Title page

MAP Protocol. Restoring physiological jaw closure and **MA**sticatory function as treatment for chronic facial **P**ain: a randomized clinical trial

Public title: Improving chewing function to treat chronic pain

ACRONYM: MAP

Universal Trial Number (UTN): U1111-*1134*-0832
ClinicalTrials.gov Identifier: NCT02144233
International Standard Randomized Controlled Trial Number Register (ISRCTN Register):
ISRCTN61654487 - http://www.controlled-trials.com/ISRCTN61654487/

Protocol number: 2
Protocol date: 2017 March 1st

Authorized signature

Name: Professor Urbano Santana-Penín
(Chair of Trial Steering Committee for final protocols and amended final protocols)

Trial Steering Committee
Urbano Santana-Penín (USP)
José López-Cedrún (JLC),
María J. Mora (MJM)
Urbano Santana-Mora (USM)

Key words. Mesh Terms:
Musculoskeletal Diseases [C05]
Jaw Diseases [C05.500]
Mandibular Diseases [C05.500.607]
Craniomandibular Disorders [C05.500.607.221]
Temporomandibular Joint Disorders [C05.500.607.221.897]
Temporomandibular Joint Dysfunction Syndrome [C05.500.607.221.897.897]
Occlusal Adjustment [E06.658.578.200]
Facial Pain [C10.597.617.364]
Chronic Pain [C10.597.617.258]
Mastication [G10.261.326.240.500]

MAP TRIAL
Name of person authorized to sign final protocol and protocol amendments for the sponsor (Chair of Trial Steering Committee)

Name: **Prof Dr Urbano Santana-Penín**
Professor and chair,
Orofacial Pain and Prosthodontics Department
Faculty of Medicine and Dentistry
Santiago de Compostela University
C/ Entrarríos s/n
15782 SANTIAGO DE COMPOSTELA, SPAIN

urbano.santana@usc.es
Tel Instit.: +34 881812350
Tel: +34 647 344 093
Fax: +34 981 562226

Principal Investigators in bold and Investigators responsible for the conduct of the MAP Trial

Dr José López-Cedrún (JLC),
Head of the Oral and Maxillofacial Surgery Department
Complejo Hospitalario Universitario A Coruña
Calle Jubias 84, 15006 A CORUÑA, Spain

lopezcedrun@centromaxilofacial.com
Tel: +34 981178000 Ext 292021
Fax: 0034 981178052

Professor María J. Mora (MJM)
Head of the Stomatology Unit
University Hospital Complex of Santiago de Compostela, and
University of Santiago de Compostela, A Coruña, Spain
15782 SANTIAGO DE COMPOSTELA, SPAIN

mariajesus.mora@usc.es

Tel: +34 981951919

Dr Urbano Santana-Mora (USM). Clinical Instructor.
Orofacial Pain and Prosthodontics Department
Faculty of Medicine and Dentistry
Santiago de Compostela University
C/ Entrarríos s/n
15782 SANTIAGO DE COMPOSTELA, SPAIN

urbanoalejandro.santana@rai.usc.es
Tel: +34 881812350
Fax: +34 981 562226

Dr Javier Collado López (JCL)
Oral and Maxillofacial Surgery Department
Complejo Hospitalario Universitario A Coruña
Calle Jubias 84, 15006 A CORUÑA, Spain

jcolmax@gmail.com
981 178000

Dr María Pombo Castro (MPC)
Oral and Maxillofacial Surgery Department
Complejo Hospitalario Universitario A Coruña
Calle Jubias 84, 15006 A CORUÑA, Spain

mariacorme@hotmail.com
981 178000

Dr Fernanda Lorenzo Franco (FLF)
Oral and Maxillofacial Surgery Department
Complejo Hospitalario Universitario A Coruña
Calle Jubias 84, 15006 A CORUÑA, Spain

JMbares@terra.com
981 178000

Dr Rocío P. García. Clinical Instructor.
Orofacial Pain and Prosthodontics Department
Facultad de Medicina y Odontología
Universidad de Santiago de Compostela
C/ Entrerríos s/n
15782 SANTIAGO DE COMPOSTELA, SPAIN

rochi_perez@hotmail.es
Tel: +34 881812349
Fax: +34 981 562226

Dr Iria L. Darriba. Clinical Instructor.
Orofacial Pain and Prosthodontics Department
Facultad de Medicina y Odontología
Universidad de Santiago de Compostela
C/ Entrerríos s/n
15782 SANTIAGO DE COMPOSTELA, SPAIN

irialopezdarriba@gmail.com
Tel: +34 881812349
Fax: +34 981 562226

Trial manager and monitor

Urbano Santana-Mora (USM)

Protocol Steering Committee:

Same as the Trial Steering Committee (see title page)

Data management team:

Teresa Pazos Fernández (TPF), JLC

Dr María Pombo Castro (MPC)

Trial Management Committee:

JLC, USP

Other individuals or groups overseeing the trial:

Prof. James H. Ware (JHW)

Written (committed) Chair:

USP

Serum Utilization Committee:

Ms Teresa Pazos Fernández (Nurse), Dr Rivas Lombardero (Head of Lab) and JLC.

