) Planned outpatient surgery, (3) Patients with known degenerative neuromuscular disease with thoracic muscular damage, (4) Patients with any physical or psychiatric condition that could impair with outcome assessment and maintaining follow-up.

Study participants are patients who meet the selection criteria and are willing and able to sign written informed consent.

Recruitment

The first patient was randomised on October 2014. Enrolment is ongoing at the time of publication.

The recruitment process is planned to fit with routine practice. Potential participants to the trial are identified at the time they attend for diagnosis and treatment choice for their breast cancer in one of the four involved tertiary-care centres. Patients who meet selection criteria receive a brief study presentation and full participant information sheet by a clinician. After

selection criteria confirmation and answering to potential further patient questions about the trial, written informed consent is obtained before surgery by the patient's surgeon.

Baseline data are collected following consent during the preoperative period.

Randomisation

Randomisation is undertaken by the surgeon (investigator) via a centralized secure web-based randomisation system. Randomisation in a 1:1 ratio is computer generated by an independent statistician from the INSERM CIC 1415 statistical unit. The allocation sequence is generated with a random permuted block design. Varying block sizes will not be revealed to ensure concealment. To avoid prognostic imbalance between the two groups, randomisation is stratified by recruiting centre and planned surgical procedure: mastectomy without axillary surgery, mastectomy with sentinel lymph node biopsy or mastectomy with standard level I/II axillary node dissection.

Study interventions

Mastectomies are performed by experienced breast surgeons using a standardized technique. The skin incision must include the tumor biopsy site, any invaded or oedematous skin, plus the nipple-areola complex. For dissecting the upper and lower skin flaps, finding the bloodless plane between the smaller lobules of the subcutaneous fat, and the larger lobules of the fat in the breast proper is required. Finally, the whole of the posterior aspect of the breast from the pectoralis major is freed. This study addresses the type of wound closure in mastectomy. So, only wound closure will be different between the two groups.

Conventional closure with drain

In the conventional closure with drain group, the skin flaps are not fixed subcutaneously but sutured at the edges, a closed suction drain is inserted under the flaps in the dead space created by the dissection at the pectoral area. The drain is stitched to the skin. The skin is closed in two layers with absorbable sutures, a deep layer of 2.0 or 3.0 vicryl sutures or

equivalent, and a subcuticular closure with absorbable 3.0 or 4.0 Monocryl sutures or equivalent. The drain is removed on the day of discharge either when drain volume is less than 50 ml over 24 hours regardless of time elapsed after surgery or at 5 days following surgery.

Quilting suture

In the quilting suture group, the skin flaps are sutured to the underlying pectoralis major with multiple parallel rows of 0/0 vicryl or equivalent. Running sutures at periodic intervals (<2cm) are placed from the skin flaps to the underlying muscle. Minor dimpling is considered acceptable and is expected to resolve. If severe dimpling is observed, stitches are removed and replaced. Efficiency of quilting suture relies on a rigorous repartition of the sutures with a special attention taken to the obliteration of the largest potential dead spaces and the empty axillary apex. The skin edges are sutured as for the control group. Closed suction will not be used for draining the pectoral area.

If an axillary lymph node dissection is required in any group (quilting suture or conventional closure), the same skin incisions used for the mastectomy are used. The axillary area is closed with vicryl sutures after the insertion of a suction drain to create a separation with the dead space, quilted or not, at the pectoral area. The drain is connected to a single suction bottle which is changed every day and the daily drain volume is monitored. The axillary drain is removed on the day of discharge either when drain volume is less than 50 ml over 24 hours regardless of time elapsed after surgery or at 5 days following surgery. Patients with axillary lymph node dissection have two drains and two bottles in the conventional closure group and only one axillary drain and one bottle in the quilting suture group.

Surgeon expertise and intervention standardisation

The licensed French doctors who will be involved in this trial as practitioners have all been certified by the French ministry of health, have at least one year of surgical experience (senior with at least one year of fellowship validated), and will have taken a course to ensure that they adhere strictly to the study protocol and are familiar with quilting suture. To standardize quilting suture across centres and surgeons, a training period of at least 2 months have been realized. This intervention has been standardized during a 2 months training period as recommended in the Randomised Trials of Non pharmacologic Treatment extension of CONSORT Statement. [26]

Study outcomes

Primary study outcome

The primary outcome is wound seroma requiring aspiration or surgical evacuation within 21 days following mastectomy. A seroma is defined as a postoperative fluid collection via palpation on clinical examination. The Common Terminology Criteria for Adverse Events (CTCAE) 4.0 which is a descriptive terminology that can be used for adverse event reporting, provide a grading scale for seromas (lymphoceles): (1) grade 1: asymptomatic, clinical or diagnostic observation only, intervention not indicated, (2) grade 2: symptomatic, medical intervention indicated, (3) grade 3: severe symptoms, radiologic endoscopic or elective operative intervention indicated. Only grade 2 and 3 seromas i.e. seromas requiring one or more aspirations or a surgical intervention will be considered as primary outcome.

This outcome was chosen as the primary outcome for three reasons. First, this outcome measure was the most used as primary outcome in reported published trials evaluating and comparing the efficacy of different methods in reducing the incidence of seromas when drainage wasn't used for all patients[27-31]. It reflects both patient morbidity and additional medical costs. Focusing on seromas requiring interventions (aspiration or surgical

intervention) is a more objective criterion than the simple presence of seroma (on physical exam or ultrasound finding). This allows to take into account only seromas having important consequences for the patient, indeed some authors discovered that 92% of their patients had seromas noted on ultrasound, but only less than half (42%) required aspiration of the seroma. [32-33]. Second, we did not wish to use the total inpatient drainage volume as a primary outcome, because it implies to use suction drains in dead space in both study groups. Using such a drain at the pectoral area while quilting the dead space is not the innovative technique we wished to test because we believe that drains themselves encourage drainage by stimulating tissue reactions or by suction. Moreover, even if we used suction drains in both groups, the patients will not be blinded because quilting suture technique is responsible of minor skin dimpling effect expected to resolve which does not exist with the conventional closure technique. Finally, the only outcome that could be blind assessed is the cosmetic result by an adjudication committee. However, this outcome is not as medically relevant as seroma requiring intervention. We therefore chose to study the cosmetic result as a secondary outcome.

In most cases, a patient will return to her initial centre if an aspiration or surgical intervention for wound seroma is needed. These interventions will be collected in the patient medical record. Nevertheless, each patient will be asked, at day 21 visit about seroma and the need for aspiration or intervention since hospital discharge. In rare cases where patients will mention seroma requiring aspiration or intervention in another centre or by their family practionner, the physician will be contacted to validate the patient report (the same procedure will be done for other wound related complications).

Secondary outcomes measurement

Secondary outcomes include:

(1) Wound-related complications:

- Wound seromas that necessitate ponction or surgical intervention within 9 months following mastectomy.

- For each patient presenting a seroma which necessitates aspiration, the total volume of aspiration and number of aspiration will be recorded.

- Wound seromas whatever their grade at day 21 and 9 months after surgery.

- Other wound- related complications such as hematoma, skin flap necrosis, surgical site infection at day 21 and 9 months

(2) Surgical morbidity: Duration of the surgical procedure and intraoperative blood loss, length of hospital stay after surgery (days), number of outpatient visits (related to mastectomy) needed following participant's discharge within the 9 months follow-up.

(3) Pain: Patient self reported pain measured with the Visual Analogue Scale pain scoring system from 0 (no pain) to 10 (unbearable pain) recorded before surgery, daily during hospitalisation and at 21 days and 9 months after surgery.

(4) Shoulder movement: The range of arm movement scored from 1 to 4 according to estimated angles of arm abduction as 1 (less than 90°), 2 (90-134°), 3 (135-179°) and 4 (180°). It will be measured by the surgeon before surgery and also at 21 days and 9 months visits.

(5) Cosmesis results: Both patient and surgeon assessments of the cosmetic results will be documented during follow-up at day 21 and 9 months, with possible response categories as follows: poor, acceptable, good and excellent. Digital photographs of the mastectomy area will be taken with standardized angles of incidence at 9 months. Results will be rated at the end of the study, by an adjudication committee blinded to treatment allocation (blinded outcome assessment) in order to obtain a blinded medical cosmetic-assessment.

