Effectivity of a joint didactic intervention by School for Patients on inappropriate control prothrombin time anticoagulated patients. Protocol for developing a randomized and controlled clinical trial.

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Study protocol

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Abstract

Background

Oral anticoagulant drugs represent an essential tool in thrombo-embolic events prevention. Most used are vitamin K antagonists, whose plasma level is monitored by measuring prothrombin time using the International Normalized Ratio. If it takes values out of the recommended range, the patient will have a higher risk of suffering from thromboembolic or hemorrhagic complications. Previous research has shown that about 33% of total patients keep values on inappropriate level. The purpose of the study is to improve International Normalized Ratio control figures by a joint didactic intervention based on the Junta de Andalucía School for Patients method that will be implemented by anticoagulated patients themselves.

Methods

A randomized clinical trial was carried out at primary care centers from one healthcare area in Málaga (Andalusia, Spain). Study population: patients included in an oral anticoagulant therapy program consisting in using vitamin K antagonists. First step detection of patients on oral anticoagulation program with International Normalized Ratio control on therapeutic level during 65% or less over total time. Second step: patients with inappropriate International Normalized Ratio control were included in two groups: Group 1 or Joint Intervention Group: patients were instructed a joint didactic intervention “from peer to peer”, by a previously trained and expert anticoagulated patient. Group 2 or Control Group: Control group performed usual clinical practice: people were schedule by nurses about one time per month, except cases in which controls were inappropriate; in those circumstances patients were schedule before that period expired. In order to built the study group and the control group, 312 individuals were required (156 in each group) to detect differences in INR figures equal or higher than 15% between both groups. Study variables time on therapeutic levels before and after intervention, sociodemographic variables, vital signs, existence of cardiovascular risk factors or accompanying diseases in the clinical records, laboratory test including complete blood count, bleeding time, and prothrombin time or partial thromboplastin time and blood chemistry, other prescribed drugs, and social support. Almost-experimental analytic study with before-after statistical analysis of the intervention were made. Lineal regression models were applied on main variables results (International Normalized Ratio value, time on therapeutic level) inputting sociodemographic variables, accompanying diseases and social support.

Background And Current Status

It has been proved that oral anticoagulant therapy (OAT) is effective in preventing situations with high risk of thromboembolic events and in treating them [1,2]. It significantly decreases ischemic stroke rates as well as their severity and associated death risk.

However, it is a therapy with special features, such as doses and response variability, the close therapeutic range, interactions with other drugs and foods, and potentially severe side effects. This fact

compels the investigators to make a close monitoring of those patients [2].

An important effect in developing cardioembolic or hemorrhagic events due to a inappropriate coagulation control using vitamin K antagonists (VKA) has been found, because control variations around 15% could result in relevant clinical problems [1].

The main AOT indications are deep vein thrombosis, pulmonary embolism, and embolic conditions prevention in patients suffering from atrial fibrillation or heart prosthetic valve wearers [3,4]. Atrial fibrillation (AF) is nowadays the pathology that requires most anticoagulant therapy indications. This fact is partially due to the population aging, since there are both incidence and prevalence increases of this arrhythmia, especially in elderly patients [5,6].

Control of patients on OAT were performed in hospitals until a few years ago. Nevertheless, changes in social and healthy contexts besides the expansion in these drugs prescriptions joined to primary health care qualification and evolution, the development of coagulation handheld measuring devices, and the need to improve patients accessibility had justified the control decentralization and due to this facts, OAT monitoring can be carried out to stable patients on primary care [7,8].

When the need of receiving anticoagulation has been stablished, this could be implemented by basically using heparin or vitamin-K antagonists (acenocoumarol or coumadin) or new direct-action oral anticoagulants as dabigatran, rivaroxaban, apixaban or edoxaban [9,10].

A method of standardizing prothrombin time results, called the international normalized ratio (INR) system, allows the investigators to obtain reliable results in different laboratories [11].

The development of coagulation handheld measuring devices to match INR in capillary blood with high sensitivity and reliability has made possible that patients on anticoagulant therapy can be controlled on primary care. This allows for comprehensive approach and control of these patients.

The number of patients with AF on anticoagulation with VKA is high, however, INR levels control results are not ideal [14,15,16].

Through educational and behavioral interventions, VKA anticoagulated patients increase their knowledge and understanding of the action mechanisms of anticoagulants drugs. As a consequence of the educational interventions, patients may increase their ability to keep an INR appropriate control.

