PRONOCOST Study

Cost-effectiveness pharmacoeconomic study of a standardized multidisciplinary weight loss method (PronoKal® Method) to improve health condition of obese patients with associated comorbidities.

Prospective registry of obese patients with comorbidities under a standardized multidisciplinary weight loss method

Protocol code: **PRO-COST-2016-02**

(Version 10.0, 25 October 2017)

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1. SUMMARY

1.1. Identification of the study

Title of study: PRONOCOST study. Cost-effectiveness pharmacoeconomic study of a standardized multidisciplinary weight loss method (PronoKal® Method) to improve health condition of obese patients with associated comorbidities.

Protocol code: PRO-COST-2016-02

1.2. Type of study

Prospective, observational, multicenter study based on a registry of patients with obesity and associated comorbidities undergoing a standardized multidisciplinary weight loss method with a 2-year follow-up.

1.3. Sponsor

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08009 Barcelona

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1.4. Study Coordinator

Dr. Lucio Criado

Clinical Medicine Specialist Accredited by the National Academy of Medicine.

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1.5. Principal investigator

Dr. Rosana Cafardo

Clinical Medicine Service of the Italian Hospital of Buenos Aires.

CABA- Argentina

1.6. Study locations

Clinical medicine outpatient facilities. Italian Hospital of Buenos Aires

Private consultation offices

01.7. Primary objective

To assess the Cost-effectiveness of a standardized weight loss method (Pronokal® Method) treatment to improve the health condition of obese patients with comorbidities and thereby reduce healthcare expenditure (pharmacological treatment, incidence of complications, use of health resources) and work absenteeism.

1.8. Secondary objectives

- Assess short and long-term weight loss and waist circumference reduction
- Assess the degree of clinical and laboratory improvement of cardiovascular risk factors (HTN, diabetes, dyslipidaemia) associated with weight loss
- Evaluate patient quality of life improvement in relation to weight loss
- Assess the tolerability and safety of the weight loss treatment.

1.9. Follow-up and duration of the study

Patients will be monitored for 2 years.

1.10. Schedule

Start of study: April 2017

End of Recruitment Period: June 2018

End of study: June 2020

2. INTRODUCTION

Obesity is a complex medical problem, which has been declared a global epidemic by the World Health Organization. The increase in its prevalence implies significant rises in healthcare system costs, both directly and indirectly, together with a quality of life deterioration.

In Argentina, as in most countries, obesity is a problem that affects more and more people. According to data published by WHO[1], the prevalence of obesity in the country has increased from 23.7% of the adult population in 2010 to 26.5% in 2014.

It is a multifactorial disease that can be associated with multiple comorbidities as it acts as a risk factor for the development of pathologies such as cardiovascular disease, type 2 diabetes (T2DM), various cancers, respiratory problems and arthritis[2].

Obesity generates a very high socioeconomic and disease burden, which compromises both the health of the population and public and private finances. The importance of treating and preventing obesity lies in reducing the impact of its complications in the quality of life and in its economic costs (including comorbidities and premature deaths attributable to overweight/obesity) that not only affect healthcare expenditure, but are also accompanied by a decrease in labour productivity[2].

Many studies have highlighted the increased costs associated with overweight and obesity, and how their progressive incidence suggests that in 15 years, in countries such as the United States or the United Kingdom, medical costs associated with the combined treatment of obesity and associated preventable diseases will increase by $48-66 billion/year and by £1.9-2 billion/year respectively[3]. Similarly, in a health survey in which data were collected from more than 17,000 people, an association between BMI and the annual rates of outpatient visits and hospitalization days, annual cost of visits, ambulatory pharmacy and laboratory services expenditure, and the total cost of health care (including inpatient and outpatient) was confirmed. Specifically, the total annual mean costs were 25% higher among subjects with a BMI of 30 to 34.9 kg/m2 compared to a BMI of 20 to 24.9 kg/m2 and 44% higher among those with a BMI of 35 kg/m2 or higher. These costs were mainly explained by the presence of coronary disease, hypertension and diabetes[4]. Other studies have also shown the impact of obesity and its complications on productivity. For example, a European study in Sweden found that obese subjects not only had a significantly higher healthcare expenditure on medication, but also that the number of sick leave days was 1.4 to 2.4 times higher and their probability of getting a disability pension multiplied from 1.5 to 2.8 times when compared to normal weight people [5].