(6) Health related quality of life: the EuroQoL-5D (EQ-5D)-5L will be collected at baseline, 21 days and 9 months visits. The EQ-5D-5L is an update of the 3L version. It still consists of

2 pages – the EQ-5D-5L descriptive system and the EQ visual Analogue scale. The descriptive system comprises the same 5 dimensions as the EQ-5D-5D-3L (mobility, self care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

(7) Direct medical costs and cost-effectiveness.

Follow-up

All patients are followed for a 9-month period, with follow-up visit at 21 days and 9 months following surgery. Those visits fit in with routine follow-up after mastectomy in the participating centres.

Blinding

It is not possible to blind patients or surgeons in our trial because of the nature of the studied intervention (surgical intervention which depends on care provider). Blinding is of great difficulty in non pharmacologic randomised trials[34-35]. Moreover, blinding of outcome assessor is not feasible for the primary outcome: seroma which require aspiration or surgical evacuation within 21 days following mastectomy. Indeed, after discharge, patients can visit at any time (in emergency or not) for a seroma or another postoperative complication. It is not possible to ensure that the gynecologist who will examine the patient is not the same as the surgeon who operated this patient. Moreover, as the patients cannot be blinded of the treatment allocation, it is difficult to ensure that they will not disclose it to the gynecologist

(outcome assessor of the trial). An adjudication committee blinded to treatment allocation aiming to *a posteriori* validates the indication of aspiration or surgical evacuation of a seroma is not relevant in this study because the decision depends on criteria that cannot be assessed retrospectively by photographs and medical records only.

Data management

Data is recorded on study specific case report forms (CRFs) via an electronic data capture system (CS Online). To maintain participant's anonymity, CRFs are identified only by a coded patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records and can be identified only by the coded patient number and initials. A data manager from the INSERM CIC 1415 biometry unit verifies the data and sends queries for missing or inconsistent data.

Sample size

The study sample size is based on a comparison of quilting suture versus conventional wound closure with drainage on seroma prevention. In our observational study data, 22% (n = 13/60) of patients undergoing mastectomy with conventional wound suture developed a seroma that required ponction or surgical intervention within 21 days following surgery. Because of the multicentric profile of our study, the rate of seroma could be greater. So we assume a rate of 30 % in the control group. In the quilting suture, we expect to observe a rate of patients developing a seroma of 15 %. With these assumptions, a two-sided type I error of 5% and 90% power, a sample size of 160 patients per group is needed. Therefore, we plan to enroll a total of 320 patients.

To recruit this number of patients a 24-month inclusion period is anticipated.

Statistical analyses

The statistical analyses will follow an intention-to-treat approach. Analyses will be conducted using two sided significance tests at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive analysis. No statistical test will be performed on baseline characteristics.

The primary outcome will be assessed as a rate, defined as the number of patients who experienced a seroma requiring aspiration or surgical intervention within 21 days following mastectomy divided by the number of patients randomised into this group. To compare the incidence rates between the two randomised groups, we will use a χ^2 test or Fisher's exact test, as appropriate.

Giving the patient profile, loss to follow-up is very unlikely. Generally, patients continue their follow-up in their original centre even if they move. However, if the case does occur, imputation of missing outcomes will be performed at least in a sensitivity analysis.

For secondary analysis, qualitative outcomes such as other postoperative wound-related complications, cosmetic results and shoulder movement will also be compared between the two arms using a χ^2 test or a Fisher's exact test. The duration of the surgical procedure, length of hospital stay, intraoperative blood loss, will be compared using Wilcoxon tests or Student t tests, as appropriate. Repeated measures such as pain evaluation and health-related quality of life will be analyzed using linear mixed-effects models to take into account the correlation of data from a given subject.

Economic evaluation

A cost-effectiveness study will be performed on the basis of resource use and HRQOL data collected alongside the trial.

Direct medical costs will be assessed from the hospital and the payer perspectives in both groups and during the whole follow-up period i.e. 9 months after randomization. For each

patient, we collect the healthcare resource use both in the hospital setting and primary care services. This covers the initial surgical stay (duration of the surgical procedure, number of consumables (drains and sutures), length of stay), subsequent hospital stays due to complications/infections, general practitioners and gynaecologist visits (over a 21-day period only), and home nursing care visits (over a 21-day period only).

To value resources, we will use the following unit costs information:

- Hospital stays: diagnosis related group payment per discharge in the French prospective payment scheme.

- Visits: General fee classification (Nomenclature Générale des Actes Professionnels) and the reimbursement rate at the date of analysis.

Health states will be valued into utility coefficients using data from the EuroQoL group (European value set). This will allow computing QALYs for each patient in both groups.

Costs and QALYs will be compared between the two groups using non parametric tests. Means and 95 % confidence intervals for costs, QALYS and incremental net monetary benefit will be estimated using the non parametric bootstrap method. Differences in costs and differences in QALYs observed in the bootstrap replicates will be represented in the cost-effectiveness plane. A cost-effectiveness acceptability curve will be computed.

Ethics and dissemination

This protocol was approved by local ethic research committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20, 16/12/2014).

In conformity with the Declaration of Helsinki, all participants will sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent will be obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. Data collected prior to participant withdrawal will be used in the trial analysis except if a participant requests removal of all her data from the database.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement to Randomised Trials of Nonpharmacologic Treatment. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not there are statistically significant. The study findings will also be presented at relevant national and international breast cancer conferences.

Discussion

Previous reports in the literature have addressed the effect of quilting versus conventional closure with drainage after mastectomy for breast cancer on patient outcome. However, the studies reported to date are limited by small sample sizes, lack of randomization, the concomitant use of drainage with quilting suture, and most studies were single centre initiatives that lacked sufficient power to inform surgical practice. Breast cancer surgeons appear to currently favour conventional wound closure with drainage, although current evidence suggests superior patients outcomes with quilting suture. The QUISERMAS trial will aim to resolve these controversies by establishing the effectiveness of each method of

mastectomy closure. This will have important clinical implications, as each wound closure type is easily applicable and already performed by breast cancer surgeons. A key limitation of the QUISERMAS trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to intervent on seroma vulnerable to bias. A strength of our study is that it is designed to be a feasible, comparative effectiveness trial design that is similar to common clinical situations. Additionally, this clinical trial protocol was conducted to conform strictly to the CONSORT statement. The results of the QUISERMAS trial will be an important contribution in breast cancer surgery literature and are likely to lead changes in mastectomy closure. We expect that this study will provide the clinical basis and evidence that is required to perform quilting suture in routine when performing mastectomies.

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Acknowledgements

The authors acknowledge Carine Coffre, Aurélie Darmaillacq and Rachel Fontenay for their constructive support during preparation and conduct of the trial.

The authors would also like to express appreciation for the contributions from patients with breast cancer who will participate in this trial.

Contributors

LO and AC helped to conceive and design the trial and wrote the manuscript. JB, BG and GB helped to conceive the trial and revised the manuscript. LO and GB will be investigators and will recruit patients and conduct the trial. AC planned the statistical analysis. LO and AC will supervise the trial. All authors read and approved the final manuscript.

Funding

This trial is supported by a grant from the French Ministry of Health (PHRC 2013).

Competing interests None.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20, 16/12/2014).

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6/7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6/7
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7/8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8 to 10
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8 and 14
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	13/14

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	15/16
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17/18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	17/18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17/18
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Dead space closure with quilting suture versus conventional closure with drainage for the prevention of seroma after mastectomy for breast cancer (QUISERMAS): protocol for a multicentre randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009903.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Oct-2015
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Epidemiology
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY

Dead space closure with quilting suture versus conventional closure with drainage for the prevention of seroma after mastectomy for breast cancer (QUISERMAS): protocol for a multicentre randomised controlled trial

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Abstract

Introduction

Postoperative wound seroma is common after mastectomy. This complication is associated with significant impact on patient outcomes and healthcare costs. The optimal closure approach for seroma prevention remains unknown but some evidence suggests that quilting suture of the dead space could lower the incidence of seroma. The aim of this trial is to compare seroma formation using quilting suture versus conventional closure with drainage in patients undergoing mastectomy.