Recent study included in Cochrane regarding to those interventions notes that education is particularly important to provide information about safety for patients suffering AF on OAT and to let patients make their own well founded decisions about treatment options and manage their OAT.

In addition, education let them make their own well founded decisions about treatment options and manage their OAT. Therefore, three research articles recently conducted in Spain show inappropriate anticoagulation control levels in patients on VKA. [17,18,19]. However, there is not enough evidence to

stablish definite conclusions about educational health interventions in INR behavior of patients suffering from AF on OAT [12,13].

Furthermore, it should be noted that these chronic patients are prone to suffer from many other conditions and as a result, they are likely to take a lot of medication. This factor has become the health self-management less effective. Hence, educative aspects aimed at self-care and effective health self-management are necessary components of educational interventions targeting this type of patients which make improve of educative aspects aimed at selfcare and effective health self-management necessary [20,21]. Selfcare support programs are presented as a tool to accomplish a change. This tool or method is also presented as an alternative to the paternalistic methodone in which citizens could receive more information about their health state (this fact is in accordance with a demonstrated rise in people's request on health issues via the internet.

Aim: The present study try to show that conducting an organized group educational intervention on VKA anticoagulated patients by using the School for Patients method will result in improved inappropriate INR control levels.

Methods

The investigators performed a randomized clinical trial over a period of 28 months. The study started on 1 of September of 2018 and will finish on 31st of December of 2020.

Study area: one healthcare area in Málaga (Spain) where 741.000 inhabitants from rural or urban population are cared for. It is organized in 33 primary care centers and 19 local doctors' offices.

Study population: patients on OAT program receiving VKA. The patients presented inappropriate INR control levels and belonged to four primary care centers representing people from different social classes in Malaga city.

Inclusion and exclusion criteria

Inclusion criteria:

Men and women over 18 eigth years old included in some of the 4 primary care centers selected.

Patients on VKA treatment for at least the last six months in primary care environment.

Patients on inappropriate INR level control.

Patients in whom we had access to, at least, 80% of their INR levels controls in last six months of treatment with VKA, although they were enrolled in another primary care center.

Patients who gave written informed consent to take part in the study.

Exclusion criteria:

Patients suffering from cognitive impairment which prevents understanding what was written in the information sheet and informed consent.

Limited mobility patients.

Terminal patients.

Alcoholism or drug addiction.

Severe psychiatric illness.

Any other reason which makes patients to be present at center´s meetings impossible.

Setting the limits and justification of the sample size.

The total population from the health centers participating in the study amounted to approximately 50.000 inhabitants.

Step I: Considering that the prevalence of patients on OAT is about 1.5% of the general population, it can be claimed that the target population to initiate our study will be 750 anticoagulated patients. Prior studies indicate [17,18,19] that at least 33% of these patients would not have an appropriate INR control level. To reach an accuracy of about 4% in the estimated proportion it must be consider the following conditions:

1) Using a normal asymptotic confidence interval with a correction to finite populations on bilaterally of 95%. 2) Assuming that the expected population is about 33%, and 3) being population total size 750, it was deemed necessary to include 312 experimental units in this study. Figure 1.

Step II: Accepting an alfa risk of 0.05 and a beta risk of 0.20 in a bilateral contrast between the study group and the control group, 312 individuals were required (156 in each group) to detect differences in INR figures equal or higher than 15% between both groups in the primary target. It has been estimated a tracking loss rate of 10% by the researchers. It was assumed a loss those individual impossible to be located, or those who did not accept to take part or those who did not attend to scheduled revisions, in accordance to the study intervention plan, as well as deceases occurring within six months since the intervention. Given the relevant impact of the development of cardioembolic or haemorrhagic events due to inappropriate INR control, changes about 15% could have great clinical relevance.

In order to reach the required sample size, all patients from the four health centers on OAT using vitamin K antagonists were studied. The investigators tried to avoid bias depending on each health center issues. Patients were selected from their own PCC once tidied by “Seguridad Social de Andalucia” user number (NUSSA). Once the inappropriate control ones were identified, they were consecutively placed considering

their social security number in every health center. After that, patients in each strate (PCC) were randomly distributed in intervention group or in control group.

It has been estimated a follow-up lost ratio about 10%. Deaths into six months from the intervention, and all individual not posible to be located, or not accepting to participate, or not attending to scheduled controls It will be considered as losts dealing with the study intervention program.

