SPECIAL ARTICLE

TRAMOMTANA (Multidisciplinary treatment of morbid obesity: Medication, behavioral therapy, nutritional support, and physical activity). From question to reality in an investigator-initiated clinical trial (II)

Juan Tur, Maria Alós, Lourdes Iglesias, Lourdes Luque, Antoni Colom, Antonio Escudero, David Martinez, Alberto Pagán, Elena Ugarriza, Marga Frontera, Gabriela Nicola, Antonio Palomero, Santiago Tofé, Juan Ramón Urgeles, María Antonia Barceló, Marta Couce, Mónica De La Peña, Miguel Fiol, Baltasar Cortés, Emma Terés, Ángela Tumbarello, Cristina Álvarez, Ramón Salinas, Vicente Pereg, Xavier González, Bartolomé Burguera

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Abstract The implementation of an intensive, multidisciplinary weight loss program in patients with morbid obesity is reported. This program is based on behavioral changes, lifestyle intervention, medication, and group therapy sessions. Our objective is to show that the results achieved with this two-year weight loss program will be at least similar to those achieved with bariatric surgery in patients with morbid obesity. We also intend to show that this multidisciplinary treatment induces an improvement in the comorbidity rate associated with lower costs for our national health system.

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KEYWORDS
Weight loss program; Health education; Research methodology; Morbid obesity; Clinical trial; Interdisciplinarity
Introduction

Obesity has become a serious public health problem and has reached pandemic levels in the United States, where 64% of the adult population (100 million people) is overweight and 30% of the population is clinically obese (body mass index [BMI] >30 kg/m²), including 14% of children and adolescents. The obesity rate in the adult Spanish population is 14.5%, and the prevalence of morbid obesity (MO) is 2%-3%. The costs of treatment for obesity represent approximately 7% of the national health budget.

There is a widespread belief in the scientific community that bariatric surgery is the only effective treatment for people with a BMI higher than 40 kg/m², but very few subjects undergoing surgery have participated in a supervised weight loss medical program prior to bariatric surgery. This, however, is a stated requirement of the consensus panel (NIH): “Potential candidates must have been shown to be unable to lose weight with non-surgical treatment.”

Different studies have shown the benefits of dietary plans, behavioral therapy programs, and physical exercise on weight loss, and the resultant improvement in obesity-associated diseases. Several studies have also shown the beneficial effect of drugs such as sibutramine and orlistat, which decrease weight and improve glycemic and lipid profiles. Subjects participating in these clinical trials also received dietary counseling.

Wadden et al. showed the efficacy of a multidisciplinary treatment including behavioral and drug therapy in patients with (non morbid) obesity. It should also be noted that the Swedish Obesity Subjects Study (SOS Study) showed that patients undergoing gastric bypass surgery lost 36% of their weight one year after bariatric surgery. However, this difference in weight loss between medical and surgical treatment is very likely to decrease over the years, particularly if the medical group is given the same degree of personalized care and follow-up usually provided to patients undergoing bariatric surgery.

Various groups have shown the benefits of bariatric surgery in patients with MO by decreasing weight and significantly relieving the complications of obesity, particularly type 2 diabetes mellitus (T2DM), hyperlipidemia, and sleep apnea. It is however clear that bariatric surgery cannot be considered in all MO patients, and it is therefore imperative to design a therapeutic strategy that may be effective in this population of patients with MO who have high rates of morbidity and mortality and high healthcare expenses.

Objectives

The primary objective of the TRAMOMTANA study is to assess, in patients with MO, the impact of an intensive, multidisciplinary, non-surgical weight loss program that includes education for nutritional health, promotion of physical activity, drugs, and support in making lifestyle changes.
The results achieved are compared to those of a surgical group consisting of MO patients undergoing bariatric surgery to treat their obesity and to those of a medical group receiving standard treatment (Fig. 1). This randomized study is planned to last 24 months, and intervention started in November 2009.

Primary analysis parameters

Primary outcome measure

- **Weight.** This study assesses monthly the impact of this medical program on body weight loss (BMI reduction). Individual weight is measured at baseline and each month during attendance at group sessions. Measurements are recorded in the case report form of each study participant.
- **Height.** This is measured at baseline.
- **Waist circumference.** Measured at study start and each month.

