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PROTOCOL

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A telephone reminder to enhance adherence to interventions in cardiovascular randomized trials: A protocol for a study within a trial (SWAT)

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Abstract

The impact of reduced adherence in randomized clinical trials is well documented in the literature. Nonadherence can negatively affect the trial sample size and estimation of the treatment effect. This protocol aims to evaluate the effects of a telephone call reminder on the adherence rates of participants to interventions in a cardiovascular randomized trial. This is a study within a trial (SWAT). The host trial is evaluating the effectiveness of a multidisciplinary 16-wk cardiovascular disease prevention program on risk factor profile among patients with carotid artery stenosis. Simultaneously, this SWAT will evaluate the effectiveness of telephone call reminders on the participants' adherence to the host trial intervention. The primary outcome is adherence to the protocol of the host trial. Secondary outcomes are level of adherence, number of dropouts, and time to drop out from the host trial.

KEYWORDS

patient compliance, randomized controlled trial, reminder systems, study within a trial (SWAT), treatment adherence and compliance

1 | INTRODUCTION

The All-Ireland Hub for Trials Methodology Research, in collaboration with the Medical Research Council Network of Hubs in the United Kingdom, have developed the study within a trial (SWAT) program, to provide studies that would investigate the effects of different methods of designing, conducting, following-up, analyzing, and interpreting evaluations of health care, within clinical trials.[1,2]

Explanatory trials where the focus is on measuring the efficacy of an intervention in ideal conditions, consider adherence to the trial intervention as an integral part of the trial methodology, and accordingly, strict treatment fidelity monitoring measures are put in place.[3] Conversely, pragmatic clinical trials seek to measure the effectiveness of an intervention in routine clinical practice environments, and more often than not, adherence to the intervention being evaluated is not considered.[4,5] Therefore, adherence in pragmatic clinical trials, like the host trial in this SWAT, presents a challenge.[6,7]

The World Health Organization (WHO) defines adherence as the extent to which a trial participant's behavior corresponds with the trial protocol in terms of taking medications as prescribed, attending clinical appointments, and/or executing lifestyle modification interventions as required.[8,9] Nonadherence has been well recognized for years to be a common issue that significantly impacts clinical outcomes and health care costs.[10–12] Poor adherence is particularly challenging in cardiovascular trials, which mostly aim to manage risk factors and improve cardiovascular disease prevention.[11,13] While accepting that routine clinical cardiovascular secondary prevention practice also suffers from low adherence rates, yet reduced adherence in cardiovascular clinical trials can have a negative effect on the trial sample size and estimation of the treatment effects.[14,15]

According to a recent report from the Non-Adherence Academic Research Consortium (NARC),[11] the collection of nonadherence data varies substantially among cardiovascular randomized trials. Even where collected, this data is rarely included in the statistical analysis to test the reliability of the effect on the primary outcome(s). The imprecision introduced by the inconsistent assessment of nonadherence in clinical trials might confound the estimate of the calculated efficacy of the study intervention.[11,16] Hence, clinical trials may not accurately answer the scientific question presented by researchers or regulators, who seek an accurate evaluation of the true efficacy and safety of treatment or interventions. Therefore, there is a need to evaluate methods used to improve adherence in this area of research.[16]

This is a protocol of a SWAT. The host trial is evaluating the effectiveness of an intensive lifestyle modification program in controlling risk factors and preventing stroke and cardiac events in patients with asymptomatic carotid artery stenosis. Concurrently, the SWAT aims to evaluate the effectiveness of telephone call reminders on participants' adherence within the host trial.

2 | DESIGN FOR THE SWAT

2.1 | Background

A great deal of effort is often expended in recruiting participants to randomized trials.[17] Following the challenge of recruiting the required number of participants, there is the problem of ensuring that all participants remain in the trial and adhere to the trial intervention as required.[6,11] Nonadherence to the trial intervention has serious implications, resulting in decreasing the statistical power of the study, impacting negatively on the trial outcomes and increasing the risk of attrition bias due to incomplete data.[14,15,18] In addition to the loss of valuable knowledge, low adherence rates can result in research resource wasting and increasing the cost of randomized trials.[15,19]

A distinction is made between intentional and unintentional nonadherence.[18,20] Unintentional nonadherence is a passive process whereby patients fail to adhere to prescribing instructions through forgetfulness, carelessness, or circumstances out of their control such as health literacy or cognitive impairment.[18,20] In contrast, intentional nonadherence is an active decision on the part of patients, which may be based on perceptions of symptom reduction, fear of side effects, fear of addiction, or perceived inefficiency of treatment.[21,22]

The issue of nonadherence is particularly problematic in cardiac rehabilitation (CR) trials. Both intentional and unintentional nonadherence were reported in secondary prevention for cardiovascular disease.[11,18,23] Evidence showed that approximately 31% of patients reported unintentional nonadherence, while 9% reported intentional nonadherence.[21] Despite the proven benefits of CR,[24,25] eligible patients do not always agree to take part in CR. Of those patients that do agree to participate, many do not adhere to the CR programs as recommended.[9,11] A recent meta-analysis included almost 400 000 patients, estimated that adherence to secondary prevention of cardiovascular disease is only 57%.[26] Similarly, an evaluation of lifestyle changes among cardiovascular patients in five European countries indicated that only 50% of patients modified their lifestyles following recommendations.[9,27] Furthermore, there is evidence that only 50% of patients adhere to cardioprotective medications 1 y after commencing treatment. Of those taking the medications, about 50% follow the treatment sufficiently to gain a therapeutic benefit.[9,28] This is similar to the estimated prevalence of poor adherence to cardiovascular prevention and medications as reported by WHO.

