Trials structured Study Protocol template

Title

COMPLIANCE: Impact of routine assessment of health-related quality of life coupled with therapeutic information on compliance with endocrine therapy in patients with non-metastatic breast cancer: protocol for a randomized controlled trial.

Names protocol contributors

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Abstract

- **Background:** *Despite its proven efficacy in reducing recurrence and improving survival, adherence to endocrine therapy (ET) is suboptimal in women with breast cancer (BC). Health-related quality of life (HRQoL) in BC has been widely studied and many positive effects have been highlighted. Recently, a link between HRQoL and compliance with ET has been suggested, which would suggest a potential role for HRQoL assessment in improving compliance with ET. With the advent of digital technologies, electronic collection of HRQoL on a tablet is now possible. Thus, we hypothesize that systematic HRQoL assessment (using a tablet, prior to each consultation, with presentation of scores to clinicians) coupled with therapeutic information could have an impact on 12-month compliance with ET in patients with non-metastatic BC.*
- **Methods:** *In this study, we will include 342 women with non-metastatic hormone receptor positive BC with an indication for treatment with ET. Patients will be randomized 1:1 by minimization and stratified by: age, stage, type of ET prescribed and presence of comorbidities or not, in 2 arms. The intervention will consist of numerical HRQoL assessment using the CHES software before each consultation (with delivery of scores to clinicians) coupled with therapeutic information. Therapeutic information will consist on 3 workshops related to understanding the prescription, nutrition and fatigue. A reminder letter will also be send to patients every month. Patients in the control group will follow standard care. HRQoL will be assessed using a classic "paper-pencil" collection at baseline in both arms to ensure comparability between arms and at 12-month. The primary endpoint is 12-month compliance with ET. Patient satisfaction with care, and clinicians' perception of the usefulness of routine HRQoL assessment will also be assessed.*
- **Discussion:** *This study will allow clinicians to identify and better understand the areas in which patients on ET have difficulties, and thus assist clinicians with patient management. Systematic evaluation of HRQoL could also provide an additional endpoint for measuring patients' health status and treatment-related symptoms, including ET. If the results of this study are positive, this intervention could be proposed as an integral part of daily clinical practice in patients treated with ET.*
- **Trial registration**: ClinicalTrials.gov NCT04176809. Registered 25 November 2019, https://clinicaltrials.gov/ct2/show/NCT04176809.

Keywords

Breast cancer, Health-related quality of life, Compliance, therapeutic information, endocrine therapy

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	COMPLIANCE: Impact of routine assessment of health-related quality of life coupled with therapeutic information on compliance with endocrine therapy in patients with non-metastatic breast cancer: protocol for a randomized controlled trial.
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Role of sponsor {5c}	All the personal of this study are working in Georges Francois Leclerc Center. The sponsor played no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. All information resulting from this study is considered confidential, at least until the appropriate analysis and control by Georges Francois Leclerc Center, the coordinating investigator, has been completed.

Introduction

Background and rationale {6a}

Currently, a large number of hormonal and cytotoxic oral therapies are available for breast cancer (BC) management. The major advantage of these therapies is their convenience due to self-administration [1,2]. Currently, in cancer treatment more than 40 oral drug specialties are reimbursed by the French health insurance system [1]. These oral forms present a new challenge in oncology, namely concerning treatment compliance. Compliance is defined as the extent to which the patient follows prescriber's recommendations [3]. Oral anticancer therapies raise concerns about poor compliance. In particular, the impact of adverse effects due to non-compliance on clinical outcomes. Non-compliance compromises overall efficacy of oral therapies and may potentially lead to treatment failure [4].

In BC, the oral form of endocrine therapy (ET) is by far the most widely investigated in terms of compliance [1]. Compliance with oral endocrine therapy is not optimal in BC. Indeed, only 59% of women treated with ET for BC remain compliant one year after prescription [5], and this percentage ranges between 41% and 72% at the end of 5 years of treatment [6]. Poor compliance with endocrine therapy is associated with decreased survival [7, 8], increased risk of recurrence [7] as well as poor prognosis [9]. To improve compliance, several studies [10-12] have implemented interventions via educational materials (sending letters, information booklets as well as telephone interviews) but none has shown a significant effect. Hadji et al in their study testing addition of educational materials to standard therapy versus the standard therapy only, in women taking Anastrozole, have shown no significant effects on compliance and persistence with adjuvant Anastrozole [10].

Concerning Ziller et al study, patients receiving additional/supplemental information appeared to have an improved adherence rate, even though differences between groups with regards to the primary endpoint were not statistically significant [11]. In another study, postmenopausal women with hormone receptor-positive (HR+) early-stage breast cancer treated with aromatase inhibitors (AI) were randomized in two groups: one receiving only AI and the other one receiving educational materials plus AI. This study has shown that education materials do not improve compliance in this patient population and has highlighted the complex nature of compliance and persistence [12].

It is interesting to note that compliance is a multidimensional phenomenon which can result from various factors related to patients (social support, patient beliefs, psychosocial factors), treatments (side effects) or health care systems (poor patient-health care provider relationship) [13].

Evaluation of the quality of care is of major importance, but to date, most quality initiatives have focused on assessing adverse events, clinical processes and cost variables. Less attention has been given to indicators of clinical improvement measured from patient's point of view [14]. To give patients the opportunity to express their perception concerning their own health, in clinical trials as well as in routine practice, it is necessary to plan and assess the use of HRQoL in clinical research and practice.