Obesity has biological, physiological, psychological, environmental and economic basis, which operate at several levels, including molecular and genetic mechanisms. Consumption habits of sugars and fats could be due to metabolic imbalances. The glycaemic index of foods, differences between individuals to metabolize glucose and insulin resistance are considered physiological causes of obesity. Psychological causes point to addictive behavioural patterns. Environmental causes emphasize

interpersonal influences and social norms and standards. And for their part, economic factors are related to the living conditions of individuals who suffer from weight problems and food prices. Thus, the increase in weight can be attributed to the consumption of foods high in calories added to increasingly sedentary life patterns.

The standardized multidisciplinary method under study (PronoKal® Method) is a personalized weight loss program under medical supervision. Its purpose is to maintain the body's weight through food re-training and the continued support of a team of dietician-nutritionists.

Based on a protein diet, this method is developed according to the characteristics of the patient and contemplates the participation of a multidisciplinary team that includes medical control, dietary-nutritional monitoring, physical activity and emotional support. Thus, the aim is, on the one hand, to produce rapid weight loss, especially at the expense of fat mass, and on the other hand to achieve a long-term maintenance of the results obtained.

Thus, in addition to a dietary pattern, the method contemplates other factors involved in the pathophysiology of obesity, such as nutritional education, physical activity and emotional support, all of which must be combined under medical supervision to ensure a safe clinical progression of the patient.

In addition to weight loss, other aspects need to be modified in the treatment of the obese patient, so that appropriate behaviours are adopted, resulting in the maintenance of the correct weight.

The basic pillars for the treatment of obesity are changes in lifestyle, including a dietary plan, adjustment of physical activity and emotional support. Thus, the management of obesity requires a multidisciplinary approach that adapts to the characteristics of the patient and allows greater effectiveness in the long term and the optimization of healthcare resources used in the fight against obesity.

Under these premises, the clinical application of the method under study is established through the intervention of a Multidisciplinary Specialist Team:

1. **Doctor:** clinical assessment, treatment prescription and patient follow-up.
2. **Physical activity:** guidance and advice to perform adequate physical activity, aimed at increasing caloric expenditure and re-adjusting the energy balance.
3. **Dietitians:** accompany and advise on nutrition and food choices throughout the treatment.
4. **Psychological support:** reinforcement of the patient's psychological status contributing to boost the patient's motivation in order to reach his/her short, medium and long-term goals.

The aim of this standardized multidisciplinary method is to decrease the weight of obese patients, which is expected to improve the comorbidities associated with obesity

The present study is designed to make a Cost-effectiveness assessment of the standardized multidisciplinary weight-loss treatment (PronoKal® Method) in obese patients with associated comorbidities, in order to improve the subjects' health condition, healthcare expenditure and work absenteeism as a consequence of their comorbidities.

3. STUDY OBJECTIVES

3.1. Primary objective

To assess the Cost-effectiveness of a standardized weight loss method (Pronokal® Method) treatment to improve the health condition of obese patients with comorbidities and thereby reduce healthcare expenditure (pharmacological treatment, incidence of complications, use of health resources) and work absenteeism.

3.2. Secondary objectives

- Assess short and long-term weight loss and waist circumference reduction
- Assess the degree of clinical and laboratory improvement of cardiovascular risk factors (HTN, diabetes, dyslipidaemia) associated with weight loss
- Evaluate patient quality of life improvement in relation to weight loss
- Assess the tolerability and safety of the weight loss treatment.

4. STUDY DESIGN

Prospective, observational, multicenter study based on a registry of patients with obesity and associated comorbidities undergoing a standardized multidisciplinary weight loss method with a 2-year follow-up.

No randomization or administration of drug treatment is intended as a consequence of the patient's participation in the study.