Methods and analysis

This is a multicentre, superiority, randomised controlled trial in women undergoing mastectomy with or without axillary involvement. Exclusion criteria include indication of bilateral mastectomy or immediate reconstruction and any physical or psychiatric condition that could impair patient's ability to cooperate with postoperative data collection or that do not allow an informed consent. Three hundred and twenty participants will be randomised in a 1:1 ratio to receive either quilting suture or conventional wound closure with drain. The primary outcome is seroma requiring either aspiration or surgical intervention within 21 days following mastectomy. Secondary outcomes include seroma regardless of whether or not it requires an intervention, surgical site infection, pain score, cosmetic result, patient's quality of life, costs and cost-effectiveness. The primary analysis will be an intention-to treat analysis performed with a χ^2 test (or Fisher's exact test).

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20,

16/12/2014). Study findings will be published in peer-reviewed journals and presented at relevant national and international breast cancer conferences.

Trial registration number:

The QUISERMAS trial is registered with clinicaltrials.gov (NCT02263651).

Strengths and limitations of this study

- QUISERMAS is the first multicentre randomised controlled trial to assess quilting suture of the dead space after mastectomy on seroma prevention.
- Surgeons and patients cannot be blinded to the surgical arm. Consequently, to reduce the risk of bias, we decided to consider for primary outcome only seroma requiring aspiration or surgical intervention.
- Cosmetic results will be assessed by an independent adjudication committee.
- An economic evaluation will be conducted alongside the trial.

Introduction

Breast cancer is the most common cancer worldwide. Surgical treatment is the preferred option and about 14.000 mastectomies are performed each year in France. [1] Postoperative seroma is a common complication after mastectomy. [2-9] This complication is secondary to the disruption of lymphatic channels that inevitably complicates extensive surgical dissection and disruption of tissue planes creating a dead space. Excessive fluid accumulation in a seroma stretches the skin, resulting in patient discomfort, impaired ipsilateral shoulder function and higher risk of surgical site infection (SSI). In rare cases, a fibrous encapsulated seroma forms that is resistant to conservative treatment and requires subsequent surgical resection. Thus, this complication may also impact healthcare costs requiring prolongation of hospital stay or unplanned outpatient visits and may delay adjuvant therapy.

Conventional wound closure commonly uses suction drain after mastectomy to prevent seroma despite seroma frequently occurs after drain removal. [10] Studies on seroma prevention have focused on the obliteration of the dead space through fibrinogen, thrombin sealants, glues or Tetracyclin with poor results. [11-20] Some recent evidence suggests that quilting suture reduces the incidence of seroma. [21-23] Quilting suture consists in suturing the skin flaps to the underlying musculature to reduce "dead space"[24]. It aims to restore the integrity of tissue planes. Ten Wolde et al [22], retrospectively analysed 176 patients (87 who underwent conventional closure and 89 quilted patients) from two consecutive groups who underwent mastectomy and/or axillary lymph node dissection (ALND), this also included patients undergoing an ALND with lumpectomy in whom only the axilla was quilted. All patients had a drain in the pectoral area that was removed on the day of discharge, at least within 36 h following surgery. The incidence of seroma decreased significantly from 80.5% to 22.5 % in the quilted group, $p<0.01$ and the volume of aspirations from 1660 ml to 611ml ($p=0.05$). Quilting closure technique was also assessed in an observational study based on 119

consecutive patients in our tertiary breast cancer unit whose fifty-nine received quilting suture (without drain) and 60 received conventional closure with drainage. The results showed a significant reduction in seroma for patients with quilting suture as compared to patients with conventional closure with drain (odds ratio [OR] = 0.26, 95% Confidence Interval = 0.08-0.86; p=0.03) The hypothesis around quilting efficacy is that dead space is the major contributor to seroma formation, and that this surgical technique applied to obliterate the dead space might reduce the incidence of this complication. [23]

As recommended in the IDEAL framework describing the stages for development of innovation in surgery, quilting suture now needs to be assessed in a controlled randomised trial. [25] Thus, the aim of our project is to assess, in a randomised controlled trial, quilting suture of the dead space without drainage at the pectoral area as compared to conventional closure with drainage on seroma prevention within 21 days following mastectomy for breast cancer.

Study objectives

Our primary objective is to assess the impact of quilting on rates of wound seroma requiring aspiration or surgical intervention within 21 days following mastectomy.

Secondary objectives are to compare quilting suture of the dead space without drainage of the pectoral area to conventional closure with drainage after mastectomy for breast cancer regarding wound-related complications, surgical morbidity, pain, shoulder movement, cosmetic results, health related quality of life, costs and cost-effectiveness.

Methods and analysis

Study design

QUISERMAS is a multicentre, superiority, randomised controlled trial with parallel groups comparing quilting suture with conventional closure with drain in the prevention of seroma in patients undergoing mastectomy with or without axillary surgery.

Setting

The trial is ongoing at the time of publication in four French university hospitals (Tours, Nantes, Poitiers, Rennes). The study is conducted in the breast surgery departments of these academic centres.

Participants

Inclusion criteria

The inclusion criteria are: (1) Female patients with operable breast cancer (invasive carcinoma and/or ductal carcinoma in situ) for whom mastectomy is recommended or preferred by the patient either alone or in association with axillary clearance either sentinel lymph node biopsy or standard level I/II axillary node dissection, (2) Age ≥18 years and ≤ 85 years,

Exclusion criteria

The exclusion criteria are: (1) Patients with an indication of bilateral mastectomy or immediate reconstruction, (2) Planned outpatient surgery, (3) Patients with known degenerative neuromuscular disease with thoracic muscular damage, (4) Patients with any physical or psychiatric condition that could impair with outcome assessment and intended follow-up.

Study participants are patients who meet the selection criteria and are willing and able to sign written informed consent.

Recruitment

The first patient was randomised on October 2014. Enrolment is ongoing at the time of publication.

The recruitment process is planned to fit with routine practice. Potential participants to the trial are identified at the time they attend for diagnosis and treatment choice for their breast

cancer in one of the four involved tertiary-care centres. Patients who meet selection criteria receive a brief study presentation and full participant information sheet by a clinician. After selection criteria confirmation and answering to potential further patient questions about the trial, written informed consent is obtained before surgery by the patient's surgeon.

Baseline data are collected following consent during the preoperative period.

Randomisation

Randomisation is undertaken by the surgeon (investigator) via a centralized secure web-based randomisation system. Randomisation in a 1:1 ratio is computer generated by an independent statistician from the INSERM CIC 1415 statistical unit. The allocation sequence is generated with a random permuted block design. Varying block sizes will not be revealed to ensure concealment. To avoid prognostic imbalance between the two groups, randomisation is stratified by recruiting centre and planned surgical procedure, either (A) mastectomy without axillary surgery, (B) mastectomy with sentinel lymph node biopsy or (C) mastectomy with standard level I/II axillary node dissection.

Study interventions

Mastectomies are performed by experienced breast surgeons using a standardized technique. The skin incision must include the tumor biopsy site, any invaded or oedematous skin, plus the nipple-areola complex. For dissecting the upper and lower skin flaps, finding the bloodless plane between the smaller lobules of the subcutaneous fat, and the larger lobules of the fat in the breast proper is required. Finally, the whole of the posterior aspect of the breast from the pectoralis major is freed. This study addresses the type of wound closure in mastectomy. So, only wound closure will differ between the two groups.

Conventional closure with drain

In the conventional closure with drain group, the skin flaps are not fixed subcutaneously but sutured at the edges, a closed suction drain is inserted under the flaps in the dead space

created by the dissection at the pectoral area. The drain is stitched to the skin. The skin is closed in two layers with absorbable sutures, a deep layer of 2.0 or 3.0 vicryl sutures or equivalent, and a subcuticular closure with absorbable 3.0 or 4.0 Monocryl sutures or equivalent. The drain is connected to a single suction bottle, which is changed every day, and the daily drain volume is monitored. The drain is removed on the day of discharge either when drain volume is less than 50 ml over 24 hours, regardless of time elapsed after surgery or at 5 days following surgery.

