Author's response to reviews

Title: A multicenter randomized controlled trial of aftercare services for Severe Mental Illness: study protocol

Authors:

Ahmad Hajebi (A-hajebi@tums.ac.ir)  
Vandad Sharifi (vsharifi@tums.ac.ir)  
Mohammad Ghadiri vasfi (ghadiri_mohamad@yahoo.com)  
Maziar Moradi Lakeh (m_moradi@tums.ac.ir)  
Mehdi Tehranidoost (tehranid@tums.ac.ir)  
Masud Yunesian (yunesianm@yahoo.com)  
Homayoun Amini (aminihom@gmail.com)  
Arash Rashidian (arashidian@tums.ac.ir)  
Seyyed Kazem Malakouti (malakoutik@gmail.com)  
Yasaman Mottaghipour (ymottaghipour@gmail.com)

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Title: A multicenter randomized controlled trial of aftercare services for severe mental illness: study protocol

Authors: Ahmad Hajebi, Vandad Sharifi, Mohammad Ghadiri vasfi, Maziar Moradi Lakeh, Mehdi Tehranidoost, Masud Yunesian, Homayoun Amini, Arash Rashidian, Seyyed Kazem Malakouti and Yasaman Mottaghipour

Dear Deesha Majithia

Executive Editor, Bio Med Central

Thank you for your kind attention. The reviewers’ comments were very helpful; we made revisions based on their thoughtful comments that led to rewriting some parts of the manuscript. In addition it should be noted that we added the name of some authors who had significant contribution to the study and their names were ignored in the original manuscript.

You can find below our detailed responses to the reviewers comments.

Best regards,

Ahmad Hajebi

Reviewer 3:

• Major revisions:
• Comment: The aftercare intervention group seems to have further subgroups—people who receive a telephone reminder + facility based delivery of aftercare intervention components, those who receive home based after care and people who can move between the groups (see Attachment 1). Though the authors have clubbed these three subgroups, there are problems in considering them as a homogenous group. Firstly, compliance or engagement with treatment is consistently associated with a number of socio demographic, health system related and illness related associations in people with severe mental illnesses. The non random allocation of participants into the 2 groups makes it very likely that systemic differences will confound the interpretation of the results. Similarly, people who potentially cross from one intervention to the other will confound the analysis, especially since there is no a priori plan to deal with this scenario.

• Response: We have had no predefined subgroups inside the aftercare intervention group. Home care and telephone follow-up are seen as components of a whole care program. We randomly assigned patients into two groups of aftercare program and control group, and then will compare the outcome of this group as a whole with the control group. However, patients inside the intervention group may receive either home care or telephone follow-up, not randomly but based on their needs. But, as mentioned by the reviewer, it is reasonable to assume that a “number of socio demographic, health system related and illness related factors” contribute to the results. Taking this into account we have considered a stratified randomization model to randomly allocate a patient with features that necessitates one model of care (i.e. home care) to be allocated evenly into intervention and control group at the start of the program. For example those with repeated hospitalization (that should receive homecare in aftercare program) were divided randomly into aftercare and control groups; in other words, there were equal number of people with such features in each group. Therefore, we have tried to minimize systematic differences between aftercare and control group. In other words we could say that we are going to test the effectiveness of a whole care program (that includes different components) with a control group of usual care. Crossing from one intervention to the other “inside” the aftercare program will not bias the results as this is another component of the program. This clarification was made in the manuscript.

• Comment: This is a non pharmacological clinical trial where the intervention is being delivered by more than one care provider in 3 different sites. In such trials, it is necessary that the clustering effect between care providers and sites are accounted for estimating the sample size. This has not been done in the protocol and needs to be incorporated.

• Response: The study was done independently in three different settings and the results for each site will be reported separately. So, we did not consider cluster effect in calculating sample size. It can be a limitation for multisite analysis.
• Comment: There is limited information available to make a clear judgment about the methods used to address bias at various stages of the study. For example, people were screened and approached for recruitment in the study 2 days in a week – this introduces the possibility of selection bias and the lack of generalizability to the larger universe of patients.

• Response: In each occasion twice a week “all” patients that were hospitalized in the last few days were screened and recruited if met criteria.

• Comment: Similarly, the method of random block sequence generation for allocation, allocation concealment and implementation process needs further details to convey the risk of unmasking at this stage.

• Response: Patients were divided randomly into two groups of intervention and control (TAU). There was equal allocation of participants between arms of the study (allocation ratio 1:1). Randomization was provided by an independent statistician at the medical university. Eligible patients were assigned to intervention or control (TAU) groups by stratified balanced block randomization method with allocation concealment. There was a psychiatrist at each center responsible for concealment procedures. After assignment, each patient of intervention group was classified according to the severity criterion by the research coordinator and then received the needed mode of care: either home care or telephone prompts for outpatient attendance. Therefore, the latter was not random but based on patient’s needs. However, to ensure comparability of intervention and control groups with regard to severity of patients’ illnesses we did a stratified randomization procedure. Patients were first categorized according to its severity that included measures for frequent admissions and/or treatment compliance. Then patients in each group of severity (high vs low) were randomized into aftercare or treatment-as-usual groups. For example, patients who had an illness with high severity that required home care (in the intervention group) were evenly randomized into two groups.

• Comment: Also, since participants and care providers are unblinded during the study, ascertainment or reporting bias is very likely, especially since care providers are involved in outcome measurements. A completely separate and independent group of researchers are recommended together with further description of how unblinding even when using dedicated researchers is to be dealt with.