5. STUDY POPULATION

Obese patients with obesity-associated comorbidities treated with the standardized multidisciplinary weight loss method (PronoKal® Method).

5.1. Inclusion criteria

- Patients of both sexes 18 years of age or older
- Patients with overweight or obesity (BMI> 30 kg/m^2) with at least one or more of the following comorbidities associated with obesity:

  - Type 2 diabetes mellitus
  - Arterial hypertension
  - Dyslipidemia
  - Hyperuricemia

  Those who are under pharmacological treatment with two or more drugs (oral antidiabetic and/or lipid-lowering agents and/or antihypertensive and/or hypouricemic agents)

- Patients who agree to attend the follow-up visits at the Pronokal centre, in Buenos Aires.
- Patients who agree to participate and provide a signed informed consent

5.2. Exclusion criteria

- Patients who do not sign the informed consent
- Pregnant or breastfeeding patients.
- Patients with severe eating disorders, alcoholism, or substance abuse.
- Patients with severe psychological disorders (e.g., schizophrenia, bipolar disorder).
- Patients with liver failure.
- Patients with kidney failure.
- Patients with type 1 DM or insulin-dependent, or currently under insulin treatment, or candidates for insulin treatment in a short period of time.
- Patients with obesity caused by other endocrine diseases (except type 2 DM).
- Patients with blood disorders.
- Patients with cancer.
- Patients with cardiovascular or cerebrovascular disease (heart rhythm disorders, recent infarction [<6m], unstable angina, decompensated heart failure, recent stroke [<6m]).
- Patients with renal lithiasis.
- Patients with cholelithiasis.

5.3. Number of patients

Expected number of subjects is 200 patients. Subjects who initiate the multidisciplinary weight loss treatment during the study inclusion period, meet the inclusion and exclusion criteria, and agree to participate and sign the informed consent will be included in the study.

6. TREATMENT DESCRIPTION

The standardized multidisciplinary method under study is a weight loss program consisting of different stages. The initial stage (stage 1) is based on a protein diet, a type of ketogenic diet very low in calories. This stage is followed by a physiological adaptation stage (stage 2) in which all food groups are reintroduced progressively, and a maintenance phase (stage 3) with long-term monitoring of the patient's weight to ensure stability of the results obtained. This program contemplates other essential aspects in the management of obese patients, such as dietary education, physical activity and psychological support throughout the treatment.

<table>
<tr><td colspan="3">80% of target weight loss</td><td>20% of target weight loss</td><td>Long-term maintenance of weight loss</td></tr>
<tr><td colspan="5">Multidisciplinary team (dietary counselling / physical activity / psychological support)</td></tr>
<tr><td colspan="3">Stage 1
Active Stage</td><td>Stage 2
Dietary re-education</td><td>Stage 3
Maintenance</td></tr>
<tr><td>Phase 1</td><td>Phase 2</td><td>Phase 3</td><td>Gradual re-introduction of different foods</td><td>Balanced diet</td></tr>
<tr><td colspan="3">VLCK diet[1]
(600-800 kcal/day)</td><td>LC diet[2]
(800-1500 kcal/day)</td><td>Maintenance diet
(1500-2250 kcal/day)</td></tr>
</table>

The stage 1 protein diet is established through the intake of high biological value proteins and low-glycaemic vegetables, supplemented with micronutrients (potassium, sodium, calcium, magnesium, vitamins and trace elements) to avoid deficiencies. This stage consists of 3 phases (Phase 1, Phase 2a and Phase 2b), in which a protein preparation and then a second protein preparation are replaced progressively by protein-rich natural foods (meat/fish/eggs). During this period of ketogenic diet, the patient will be visited by the doctor every fortnight.

The ketogenic stage 1 of the method will be maintained for 2 months for those patients with an initial BMI of 30 to 35 kg/m^2 and for 3 months for those patients with initial BMI > 35 kg/m^2.