Quilting suture

In the quilting suture group, the skin flaps are sutured to the underlying pectoralis major with multiple parallel rows of 0/0 vicryl or equivalent. Running sutures at periodic intervals (<2cm) are placed from the skin flaps to the underlying muscle. Minor dimpling is considered acceptable and is expected to resolve. If severe dimpling is observed, stitches are removed and replaced. Efficiency of quilting suture relies on a rigorous repartition of the sutures with a special attention taken to the obliteration of the largest potential dead spaces and the empty axillary apex. The skin edges are sutured in the same way as for the control group. Closed suction is not used for draining the pectoral area.

If an axillary lymph node dissection is required in any group (quilting suture or conventional closure), skin incisions performed for the mastectomy are used. After the insertion of a suction drain, the axillary area is closed with vicryl sutures to create a separation with the dead space, quilted or not, at the pectoral area. The drain is connected to a single suction bottle which is changed every day and the daily drain volume is monitored. The axillary drain is removed on the day of discharge either when drain volume is less than 50 ml over 24 hours regardless of time elapsed after surgery or at 5 days following surgery. Consequently, patients with axillary lymph node dissection have two drains and two suction bottles in the

conventional closure group and only one axillary drain and one suction bottle in the quilting suture group.

Surgeon expertise and intervention standardisation

The licensed French doctors who are involved in this trial as practitioners have all been certified by the French ministry of health, have at least one year of surgical experience (senior with at least one year of fellowship validated), and will have taken a course to ensure that they adhere strictly to the study protocol and are familiar with quilting suture. To standardize quilting suture across centres and surgeons, a training period of at least 2 months is required as recommended in the Randomised Trials of Non pharmacologic Treatment extension of CONSORT Statement. [26]

Study outcomes

Primary outcome

The primary outcome is wound seroma requiring aspiration or surgical evacuation within 21 days following mastectomy. A seroma is defined as a postoperative fluid collection via palpation on clinical examination. The Common Terminology Criteria for Adverse Events (CTCAE) 4.0 which is a descriptive terminology used for adverse event reporting, provides a grading scale for seromas (lymphoceles): (1) grade 1: asymptomatic, clinical or diagnostic observation only, intervention not indicated, (2) grade 2: symptomatic, medical intervention indicated, (3) grade 3: severe symptoms, radiologic endoscopic or elective operative intervention indicated. Only grade 2 and 3 seromas i.e. seromas requiring one or more aspirations or a surgical intervention will be considered as primary outcome.

This outcome was chosen as the primary outcome for three reasons. First, this outcome measure was the most used as primary outcome in reported published trials evaluating and comparing the efficacy of different methods in reducing the incidence of seromas when

drainage wasn't used for all patients[27-31]. It reflects both patient morbidity and additional medical costs. Focusing on seromas requiring interventions (aspiration or surgical intervention) is a more objective criterion than the simple presence of seroma (on physical exam or ultrasound finding). This allows to take into account only seromas having important consequences for the patient, indeed some authors discovered that 92% of their patients had seromas noted on ultrasound, but only less than half (42%) required aspiration of the seroma. [32-33]. Second, we did not wish to use the total inpatient drainage volume as a primary outcome, because it implies to use suction drains in dead space in both study groups. Using such a drain at the pectoral area while quilting the dead space is not the innovative technique we wished to test because we believe that drains themselves encourage drainage by stimulating tissue reactions or by suction. Moreover, even if we used suction drains in both groups, the patients will not be blinded because quilting suture technique is responsible of minor skin dimpling effect expected to resolve which does not exist with the conventional closure technique. Finally, the only outcome that could be blind assessed is the cosmetic result by an adjudication committee. However, this outcome is not as medically relevant as seroma requiring intervention. We therefore chose to study the cosmetic result as a secondary outcome.

In most cases, a patient will return to her initial centre if an aspiration or surgical intervention for wound seroma is needed. These interventions will be collected in the patient medical records. Nevertheless, each patient will be asked, at day 21 visit about seroma and the need for aspiration or intervention since hospital discharge. In rare cases where patients will mention seroma requiring aspiration or intervention in another centre or by their family practionner, a physician will be contacted (either by phone or email) to validate the patient report (the same procedure will be done for other wound related complications).

Secondary outcomes

Secondary outcomes include:

(1) Wound-related complications:

- Wound seromas that necessitate aspiration or surgical intervention within 9 months following mastectomy.

- For each patient presenting a seroma that necessitates aspiration, the total volume of aspiration and number of aspirations will be recorded.

- Wound seroma whatever the grade at day 21 and 9 months after surgery.

- Other wound- related complications such as hematoma, skin flap necrosis, surgical site infection at day 21 and 9 months after surgery.

(2) Surgical morbidity: Duration of the surgical procedure and intraoperative blood loss, length of hospital stay after surgery (days), number of outpatient visits (related to mastectomy) needed following participant's discharge within the 9 months follow-up.

(3) Pain: Patient self reported pain measured with the Visual Analogue Scale pain scoring system from 0 (no pain) to 10 (unbearable pain) recorded before surgery, daily during hospitalisation and at 21 days and 9 months after surgery.

(4) Shoulder movement: The range of arm movement scored from 1 to 4 according to estimated angles of arm abduction as 1 (less than 90°), 2 (90-134°), 3 (135-179°) and 4 (180°). It will be measured by the surgeon before surgery and also at 21 days and 9 months after surgery.

(5) Cosmetic results: Both patient and surgeon assessments of the cosmetic results will be documented at day 21 and 9 months after surgery, with possible response categories as follows: poor, acceptable, good and excellent. Digital photographs of the mastectomy area will be taken with standardized angles of incidence at 9 months. Results will be rated at the end of the study, by an adjudication committee blinded to treatment allocation in order to obtain a blinded surgical cosmetic-assessment.

(6) Health related quality of life: the EuroQoL-5D (EQ-5D)-5L will be collected at baseline, 21 days and 9 months visits. The EQ-5D-5L is an update of the 3L version. It still consists of 2 pages – the EQ-5D-5L descriptive system and the EQ visual Analogue scale. The descriptive system comprises the same 5 dimensions as the EQ-5D-5D-3L (mobility, self care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

(7) Direct medical costs and cost-effectiveness.

Follow-up

During follow-up, patients will receive usual care. All patients are followed for a 9-month period, with follow-up visit at 21 days and 9 months following surgery. Those visits fit in with routine follow-up after mastectomy in the participating centres.

Blinding

It is not possible to blind patients or surgeons in our trial because of the nature of the studied intervention, surgical intervention that depends on care provider, as for a large part of other non pharmacologic interventions[34-35]. Moreover, blinding of outcome assessor is not feasible for the primary outcome: seroma that require aspiration or surgical evacuation within 21 days following mastectomy. Indeed, after discharge, patients can visit at any time (in emergency or not) for a seroma or another postoperative complication. It is not possible to ensure that the clinician who will examine the patient is not the same as the surgeon who operated this

patient. Moreover, as the patients cannot be blinded to the treatment allocation, it is difficult to ensure that they will not disclose it to the surgeon (outcome assessor of the trial). An adjudication committee blinded to treatment allocation aiming to *a posteriori* validates the indication of aspiration or surgical evacuation of a seroma is not relevant in this study because the decision depends on criteria that cannot be assessed retrospectively by photographs and medical records only.

Data management

Data is recorded on study specific case report forms (CRFs) via an electronic data capture system (CS Online). To maintain participant's anonymity, CRFs are identified only by a coded patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records and can be identified only by the coded patient number and initials. A data manager from the INSERM CIC 1415 biometry unit verifies the data and sends queries for missing or inconsistent data.

Sample size

The study sample size is based on a comparison of quilting suture versus conventional wound closure with drainage on seroma prevention. In our observational study data, 22% (n = 13/60) of patients undergoing mastectomy with conventional wound suture developed a seroma that required aspiration or surgical intervention within 21 days following surgery. Because of the multicentre profile of our study, the rate of seroma could be greater. We thus assume a rate of 30 % in the control group. In the quilting suture, we expect to observe a rate of patients developing a seroma of 15 %. With these assumptions, a two-sided type I error of 5% and 90% power, a sample size of 160 patients per group is needed. Therefore, we plan to enroll a total of 320 patients.

To recruit this number of patients a 24-month inclusion period is anticipated.