Secondary outcome measures

- **Blood glucose and glycosylated hemoglobin.** The TRAMOMTANA study includes fasting measurements of glycosylated hemoglobin and blood glucose at baseline and every 6 months. These tests are performed at the central laboratory of Hospital Universitario Son Espases (HUSE). In addition, the endocrinology group supervises the use of drugs for the treatment of diabetes.
- **Albuminuria.** Kidney function control.
- **Blood pressure.** This is measured at baseline and every month during group sessions. In addition, the endocrinology group supervises the use of drugs for the treatment of hypertension.
- **Lipid/lipoprotein levels** (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides). These are measured at the HUSE central laboratory every 6 months. Plasma samples are stored at -80°C in freezers. Fasting blood samples are collected at baseline and every 6 months.
- **Number of episodes of obstructive sleep apnea.**
- **Body composition.** This is assessed by DEXA and bioimpedance at baseline and every year.

Other test parameters

- **Psychological and quality of life parameters:**
  - Anxiety. Assessed using the Hamilton scale. At baseline and every year.
  - Depression. Assessed using the Hamilton scale. At baseline and every year.
  - Impulsiveness. Assessed by the Plutchik test. At baseline and every year.
  - Sexual satisfaction. Assessed using the Golombok Rust Inventory of Sexual Satisfaction (GRISS). At baseline and every year.
  - Eating disorders. Assessed using the Eating Disorders Inventory-2 (EDI-2). At baseline and every year.
  - Health-related quality of life. Assessed using the generic SF-36 Health Survey. At baseline and every year.
- **Number of hospital admissions.** The relative impact of program intervention in the number of hospital admissions required by participants is characterized.
- **Costs and cost-effectiveness.** TRAMOMTANA estimates the cost and cost-effectiveness associated with this intensive multidisciplinary intervention as compared to surgical treatment.

Participating subjects were recruited over 6 months at the endocrinology clinics and the surgery department of Hospital Universitario Son Dureta.

During the screening visit, participant compliance with the inclusion criteria was verified, informed consent was obtained, blood tests were reviewed, and randomization was performed.

During the first visit, the principal investigator or a designee reviewed the project with the subjects. The potential benefits and risks of participation in this study were reviewed, and any questions the subjects had about their participation in the study were answered. During these visits, the participants were also informed of the different follow-up consultations they would have to attend (endocrinology, nursing, psychiatry, sports medicine, and physical therapy) and of their mandatory participation in group sessions. All recruited subjects and their relatives were also invited to attend, if they so wished, an information session with the staff responsible for the study where the risks were detailed and any questions were answered, in accordance with the Declaration of Helsinki for biomedical research. There was some flexibility in the number of visits required for this process, but it was thought that all of these aspects should be addressed as comprehensively as possible before randomization. Subjects were randomized in a 1:1 ratio to one of the abovementioned groups. Statistical software was used for this randomization.

The final date of the trial will be December 31, 2011, as the duration of the intervention period is 2 years. Since the assessment of the changes occurring during that period is a study objective, the study will not end before that date.

The TRAMOMTANA study is intended to show, in the intervention group, the strong therapeutic component of communication and intensive care. Study participants are given a mobile telephone number (6262XXX89, from 08 to 20 h seven days a week) so as to maintain interaction throughout the study. This, together with the blog http://tramontana.blogspot.com, are tools that allow for direct communication between the participants and the team and, once the study is completed, for the dissemination of the results, whether positive or negative, through this channel and/or the different scientific publications that may result.

Study design

TRAMOMTANA is a randomized, parallel-group clinical trial to explore the impact of a multidisciplinary program on weight loss, metabolic profile, and associated diseases in MO patients. It should be noted that prior studies comparing the effect of gastric bypass to lifestyle changes in patients with MO were not randomized.

Participants who met the inclusion criteria and did not want to undergo bariatric surgery were enrolled into the
medical treatment arm and were randomized to one of the following:

- Intensive multidisciplinary group (n = 60). This group receives treatment combining lifestyle changes (dietary changes, increased physical activity) and support in the process of change, based mainly on the acquisition of tools and knowledge. The group is supervised by a team consisting of a nutritional nurse, a sports physician, a physical therapist, and an endocrinologist. Staff members from the department of psychiatry/psychology also participate in group therapy sessions.

