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Usefulness of a run-in period to reduce drop-outs in a randomized controlled trial of a behavioral intervention

Michelle Ulmer [a,*], Donald Robinaugh [a], Jennifer P. Friedberg [a,b], Stuart R. Lipsitz [c], Sundar Natarajan [a,b]

[a] VA New York Harbor Healthcare System, New York, NY, United States
[b] New York University School of Medicine, New York, NY, United States
[c] Brigham and Womens Hospital, Harvard Medical School, Boston, MA, United States

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ABSTRACT

Objectives: We evaluated the usefulness of a simple run-in period to reduce drop-outs in a behavioral intervention to improve blood pressure (BP). In a pilot study where a run-in period was not used, we had a 25% drop-out rate.
Methods: A prospective evaluation was performed in the context of a blinded 3-arm randomized trial. Participants are eligible if they have uncontrolled BP on 2 consecutive visits. Potential participants are approached during a routine visit, informed, consented and enrolled. After a 1-month run-in period during which all participants receive a phone call to: i) verify phone availability, ii) get basic information on treatment, and iii) confirm the baseline visit, participants return for a baseline visit. They are then randomized to one of the three treatment arms: usual care, non-tailored counseling, or tailored counseling. Participants make return visits at 3, 6 and 12 months.
Results: Of the 1275 potential participants who received detailed study information, 301 consented to participate, of whom 226 were enrolled. During the run-in period, 73 withdrew consent and 153 participants were randomized; 7 subsequently dropped out. There were no differences ($p>.1$) between the 73 cancelled and the 153 randomized patients. There were fewer drop-outs than in the pilot study (5% vs. 25%, $p<.0001$).
Conclusions: The run-in period reduces the number of drop-outs after randomization and improves statistical power. In order to retain external validity, it is important to compare participants who remain in the study and those that cancel, and incorporate that in generalizing from the study.

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1. Background

A run-in period in a randomized clinical trial (RCT) can be defined as a specified period of time after enrollment and prior to randomization that is allotted to further measure a participant's eligibility and commitment to a study [1,2]. The purpose of a run-in period is twofold: 1) it allows the participant to think further about the study and their participation, and 2) it permits the researcher to gauge to what extent the participant will adhere to the requirements of the study. By including a run-in period in a trial, one can distinguish between those participants who are more committed to the study, and those who are not as committed, thus allowing the research team to estimate which participants will be less likely to drop out and more likely to complete the study [3]. One can make this distinction by giving the participant a small taste of what they will eventually do if they continue their participation in the

* Corresponding author. 423 East 23rd Street, Room 13109-C, New York, NY 10010, United States. Tel.:+1 212 686 7500x7927; fax: +1 212 951 5981.
E-mail addresses: michelle.ulmer@va.gov, meu202@nyu.edu (M. Ulmer).

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study. The logic behind doing this is that if participants have an idea of what the study entails before actually going through the study procedures, they can decide early on, prior to randomization, whether or not they would like to continue on with their participation given the responsibilities put forth in the run-in period.

When evaluating the outcomes of a RCT, it is of great importance to obtain complete information on randomized participants, and this can be achieved by retaining as many participants as possible. For studies that require multiple visits or interventions, a run-in period can increase the likelihood of follow-up and decrease the number of drop-outs or incomplete data after randomization, thus allowing for more precise statistical analyses, greater internal validity and stronger statistical power [4,5].

Though randomization is critical to a RCT, it is equally important that the subjects included in the analysis yield an unbiased assessment of treatment effects, i.e. that missing data is random [6,7]. Participant drop-out is probably the most common reason for non-random missing data and a central focus of any trial is to reduce drop-outs. While it may seem that drop-outs will not affect power in an intent-to-treat (ITT) design, since participants are analyzed as randomized irrespective of whether the participant received or complied with the whole treatment, the reality is more complex. Though ITT incorporates drop-outs, such analyses yield smaller, more conservative, treatment differences because drop-outs do not get the full intervention and the treatment effect is thereby diluted [8–10]. As an example, if 30% of participants drop out of the intervention arm of a placebo-controlled trial, only 70% can get the treatment to benefit from it. In this case, if the sample size estimate in the study design does not take into account this drop-out rate, then the trial could be under-powered.