Statistical analyses

The statistical analyses will follow an intention-to-treat approach. Analyses will be conducted using two sided significance tests at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive statistics. No statistical tests will be performed on baseline characteristics.

The primary outcome will be assessed as a rate, defined as the number of patients who experienced a seroma requiring aspiration or surgical intervention within 21 days following mastectomy divided by the number of patients randomised into this group. To compare the incidence rates between the two randomised groups, we will use a χ^2 test or Fisher's exact test, as appropriate.

Giving the patient profile, loss to follow-up is very unlikely. Generally, patients continue their follow-up in their original centre even if they move. However, if the case does occur, imputation of missing outcomes will be performed at least in a sensitivity analysis.

For secondary analysis, qualitative outcomes such as other postoperative wound-related complications, cosmetic results and shoulder movement will also be compared between the two arms using a χ^2 test or a Fisher's exact test. The duration of the surgical procedure, length of hospital stay, intraoperative blood loss, will be compared using Wilcoxon tests or Student t tests, as appropriate. Repeated measures such as pain evaluation and health-related quality of life will be analyzed using linear mixed-effects models to take into account the correlation of repeated measures from a given subject.

Economic evaluation

A cost-effectiveness study will be performed on the basis of resource use and HRQOL data collected alongside the trial.

Direct medical costs will be assessed from the hospital and the payer perspectives in both groups and during the whole follow-up period i.e. 9 months after surgery. For each patient, we will collect the healthcare resource use both in the hospital setting and primary care services. This covers the initial surgical stay (duration of the surgical procedure, number of consumables (drains and sutures), length of stay), subsequent hospital stays due to complications/infections, general practitioners and gynaecologist visits (over a 21-day period following surgery only), and home nursing care visits (over a 21-day period only).

To value resources, we will use the following unit costs information:

- Hospital stays: diagnosis related group payment per discharge in the French prospective payment scheme.

- Visits: General fee classification (Nomenclature Générale des Actes Professionnels) and the reimbursement rate at the date of analysis.

Health states will be valued into utility coefficients using data from the EuroQoL group (European value set). It will allow computing QALYs for each patient in both groups.

Costs and QALYs will be compared between the two groups using non parametric tests. Means and 95 % confidence intervals for costs, QALYS and incremental net monetary benefit will be estimated using the non-parametric bootstrap method. Differences in costs and differences in QALYs observed in the bootstrap replicates will be represented in the cost-effectiveness plane. A cost-effectiveness acceptability curve will be computed.

Ethics and dissemination

This protocol was approved by local ethic research committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20, 16/12/2014).

In conformity with the Declaration of Helsinki, all participants will sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent will be obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. In that event, data collected prior to participant withdrawal will be used in the trial analysis except if a participant requests removal of all her data from the database. Sponsor of the study may audit trial conduct as deemed appropriate. A formal amendment to the local research ethics committee will be required for any amendments to the study protocol which may impact the conduct of the study, or the potential safety of or benefits to patients will require, if needed an amendment will also be required from the National regulatory Agency for Security of Medicines and healthcare products (ANSM). Any protocol amendments will be communicated to investigators and oversight authority but also to trial participants and registries, if deemed necessary.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement to Randomised Trials of Non pharmacologic Treatment. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant.. Authors will be individuals who have made key contributions to study design and conduct. Trial findings will also be submitted for presentation at scientific meetings. The study findings will also be presented at relevant national and international breast cancer conferences.

Discussion

Previous reports in the literature have addressed the effect of quilting versus conventional closure with drainage after mastectomy for breast cancer on patient outcome. However, the studies reported to date are limited by small sample sizes, absence of randomization, concomitant use of drainage with quilting suture, and most studies were single centre initiatives that lacked sufficient power to inform surgical practice. Breast cancer surgeons appear to currently favour conventional wound closure with drainage, although current evidence suggests better patient outcomes with quilting suture. The QUISERMAS trial will aim to resolve these controversies by establishing the effectiveness of each method of mastectomy closure. This will have important clinical implications, as each wound closure type is easily applicable and already performed by breast cancer surgeons. A key limitation of the QUISERMAS trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to intervent on seroma vulnerable to bias. A strength of our study is that it is designed to be a feasible, comparative effectiveness trial design that is similar to common clinical situations. Additionally, this clinical trial protocol was conducted to conform strictly to the CONSORT statement. The results of the QUISERMAS trial will be an important contribution in breast cancer surgery literature and are likely to lead changes in mastectomy closure. We expect that this study will provide the clinical basis and evidence that is required to perform quilting suture in routine when performing mastectomies.

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Acknowledgements

The authors acknowledge Carine Coffre (data manager), Aurélie Darmaillacq (clinical research associate) and Rachel Fontenay (health economist) for their constructive support during preparation and conduct of the trial.

The authors would also like to express appreciation for the contributions from patients with breast cancer who will participate in this trial.

Contributors

LO and AC helped to conceive and design the trial and wrote the manuscript. JB, BG and GB helped to conceive the trial and revised the manuscript. LO and GB will be investigators and will recruit patients and conduct the trial. AC planned the statistical analysis. LO and AC will supervise the trial. All authors read and approved the final manuscript.

Funding

This trial is supported by a grant from the French Ministry of Health (PHRC 2013).

Competing interests No, there are no competing interests.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20, 16/12/2014).

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1,3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	__19_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1_____
	5b	Name and contact information for the trial sponsor	___1,19_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__The funder have no role in the cites actions
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___7,8,14 to 17

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____5,6_____
	6b	Explanation for choice of comparators	____6_____
Objectives	7	Specific objectives or hypotheses	_____6, 10 to 13
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____2,6_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____8 to 10_
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____10_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____13____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__10 to 13_
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____7,8__

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____14,15___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____7, 14, 15_
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____13,14___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____14 to 16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____13_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____14_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____15,16__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__NA_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____1, 15_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_the trial does not require a DMC because we are only evaluating the closure technique and both techniques are known to be of minimal risk for patients____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____17____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____17_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____17_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____8_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____14___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____19____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__The chief investigator will be given an access to the cleaned data set_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____17_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____17_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____17_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___Available from request to the first author_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Dead space closure with quilting suture versus conventional closure with drainage for the prevention of seroma after mastectomy for breast cancer (QUISERMAS): protocol for a multicentre randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009903.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Oct-2015
Complete List of Authors:	Ouldamer, Lobna; CHRU de Tours, Gynecology Bonastre, Julia; Gustave Roussy, Service de Biostatistique et d'Epidemiologie; CESP, Centre for Research in Epidemiologie and Population Health INSERM U1018 Paris-Sud Univ Brunet-Houdard, solene; Université François-Rabelais de Tours, PRES Centre Val de Loire Université, ; CHRU de Tours, Unité d'Evaluation Médico-Economique Body, Gilles; CHRU de Tours, Department of Gynecology; Université François-Rabelais de Tours, PRES Centre Val de Loire Université, Giraudeau, Bruno; Université François-Rabelais de Tours, PRES Centre Val de Loire Université, ; CHRU de Tours, INSERM CIC 1415 Caille, Agnès; Université François-Rabelais de Tours, PRES Centre Val de Loire Université, ; CHRU de Tours, INSERM CIC 1415
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Epidemiology
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY

Dead space closure with quilting suture versus conventional closure with drainage for the prevention of seroma after mastectomy for breast cancer (QUISERMAS): protocol for a multicentre randomised controlled trial

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Abstract

Introduction

Postoperative wound seroma is common after mastectomy. This complication is associated with significant impact on patient outcomes and healthcare costs. The optimal closure approach for seroma prevention remains unknown but some evidence suggests that quilting suture of the dead space could lower the incidence of seroma. The aim of this trial is to compare seroma formation using quilting suture versus conventional closure with drainage in patients undergoing mastectomy.

Methods and analysis

This is a multicentre, superiority, randomised controlled trial in women undergoing mastectomy with or without axillary involvement. Exclusion criteria include indication of bilateral mastectomy or immediate reconstruction and any physical or psychiatric condition that could impair patient's ability to cooperate with postoperative data collection or that do not allow an informed consent. Three hundred and twenty participants will be randomised in a 1:1 ratio to receive either quilting suture or conventional wound closure with drain. The primary outcome is seroma requiring either aspiration or surgical intervention within 21 days following mastectomy. Secondary outcomes include seroma regardless of whether or not it requires an intervention, surgical site infection, pain score, cosmetic result, patient's quality of life, costs and cost-effectiveness. The primary analysis will be an intention-to treat analysis performed with a χ^2 test (or Fisher's exact test).