Study design: randomized clinical trial.

Description of the intervention:

The study was carried out in a 28 months period. It started on 1 of September of 2018 and it will finish on 31st of December of 2020.

Patients in each strate (PCC) were randomly distributed in intervention group or in control group (a random numbers table was used). After assignment to intevention, participant name will be deleted in order to mask the data by the nurses in charge of the recruitment. The outcome assessors do not know the patients identity. The masking was carried out by replacing the patients identification data for an assignment number.

All patients under study received an information sheet and they signed informed consent forms when they attended to INR control. The investigators tried the involvement of every person so that patients included in intervention group were telephoned in previous weeks in order to get the attendance to group meetings (as far as three times and in different times if was necessary) by a nurse. They were recalled the day before the meeting. After that, the intervention was carried out and it was based in the patients attendance to one educational session leaded by an expert patient (member of “Málaga anticoagulated patients association). This person had been previously trained by health professionals and he was able to apply a leader roll as instructor, supporting in their knowledge and experience. Press material and a question form had been worked out for the intervention group to start the meeting. (Anexo VII). The patients had to answer the form questions about their vitamin-K antagonists knowledge. Then, the expert patient answered to everyone “¿what obstacles could we find in order to reach an appropriate anticoagulation degree?”. The instructor relied on the support of short PowerPoint presentations as well as on graphic material explaining their subjects to the patients. The main explanations for inappropriate control levels were exposed by the expert patient: other drugs consumption, inadequate food, adherence to treatment, etc. Brainstorm, Phillips technique 6.6, Role Playing and a table including main ideas provided by patients were performed in order to keep their INR levels at appropriate range, and the impediments they faced for reaching them were also included. All of this was made for complementing the knowledge transmitted by health professionals. A sanitary professional carried out observation and energizer tasks if was necessary.

Group meetings with educational sessions were organised in a primary health center, and they took place from Monday to Thursday in the evening (according to the onvenience of the center) with a last of 90

minutes each. It had been estimated eleven sessions to teach including 15 persons each as a maximum in order to complete one session per person; but always in the same classroom and under the management of the expert patient and the observation of the main researcher.

Every patient had to attend to one group meeting (intervention group). Control group performed usual clinical practice: people were schedule by nurses about one time per month, except cases in which controls were inappropriate; in those circumstances patients were schedule before that period expired. Patients in control group did not attend to any group session. Both groups followed with their usual INR controls, carrying out the needed number of measuring under the guidance of health professionals involved in appropriate INR control in all patients.

And the last step, once the intervention had been carried out to every indicated patient, INR figures and data were collected within the next six months in order to analyse them.

The study participants could withdraw the informed consent at any time and they could leave the study if they did not complete the six months of INR control after the educational intervention. The main reasons for discontinuing or modifing interventions asigned to each study participant were withdraw request, a participant death or stop using antivitamin K drugs. Unmasking is allowed in that cases.

Protocol amendments will be reported to research ethics committee and to funding foundation (FIMABIS) and trial sponsor (FJNM).

Data collecting: All variables detailed below were collected as long as they were suitable in digital medical history or it could be directly obtained from the patient during the medical interview, without the need of changing health center usual clinical practice, over the 6 months prior to the intervention. The data were collected in some collection sheets and kept by the principal investigator as follows:

First step: patients on OAT program enrolled in several primary health centers belonging to a healthcare area of Málaga were evaluated at the study moment attending to their clinical characteristics. The measurements obtained from the digital clinical history in the last six months before the beginning of the study were recorded, as well as the rest of variables, in some collection sheets.

Second step: Once the study of the VKA anticoagulation control degree was performed, patients on inappropriate control were selected. A list of patients with deficient INR control in participant health centers was made. It was considered an inappropriate INR control when the therapeutic INR values percentages (TRT) was less than 65%, using Rosendaal method to obtain them. In case of no availability, INR control was considerate inappropriate when therapeutic INR values percentage resulted less than 60%. In any of the assumptions, the assessment period was at least the last six months.