Stage 2 begins after the initial loss of most of the weight to be lost (ideally 80%), with the progressive introduction of different foods, while reducing protein preparations at the same time. In this way the weight loss indicated by the doctor is finally reached and the food balance is also achieved. This stage will be maintained for a period of 4 months in patients with an initial BMI of 30 to 35 kg/m^2 and for 6 months for those patients with initial BMI> 35 kg/m^2.

The last stage of the method begins at this moment, which involves the long-term maintenance of the lost weight, with the supervision and monitoring of specialized dietitians/nutritionists who advise patients in terms of consolidation of their new dietary habits, that is, the establishment of a balanced diet, which is the ultimate goal of the method.

The method must be implemented under strict medical supervision to ensure the efficacy and, above all, the safety of the program. In addition, the program is supported

by dietitians/nutritionists who help control the patient's progress (with continuous on-site and/or telephone follow-up over the 2 years of treatment) and a team of psychological counselling professionals and experts in physical activity.

7. STUDY PROCEDURES

7.1. Start of study

The investigating physician will be responsible for assessing the appropriateness of the treatment for each patient, regardless of their participation in this study.

Patients will be recruited consecutively as they go to the clinic and are prescribed treatment with the standardized multidisciplinary method. Before being included, the investigator must check the inclusion and exclusion criteria, and obtain their informed consent.

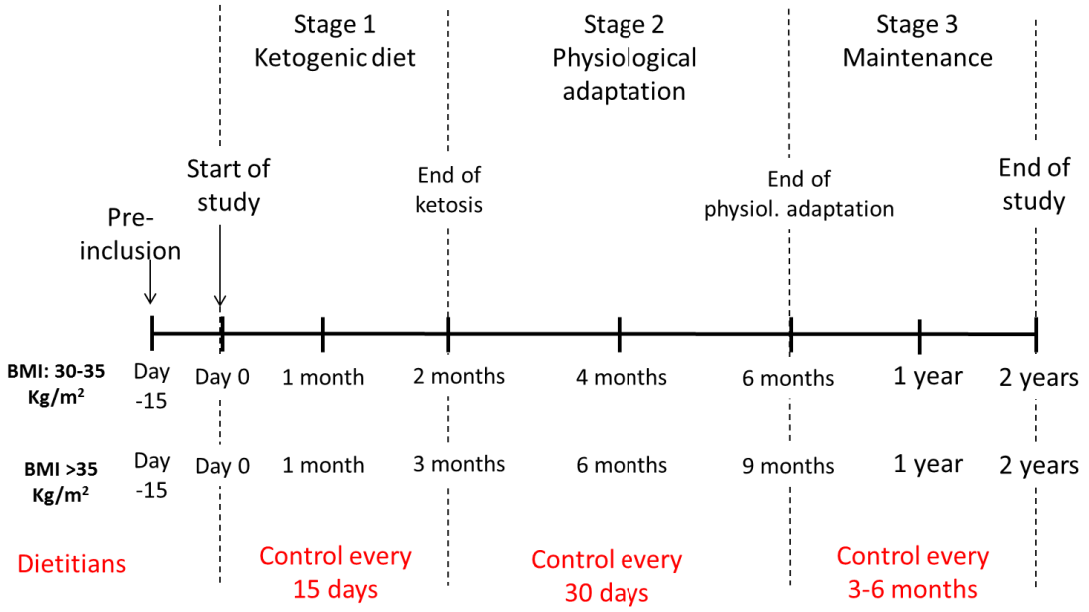
7.2. Follow-up period

The expected follow-up period for each patient will be 2 years from the time of inclusion, recording data during the weight loss and maintenance periods. The registry of patient data for this study will be made by the doctor and the dietitians/nutritionists who will regularly see the patient in the face-to-face visits at the Pronokal centre. For this, a specific form will be designed in which information about the variables to be studied will be collected.

Before starting treatment with the standardized multidisciplinary method and its inclusion in the study, the physician will have performed a first patient pre-inclusion visit (day -15) to request complementary tests (laboratory and ECG) and rule out the existence of contraindications to the ketogenic diet part of the weight loss program.