Health-related quality of life (HRQoL) is gathering increasing interest in oncology, as reflected by the number of scales being developed and the increased use of HRQoL measurement as an outcome in randomized controlled trials. Reasons for this growing interest may be related to significant treatment toxicities but also to the fact that HRQoL has been shown to be a prognostic factor for survival [15, 16]. In many cases, symptom palliation of and improvement of HRQoL are the main goals of treatment, rather than increased survival. Thus, the American Society of Clinical Oncology (ASCO) and the Food and Drug Administration (FDA) recommend HRQoL as the second endpoint after overall survival and the primary endpoint of treatment efficacy, if treatment has no effect on overall survival. Over the past decade, HRQoL in BC has been widely studied and many determinants have been identified [17, 18].

Routine evaluation of HRQoL was shown to have a positive impact on communication between patients and medical staff [19] and on clinical parameters such as the duration of the treatment without relapse and survival [20, 21]. Recently, it has been suggested that there may be a link between HRQoL and compliance with oral endocrine therapy. Indeed, Pinheiro et al, reported that women with poorer HRQoL were more likely at risk of non-adherence [22], in a study addressing the association between HRQoL and under-use of endocrine therapy in women with hormone-sensitive BC. This result suggests that focusing on a modifiable factor such as HRQoL could be a way to improve compliance with oral endocrine therapy. In addition, to date, the modulatory effect of HRQoL on compliance with oral treatments in BC has never been studied.

With the advent of digital technologies, it is now possible to perform HRQoL measurements using a tablet with instantaneous score generation [23]. This mode of measurement provides real time results to clinicians (through graphics) and generates alerts (color codes) if HRQoL scores are deteriorated, allowing adjustment of patient support in a personalized way. From the patient's point of view, the inclusion of numerical assessment in the process of data collection has shown benefits in disease management and symptom control [24], improving survival [20] and patient-clinician communication [19]. Moreover, it also potentially facilitates clinical decision through the systematic and continuous collection of symptom data [25].

Since compliance is a multidimensional phenomenon, any attempt to improve it should encompass several

potential contributors.

Objectives {7}

We hypothesize that electronic measurement of HRQoL (before each consultation with scores communicated immediately to clinicians who can discuss it with patients), coupled with therapeutic information, will improve 12-month compliance rate with ET in patients with non-metastatic BC. At a later step, we will assess the role of social support and psychological distress as potential modulators of compliance with ET, the capacity of HRQoL to predict compliance with ET, patient satisfaction with care and physician's perception regarding the clinical utility of routine HRQoL evaluation.

Trial design {8}

To achieve study aims, we will carry out a randomized, interventional, prospective study. Eligible patients who agree to participate will be randomized into two parallel arms (ratio 1:1) by the minimization technique with stratification by age, stage, presence or absence of comorbidities and type of ET prescribed.

Methods: Participants, interventions and outcomes

Study setting {9}

Patients will be recruited at Dijon cancer center (Georges François Leclerc-Unicancer center) in France.

Eligibility criteria {10}

Women aged 18 and over, with non-metastatic hormone receptor positive breast cancer will be included in this study. These women will have to be at the end of primary treatment, have an indication for endocrine therapy treatment during 5 to 10 years, be affiliated to a French social security scheme or beneficiary of such a scheme and have agreed to participate by signing a written consent. Patients who participate in another clinical trial where HRQoL is assessed will not be included, as well as women for whom HRQoL evaluation is not possible (cognitive disorders, psychiatric disorders, people who do not speak French).

Who will take informed consent? {26a}

The study will be proposed to eligible patients by their doctors (oncologists, surgeons, radiation oncologists). Patients will then be referred to the clinical research associates, whose role will be take informed consent from participants who agree to be included in the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. Participants will also be asked for permission for the research team to share relevant data with people from the Universities taking part in the research or from regulatory authorities, where relevant.
This trial does not involve collecting biological specimens for storage.

Interventions

Explanation for the choice of comparators {6b}

Patients in the control arm will receive standard care. They will not undergo digital HRQoL collection, and therapeutic information workshops will not be proposed to them. Nevertheless, HRQoL will be evaluated at baseline using the FACT-G questionnaire to ensure the comparability of groups concerning HRQoL at inclusion, and again at 12 months. This HRQoL assessment will be performed using a traditional paper questionnaire and scores will not be provided to clinicians. The particularity of this HRQoL assessment is that it will be done in both groups. We have choose a standard care for patients in control groups in other to be able in case of positive results to implement this intervention in our routine care.

Intervention description {11a}

The intervention will be done in the interventional arm. It will consist in an electronic measurement of patient HRQoL before each consultation with delivery scores to clinicians, who can discuss it with patients and couple it with therapeutic information.

Assessment of HRQoL

Patients will complete the EORTC-QLQ-C30 and the EORTC-QLQ-BR23 questionnaires before their consultation, via a touch pad or from their home via a secure web portal. Patients will complete the questionnaires via the CHES software [26]. The CHES software was developed by Evaluation Software Development (ESD) in collaboration with the EORTC Quality of Life Group to facilitate the inclusion of HRQoL measurement instruments in research projects and daily clinical practice. This mode of collection provides clinicians with real-time results, and generates alerts in the event of clinically significant deterioration of patients' HRQoL scores, allowing them to tailor treatment in a personalized manner. The scores will then be generated and provided to patients and clinicians in a graphic form, describing scores course. Access to CHES web portal will also be open to patients outside consultation time points, to enable them to monitor HRQoL if necessary. If minimal HRQoL impairment is observed (decrease lower than 20 points) [27], self-help tools can be generated, providing patients with indications on how to deal with certain adverse effects. Moreover, if a significant deterioration in HRQoL (decrease higher than 20 points) [27], the clinical research assistant will receive an alert and, if necessary, will forward the information to the medical team for appropriate care.