Variables. Operative definition

The main variable to assess in this study was time on INR therapeutic levels in the last six months receiving VKA treatment. Appropriate INR level control was assessed in two ways: measuring the

therapeutic INR values percentages or Time percentages in therapeutic values estimated using Rosendaal method. It supposed to record the figure of INR value and the date in which the test was carried out. The therapeutic INR values percentages are defined by their acceptable values according to the pathology the patient suffers. It use to be from 2 to 3 if it is about atrial fibrillation or from 2.5 to 3.5 if thromboembolism prevention is carried out after a heart valve surgery has been performed. So, this quantitative variable had to be measured to calculate patients percentage on appropriate range, according to the patient condition.

Independent variables also called study variables are those which could affect to result variable. We classified them in eight groups to make easier their analysis.

Sociodemographic: age and gender, marital status, employment situation, social and family support.

Somatometry and vital signs: Height, weight, body mass index (BMI), diastolic and systolic blood pressure, and heart rate.

Cardiovascular risk factors: smoking habit, diabetes, arterial hypertension, dyslipidaemia and chronic renal failure.

Cardiovascular conditions: atrial fibrillation (AF), interventional cardiac valve diseases with or without AF, ischemic cardiopathy, thromboembolic diseases history (stroke, transient ischemic attack), hemorrhagic stroke, congestive heart failure.

Blood test: Complete blood count, bleeding time and prothrombin time or partial thromboplastin time, glomerular filtration rates, total cholesterol, HDL and LDL cholesterol and triglycerides. They were obtained from the last blood test carried out to the patient.

Use of accompanying medication: total number of drugs, anticoagulant type.

Consumption of “gastric protector” or non-steroidal anti-inflammatories.

Dietary habits: usual consumption of food rich in vitamin K, alcohol consumption, frequent diet transgressions.

Primary Outcome Measure:

1.Time on INR therapeutic levels in the last six months receiving VKA treatment: Appropriate INR level control was assessed in two ways: measuring the therapeutic INR values percentages or Time percentages in therapeutic values estimated using Rosendaal method [Time Frame: 0 and 6 months]

Secondary Outcome Measures:

2. Sociodemographic

Record of age and gender. [Time Frame: Start of the study.]

3. Body mass index (BMI)

Determination of the body mass index calculated as the weight measured in kilograms

(kg) divided by the height measured in meters squared (weight / height2) (Kg /m2).

[Time Frame: 0 and 6 months.]

4. Diastolic and systolic blood pressure

Determination of diastolic and systolic blood pressure measured in millimeters of

mercury (mm / Hg), average of 2 determinations. [Time Frame: 0 and 6 months.]

5. Heart rate

Determination of the number of heart beats per minute, average of 2 determinations of.

[Time Frame: 0 and 6 months.]

6. Smoking habit

Incidence of smoker's habit status in the electronic medical record. [Time Frame: 0 and 6 months.]

7. Diabetes

Incidence of the condition of diabetes in the electronic medical record. [Time Frame: 0 and 6 months.]

8. Arterial hypertension

Incidence of diagnosis of hypertension in the electronic medical record. [Time Frame: 0 and 6 months.]

9. Dyslipidemia

Incidence of the diagnosis of dyslipidemia in the electronic medical record.

[Time Frame: 0 and 6 months.]

10. Chronic renal failure

Incidence of the diagnosis of chronic renal failure in the electronic medical record.

[Time Frame: 0 and 6 months.]

11. Atrial fibrillation

Incidence of diagnosis of atrial fibrillation in the electronic medical records of patients.

[Time Frame: 0 and 6 months.]

12. Interventional cardiac valve diseases with or without atrial fibrillation

Incidence of diagnosis of interventional cardiac valve diseases in the electronic medical

records of patients. [Time Frame: 0 and 6 months.]

13. Ischemic cardiopathy

Incidence of diagnosis of Ischemic cardiopathy in the electronic medical records of

patients. [Time Frame: 0 and 6 months.]

14. Thromboembolic diseases history (stroke, transient ischemic attack)

Incidence of diagnosis of thromboembolic diseases history (stroke, transient ischemic attack) in the electronic medical records of patients. [Time Frame: 0 and 6 months.]

15. Hemorrhagic stroke

Incidence of diagnosis of hemorrhagic stroke in the electronic medical records of patients.

[Time Frame: 0 and 6 months.]

16. Congestive heart failure

Incidence of diagnosis of congestive heart failure in the electronic medical records of patients.

[Time Frame: 0 and 6 months.]

17. Glomerular filtration rates

Determination of total Glomerular filtration rates in mL/min/1,73 m2. Change of basal to 12 months.