The study will begin with the baseline visit (day 0) in which the inclusion and exclusion criteria will be confirmed, the signing of informed consent will be obtained and the multidisciplinary treatment will be prescribed, followed by 6 control visits: 2 visits during the ketogenic stage (1-month after the start and at the end of ketosis), 2 visits during the physiological adaptation phase (at 4 or 5 months and at the end of stage 2) and 2 follow-up visits during the maintenance up to the 2-year completion. Regardless of the visits established in this protocol, the doctor will make as many visits as he/she deems necessary for good patient control.

On the other hand, dietitians/nutritionists, according to the methodology of the program, will carry out a face-to-face follow-up of the patient, which will be fortnightly during the ketogenic diet, monthly during the physiological adaptation of stage 2 and quarterly or semi-annual during the maintenance stage.



In the **pre-inclusion visit (day -15)**, the physician will perform a first clinical assessment of the patient. He/she will record the sociodemographic data, history of diabetes, comorbidities, pharmacological treatments. He/she will request complete laboratory tests and will perform an electrocardiogram to rule out contraindications and verify the inclusion/exclusion criteria. The said laboratory tests will include:

- Complete blood count and leukocyte formula
- Hydrocarbon metabolism: fasting glycemia, HbA1c, insulinemia
- Lipid profile: total cholesterol, LDL-C, HDL-C, triglycerides
- Transaminases: GOT, GPT, gammaGT
- Renal profile: creatinine, glomerular filtration, creatinine clearance, microalbuminuria
- Nitrogen balance: urea, uric acid
- Thyroid profile: TSH, T3, T4
- Ionogram: Na, K, Cl, Ca, Mg

In the **initial visit (day 0):** In this visit, a physical examination will be performed and data related to weight (weight, BMI, waist circumference), as well as data on comorbidities associated with obesity (type of pathology, pharmacological treatment, complications in the last year) will be recorded. After checking the inclusion/exclusion criteria, the patient information sheet will be given and the informed consent will be obtained. During this visit, the patient's quality of life will be assessed (with the SF-12 quality of life questionnaire) and treatment will be prescribed according to the method (PronoKal® Method), which will begin with phase 1 of the active stage.

In the **follow-up visits - Recorded by the doctor.** In the regular check-ups throughout the course of treatment, the physician will record: any discomfort or side effect related to weight loss treatment and whether there has been any change in the comorbidities associated with obesity (laboratory results, medication, complications, etc.). At the end of each stage the doctor will assess the patient's quality of life through a questionnaire.

In the **follow-up visits - Recorded by dietitians/nutritionists.** During the interviews that the dietitians/nutritionists will have with the patients, and parallel to the doctor's records, the following details will be recorded:

- Clinical data: anthropometric data and blood pressure
- Medication changes
- Onset of complications (e.g., hypertensive crisis, ...)
- Hospital admissions
- Work absenteeism: number of days and cause....

In case of early withdrawal from the study, the doctor will write the dropout date and the reason, in study completion form.

7.3. Duration of study

For each patient initiating treatment, a minimum follow-up period of 2 years will be observed.

8. SOURCE OF INFORMATION AND DATA MANAGEMENT.

8.1. Source of information

The information for this study will be obtained from the patient's medical records and the interview that the physician and dietitians/nutritionists carry out with the patient. All information will be recorded on the forms designed for this purpose (Annex 3) and subsequently submitted to the coordinating center, prior express authorization of the patient by signing the Informed Consent, for its statistical analysis.

The corresponding data will be saved in a file owned by PronoKal Group®, who will manage the information according to Organic Law 15/1999 relative to Protection of Personal Data.

8.2. Monitoring

In this study, a remote monitoring of the inclusion and follow-up of patients will be carried out by:

Responsible of Monitoring

CROSSDATA - Punta Alta
Enric Granados 145, 2º-1º
08008 Barcelona
Tel. +34 935 177 609

9. ENDPOINTS

9.1. Primary endpoints

The primary variables to be recorded for the study objectives are:

- Consumption of health resources: visits, laboratory controls, admissions ...
- Changes in pharmacological treatment
- Work absenteeism

9.2. Secondary endpoints

- Body weight and waist circumference
- Changes in clinical parameters: glycaemic profile, lipid profile, blood pressure
- Score in the SF-12 quality of life questionnaire
- Onset of side effects
- Onset of serious adverse reactions during the protein diet's follow-up.