Therapeutic information

Therapeutic information will consist on workshops on various themes and will be coordinated by a pharmacist in charge of therapeutic education in Dijon cancer center. This healthcare professional will be responsible for the organization and implementation of these workshops. Workshops will be performed by pharmacists, nurses or dieticians. Only attendance Workshop 1 will be required, other workshops will be optional.

Workshop 1, will deal with “understanding the prescription”. The aim is to inform patients about their ET and treatment benefits. It also helps patients to recognize and react to the occurrence of possible adverse effects, and anticipate their occurrence through appropriate preventive means. This workshop will be held within 2 months after the first prescription of endocrine therapy. This workshop will be performed by pharmacists with training in therapeutic education.

Two additional optional workshops on nutrition (Workshop 2) and fatigue (Workshop 3) will be offered. This workshops will be collective and performed by a dieticians and nurses, respectively. Workshop 2, on Nutrition, will focus on the benefits of exercise and the need to adopt an appropriate diet. Patients will have the opportunity to express their representations and experiences related to their diet and the consequences of

disease and treatments on diet. Workshop 3, on fatigue, will address the recognition of fatigue and early management of this symptom. Patients can describe their experiences of fatigue and how their life is affected by it. Moreover, they can identify possible causes and finally discuss solutions to better this symptom.
Every month, a letter encouraging patients to regularly take their medication will be sent. This letter, derived from Hadji's work [10], will also include some tips on how to deal with some particular side effects of endocrine therapy.

Criteria for discontinuing or modifying allocated interventions {11b}

Patient have the right to withdraw his consent at any time of the study. Patients who withdraw from the study will continue to receive standard care.

Strategies to improve adherence to interventions {11c}

Every month, a letter encouraging patients to regularly take their medication will be sent. This letter will also play the role of a reminder for patients in interventional group.

Relevant concomitant care permitted or prohibited during the trial {11d}

None

Provisions for post-trial care {30}

There is no anticipated harm and compensation for trial participation and there will be no provision for post-trial care, other than continuation of standard care.

Outcomes {12}

Primary endpoint

The primary endpoint of this study is 12-month compliance with ET, as evaluated using the Morisky Green Levine scale (MGL). Patients will be considered as compliant if they have a high adherence in MGL scale corresponding to a score of 4.

Secondary endpoints

The secondary endpoints will be anxiety and depression assessed by the HADS questionnaire, social support assessed by Sarason's SSQ6 questionnaire and HRQoL assessed by the FACT-G questionnaire.
HRQoL data using FACT-G questionnaire will be assessed at inclusion in both arms to ensure comparability between groups and at 12 months, to assess the predictive value of HRQoL on compliance to endocrine therapy.
Patient satisfaction with care will be assessed by the EORTC-SAT-C33 and EORTC-OUT-PATSAT-7 questionnaires.
Physician perception regarding the utility of systematic HRQoL evaluation will be assessed using an ad hoc questionnaire derived from the work of Velikova [19, 28], including the perceived utility and satisfaction of routine assessment HRQoL, reasons for use/non-use and the intention to adopt this assessment in routine care.

Participant timeline {13}

See SPIRIT Figure for more information.

Sample size {14}

A total of 342 patients with non-metastatic BC are required, based on the following assumptions: an estimated compliance rate of 59% [5] in patients with non-metastatic breast cancer one year after the first prescription of ET, a bilateral risk alpha of 5%, a statistical power of 80%, to show a 15% difference in compliance between patients in the intervention arm and those in the control arm 1 year after the first prescription, it is necessary to include 155 patients per arm (bilateral chi-square test). Taking into account a loss to follow-up rate of 10%, a total of 171 patients will be included in each arm (nQuery Advisor V7).

Recruitment {15}

Eligible patients will be identified by a clinical research associate in multidisciplinary consultation meeting. After that, they will inform investigators of the study. The doctors (oncologists, surgeons, radiation oncologists) will propose the study to patients who were eligible.

Assignment of interventions: allocation

Sequence generation {16a}

The Method of generating the allocation sequence will be a computer-generated random numbers with age, stage, presence or absence of comorbidities and type of ET prescribed being the factors for stratification.

Concealment mechanism {16b}

Eligible patients who agree to participate will be randomized into two parallel arms (ratio 1:1) by the minimization technique.

Implementation {16c}

The investigator or the surrogate person choose by the investigators will generate the allocation sequence, enroll participants, and assign participants to interventions.

Assignment of interventions: Blinding

Who will be blinded {17a}

No blinding only data analysts will be blinded.