[Time Frame: 0 and 6 months.]

18. Total cholesterol

Determination of total cholesterol measured in milligrams per deciliter (mg/dl). Change of basal to 12 months. [Time Frame: - 6 and 6 months.]

19. HDL Cholesterol

Determination of HDLc (high-density lipoprotein colesterol). LDLc measured in milligrams per deciliter (mg/dl)., (low-density lipoprotein colesterol). HDLc measured in milligrams per deciliter (mg/dl). Change of basal to 6 months. [Time Frame: –6 and 6 months.]

20. LDL cholesterol

Determination of LDLc (low-density lipoprotein cholesterol). LDLc measured in milligrams per deciliter (mg/dl). Change of basal to 6 months. [Time Frame: - 6 and 6 months.]

21. Triglycerides

Determination of total triglycerides measured in milligrams per deciliter (mg/dl). Change of basal to 12 months. [Time Frame: - 6 and 6 months.]

22. Total number of drugs

Determination of the total number of different medications prescribed in the electronic

medical records of patients. Change of basal to 12 months [Time Frame: - 6 and 6 months.]

23. Anticoagulant type

Determination of the anticoagulant type prescribed in the electronic medical records of patients. Change at baseline and at 12 months. [Time Frame: - 6 and 6 months.]

24. Consumption of “gastric protector”

Determination of the Consumption of “gastric protector” prescribed in the electronic medical records of patients. Change at baseline and at 12 months. [Time Frame: - 6 and 6 months.]

25. Usual consumption of food rich in vitamin K

Change in usual consumption of food rich in vitamin K. Change at baseline and at 12 months

[Time Frame: - 6 and 6 months.]

26. Alcohol consumption

Change in usual alcohol consumption. Change at baseline and at 12 months [Time Frame: - 6 and 6 months.]

Eligibility: Minimum Age: 18 years. Sex: All. Accepts Healthy Volunteers: no.

Statistical analysis

First of all, a descriptive analysis of the study variables was carried out. Continue variables values were summed up in an index which showed means and standard deviation or medians according to the variable distribution (symmetric or asymmetric respectively), values range: maximum and minimum. Categorical variables were presented using absolute and relative frequencies. Chi-square test were applied to analyse the observed differences in qualitative variables frequencies or Fisher test if under 5

waited values percentage amount more than 20%. Odds ratio and its confidence intervals at 95% were calculated in the case of two-dimensional indexes.

Student-t test for paired samples was applied to study the differences in continuous variables, before and after the intervention, in case that normality requirement could be accepted, what it could be proved by using Shapiro-Wilk test. In order to compare obtained values in experimental group and in control group Student-t test was used for independent groups or its non-parametrical equivalent Mann-Whitney test. If normality could not be accepted, non-parametrical Wilcoxon test should have been applied. In case of obtaining significantly statistical results, confidence intervals at 95% should have been calculated. Multiple lineal regression models should have been used to determine associated factors to inappropriate INR control.

Statistical analysis was done using R software 3.0 version (Foundation for Statistical

Computing, Vienna, Austria; available at http://www.R-project.org 1.5.11.

Risks or limitations and viability

Some of the studied variables may not be collected in the digital clinical history which is the main data collecting source. To solve this limitation and considering that patients have to attend necessarily to INR controls in health center, the lack data were recovered performing a clinical interview. Furthermore, we could face to low group meetings attending due to lack of interest or lack of motivation of the studied individual. Patients who did not attend a meeting were called again to participate in next group session. “Hawthorne effect” could result in patients when they felt that they were being observed, what made them to comply the advices in a more strictly way. Furthermore, the main investigator attended to the intervention group meetings what may result in bias when he interpreted the outcomes.

Timetable and work programme

The study is being carried out in a 28 months period. The assembly of the project took place on one day at Primary Care Center *Ciudad Jardin* practice classroom for all health care members involved in the research, so as the expert patient who executed the intervention to develop and plan the implementation of the research strategy.

Nurses reported to participants about the study strategies and they collected the informed consent from the participants.