- Medical group with standard treatment (standard group) (n = 60).

- Surgical group (n = 60). Patients who met the criteria for bariatric surgery and wished to undergo the procedure were included in this group, consisting of 60 subjects undergoing bariatric surgery.

All three participating groups attended a baseline visit with the different members of the healthcare staff, including an endocrinologist, a nurse, a psychiatrist, a physical therapist, and a sports physician.

The intensive multidisciplinary (experimental) group returns for regular visits to these specialists every 3 months and also attends group sessions - on a weekly basis for the first 3 study months and every 15 days for the subsequent 21 months.

Selection of study population

One hundred and forty of the 180 subjects with MO (BMI >40 kg/m²) aged 18-65 years and with one or more comorbidities who planned to participate in the study have already been included at the time of writing.

To be eligible to participate in the TRAMOMTANA study, subjects must have MO with T2DM and/or comorbidities, a moderate risk of occurrence of cardiovascular disease, and willingness to adhere to the protocol described as intervention and to be randomized to participate in the study.

Inclusion criteria

- Age ranging from 18 to 65 years.
- Males of females of any ethnic group with BMI >40 kg/m².
- Blood pressure < 160/100 mmHg (systolic/diastolic). Patients whose blood pressure exceeds these levels at the screening visit can start antihypertensive treatment. Such patients may be re-evaluated for eligibility based on blood pressure 3 months later.
- Patients with or without a diagnosis of T2DM. T2DM is diagnosed according to the 1997 American Diabetes Association criteria: fasting blood glucose > 126 mg/dL, hyperglycemic symptoms with plasma glucose values > 200 mg/dL or blood glucose > 200 mg/dL 2 h after an oral glucose load of 75 g. Subjects treated with both oral medication and insulin are eligible to participate in this study.
- HbA₁c concentration less than 11%. Patients whose HbA₁c exceeds this level at the screening visit can start hypoglycemic treatment but may be re-evaluated for eligibility based on HbA₁c after 3 months.
- Fasting triglyceride levels less than 600 mg/dL.
- Patients with or without cardiovascular disease. Potential study subjects include those with a history of uncomplicated myocardial infarction, coronary artery bypass, percutaneous coronary angiography, coronary stents, chronic stable angina, complex arrhythmia at rest or induced by exercise, and congestive heart disease (stable NYHA class I or II) if more than 3 months have elapsed since the last episode. All subjects have to perform an exercise test and be re-evaluated by the cardiology department before participating in this study.
- The patient has voluntarily signed and dated the informed consent form approved by the ethics committee after being informed about the nature of the study and having had the opportunity to ask questions. The signature of informed consent before any study-specific procedure is performed is indispensable.

Participants should be willing to change their lifestyle habits and to use drugs for weight reduction.

Exclusion criteria

- Patient unable or unwilling to sign consent or attend group sessions or visits.
- Current diagnosis of schizophrenia or other type of psychosis, or bipolar disorder.
- Hospitalization for treatment of depression in the previous 6 months.
- History of alcohol or drug abuse in the previous 12 months.
- History of weight loss greater than 10 kg in the previous 3 months.
- Inability to walk 50 m.
- History of bariatric surgery or bowel resections.
- Chronic corticosteroid treatment.
- Pregnancy.
- Cancer requiring treatment in the previous 5 years, except for skin cancer (other than melanoma), or clearly cured cancer in the investigator’s opinion.
- HIV-positive patient.
- Active tuberculosis.
- Cardiovascular disease (myocardial infarction or cardiac procedure in the previous 3 months).
- Any abnormality during the exercise test.
- Renal disease: serum creatinine > 1.4 mg/dL (females) or > 1.5 mg/dL (males), or current dialysis treatment.
- Chronic obstructive pulmonary disease.
- Chronic B or C hepatitis or cirrhosis.
- Inflammatory bowel disease.
- Cushing’s syndrome.
- Acromegaly.
- Lower limb amputation due to non-traumatic reasons.
- Any major organ transplant (excluding cornea or hair transplant).