Procedure for unblinding if needed {17b}

The design is an open label trial with only data analysts being blinded so unblinding will not occur.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data collected

Sociodemographic characteristics (age, sex, level of education, family situation, socio-professional category, work time), medical and surgical history, date of tumor diagnosis, tumor characteristics, previous treatments, patient clinical characteristics at inclusion and at each follow-up visit (weight, height, overall patient condition), concomitant treatment, type of endocrine therapy received, HRQoL data (FACT-G), anxiety and depression (HADS), social support (SSQ6), treatment modification (change in the type of endocrine therapy), treatment-related toxicities and their grade will be collected. Patient satisfaction with provided care will be measured

using the EORTC-SAT-C33 and the EORTC-OUT-PATSAT-7. Clinicians' perceptions of systematic health-related quality of life assessment (utility and perceived satisfaction, reasons for use or non-use, and the intention to adopt it in practice) will be collected via an ad hoc questionnaire. Sociodemographic data and reasons for refusing to participate will also be documented for patients who refuse to participate. Data on patients' withdrawal or death will be documented in the case report form. Reasons for study withdrawal should also be documented. All data from this study will be transcribed in an electronic case report form (Clinsight).

Questionnaires and tools

EORTC-QLQ-C30 and EORTC-QLQ-BR23 questionnaires

The cancer-specific EORTC-QLQ-C30 questionnaire and its breast cancer-specific QLQ-BR 23 module are available in French and are validated tools to assess HRQoL in cancer and more specifically in BC [29]. The EORTC-QLQ-C30 questionnaire renders possible to assess one dimension of HRQoL / overall health, five functional dimensions (physical, current activities, cognitive, emotional and social), eight dimensions of symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation and diarrhea) and a scale of financial difficulties. The EORTC-QLQ-BR23 consists of 23 questions which assess four functional dimensions (body image, sexual activity, sexual pleasure and future perspectives) and four dimensions of symptoms (side effects of systemic therapy, breast symptoms, symptoms at the arm and upset by hair loss). Scores are generated per dimension in accordance with the EORTC [30] scoring rules. These scores vary from 0 (worst) to 100 (best) for the functional and global health parameters and from 0 (best) to 100 (worst) for symptom parameters.

MGL questionnaire

The 4-item Morisky Green Levine Medication Adherence Scale (MGL) was developed to measure adherence to treatment by Morisky et al [31]. It has a range of 0 to 4, where 0 is very low and 4 is highest. Patients are categorized according to three levels of adherence: high (score equal to 4), moderate (score equal to 2 or 3) and low (score equal to 0 or 1).

HADS questionnaire

The Hospital Anxiety and Depression Scale (HADS) is an instrument for detecting anxiety and depressive disorders. It was validated and adapted in French in 1989 by Lepine et al [32]. This scale has 14 items rated from 0 to 3 and covers 2 dimensions. Seven questions related to the anxiety dimension and seven other related to the depressive dimension, yielding 2 scores, A (Anxiety) and D (Depression). The maximum score for each dimension is 21. A score of 11 or higher indicates the probable presence of the disorder.

FACT-G questionnaire

The FACT-G (Functional Assessment of Cancer Therapy-General) is a 27-question tool validated in cancer patients and has four subscales to assess wellbeing. The FACT-G instrument assesses 4 HRQoL domains: physical well-being (7 items); social and/or family well-being (7 items); emotional well-being (6 items); and functional well-being (7 items). Respondents use a 5-point Likert-type scale which rates the relevant domain from 0 (not at all) to 4 (very much). From these subscales a global score is obtained [33, 34]. The FACT-G total score vary from 0 to 108. The higher the score, the better the HRQoL.

EORTC PATSAT-C33 and EORTC-OUT-PATSAT-7 questionnaires

The EORTC-PATSAT-C33 questionnaire and its EORTC-OUT-PATSAT7 ambulatory context-specific

supplementary module were developed to assess perceptions of cancer patients regarding the quality of care received [35]. They consist of 33 and 7 items, respectively. The EORTC-PATSAT-C33 questionnaire includes three sections on the perceived quality of care provided by physicians, radiotherapy nurses / technicians and services / care organization. The clinician section includes three dimensions that address technical skills (3 items), quality and quantity of information exchanged (3 items) and behavior (4 items). The radiotherapy nurses / technicians section has two dimensions: information provision and reactivity (3 items) and affective behavior (4 items). The service and organization of care section has three dimensions: coordination (4 items), interaction with the healthcare team (7 items) and five single items.

The complementary EORTC-OUT-PATSAT7 includes two dimensions dealing with convenience of care (3 items) and transition (3 items) and a single item on continuity of care. The instructions invite patients to evaluate the most recent care experience and to specify the cancer care setting. The score vary from 0 to 100. A higher score indicates higher level of satisfaction.

SSQ6 questionnaire

Social support will be evaluated by Sarason's six-item Social Support questionnaire (SSQ6), validated and adapted in French by Rascle et al. in 2005 [36]. This questionnaire reflects the support available in patients' environment. Social support is measured across 2 dimensions: support availability, through the number of contacts that the patient can count on (0 to 9 people) and quality of support, through patient satisfaction with support received.

Each item represents a situation in which the patient may need support. Patient is asked to cite the number of people that she could count on in that particular situation. Concerning the second item, the patient is asked to assess satisfaction with the support provided. The scores are generated according to Sarason's recommendations. A score is calculated for each dimension. Support availability score is calculated as the sum of the number of people available for the 6 items, this score ranges from 0 to 54, with 54 representing the highest availability. The social support satisfaction score is calculated by the sum of the satisfaction of the 6 items. This score ranges from 6 to 36, with 36 representing the highest level of satisfaction [37].