First step, at the start of the study, a retrospective data collecting of the six months prior to the intervention from all patients who met all the selection requirements included in OAT program were completed. Once the anticoagulated patients had been analysed and the list of the patients on inappropriate control have been completed, a random sampling in every health center were done in order to build two groups: *intervention group and control group.*

Intervention group were performed to indicated patients. Nurse students took on the telephone calls to schedule intervention group patients for group meetings attendance. The main researcher joined with the expert patient had to attend to every group meeting, but the researcher only acted as an observer. Every participant center relied on nurses (10 partners) and two resident medical interns (learning Family and Community Medicine) to complete this task. Due to their frequent contacts with anticoagulated patients, nurses instructed them about study issues and collected the signed written inform consent, as well as they concerned about data collected, INR figures and patients studied variables. A portfolio with the collecting data forms was distributed to every participant. It was employed for the patients to collect their data which were transcript to a digital book that was identical for every participant center and it was used as a basis for the randomization. Two resident medical interns handled all computerised recordings.

After that, the intervention was carried out and it was based in the patients attendance to one meeting leaded by an expert patient. Due to lack of space and in order to improve the patients understanding, and according to the convenience of the center, the meeting was performed in different evenings but always in the same classroom and under the management of the expert patient and the observation of the main researcher.

And the last step consisted in collecting INR control data. In control group as well as in intervention one, INR control data had been obtained within six months from the activity date. Then, a new assembly with researchers team was carried out. Once this period has expired, a comparative before-after statistic study in every studied subject and between intervention and control group were be done. Figure 2.

Data monitoring committee is composed by main researcher (LGM), and doctors ABO and RRG.

All researches have accessed to the final data set. Results will be reported to participants. within the six months after statistycal análisis is completed.

Legal and ethical issues

This project will be performed respecting the principles of the Declaration of Helsinki (Fortaleza Revision. 2013), and Good Clinical Practice. Personal data will be treated following European Parlament Resolution 2016/679 and 27th of April of 2016 Council wich concerns to personal data treatment and protection.

The study protocol was approved by research ethical committee which belongs to General Healthcare Area of Málaga, previously to the beginning of the patients recruitment.

Data confidentiality is always an imperative condition and the data use was strictly done to reach the protocolized aims and to notify to competent authorities.

List Of Abbreviations

DAOA: Direct action oral anticoagulants

VKA: Vitamin K antagonists.

HC: Health center

AF: Atrial fibrillation

AH: Arterial hypertension

BMI: Body mass index

INR: International normalized ratio

OAT: Oral anticoagulant therapy

TRT: Time in therapeutic rangue

Declarations

Personal data of patients who compromise their anonymity are not included. The declaration of the identifying data of the participants is not aplicable.

Ethics approval and consent to participate

The Ethics and Research Committee of Malaga granted the approval for this trial. The regulations on Good Clinical Practice will be observed at all times, as well as the ethical principles established for the research on human beings stipulated in the Declaration of Helsinki and further amendments thereto. The clinical information will remain separate from the identification details and the databases will be coded and stored in specific computers solely intended for the project. All the records will be made observing all the dispositions from the legislation in force with regard to personal data protection according to the Act 15/1999 dated 13 December, as well as on safety files which may store personal data information, and more specifically, with regard to the access through communication networks (Royal Decree 994/1999 dated 11 June) and access to confidential information for scientific purposes from the Commission Regulation CE No. 831/2002 by the European Union and Act 41/2002 dated 14 November, which is considered the legal standard on Patient's Autonomy and Rights and Duties in terms of Clinical Information and Documentation. The staff responsible for such purpose will manage the data according to the instructions provided by the person responsible for the treatment. Such data will not be applied or used for a different purpose than those stated in the respective authorization; neither will they be reproduced to other people even for registration purposes. Once the aim of the trial has been carried out, the personal data collected will be destroyed, deleted, or given back to the person responsible for the treatment, along with any other media or documents containing any personal data related to the project. Every patient will be informed verbally and in writing about the objectives of the project and its methodology. Each individual will sign the respective informed consent form.

Consent for publication

All the authors gave their consent to take part in the study.

Data and material availability: available upon justified request to the author.

Trial status

The randomized trial is currently in the phase of patient's follow-up. Latest version (submitted September 25, 2018) on ClinicalTrials.gov NCT03647254: version 2. Latest version (submitted September 25, 2018) on ClinicalTrials.gov NCT03647254: version 2. The recruitment date of the first patient is September 1, 2019. The date of recruitment of the last patient is December 31, 2020.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

Authors have been chosen considering their contribution in the research protocol development and implementation. LGM has taken part in the original conception and design of this study and drafted the first version of this project as well as the manuscript. AHN, RRG, JMN, RPR, ILP, ABO, MGJ, MPFL, DLN, USC, CBG and FJNM have taken part in the conception and design of the study and critically reviewed the draft of the manuscript, providing a key intellectual contribution to the final version. All authors have read and approved the final manuscript. All subjects that are part of the paper has been revised and discussed by all authors in order to be exposed as clearly as possible.