Criteria and specific procedures for subject withdrawal

- A subject or his legal representative request study withdrawal.
• The investigator considers withdrawal to be in the best interest of the subject.
• If an adverse event is reported, safety problems or protocol non-compliance.
• A participant will immediately be withdrawn from the study if, in the investigator’s judgment, clinically significant abnormal laboratory results or events that prevent study continuation have occurred.

Patients in this study will not be replaced, but as noted in the methods section, every effort will be made to motivate and encourage patients so that the drop-out rate is as low as possible.

Once the two-year intervention phase is completed, the impact of our intervention will continue to be assessed in the subjects every 3 months (for 6 months) and every 6 months (for 2 years). Table 1 details the study phases.

Efficacy and safety assessments/variables

Study procedures

• Baseline visit. Baseline data were collected during the first research visits and before the start of intervention (measurement 1). Different plasma measurements are made every 3 months to determine the effect of intensive weight loss intervention.
• Follow-up visits. Follow-up data are collected during the regularly scheduled visits and interviews (detailed in Table 2). The patients return for clinical visits every 3 months. Questionnaires are sent to all participants. At these clinical visits to the different specialists (psychiatrist, dietitian, surgeon, and endocrinologist), the patient’s medical history is taken down and the subjects relevant to each specialty are reviewed. Special emphasis is given to the review of drugs used, the review of clinical tests and the assessment of comorbidities, problems with cardiovascular disease, other diseases, surgical procedures, and hospital admissions. During visits to the research team, aspects related to the patient’s quality of life are addressed.

Medical group with standard treatment (60 patients)
The standard medical group makes regular visits to the hospital, in addition to baseline visits to the endocrinologist and follow-up visits to the endocrinologist and/or dietician at months 1, 6, 12, 18, and 24.

Intensive multidisciplinary group (60 patients)
The intensive multidisciplinary group receives treatment combining lifestyle changes, increased physical activity, and support in the change process. The goal is sustained weight loss.

Subjects included in the intensive multidisciplinary group alternate group sessions every 7 days with individual medical visits every 3 months.

These subjects are seen every 3 months by this same group of professionals to assess their progress and comorbidity status. During the first month of intervention, the following psychometric tests are administered:

Table 1 Work plan.

<table>
<thead>
<tr>
<th>1st phase. Recruitment phase (six months)</th>
</tr>
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<tbody>
<tr>
<td>• Participants were recruited during a 6-month period</td>
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<tr>
<td>• Sample collection for measurement of baseline hormone, biochemical, and inflammation marker levels</td>
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<tr>
<td>• Implementation of contents of group therapy sessions</td>
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<tr>
<td>• Administration of psychometric tests and questionnaire preparation</td>
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<tr>
<th>2nd phase. Intervention phase (2 years)</th>
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<tbody>
<tr>
<td>Intensive medical group (60 patients)</td>
</tr>
<tr>
<td>• Months 1-2. Baseline visits to psychiatry, dietetics, exercise physiologist, and endocrinologist</td>
</tr>
<tr>
<td>• Months 3-24. Monitoring visits to physical exercise, dietetics, and endocrinologist every 3 months</td>
</tr>
<tr>
<td>• Months 1-3. A weekly group meeting for the first 3 months. Nutritional group sessions to alternate with behavioral therapy and physical activity</td>
</tr>
<tr>
<td>• Months 3-24. A group meeting every 15 days. Nutritional group sessions to alternate with behavioral therapy and physical activity</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard medical group (60 patients)</th>
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<tbody>
<tr>
<td>• Months 1-2. Baseline visits to psychiatry, dietetics, and endocrinologist</td>
</tr>
<tr>
<td>• Months 3-24. Follow-up visits to endocrinologist and/or dietician at months 1, 6, 12, 18, and 24</td>
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<tr>
<th>Surgical group (60 patients)</th>
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<tr>
<td>• Months 1-2. Baseline visits to psychiatrist, dietician, and endocrinologist</td>
</tr>
<tr>
<td>• Months 3-24. Follow-up visits to surgeon and/or endocrinologist and/or dietician at weeks 2 and months 1, 3, 6, 9, 12, 15, 18, and 24</td>
</tr>
<tr>
<td>• Sample collection at each visit for measurement of hormone, biochemical, and inflammation marker levels as noted in Table 1</td>
</tr>
<tr>
<td>• Testing of samples taken at the different visits for the measurement of circulating hormone levels as noted in Table 1</td>
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<tr>
<td>• Analysis of the results obtained in both groups. Statistical study of the results</td>
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<tr>
<th>3rd phase. Analysis phase (six months)</th>
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<tbody>
<tr>
<td>• Review of the results of the different tests and questionnaires. Three-monthly evaluation of participating subjects (impact of our intervention) before they are switched to the usual six-monthly visits</td>
</tr>
<tr>
<td>• Result preparation and reporting. Statistical study of the results</td>
</tr>
<tr>
<td>• The possibility of conducting a multicenter study in Europe and the United States will be considered</td>
</tr>
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</table>
Structured interview to assess obesity.
Hamilton anxiety scale.
Hamilton depression scale.
Plutchik impulsiveness scale (IS).
Eating Disorder Inventory (EDI-2).
SF-36 Health Survey generic health-related quality of life questionnaire.