Ad hoc questionnaire

This ad-hoc questionnaire derived from the work of Velikova [19, 28] will assess the perception of doctors concerning the interest of systematic HRQoL evaluation. It evaluates the following criteria: usefulness of the systematic evaluation of HRQoL, perceived satisfaction with systematic evaluation of HRQoL, reasons to use it or not in current clinical practice and whether or not to adopt it routinely.

CHES

For this study, a French version of the CHES web-based solution will be available. Each patient will be represented by an identifier, to guarantee the data confidentiality and anonymous exploitation of database for statistical purposes. CHES offers a cross-sectional presentation (presentation of scores for each dimension) and a presentation of the longitudinal course of HRQoL for each dimension of the questionnaires. CHES also minimizes input errors, reduces the number of missing data related to data collection, and avoids ambiguities in the responses. This software also allows remote access via a platform that will allow patients, who desire (outside the consultations) to give an input on their HRQoL, in the event of a deterioration or improvement perceived at the clinical level.

Plans to promote participant retention and complete follow-up {18b}

We have plan for patients in the intervention group to do the optional workshops coupled with their visit in the hospital. This was set up to avoid patients to come to the hospital only for the workshops since transport fees is not reimbursed in this study. For the promotion of a complete follow-up, the encouragement letter send every month to the patients will also play a role of reminder.

Data management {19}

All information required by the protocol will be reported for each patient in an electronic case report form (eCRF). The data should be collected in the patient's file as they are obtained, and reported in the eCRF via a given access to the Clinsight © tool.

An explanation will be given for each missing data and the consistency of the data entered will be verified.

All data from this study will be transcribed in an electronic observation booklet (Clinsight) by a person designated by the investigator (CRA of the site). A record of all changes made to the notebooks will be kept (Audit Trail of Clinsight).

In order to attest to the authenticity and accuracy of the data contained in the observation booklet, the investigator will sign via an electronic signature as part of an eCRF.

The data will be collected on an electronic observation book under the responsibility of the investigator or the person that the investigator has delegated for this function (CRA, etc.) on a hosted e-CRF (and saved on a daily basis) by a provider and protected by a password changing every 3 months.

A data extraction in SAS version 9.4 or R or STATA will be requested for the analysis, in order to be able to import into the appropriate statistical analysis software. The data file and the corresponding formats will be replayed and saved according to the standard operating procedures of the Georges Francois Leclerc Center (CGFL).

The data will be saved on the internal network of the CGFL in a directory dedicated to the study, directory accessible only to the statistician. The internal network of the CGFL is secured by a firewall that protects the CGFL network from any external intrusion. A proxy server also controls web browsing and anti-virus software examines all files and pages copied from external servers to the CGFL. Each person wishing to connect to the CGFL network must first identify himself using an identifier provided by the CGFL IT Services and with his personalized password during the first connection.

In accordance with the decree of 8 November 2006 fixing the period of conservation by the sponsor and the investigator of documents and data relating to a biomedical research on a medicinal product for human use, at the end of the research:

All the documents (different versions of the protocol, notebooks, investigative file, consents, correspondences, etc.) appearing on paper will be archived, in each center, and at the promoter, for at least 15 years.

The data on computer media will be kept until the completion of the final report of the research and archived for at least 15 years.

The entry will be made on e-CRF, terminal controls will be programmed according to the data-management manual and will therefore require the correction of the data as soon as it is entered. Depending on the specifications, data validation may be carried out for the statistical analysis, and requests for correction will be issued to the investigator or to the study's clinical research associate, which undertakes to complete and correct the data in result.

The database will be frozen once the consistency checks are no longer anomalies and following a decision by

the project manager in consultation with the methodologist.

Confidentiality {27}

The investigator undertakes, for himself and for all those who have to follow the progress of the trial, to guarantee the confidentiality of all the information provided by the Center Georges François Leclerc until the publication of the results of the 'trial. This confidentiality requirement will not apply to information that the investigator will be required to provide to patients as part of their participation in the trial or to previously published information.

The investigator undertakes not to publish, disclose or use, in any way whatsoever, directly or indirectly, scientific or technical information related to the trial. The essay may not be the subject of any written or oral commentary without the agreement of the promoter (CGFL); all the information communicated or obtained during the execution of the test belonging to the promoter, who may freely dispose of it.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

See above 26b there will be no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive analysis

A descriptive analysis of patients' clinical and socio-demographic characteristics at inclusion will be performed for each arm. Data will be expressed as number and percentage for categorical variables, and as mean± standard deviation (SD), or median and interquartile range [IQR] for continuous variables, as appropriate. The number of missing data will be specified. The number of patients with available data will also be specified for quantitative variables. Normality will be tested using the Shapiro-Wilk test. According to data distribution, independent Student t tests or non-parametric Mann-Whitney tests will be used to compare results between groups. The basic categorical characteristics will be compared using tests of Chi square or Freeman Halton according to the number of the variable categories. Continuous variables can be transformed into categorical variables according to thresholds defined by literature.

Analysis of the primary endpoint

Compliance with endocrine therapy at 12 months equal the percentage of patients with a score of four in Morisky Green Levine scale.