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Figures

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Figure 1

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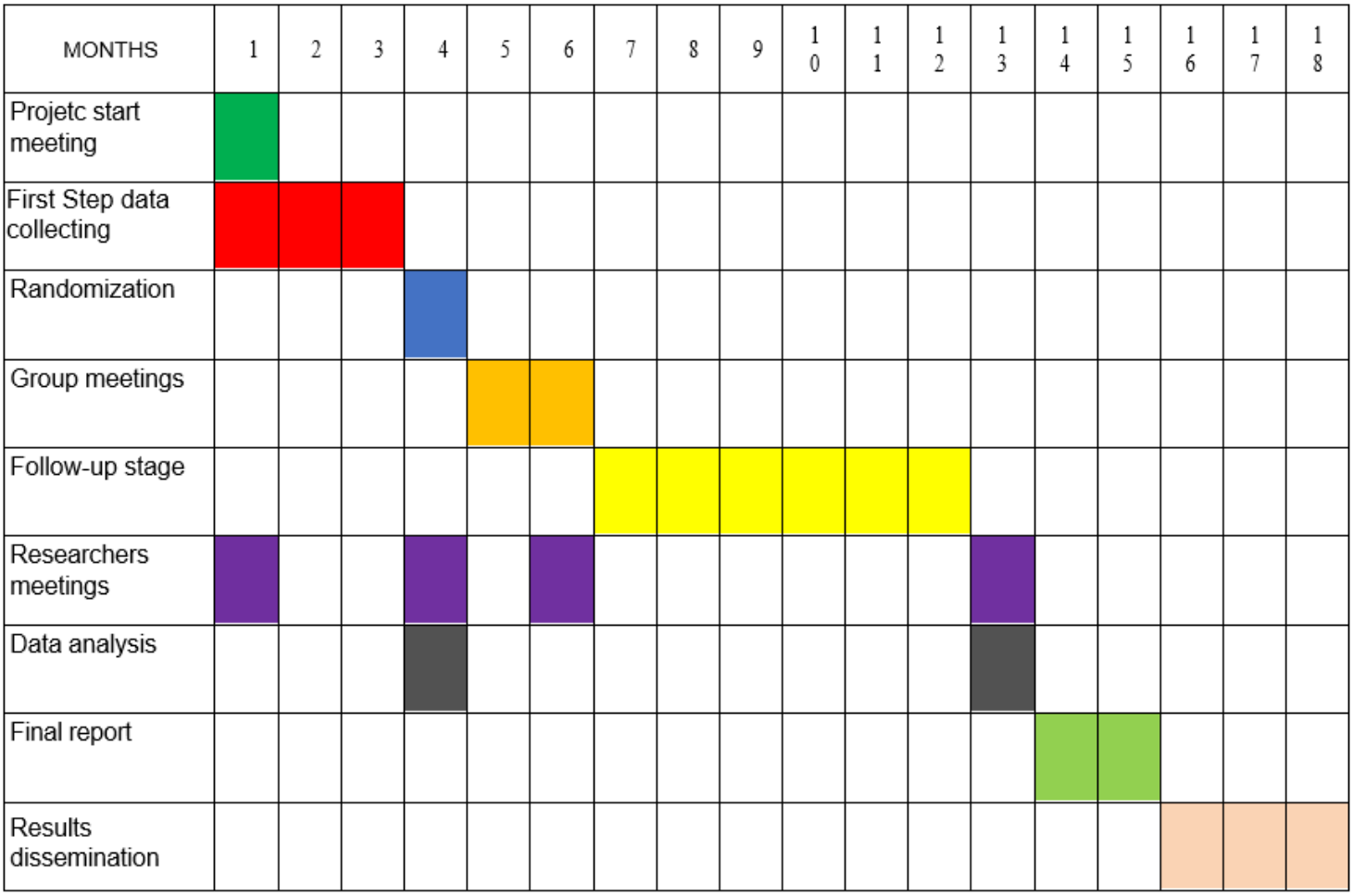

Figure 2

Timetable.

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