Data and Safety Monitoring Board (DSMB): (please see *item* 21a)

Prof. Dr. Pentti Alanen (Chair).	alanenpentti@gmail.com
Prof. Dr. Julián Álvarez Escudero (Expert in Pain Medicine)	julian.alvarez.escudero@sergas.es
Prof. Dr. Joao C. Pinho (Expert in TMD).	pinhojc@gmail.com
Prof. Dr. Carmen Carollo (Statistician).	mdelcarmen.carollo@usc.es
Dr. Francisco Gude (Statistician).	francisco.gude.sampedro@sergas.es

Trial Coordinator and Sponsor's Representative

Prof Dr Urbano Santana-Penin
Facial Pain and Prosthodontics, Faculty of Medicine and Dentistry, University of Santiago de Compostela, C/ Entrerrios s/n. 15782 Santiago de Compostela, Spain.
Tel: +34 647344093.
Fax: +34 981562226.
E-mail: urbano.santana@usc.es

Principal Coordinating Investigator

Dr José López-Cedrún
Head of the Oral and Maxillofacial Surgery Department, University Hospital Complex of A Coruña, Calle Jubias 84, 15006 La Coruña, Spain.
Phone: +34 981178000 Ext 292021.
FAX: +34 981178052
E-mail: lopezcedrun@centromaxilofacial.com

Trial Statistician

Prof. James H. Ware
Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, US.
E-mail: ware@hsph.harvard.edu

Background
Chronic temporomandibular joint (TMJ) disorders (TMD) are the main cause of facial pain, and the second cause of musculoskeletal pain after low-back pain. The cause of TMD is unknown and therapy is usually empirical. Systematic reviews have shown that more research is needed to elucidate the benefits of occlusal adjustment for TMD. The risk factors for chronic unilateral TMD include dental (occlusal) premature contacts and habitual chewing on the affected side; therefore, a new occlusal therapy is proposed to restore physiological jaw closure and chewing function.

Aims
The primary endpoint will be the average change in pain score from baseline to the six-month assessments. Efficacy will be demonstrated by superior pain relief with the active treatment compared with the placebo.

Methods

Study design

A phase 3, randomized, single (extensible to up three) centre, 6-month parallel-group, patient- and observer-blinded, placebo-controlled clinical trial to assess the efficacy of occlusal adjustment on recovery of physiological jaw closure and chewing function in patients with TMD.

Study population

Inclusion criteria: TMD patients, aged 18-65 years with full dentates and normo-occlusion suffering significant pain (pain scores ≥4 and ≤9; method: visual analogue/numerical rating scale (VAS/NRS); 0 = no pain, 10 = worst imaginable pain). Main exclusion criterion is the requirement of excessive enamel removal to equilibrate the dental articulation (occlusion).

Intervention
Active therapy will consist of the elimination of premature tooth contacts and the reduction of the steeper lateral anterior guidance. *Placebo* therapy will be conducted in a manner identical to the active adjustment, but no enamel will be removed.

Outcomes

Main outcome: self-reported pain intensity on the affected side measured by the VAS and/or NRS scale. Secondary outcomes: maximum comfortable mouth opening (using a Boley gauge), chewing function (observed on the habitual chewing side) and quality of life using self-administered tests. Time frame: baseline and both 3- and 6-months follow-up.

Sample size estimation

Based on data from a previous study, we assume a standard deviation of 2.4 for this variable. We will test the null hypothesis of no treatment effect at the two-sided 0.05 level. With a fixed sample size design, a total sample size of 88 subjects (extended to 110 for drop-outs) with complete follow-up would provide power of 0.8 to detect changes in pain score of 1.5 units between the active and placebo treatment groups.

Interim analysis plan and stopping rules

The Data and Safety Monitoring Board will be responsible for activating early stopping. The study will employ an interim analysis plan with a single interim analysis after 70% of participants have completed the six-month follow-up visit. Using the Lan-DeMets version of the O'Brien-Fleming stopping rule, the critical value for statistical significance at the interim analysis (under both intention-to-treat and *per-protocol* sets) will be +2.438, corresponding to a nominal two-sided P value of 0.0146.

Statistical analysis plan

For analysis of baseline characteristics, qualitative variables will be expressed as frequencies and percentages (25th -75th percentiles) and continuous variables as means (standard deviation). Fisher´s exact or McNemar tests will be used to compare the distributions of binary variables; Student t test or measurements repeated analysis of variance will be used to compare normal variables, and the Wilcoxon or Mann-Whitney U test for non-normally distributed continuous variables.

All analyses will be conducted by two independent statisticians according to the intention-to- treat approach (the primary outcome was also analyzed as per protocol).

The objective of this analysis is to adjust regression models that explain the outcomes of interest as a function of time and group. Based on the properties of the analized variables, the model fit of the analyses based on the linear mixed-effects model or the beta mean regression model with mixed effects, using the Akaike Information Criterion or the Bayes Information Criterion. Plots of residuals were used to check that the model assumptions were met and to assess goodness of fit. Statistical significance level was set at 0.05. All the analyses were conducted using the software R (R Development Core Team), including the "lme4" and the "gamlss" packages or IBM SPSS24.

Sponsor
University of Santiago de Compostela, Praza Obradoiro s/n, 15782 Santiago de Compostela, Spain

Funder
Ministry of Science and Innovation of the Government of Spain (Grant nº PI11/02507).

European Development Fund (EDF). Fondo Europeo de Desarrollo Regional (FEDER) . "Una manera de hacer Europa"

Autonomic Committee of the Research Ethics of Galicia: CAEI approval number 2009/017; updated on November 29, 2013).

Date trial started
11th August, 2014.

Expected end date
July, 2017.

The authors state that there are no conflicts of interest to report.