HRQoL analysis

All HRQoL scores will be calculated according to FACT-G guidelines and described according to the arm (interventional arm or control arm). A logistic regression model will be used to assess the capacity of HRQoL to predict 12-month compliance with endocrine therapy. The modulatory potential of social support on compliance will be assessed using an interaction term between the availability / satisfaction of social support that patients receive and HRQoL in a logistic regression model. The modulatory potential of psychological

distress on compliance will be assessed using an interaction term between patient anxiety / depression and HRQoL in a logistic regression model.
The significance level for the statistical analyses is fixed at $p < 0.05$ and all tests will be bilateral. The data analysis will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analysis
Contamination-based intent-to-treat analysis will be conducted to account for potential cross-contamination between the arms.

Interim analyses {21b}

An interim analysis will be conducted when half of the patients in the study have been included and the evaluation of the primary endpoint in these patients completed.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

An analysis of missing HRQoL data profiles will also be performed. If a Missing Not At Random (MNAR) profile is demonstrated / suspected, multiple imputation of missing data can be performed in sensitivity analysis, taking into account the variables associated with the occurrence of missing data.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

A steering committee will be set up as part of this study. This committee will be made up of the following members: Dr. Isabelle DESMOULINS, Dr. Karine PEIGNAUX, Tienhan Sandrine DABAKUYO YONLI, Dr. Cyril DI MARTINO, Ariane MAMGUEM KAMGA, and Oumar BILLA.

Composition of the data monitoring committee, its role and reporting structure {21a}

Since no serious adverse events related to patient participation are expected in this study, we do not wish to set up an independent monitoring committee. Nevertheless, a steering committee will be set up as part of this study. He will take all the decisions concerning the study (amendments, opening of new centers, etc.). This committee will be made up of the following members: Dr. Isabelle DESMOULINS, Dr. Karine PEIGNAUX, Tienhan Sandrine DABAKUYO YONLI, Dr. Cyril DI MARTINO, Ariane MAMGUEM KAMGA, and Oumar BILLA.

Adverse event reporting and harms {22}

As soon as an investigator becomes aware of an adverse event, incident or risk of a serious incident, he / she transmits it directly to the concerned vigilance according to the procedures in force in the establishment and by stating in the declaration that the patient is included in the study ACRONYM STUDY + ID RCB ID.

The intervention implemented in this study is a low risk intervention. Indeed, the procedure set up consists of the administration of HRQoL questionnaires as well as workshops therapeutic information. Since the patients in this study are on endocrine therapy, the standard procedure for the reporting of adverse events related to endocrine therapy will be implemented. The principal investigator will be responsible for ensuring this.

Frequency and plans for auditing trial conduct {23}

There is no Data Monitoring Committee as this is a low-risk intervention. Nevertheless, a steering committee will be set up as part of this study. They will gathered 2 times per year during the enrolment phase to see if the trial need to be adjust and only once per year during the follow-up phase. But they can also gathered in extraordinary session when is needed.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any modification of the protocol of the study will be the subject of a request for amendment to the regulatory authorities. In case of modification, approved by the regulatory authorities, the investigators of the study will be informed.

Dissemination plans {31a}

All information resulting from this study is considered confidential, at least until the appropriate analysis and control by the sponsor, the coordinating investigator, has been completed. All publications, abstracts or presentations including the results of the trial will require the approval of the sponsor. In addition, all communications, manuscripts or presentations must include a section that mentions the Center Georges François Leclerc, investigators, that have contributed to the conduct of the study. Similarly, the publications of the ancillary results (ancillary studies) will include the name of the person who performed the additional work as well as the names of all the other persons concerned by this additional work as well as the name of the coordinator.

Discussion

This study will evaluate the usefulness of systematic assessment of HRQoL coupled with therapeutic information to enhance compliance with endocrine therapy in patients with non-metastatic breast cancer. To take into account that compliance decreases over time, a reminder to encourage patients to take endocrine therapy was included in the intervention and will be sent every month.

A steering committee has also been set and will be responsible for all the decisions concerning the study.

In the future, if results are positive, this intervention will be implemented in clinical practice, therefore we have chosen to be as close as possible to routine clinical practice. Routinely, women with HR+ breast cancer treated with endocrine therapy will have a consultation 2 to 3 times a year. HRQoL will be assessed before each consultation and will be monitored three times during study duration.

This routine HRQoL assessment would enable clinicians to identify and better understand the areas in which patients treated with endocrine therapy most need support, therefore guiding patient individual management.

Systematic assessment of HRQoL could also provide an additional endpoint for measuring patient status and treatment-related symptoms, including endocrine therapy.

If study results are positive, electronic assessment of HRQoL coupled with therapeutic information could be offered in daily clinical practice as an integral part of the care process for patients treated with endocrine therapy. Moreover, this intervention could be generalized to other centers in France, considering that every cancer center has a service dedicated to therapeutic information.

Trial status

Protocol version 1.1

Date: 20/08/2019

Beginning of the recruitment: January 2020

Approximate date when recruitment will be completed: December 2022

Abbreviations

BC: Breast Cancer

ET: Endocrine Therapy

HRQoL: Health-related quality of life

HR+: Hormone receptor positive

FACT-G: Functional Assessment of Cancer Therapy- General

ASCO: American Society of Clinical Oncology

FDA: Food and Drug Administration

EORTC: European Organization for Research and Treatment of Cancer

ESD: Evaluation Software Development

HADS: Hospital Anxiety and Depression Scale

SSQ6: Sarason Social Support Questionnaire

SD: Standard Deviation

IQR: Interquartile Range

MNAR: Missing Not At Random

SAS: Statistical Analysis System

CHES: Computer-based Health Evaluation System

Declarations

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Authors' contributions {31b}

AKM and TSDY conceived the study and wrote the protocol. They also provided support in methodological aspects, statistical analyses. CDM helped to design therapeutic information workshops. SPB and AA provided support in methodological aspects (particularly routine HRQoL monitoring through the CHES software) and statistical analyses. PA has provided support in methodological aspects. All authors read and approved the final manuscript.