These tests will be repeated annually to assess the impact of intervention.

These patients also participate in guidance sessions twice monthly. Each group consists of 13-14 subjects. Aspects addressed during these sessions include:

- Health education on impulse control, management of stress and contingencies, change in intake patterns, and healthy nutrition.
- Health education aspects including nutritional advice, physical activity, social aspects and lifestyle changes, using motivation and stimulus control techniques. Group sessions follow the guidelines detailed in the manual Learn Program for Weight Management.
- Physical activity aspects. Physical activity is a key component that contributes to long-term weight loss, improves cardiorespiratory and muscular fitness, and reduces risk factors for cardiovascular and metabolic disease. Controlled trials using physical activity as the dominant part of weight loss intervention have shown significant reductions in the incidence of diabetes and hypertension.

The physical activity program of this study motivates participants to gradually increase their physical activity to 120 min. The sports medicine department performs an individual assessment at baseline. General information about the benefits of physical activity is provided through group sessions. Any questions or problems that may arise during the practice of physical activity are also addressed in these sessions.

We try to provide a place where the subjects may perform a supervised exercise session once a month to stimulate both social support for and the practice of exercise.

This group of patients was eligible for drug treatment, and 40% of them received sibutramine at no cost through our hospital pharmacy for a period of 3 months, until this drug was withdrawn from the market. Twenty percent of these patients have also received treatment with Xenical® at some time.

The possibility of drug treatment disappeared when Reductil® was withdrawn from the market.

The goal was to induce a 15%-25% weight reduction in the first year and a 20%-35% reduction in the second year, and to progressively increase physical activity (mainly consisting of walking for up to 120 min per week).

### Surgical group (60 patients)

These patients were selected from our waiting list for bariatric surgery and followed the standard screening and treatment protocol established at our hospital. Patients who met the inclusion criteria were seen by the dietician, endocrinologist, psychiatrist, and surgeon.

Anthropometric, metabolic, and hormonal (leptin, ghrelin, adiponectin, insulin, PYY) measurements and the evaluation of different events were performed during the first clinical visit (screening) and then at 3, 6, 9, 12, 15, 18, 21, and 24 months in both the medical and surgical groups.

### Statistical methods and sample size estimation

#### Rationale for sample size

Approximately 180 subjects were recruited into this study. Subjects with BMI > 40 kg/m² who met three of the inclusion
criteria and none of the exclusion criteria were eligible to participate in the study.

Sample size was calculated in order to have an adequate power (> 80%) for detecting clinically significant effects in terms of standardized differences in the percent change from baseline to after intervention (2 years). Because of the longitudinal nature of the study and the need for changes in feeding habits, a 20% drop-out rate was expected.

As stated above, different approaches were used to reduce this rate as much as possible. Although a conventional “intent-to-treat” approach was used for managing protocol deviations, sample size was conservatively increased in order to be able to randomize 60 subjects to each medical arm of the study: the standard medical group and the intensive multidisciplinary group.