A Cochrane systematic review evaluating the effectiveness of methods and strategies to promote patients' adherence in CR programs[16] demonstrated that there is a need to devise strategies to improve adherence in such programs and evaluate their effectiveness.[16] Telephone reminders to nonresponders were effective in increasing recruitment to trials.[17] As yet, this strategy has not been tested to improve adherence to trial interventions. Telephone reminder intervention could have a greater effect on nonintentional nonadherence in CR trials. This SWAT aims to assess the effectiveness of telephone reminders on participants' adherence within the cardiovascular host trial.

2.2 | Intervention and comparator

Participants who have been recruited and randomized to the intervention arm in the host randomized control trial will be further randomized for this SWAT. Patients in the intervention arm of the host trial will attend a 16-wk multidisciplinary lifestyle program, which includes healthy lifestyle changes such as smoking cessation, healthy food choices, increasing physical activity levels, and management of dyslipidemia, diabetes, and hypertension. The intervention program of the host trial program will consist of 16 sessions of 2.5 h each per week. Each of the weekly sessions will incorporate an individualized meeting between a multidisciplinary healthcare team (which includes a physiotherapist, dietitian, nurse, and physician) and each patient. The multidisciplinary team will review the progress of each patient and health goals. The weekly sessions will also include a 1-h group exercise program and an educational workshop.

Participants allocated to the intervention arm of this SWAT will receive telephone call reminders to attend the lifestyle intervention program in the host trial. To ensure standardization of the SWAT intervention, the telephone reminder is a scripted text, where the participant is reminded of their appointment date and time (Appendix). There will be 16 appointments (one appointment every week) for the lifestyle intervention program in the host trial. Therefore, the SWAT participants will receive a telephone call reminder every week over the 16-wk of the lifestyle intervention program. A telephone call reminder will be received two business days before each appointment. Up to three calls will be made if the line was busy or there was no answer. For confidentiality reasons, no messages will be left on voicemail.

Participants allocated to the control group in this SWAT will not receive any telephone reminders. At baseline assessment, patients will be given a schedule of their visits throughout the intervention period. These patients will have no telephone call reminders before their appointments.

2.3 | Method for allocating to intervention or comparator

Patients will be allocated to the telephone reminder intervention or to control group via sealed randomization envelopes, in an equal ratio of 1:1. The investigator will not be able to identify to which arm each patient will be allocated until the sealed envelope has been opened. The randomization scheme will be produced using the PROC PLAN procedure of the SAS software package.

2.4 | Definition of outcomes

2.4.1 | Primary outcome

- Adherence to the protocol of the host trial.

2.4.2 | Secondary outcome

- Level of adherence to the protocol of the host trial.
- Number of dropouts from the host trial.
- Time to drop out from the host trial.

In the context of this study, the primary outcome of adherence is defined as 100% attendance. The secondary endpoint of the level of adherence is measured as the percentage of attendance of all allocated visits, within the host trial.

2.5 | Analysis plan

Analyses will include appropriate descriptive analyses, and between-group comparisons using SPSS software. The primary analysis is the difference in adherence rate between those receiving the telephone reminders and those not receiving the reminders. This will be done using the chi-square test. Odds ratios and 95% confidence intervals will be calculated. The secondary analysis is time to dropout. This will be plotted by Kaplan-Meier survival curves and using the log-rank test to compare the two randomized groups. Cox regression will be used to adjust for age, gender, treatment allocation in the host clinical trial. Analyses will be undertaken on an intention-to-treat basis, using two-sided statistical significance at the 5% level. Data will be presented as proportions and percentages (adherence rate) or as the median, standard error, and interquartile range (time to the response).

2.6 | Possible problems

Ethical approvals for the SWAT and the host trial and have been sought and granted; therefore, we do not anticipate any ethical issues arising. The SWAT protocol has been registered in the SWAT Repository of the Northern Ireland Network for Trials Methodology Research (SWAT number 81). However, there is currently no evidence to support the effectiveness of telephone reminders to improve adherence in a randomized trial. A priori, we cannot pre-empt those telephone reminders may have an adverse effect on adherence.

Adherence in this study is presented as a trial methodology issue. However, adherence to the intervention might also be seen as an issue for intervention delivery. We argue that this SWAT is not designed to investigate the outcomes of the host trial intervention. The SWAT will demonstrate the effect of telephone call reminders on patient adherence rates, which could be used in clinical trials going forward. Nevertheless, if within the host trial, we do find that patients randomized to either arm of this SWAT study show improved outcomes within the intervention arm of the host trial, then we could assess if telephone reminders should be considered as part of the host intervention delivery into routine care. As such, it could have further implications on routine clinical practice.

CONFLICT OF INTEREST

None.

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APPENDIX

Reminder Call Script

This is [the hospital name/health network name/and study name] at [the department name], calling to remind you about an appointment for [patient's name] on [day and date] at [time] at [the cardiac rehabilitation center name]. Please arrive 15 min prior to your appointment time to allow the registration process. If you have any questions, do not hesitate to contact the study investigators on [phone number]. We look forward to welcoming you. Thank you.