Funding {4}

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Availability of data and materials {29}

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate {24}

The protocol falls within the scope of interventional biomedical research and has been approved by regulatory authorities. This study has also been registered with the Competence Authority (IDRCB number: 2019-A01323-54). The information collected during this study is subject to computer processing in accordance with MR001 reference methodology. The declaration of conformity with the MR001 reference methodology has also been done (N ° 1878714) for interventional studies for treatment of informatics data. Every woman eligible for this study will have to sign an informed consent before enrollment. Prior consent signature, women should have received a clear information on the study and a delay will be given before informed consent signature.

Consent for publication {32}

These are available from the corresponding author on request.

Competing interests {28}

The authors declare that they have no competing interests.

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References

1. *Huiart L, Bardou VJ, Giorgi R. L'adhésion thérapeutique aux traitements oraux : enjeux en oncologie - l'exemple du cancer du sein [The importance of adherence to oral therapies in the field of oncology: the example of breast cancer]. Bull Cancer. 2013; 100(10):1007–1015. doi:10.1684/bdc.2013.1830*
2. *Ayres LR, Baldoni Ade O, Borges AP, Pereira LR. Adherence and discontinuation of oral hormonal therapy in patients with hormone receptor positive breast cancer. Int J Clin Pharm. 2014; 36:45–55. doi:10.1007/s11096-013-9833-5*
3. *Hugtenburg JG, Timmers L, Elders PJ, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient Prefer Adherence. 2013; 7:675–682. Published 2013 Jul 10. doi:10.2147/PPA.S29549*
4. *Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. Diabetes Care. 2012; 35(12):2533–2539. doi:10.2337/dc12-0572*
5. *Cheung WY, Lai EC, Ruan JY, Chang JT, Setoguchi S. Comparative adherence to oral hormonal agents in older women with breast cancer. Breast Cancer Res Treat. 2015; 152(2):419–427. doi:10.1007/s10549-015-3455-7*
6. *Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat. 2012; 134(2):459–478. doi:10.1007/s10549-012-2114-5*
7. *Weaver KE, Camacho F, Hwang W, Anderson R, Kimmick G. Adherence to adjuvant hormonal therapy and its relationship to breast cancer recurrence and survival among low-income women. Am J Clin Oncol. 2013; 36(2):181–187. doi:10.1097/COC.0b013e3182436ec1*
8. *Hsieh KP, Chen LC, Cheung KL, Chang CS, Yang YH. Interruption and non-adherence to long-term adjuvant hormone therapy is associated with adverse survival outcome of breast cancer women--an Asian population-based study. PLoS One. 2014; 9(2):e87027. Published 2014 Feb 21.*
9. *Taketani K, Tokunaga E, Yamashita N, et al. Early discontinuation of adjuvant hormone therapy is associated with a poor prognosis in Japanese breast cancer patients. Surg Today. 2014; 44(10):1841–1846. doi:10.1007/s00595-013-0762-7*
10. *Hadji P, Blettner M, Harbeck N, et al. The Patient's Anastrozole Compliance to Therapy (PACT) Program: a randomized, in-practice study on the impact of a standardized information program on persistence and compliance to adjuvant endocrine therapy in postmenopausal women with early breast cancer. Ann Oncol. 2013; 24(6):1505–1512. doi:10.1093/annonc/mds653*
11. *Ziller V, Kyvernitakis I, Knöll D, Storch A, Hars O, Hadji P. Influence of a patient information program on adherence and persistence with an aromatase inhibitor in breast cancer treatment--the COMPAS study. BMC Cancer. 2013; 13:407. Published 2013 Sep 4. doi:10.1186/1471-2407-13-407*