A 5% type 1 error, with an 80% power and a baseline BMI of 45 kg/m², with a standard deviation of 4-5 kg/m², was assumed. In addition, based on the inclusion criteria and on our prior experience with previous clinical trials, we knew that there would be statistically significant differences between the groups in BMI reduction. This reduction would have to be at least 4 units in kg/m² between the groups, equivalent to a 10% reduction in BMI. If a greater BMI reduction or a lower standard deviation was finally obtained, the statistical precision of all comparisons would be even better.

Statistical analysis

A 20% drop-out rate was expected, which would leave approximately 48 evaluable patients in each arm. This proportion would guarantee a statistical power > 99% for detecting differences in the groups, and an 80% power for detecting differences between the study arms (alpha 0.05). The population to be analyzed will consist of participants recruited for the study who meet the inclusion/exclusion criteria and have data available for the main variables (weight, BMI, and waist circumference). A descriptive statistical analysis will be performed of all collected variables to identify maximum and minimum values and outliers, and to detect and clean errors. Descriptors of central tendency of continuous variables will be generated. For all other variables, frequencies will be noted and clusterings will be done (Table 3). A Kolmogorov-Smirnov test will be used to assess the normal distribution of continuous variables. If one or more variables are not normally distributed, a standardized distribution will be obtained through logarithmic conversion to allow for the use of non-parametric tests. The results of the normally distributed variables used will be provided as mean ± standard deviation, and those with a non-gaussian distribution will be displayed as median (range). Differences in sociodemographic, clinical, and laboratory parameters between patients in each group and in the different assessment periods will be analyzed using a Student’s test and an ANOVA test (continuous variables) and a Chi-square test (categorical variables). Similarly, correlations between variables will be analyzed using Pearson and Spearman correlation coefficients for normal and non-normal pairs respectively. Data analysis will be performed in the 6 months following study completion by the statistical unit of the Fundación en Investigación Sanitaria de les Illes Balears (FISIB).

Ethical conduct of the study

This project is being conducted at the research unit (CAIBER) of Hospital Universitario Son Dureta (currently Son Espases) (Palma de Majorca) and in cooperation with the departments of endocrinology, general surgery, pharmacy, clinical laboratory, biobank, pathology, respiratory tract, and cardiology of Hospital Universitario Son Dureta (currently Son Espases) in compliance with the protocol, International Conference of Harmonization guidelines (ICH-GCP), the applicable regulations and guidelines governing the conduct of clinical studies, and the ethical principles arising from the Declaration of Helsinki.

The biobank is responsible for the collection and storage of blood samples to be taken during this study. The biobank is financed with funds from the Instituto de Salud Carlos III and its offices and laboratories are located in the premises of the pathology department.

Communication policy and dissemination of results

The sponsor, Hospital Universitario Son Dureta/Son Espases, is committed to publishing the results of the trial regardless of whether they are positive or negative. The results of this study will be disseminated at several levels:

- Presentation of interim and final reports as communications to national and international meetings and congresses.
- Preparation of original research papers for publication in national and international scientific journals.

A CD-ROM reporting the main aspects of the study will also be prepared and sent to all participants, all scientific societies related to the specialties concerned, and to the political authorities concerned with public health, nutrition, and physical activity in the Balearic Islands autonomous region.

All information recorded as a result of this study will be considered confidential. The applicable Spanish data protection law (Organic Act 15/1999, of December 13, on personal data protection) will be respected at all times.

The TRAMONTANA study was approved by the relevant ethics committee and the Spanish Medicines Agency and registered in EudraCT in 2009, and was started in the third quarter of that same year.

At the time of writing, recruitment for the intervention group has already been completed, while recruitment rates of 90% and 70% have been reached in the standard medical and surgical groups respectively.

Conflict of interest

The authors state that they have no conflict of interest.
Table 3  Frequency and content of group sessions.

<table>
<thead>
<tr>
<th>Content</th>
<th>FIRST YEAR</th>
<th>Second year</th>
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<tr>
<td></td>
<td>First</td>
<td>Second</td>
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<tr>
<td>Physical activity</td>
<td>Weekly</td>
<td>Bimonthly</td>
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<tr>
<td>Nutrition</td>
<td>Weekly</td>
<td>Bimonthly</td>
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<tr>
<td>Support to change</td>
<td>Weekly</td>
<td>Bimonthly</td>
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References