Several papers describe different ways the typical placebo run-in period has been used when a new medication or a new use for a medication is tested [8,11–16]. In some of these studies, the run-in was used to screen and randomize adherent participants [17]; in others it was used to filter out those who respond to the placebo, to filter out those who do not respond to the active drug, or those who respond adversely to it, though these uses of the run-in have given rise to concerns [12].

Because of the complexities of standardizing and evaluating behavioral interventions, RCTs of behavioral interventions to target chronic medical conditions or adherence to medical regimens are more difficult to execute than drug trials. Of those behavioral trials that have been conducted, most (including the pilot study to the RCT described in this paper) had a large proportion of drop-outs. Since the concerns identified in drug trials [12] are not directly applicable to behavioral trials, and since drop-outs are such a problem, a run-in period may be well-suited for such trials. Few (if any) studies have empirically evaluated the usefulness of a run-in period in retaining participants in behavioral RCTs and its effect on external validity.

To evaluate the feasibility and potential effectiveness of a novel behavioral intervention to lower blood pressure, we conducted a pilot study, where 120 participants were enrolled and randomized. The pilot study was followed by a more rigorous randomized trial to test the same intervention (n=226 enrolled, n=153 randomized). The larger RCT is identical to the pilot study in that the same intervention and similar procedures were used. The pilot study differed in one important design aspect, however; the use of a run-in period was not implemented. Out of the 120 enrolled and randomized participants in the pilot study, only 90 completed the study at 6 months. Based on these numbers, the projected drop-out rate for the current study would have been 25%. We therefore decided to include a simple run-in period of 4 weeks in the current study in order to decrease the number of participant drop-outs after randomization.

In this paper, we assess the effectiveness of a run-in period in decreasing the number of participants who drop out, thereby increasing the amount of complete data and the number of participants who return for follow-up. We also evaluate and discuss the generalizability of the study results when a run-in period is implemented.

2. Methods

After seeing a 25% drop-out rate following randomization in the pilot study, we performed a prospective evaluation of a run-in period on the drop-out rate after randomization in the context of a blinded 3-arm randomized trial. In particular, we hypothesized that the run-in period would reduce the 25% drop-out rate seen after randomization in the pilot study to 10%. With 120 participants enrolled and randomized in the pilot study, we needed 120 participants randomized after the run-in period in the current RCT in order to test if the run-in period truly reduces the drop-out rate after randomization to 10%. To determine the significance of this reduction, Fisher's exact test with 80% power and a 2-sided .05 significance level was used.

These analyses are part of a larger randomized controlled trial of a telephone-delivered behavioral intervention for enhancing adherence to treatment and improving blood pressure in participants with uncontrolled hypertension. The specific purpose of the clinical trial is to compare the effect of a tailored behavioral intervention on blood pressure, diet, medication, and physical activity adherence to that of a non-tailored behavioral intervention and treatment as usual.

We enrolled participants to this study from the VA New York Harbor Healthcare System. In order to be eligible for the study, the participants must have had uncontrolled hypertension as defined by the Joint National Committee [18]. In addition, a potential participant had to be at least 21 years old and must have been prescribed an antihypertensive medication at least six months prior to enrollment. A potential participant was excluded if he/she had several severe comorbid diseases. Participants were also excluded if they planned to relocate out of the New York City area during the course of their potential participation (1 year), or if they did not have a working telephone.

A research assistant (RA) approached a potential participant during a routine health care visit to provide an explanation of the study if he/she met all of the inclusions and none of the exclusions. If the individual was interested in participating, the RA then screened him or her by administering a series of questions and taking 3 BP measurements. Upon further evaluation, if the participant still met the inclusion/exclusion criteria and the average of the