12. *Markopoulos C, Neven P, Tanner M, et al. Does patient education work in breast cancer? Final results from the global CARIATIDE study. Future Oncol. 2015; 11(2):205–217. doi:10.2217/fon.14.179*
13. *Hadji P. Improving compliance and persistence to adjuvant tamoxifen and aromatase inhibitor therapy. Crit Rev Oncol Hematol. 2010; 73(2):156–166. doi:10.1016/j.critrevonc.2009.02.001*
14. *Madan A, Borckardt JJ, Connell A, et al. Routine assessment of patient-reported outcomes in behavioral health: room for improvement. Qual Manag Health Care. 2010; 19(1):70–81. doi:10.1097/QMH.0b013e3181ccbc53*
15. *Epplein M, Zheng Y, Zheng W, et al. Quality of life after breast cancer diagnosis and survival. J Clin Oncol. 2011; 29(4):406–412. doi:10.1200/JCO.2010.30.6951*
16. *Takada K, Kashiwagi S, Fukui Y, Goto W, Asano Y, Morisaki T et al. Prognostic value of quality-of-life scores in patients with breast cancer undergoing preoperative chemotherapy. BJS Open. 2018; 3(1):38–47. Published 2018 Nov 26. doi:10.1002/bjs5.50108*
17. *Chu WO, Dialla PO, Roignot P, Bone-Lepinoy MC, Poillot ML, Coutant C et al. Determinants of quality of life among long-term breast cancer survivors. Qual Life Res. 2016 Aug; 25(8):1981-90. doi:10.1007/s11136-016-1248-z.*
18. *Lavdaniti M, Owens DA, Liamopoulou P, Marmara K, Zioga E, Mantzanas MS et al. Factors Influencing Quality of Life in Breast Cancer Patients Six Months after the Completion of Chemotherapy. Diseases. 2019; 7(1):26. Published 2019 Feb 24. doi:10.3390/diseases7010026*
19. *Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol. 2004; 22(4):714–724. doi:10.1200/JCO.2004.06.078*
20. *Basch E, Dueck AC, Kris MG,* Scher *HI, Hudis CA,* Sabbatini *P et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial [published correction appears in J Clin Oncol. 2016 Jun 20;34(18):2198] [published correction appears in J Clin Oncol. 2019 Feb 20;37(6):528]. J Clin Oncol. 2016;34(6):557–565. doi:10.1200/JCO.2015.63.0830*
21. *Denis F, Lethrosne C, Pourel N, Molinier O, Pointreau Y, Domont J et al. Randomized Trial Comparing a Web-Mediated Follow-up With Routine Surveillance in Lung Cancer Patients [published correction appears in J Natl Cancer Inst. 2018 Apr 1; 110(4):436]. J Natl Cancer Inst. 2017; 109(9):10.1093/jnci/djx029. doi:10.1093/jnci/djx029*
22. *Pinheiro LC, Wheeler SB, Reeder-Hayes KE, Samuel CA, Olshan AF, Reeve BB. Investigating Associations Between Health-Related Quality of Life and Endocrine Therapy Underuse in Women With Early-Stage Breast Cancer. J Oncol Pract. 2017; 13(5):e463–e473. doi:10.1200/JOP.2016.018630*
23. *Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014; 32(14):1480–1501. doi:10.1200/JCO.2013.53.5948*
24. *Ruland CM, Andersen T, Jeneson A, Moore S, Grimsbø GH, Børøsund E et al. Effects of an internet support system to assist cancer patients in reducing symptom distress: a randomized controlled trial.*

Cancer Nurs. 2013; 36(1):6–17. doi:10.1097/NCC.0b013e31824d90d4

25. *Eggersmann TK,Harbeck N, Schinkoethe T, Riese C. eHealth solutions for therapy management in oncology. Breast Cancer Manag. 2018; 6(3):101–106. https://doi.org/10.2217/bmt-2017-0005*
26. *Holzner B, Giesinger JM, Pinggera J, Zugal S, Schöpf F, Oberguggenberger AS et al. The Computer-based Health Evaluation Software (CHES): a software for electronic patient-reported outcome monitoring. BMC Med Inform Decis Mak. 2012; 12:126. Published 2012 Nov 9. doi:10.1186/1472-6947-12-126*
27. *Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998; 16(1):139–144. doi:10.1200/JCO.1998.16.1.139*
28. *Velikova G, Keding A, Harley C, Cocks K, Booth L, Smith AB et al. Patients report improvements in continuity of care when quality of life assessments are used routinely in oncology practice: secondary outcomes of a randomised controlled trial. Eur J Cancer. 2010;46(13):2381–2388. doi:10.1016/j.ejca.2010.04.030*
29. *Aaronson, NK, Ahmedzai, S, Bergman, B, Bullinger M, Cull A, Duez NJ et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993; 85(5):365–376. doi:10.1093/jnci/85.5.365*
30. *Fayers, P.M., Aaronson, N.K., Bjordal, K., Groenvold, M., Curran, D., Bottomley, A., on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 Scoring Manual. 3rd edn. EORTC, Brussels; 2001*
31. *Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986; 24:67–74.*
32. *Lepine JP, Godchau M, Brun P. Anxiety and depression in inpatients. Lancet. 1985; 2(8469-70):1425–1426. doi:10.1016/s0140-6736(85)92589-9*
33. *Costet N, Lapierre V, Benhamou E, Le Galès C. Reliability and validity of the Functional Assessment of Cancer Therapy General (FACT-G) in French cancer patients. Qual Life Res. 2005; 14(5):1427–1432. doi:10.1007/s11136-004-5531-z*
34. *Conroy T, Mercier M, Bonneterre J, Luporsi E, Lefebvre JL, Lapeyre M, Puyraveau M, Schraub S. French version of FACT-G: validation and comparison with other cancer-specific instruments. Eur J Cancer. 2004; 40(15):2243–2252. doi:10.1016/j.ejca.2004.06.010*
35. *Brédart A, Anota A, Young T, Tomaszewski KA, Arraras JI, Moura De Albuquerque Melo H et al; EORTC Quality of Life Group. Phase III study of the European Organisation for Research and Treatment of Cancer satisfaction with cancer care core questionnaire (EORTC PATSAT-C33) and specific complementary outpatient module (EORTC OUT-PATSAT7). Eur J Cancer Care (Engl). 2018; 27(1):10.1111/ecc.12786. doi:10.1111/ecc.12786*
36. *Rascle N, Bruchon-Schweitzer M, Sarason IG. Short form of Sarason's Social Support Questionnaire: French adaptation and validation. Psychol Rep. 2005;97(1):195–202. doi:10.2466/pr0.97.1.195-202*
37. *Bruchon-Schweitzer M. Psychologie de la santé. Modèles, concepts et méthodes. 1er éd. Paris : Dunod; 2002A.*