Ethics and dissemination:

Written informed consent will be obtained from all participants. This study was approved by Tours Research ethics committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20,

16/12/2014). Study findings will be published in peer-reviewed journals and presented at relevant national and international breast cancer conferences.

Trial registration number:

The QUISERMAS trial is registered with clinicaltrials.gov (NCT02263651).

Strengths and limitations of this study

- QUISERMAS is the first multicentre randomised controlled trial to assess quilting suture of the dead space after mastectomy on seroma prevention.
- Surgeons and patients cannot be blinded to the surgical arm. Consequently, to reduce the risk of bias, we decided to consider for primary outcome only seroma requiring aspiration or surgical intervention.
- Cosmetic results will be assessed by an independent adjudication committee.
- An economic evaluation will be conducted alongside the trial.

Introduction

Breast cancer is the most common cancer worldwide. Surgical treatment is the preferred option and about 14.000 mastectomies are performed each year in France. [1] Postoperative seroma is a common complication after mastectomy. [2-9] This complication is secondary to the disruption of lymphatic channels that inevitably complicates extensive surgical dissection and disruption of tissue planes creating a dead space. Excessive fluid accumulation in a seroma stretches the skin, resulting in patient discomfort, impaired ipsilateral shoulder function and higher risk of surgical site infection (SSI). In rare cases, a fibrous encapsulated seroma forms that is resistant to conservative treatment and requires subsequent surgical resection. Thus, this complication may also impact healthcare costs requiring prolongation of hospital stay or unplanned outpatient visits and may delay adjuvant therapy.

Conventional wound closure commonly uses suction drain after mastectomy to prevent seroma despite seroma frequently occurs after drain removal. [10] Studies on seroma prevention have focused on the obliteration of the dead space through fibrinogen, thrombin sealants, glues or Tetracyclin with poor results. [11-20] The comparator in these studies was almost always conventional wound closure with suction drains as it is the most common practice. Some recent evidence suggests that quilting suture reduces the incidence of seroma. [21-23] Quilting suture consists in suturing the skin flaps to the underlying musculature to reduce "dead space"[24]. It aims to restore the integrity of tissue planes. Ten Wolde et al [22], retrospectively analysed 176 patients (87 who underwent conventional closure and 89 quilted patients) from two consecutive groups who underwent mastectomy and/or axillary lymph node dissection (ALND), this also included patients undergoing an ALND with lumpectomy in whom only the axilla was quilted. All patients had a drain in the pectoral area that was removed on the day of discharge, at least within 36 h following surgery. The incidence of seroma decreased significantly from 80.5% to 22.5 % in the quilted group, $p<0.01$ and the volume of aspirations

from 1660 ml to 611ml (p=0.05). Quilting closure technique was also assessed in an observational study based on 119 consecutive patients in our tertiary breast cancer unit whose fifty-nine received quilting suture (without drain) and 60 received conventional closure with drainage. The results showed a significant reduction in seroma for patients with quilting suture as compared to patients with conventional closure with drain (odds ratio [OR] = 0.26, 95% Confidence Interval = 0.08-0.86; p=0.03) The hypothesis around quilting efficacy is that dead space is the major contributor to seroma formation, and that this surgical technique applied to obliterate the dead space might reduce the incidence of this complication. [23] As recommended in the IDEAL framework describing the stages for development of innovation in surgery, quilting suture now needs to be assessed in a controlled randomised trial. [25] Thus, the aim of our project is to assess, in a randomised controlled trial, quilting suture of the dead space without drainage at the pectoral area as compared to conventional closure with drainage on seroma prevention within 21 days following mastectomy for breast cancer.

Study objectives

Our primary objective is to assess the impact of quilting on rates of wound seroma requiring aspiration or surgical intervention within 21 days following mastectomy.

Secondary objectives are to compare quilting suture of the dead space without drainage of the pectoral area to conventional closure with drainage after mastectomy for breast cancer regarding wound-related complications, surgical morbidity, pain, shoulder movement, cosmetic results, health related quality of life, costs and cost-effectiveness.

Methods and analysis

Study design

QUISERMAS is a multicentre, superiority, randomised controlled trial with parallel groups comparing quilting suture with conventional closure with drain in the prevention of seroma in patients undergoing mastectomy with or without axillary surgery.

Setting

The trial is ongoing at the time of publication in four French university hospitals (Tours, Nantes, Poitiers, Rennes). The study is conducted in the breast surgery departments of these academic centres.

Participants

Inclusion criteria

The inclusion criteria are: (1) Female patients with operable breast cancer (invasive carcinoma and/or ductal carcinoma in situ) for whom mastectomy is recommended or preferred by the patient either alone or in association with axillary clearance either sentinel lymph node biopsy or standard level I/II axillary node dissection, (2) Age ≥18 years and ≤ 85 years,

Exclusion criteria

The exclusion criteria are: (1) Patients with an indication of bilateral mastectomy or immediate reconstruction, (2) Planned outpatient surgery, (3) Patients with known degenerative neuromuscular disease with thoracic muscular damage, (4) Patients with any physical or psychiatric condition that could impair with outcome assessment and intended follow-up.

Study participants are patients who meet the selection criteria and are willing and able to sign written informed consent.

Recruitment

The first patient was randomised on October 2014. Enrolment is ongoing at the time of publication.

The recruitment process is planned to fit with routine practice. Potential participants to the trial are identified at the time they attend for diagnosis and treatment choice for their breast

cancer in one of the four involved tertiary-care centres. Patients who meet selection criteria receive a brief study presentation and full participant information sheet by a clinician. After selection criteria confirmation and answering to potential further patient questions about the trial, written informed consent is obtained before surgery by the patient's surgeon.

Baseline data are collected following consent during the preoperative period.

Randomisation

Randomisation is undertaken by the surgeon (investigator) via a centralized secure web-based randomisation system. Randomisation in a 1:1 ratio is computer generated by an independent statistician from the INSERM CIC 1415 statistical unit. The allocation sequence is generated with a random permuted block design. Varying block sizes will not be revealed to ensure concealment. To avoid prognostic imbalance between the two groups, randomisation is stratified by recruiting centre and planned surgical procedure, either (A) mastectomy without axillary surgery, (B) mastectomy with sentinel lymph node biopsy or (C) mastectomy with standard level I/II axillary node dissection.

Study interventions

Mastectomies are performed by experienced breast surgeons using a standardized technique. The skin incision must include the tumor biopsy site, any invaded or oedematous skin, plus the nipple-areola complex. For dissecting the upper and lower skin flaps, finding the bloodless plane between the smaller lobules of the subcutaneous fat, and the larger lobules of the fat in the breast proper is required. Finally, the whole of the posterior aspect of the breast from the pectoralis major is freed. This study addresses the type of wound closure in mastectomy. So, only wound closure will differ between the two groups.

Quilting suture

In the quilting suture group, the skin flaps are sutured to the underlying pectoralis major with multiple parallel rows of 0/0 vicryl or equivalent. Running sutures at periodic intervals

(<2cm) are placed from the skin flaps to the underlying muscle. Minor dimpling is considered acceptable and is expected to resolve. If severe dimpling is observed, stitches are removed and replaced. Efficiency of quilting suture relies on a rigorous repartition of the sutures with a special attention taken to the obliteration of the largest potential dead spaces and the empty axillary apex. The skin edges are sutured in the same way as for the control group. Closed suction is not used for draining the pectoral area.