10. STATISTIC ANALYSIS

10.1. Descriptive statistics

Descriptive statistics will be made of all the variables collected in the Case Report Form, building frequency tables for the nominal-type variables and measurements of central tendency and dispersion for continuous variables. The 95% confidence intervals (95% CI) will be estimated for the latter.

10.2. Analysis of objectives

The primary objective analysis will include:

- Costs of weight loss treatment estimated from the cost of: protein products and dietary supplements + number of control visits + number of laboratory tests performed
- Healthcare expenditure estimated as the sum of the following costs: pharmacological treatment of associated comorbidities, incidence of

complications (visits to his/her primary care physician, a specialist or emergency department for acute complications, treatment of acute complications, number of hospital admission days, antibiotic treatment), consumption of health resources (visits to the general practitioner, visits to specialists, laboratory tests)

- Work absenteeism, estimate of the number of work leave days + hours of work absenteeism due to health problems or medical visits.

In order to evaluate if the weight loss treatment is improving the health of patients and reducing health expenditure and absenteeism, the healthcare expenses and work absenteeism estimated from the doctor's records corresponding to the 6 months prior to the initiation of the weight loss treatment will be compared with data recorded at follow-up visits over the 2-year follow-up. Likewise, the doses and number of drugs required by patients for the treatment of their comorbidities before the weight loss and at the control visits during weight loss and up to completing the 2 years of follow-up will be compared.

As secondary objectives, the efficacy of the weight loss treatment will be studied by comparing the anthropometric parameters of the initial visit with those of the follow-up visits (weight, body mass index and waist circumference). Likewise, any improvement in laboratory parameters and blood pressure during the follow-up will be studied. Changes in quality of life scores (SF-12) will also be assessed between the initial visit and the end of each treatment stage.

For all objectives, the comparisons between qualitative variables will be made using the Chi square test or the Fisher exact test, and the comparison between quantitative variables will be performed using the Student's t-test (in the case of 2 groups) or by the one-way ANOVA test (for 3 or more groups). If the conditions for the Student's t-test or the Anova test are not met, the non-parametric Mann-Whitney U test (2 groups) or the Kruskal-Wallis test (for 3 more groups) will be used.

Safety and tolerability will be analysed by descriptive statistics of all side effects or adverse reactions reported by patients throughout the study.

For all tests, the significance level will be set at $p < 0.05$.

11. RECORDING ADVERSE REACTIONS

During the entire follow-up period, the physician should report any suspicion of a serious adverse reaction observed in the patient under treatment by completing a Serious Adverse Reaction Report form, forwarding it to the coordinating center (Annex 5).

SERIOUS ADVERSE REACTION: refers to any adverse reaction that can be classified in one or more of the following categories:

- Fatal
- Life-threatening
- Causes persistent or significant disability
- Causes hospitalization or prolongs hospital stay

Congenital anomalies/birth defects and serious adverse clinical consequences associated with use under conditions other than those set out in the Summary of Product Characteristics (SmPC), overdose or abuse are also included.
Medical judgment should be implemented when deciding whether an event or reaction is serious in other situations. Major adverse reactions or events that do not pose an immediate danger to life or cause death or hospitalization but which may endanger the patient should be considered serious.

12. ETHICAL ASPECTS

12.1 General

This study will be carried out in accordance with current regulations, international accepted ethical standards of Good Clinical Practice (CPMP/ICH/135/95) and the principles established in the latest version of the Declaration of Helsinki.

12.2. Informed consent

Prior to inclusion in the study, the study doctor should provide the patient with information about the study (Annex 1), propose participation in the same, answer any questions and request the completion of the informed consent (Annex 2), which he/she will keep in his/her own files.

12.3. Confidentiality of data

The data of the different participating subjects will become part of a totally confidential electronic file owned by Pronokal Group.

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