Conventional closure with drain

In the conventional closure with drain group, the skin flaps are not fixed subcutaneously but sutured at the edges, a closed suction drain is inserted under the flaps in the dead space created by the dissection at the pectoral area. The drain is stitched to the skin. The skin is closed in two layers with absorbable sutures, a deep layer of 2.0 or 3.0 vicryl sutures or equivalent, and a subcuticular closure with absorbable 3.0 or 4.0 Monocryl sutures or equivalent. The drain is connected to a single suction bottle, which is changed every day, and the daily drain volume is monitored. The drain is removed on the day of discharge either when drain volume is less than 50 ml over 24 hours, regardless of time elapsed after surgery or at 5 days following surgery. Conventional closure with drain was chosen as the comparator group as it is the current practice in the centres where the study is conducted and more generally in European countries. [10]

If an axillary lymph node dissection is required in any group (quilting suture or conventional closure), skin incisions performed for the mastectomy are used. After the insertion of a suction drain, the axillary area is closed with vicryl sutures to create a separation with the dead space, quilted or not, at the pectoral area. The drain is connected to a single suction bottle which is changed every day and the daily drain volume is monitored. The axillary drain is removed on the day of discharge either when drain volume is less than 50 ml over 24 hours

regardless of time elapsed after surgery or at 5 days following surgery. Consequently, patients with axillary lymph node dissection have two drains and two suction bottles in the conventional closure group and only one axillary drain and one suction bottle in the quilting suture group.

Surgeon expertise and intervention standardisation

The licensed French doctors who are involved in this trial as practitioners have all been certified by the French ministry of health, have at least one year of surgical experience (senior with at least one year of fellowship validated), and will have taken a course to ensure that they adhere strictly to the study protocol and are familiar with quilting suture. To standardize quilting suture across centres and surgeons, a training period of at least 2 months is required as recommended in the Randomised Trials of Non pharmacologic Treatment extension of CONSORT Statement. [26]

Study outcomes

Primary outcome

The primary outcome is wound seroma requiring aspiration or surgical evacuation within 21 days following mastectomy. A seroma is defined as a postoperative fluid collection via palpation on clinical examination. The Common Terminology Criteria for Adverse Events (CTCAE) 4.0 which is a descriptive terminology used for adverse event reporting, provides a grading scale for seromas (lymphoceles): (1) grade 1: asymptomatic, clinical or diagnostic observation only, intervention not indicated, (2) grade 2: symptomatic, medical intervention indicated, (3) grade 3: severe symptoms, radiologic endoscopic or elective operative intervention indicated. Only grade 2 and 3 seromas i.e. seromas requiring one or more aspirations or a surgical intervention will be considered as primary outcome.

This outcome was chosen as the primary outcome for three reasons. First, this outcome measure was the most used as primary outcome in reported published trials evaluating and comparing the efficacy of different methods in reducing the incidence of seromas when drainage wasn't used for all patients[27-31]. It reflects both patient morbidity and additional medical costs. Focusing on seromas requiring interventions (aspiration or surgical intervention) is a more objective criterion than the simple presence of seroma (on physical exam or ultrasound finding). This allows to take into account only seromas having important consequences for the patient, indeed some authors discovered that 92% of their patients had seromas noted on ultrasound, but only less than half (42%) required aspiration of the seroma. [32-33]. Second, we did not wish to use the total inpatient drainage volume as a primary outcome, because it implies to use suction drains in dead space in both study groups. Using such a drain at the pectoral area while quilting the dead space is not the innovative technique we wished to test because we believe that drains themselves encourage drainage by stimulating tissue reactions or by suction. Moreover, even if we used suction drains in both groups, the patients will not be blinded because quilting suture technique is responsible of minor skin dimpling effect expected to resolve which does not exist with the conventional closure technique. Finally, the only outcome that could be blind assessed is the cosmetic result by an adjudication committee. However, this outcome is not as medically relevant as seroma requiring intervention. We therefore chose to study the cosmetic result as a secondary outcome.

In most cases, a patient will return to her initial centre if an aspiration or surgical intervention for wound seroma is needed. These interventions will be collected in the patient medical records. Nevertheless, each patient will be asked, at day 21 visit about seroma and the need for aspiration or intervention since hospital discharge. In rare cases where patients will mention seroma requiring aspiration or intervention in another centre or by their family

practionner, a physician will be contacted (either by phone or email) to validate the patient report (the same procedure will be done for other wound related complications).

Secondary outcomes

Secondary outcomes include:

(1) Wound-related complications:

- Wound seromas that necessitate aspiration or surgical intervention within 9 months following mastectomy.

- For each patient presenting a seroma that necessitates aspiration, the total volume of aspiration and number of aspirations will be recorded.

- Wound seroma whatever the grade at day 21 and 9 months after surgery.

- Other wound- related complications such as hematoma, skin flap necrosis, surgical site infection at day 21 and 9 months after surgery.

(2) Surgical morbidity: Duration of the surgical procedure and intraoperative blood loss, length of hospital stay after surgery (days), number of outpatient visits (related to mastectomy) needed following participant's discharge within the 9 months follow-up.

(3) Pain: Patient self reported pain measured with the Visual Analogue Scale pain scoring system from 0 (no pain) to 10 (unbearable pain) recorded before surgery, daily during hospitalisation and at 21 days and 9 months after surgery.

(4) Shoulder movement: The range of arm movement scored from 1 to 4 according to estimated angles of arm abduction as 1 (less than 90°), 2 (90-134°), 3 (135-179°) and 4 (180°). It will be measured by the surgeon before surgery and also at 21 days and 9 months after surgery.

(5) Cosmetic results: Both patient and surgeon assessments of the cosmetic results will be documented at day 21 and 9 months after surgery, with possible response categories as follows: poor, acceptable, good and excellent. Digital photographs of the mastectomy area

will be taken with standardized angles of incidence at 9 months. Results will be rated at the end of the study, by an adjudication committee blinded to treatment allocation in order to obtain a blinded surgical cosmetic-assessment.

(6) Health related quality of life: the EuroQoL-5D (EQ-5D)-5L will be collected at baseline, 21 days and 9 months visits. The EQ-5D-5L is an update of the 3L version. It still consists of 2 pages – the EQ-5D-5L descriptive system and the EQ visual Analogue scale. The descriptive system comprises the same 5 dimensions as the EQ-5D-5D-3L (mobility, self care, usual activities, pain/discomfort, anxiety/depression). However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

(7) Direct medical costs and cost-effectiveness.

Follow-up

During follow-up, patients will receive usual care. All patients are followed for a 9-month period, with follow-up visit at 21 days and 9 months following surgery. Those visits fit in with routine follow-up after mastectomy in the participating centres. Schedule of enrolment, intervention and assessments are presented in table 1.

Timepoint	Baseline (inclusion)	Surgery Day 0	Hospitalization daily	Follow-up Day 21 (+/- 5 days)	Follow-up 9 months (+/- 15 days)
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Clinical Exam	X		X	X	X
Previous medical examination	X				

(Mammogram, Breast ultrasound, Breast MRI if required)					
Randomization (as close as possible to the surgery)		X			
INTERVENTION					
Quilting suture		X			
Conventional closure with drain		X			
ASSESSMENTS					
Wound seroma evaluation			X	X	X
Other wound complications			X	X	X
Pain score	X		Day 1 after surgery only, 1st evaluation after 6 am	X	X
Photographs (for cosmesis assessment)					X
Range of arm movement	X			X	X
EQ-5D-5L questionnaire and cost evaluation	X			X	X
Patient/ Surgeon reported cosmesis assessment				X	X
Adverse Events			X	X	X

Table 1: Schedule of enrolment, intervention and assessments

Participant retention is promoted through the eligibility criteria (exclusion of patients with any physical or psychiatric condition that could impair with outcome assessment and intended follow-up). Moreover, loss to follow is unexpected because of the nature of the disease and relatively short follow-up i.e. 9 months.

Blinding

It is not possible to blind patients or surgeons in our trial because of the nature of the studied intervention, surgical intervention that depends on care provider, as for a large part of other non pharmacologic interventions[34-35]. Moreover, blinding of outcome assessor is not feasible for the primary outcome: seroma that require aspiration or surgical evacuation within 21 days following mastectomy. Indeed, after discharge, patients can visit at any time (in emergency or not) for a seroma or another postoperative complication. It is not possible to ensure that the

clinician who will examine the patient is not the same as the surgeon who operated this patient. Moreover, as the patients cannot be blinded to the treatment allocation, it is difficult to ensure that they will not disclose it to the surgeon (outcome assessor of the trial). An adjudication committee blinded to treatment allocation aiming to *a posteriori* validates the indication of aspiration or surgical evacuation of a seroma is not relevant in this study because the decision depends on criteria that cannot be assessed retrospectively by photographs and medical records only.

Data management

Data is recorded on study specific case report forms (CRFs) via an electronic data capture system (CS Online). To maintain participant's anonymity, CRFs are identified only by a coded patient number and initials. All records that contain patient names or other identifying information will be stored separately from the study records and can be identified only by the coded patient number and initials. A data manager from the INSERM CIC 1415 biometry unit verifies the data and sends queries for missing or inconsistent data.

Sample size

The study sample size is based on a comparison of quilting suture versus conventional wound closure with drainage on seroma prevention. In our observational study data, 22% (n = 13/60) of patients undergoing mastectomy with conventional wound suture developed a seroma that required aspiration or surgical intervention within 21 days following surgery. Because of the multicentre profile of our study, the rate of seroma could be greater. We thus assume a rate of 30 % in the control group. In the quilting suture, we expect to observe a rate of patients developing a seroma of 15 %. With these assumptions, a two-sided type I error of 5% and

90% power, a sample size of 160 patients per group is needed. Therefore, we plan to enroll a total of 320 patients.

To recruit this number of patients a 24-month inclusion period is anticipated.

Statistical analyses

The statistical analyses will follow an intention-to-treat approach. Analyses will be conducted using two sided significance tests at the 5% significance level. A participant flow diagram will be reported. Group characteristics at baseline will be studied with descriptive statistics. No statistical tests will be performed on baseline characteristics.

The primary outcome will be assessed as a rate, defined as the number of patients who experienced a seroma requiring aspiration or surgical intervention within 21 days following mastectomy divided by the number of patients randomised into this group. To compare the incidence rates between the two randomised groups, we will use a χ^2 test or Fisher's exact test, as appropriate.

Giving the patient profile, loss to follow-up is very unlikely. Generally, patients continue their follow-up in their original centre even if they move. However, if the case does occur, imputation of missing outcomes will be performed at least in a sensitivity analysis.

For secondary analysis, qualitative outcomes such as other postoperative wound-related complications, cosmetic results and shoulder movement will also be compared between the two arms using a χ^2 test or a Fisher's exact test. The duration of the surgical procedure, length of hospital stay, intraoperative blood loss, will be compared using Wilcoxon tests or Student t tests, as appropriate. Repeated measures such as pain evaluation and health-related quality of life will be analyzed using linear mixed-effects models to take into account the correlation of repeated measures from a given subject.

Economic evaluation

A cost-effectiveness study will be performed on the basis of resource use and HRQOL data collected alongside the trial.

Direct medical costs will be assessed from the hospital and the payer perspectives in both groups and during the whole follow-up period i.e. 9 months after surgery. For each patient, we will collect the healthcare resource use both in the hospital setting and primary care services. This covers the initial surgical stay (duration of the surgical procedure, number of consumables (drains and sutures), length of stay), subsequent hospital stays due to complications/infections, general practitioners and gynaecologist visits (over a 21-day period following surgery only), and home nursing care visits (over a 21-day period only).

To value resources, we will use the following unit costs information:

- Hospital stays: diagnosis related group payment per discharge in the French prospective payment scheme.

- Visits: General fee classification (Nomenclature Générale des Actes Professionnels) and the reimbursement rate at the date of analysis.

Health states will be valued into utility coefficients using data from the EuroQoL group (European value set). It will allow computing QALYs for each patient in both groups.

Costs and QALYs will be compared between the two groups using non parametric tests. Means and 95 % confidence intervals for costs, QALYS and incremental net monetary benefit will be estimated using the non-parametric bootstrap method. Differences in costs and differences in QALYs observed in the bootstrap replicates will be represented in the cost-effectiveness plane. A cost-effectiveness acceptability curve will be computed.

Monitoring

No Data Monitoring Committee was formed because of the short duration of patient participation and known minimal risks for both arms. We did not plan any interim analysis.

Adverse events will be collected and reported according using the usual reported system of the sponsor.

Ethics and dissemination

This protocol was approved by local ethic research committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20, 16/12/2014).

In conformity with the Declaration of Helsinki, all participants will sign a written informed consent form that describes this study and provides sufficient information for patients to make an informed decision about their participation. Consent will be obtained from patients before they undergo any study procedure. Participants may withdraw from the study at any time during the clinical trial without any impact on their care. In that event, data collected prior to participant withdrawal will be used in the trial analysis except if a participant requests removal of all her data from the database. Sponsor of the study may audit trial conduct as deemed appropriate. A formal amendment to the local research ethics committee will be required for any amendments to the study protocol which may impact the conduct of the study, or the potential safety of or benefits to patients will require, if needed an amendment will also be required from the National regulatory Agency for Security of Medicines and healthcare products (ANSM). Any protocol amendments will be communicated to investigators and oversight authority but also to trial participants and registries, if deemed necessary. The chief investigator will be given an access to the cleaned dataset.

Reports will follow international guidelines: CONSORT Statement and Extension of the CONSORT Statement to Randomised Trials of Non pharmacologic Treatment. Research findings will be submitted for publication in peer-reviewed journals regardless of whether or not they are statistically significant. Authors will be individuals who have made key contributions to study design and conduct. Trial findings will also be submitted for

presentation at scientific meetings. The study findings will also be presented at relevant national and international breast cancer conferences.

Discussion

Previous reports in the literature have addressed the effect of quilting versus conventional closure with drainage after mastectomy for breast cancer on patient outcome. However, the studies reported to date are limited by small sample sizes, absence of randomization, concomitant use of drainage with quilting suture, and most studies were single centre initiatives that lacked sufficient power to inform surgical practice. Breast cancer surgeons appear to currently favour conventional wound closure with drainage, although current evidence suggests better patient outcomes with quilting suture. The QUISERMAS trial will aim to resolve these controversies by establishing the effectiveness of each method of mastectomy closure. This will have important clinical implications, as each wound closure type is easily applicable and already performed by breast cancer surgeons. A key limitation of the QUISERMAS trial is that surgeons and patients cannot be blinded to the surgical arms. This leaves the assessment of outcomes and decisions to intervent on seroma vulnerable to bias. A strength of our study is that it is designed to be a feasible, comparative effectiveness trial design that is similar to common clinical situations. Additionally, this clinical trial protocol was conducted to conform strictly to the CONSORT statement. The results of the QUISERMAS trial will be an important contribution in breast cancer surgery literature and are likely to lead changes in mastectomy closure. We expect that this study will provide the clinical basis and evidence that is required to perform quilting suture in routine when performing mastectomies.

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Acknowledgements The authors acknowledge Carine Coffre (data manager), Aurélie Darmaillacq (clinical research associate) and Rachel Fontenay (health economist) for their constructive support during preparation and conduct of the trial.

The authors would also like to express appreciation for the contributions from patients with breast cancer who will participate in this trial.

Contributors LO and AC helped to conceive and design the trial and wrote the manuscript. JB, BG and GB helped to conceive the trial and revised the manuscript. LO and GB will be investigators and will recruit patients and conduct the trial. AC planned the statistical analysis. LO and AC will supervise the trial. All authors read and approved the final manuscript.

Funding This trial is supported by a grant from the French Ministry of Health (PHRC 2013). The funding source has no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Competing interests No, there are no competing interests.

Ethics approval Tours Research Ethics Committee (CPP TOURS - Region Centre - Ouest 1, 2014-R20, 16/12/2014).

Data sharing statement Public Access There are no plans to grant public access to the full protocol, participant-level data or statistical code.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1,3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	__19_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1_____
	5b	Name and contact information for the trial sponsor	___1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___7,8,14 to 17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____5,6_____
	6b	Explanation for choice of comparators	____5,6, 11___
Objectives	7	Specific objectives or hypotheses	_____6, 10 to 13
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____2,6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____8 to 10_
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____10_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____13____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__10 to 13_
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	a table was added

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____14,15___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____7, 14, 15_
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____13,14___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____14 to 16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____15_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____14_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____15,16__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__NA_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____1, 15_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_the trial does not require a DMC because we are only evaluating the closure technique and both techniques are known to be of minimal risk for patients____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____17____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available from request to the first author

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.