• Response: We were unable to blind the care providers and the subjects; therefore, we agree that bias in reporting is possible. However, we chose
assessors not from care providers to minimize this form of bias.

- Comment: There is little detail on how the fidelity and quality assurance of the intervention is to be monitored across the sites/practitioners. This is an essential component of multi site trials of complex, non pharmacological intervention trials and needs to be specified clearly. It might be useful to consider collecting process indicators to describe the key stages of the intervention delivery (number of home based or facility based sessions delivered, number and % who drop out or refuse intervention etc) as this information will be necessary to compare the similarity of the intervention delivery across the 3 sites.

- Response: A single team trained all the care providers and evaluators in different sites with a single training module. A single guideline was used by all care providers. The supervisors in each center used the same protocol for supervision that consisted of weekly meetings, checking the data collection procedures, supervision of training sessions, etc. The same supervision procedure was employed for the whole process of case recruitment and data collection. Detailed procedures were added to the manuscript.

- Comment: The section on statistical analysis is rather bare and needs much greater elaboration. Specifically, the details of the descriptive statistics needs to be detailed, the method of dealing with missing values through imputation needs to be specified, any potential subgroup analysis (by site or gender etc) needs to be spelt out as well as more details of the economic analysis planned.

- Response: Descriptive summaries of socio-demographic and clinical data will be provided for all subjects at different time points. These include means and standard deviations, or proportions. The clinical ratings will be summarized in terms of the total score, and the proportion of patients improving from baseline.

- Comment: Obtaining informed consent for participation from subjects who are just recovering from an acute episode of schizophrenia, severe enough to warrant admission, poses complex ethical and procedural challenges. The informed consent procedure needs to account for and describe how these challenges (like decisional capacity assessment, methods of information provision to address cognitive deficits, literacy levels etc) need further elaboration.

- Response: Patients who met the inclusion criteria were informed with verbal and written information regarding the study and then both patients and their guardians were asked to give a written informed consent if they agreed to participate in this study. This was done by the research coordinator at each
center. Consent procedures had been designed in a non-technical language. It was matched to the literacy levels of the participant and caregiver and was designed in a manner to increase the intake of information. For those patients who meet all inclusion criteria, the research coordinator established a meeting with the patients and their families. In the meeting he/she explained the trial and the purposes of the trial and tried to respond to all their questions. Then he asked the patients and the caregivers whether they were interested in participating in the trial. If both were interested to participate, he took written consent. If not, they excluded from the trial and received treatment as usual. The consent procedures and interventions have been approved by the Ethical Committee in Tehran University of Medical Sciences. Subjects had the right to quit whenever they like it. Those who did not consent to participate in the study received the routine and conventional care. These details were added to the manuscript.

• Comment: Similarly, specific mention needs to be made of the serious adverse events monitoring (death, suicide attempt, serious medication related side effects) and reporting process as well as details of the trial monitoring committee that will oversee the methodological and ethical standards of the trial, as well as take decisions on any interim analysis and trial termination.

• Response: In each center there was an external supervisor assigned from Vice Chancellor of Research who oversaw the whole procedure of research and he received progress reports of the project in each center and if necessary he had to make decisions with regard to unwanted events. Monitoring included cases of readmissions and every adverse event such as death and suicide.

• Minor essential revisions:

• Comment: Overall, the authors would need to follow the CONSORT statement for the reporting of non-pharmacological trials in further revisions of the protocol. There is a need for further language edits (especially around the terminology used for subjects at various times in the protocol) and to shorten the description of the intervention components.

• Response: Modifications were done.

Reviewer 2:

• Comment: The authors should see to (again) that the protocol adheres to CONSORT guidelines.

• Response: Modifications were done.

• Comment: Please be clear about number ingredients of the intervention and their contents. E.g. on p. 4 it says “It has three main parts…” followed by a description of 4 parts. Later on (p. 13), the description of the intervention has
different parts again, including “a program for rehabilitation” which has not been mentioned before.

• Response: Aftercare services have three main components but the first part (treatment follow-up) consists of two modes of care: home care and telephone follow-up. As we have explained in the text, the participants have received one of them based on their need.

The text in the P. 4 was corrected as follow: It has three main components; treatment follow-up, family psychoeducation, and social skills training.

The text in the p. 13 was corrected as follows: The major rehabilitative component of the service included social skills training that was started after the period allocated to family psychoeducation (usually after 3 months of inclusion in the study).

• Comment: p. 8: Please specify how the Iranian Ministry of Health can have designed that trial (p. 8). What was the authors’ role in this? Are they employed by the MoH?

• Response: Ministry of Health ordered a protocol for aftercare services and provided the grant to the University to be granted to the authors as the research budget.

• Comment: Aims and endpoints should be the same. E.g. there is an apparent conflict between “This study aims at evaluating the clinical effectiveness…” (P: 7, “overall aims”) and primary outcome length of stay (p. 11).

• Response: We think that “length of hospital stay” could be considered as one of the most important indicators for evaluating the clinical effectiveness of services, because re-hospitalization usually follows relapse or recurrence of signs and symptoms, particularly in patients with severe mental illness.

• Comment: p. 11, last item: “direct cost-effectiveness…” cannot be a secondary outcome measure. Authors should specify how they will collect costs.

• Response: We corrected the paragraph as follows: The primary outcome measures were the length of hospital stay and any psychiatric rehospitalization during the 12 months post discharge. The secondary outcome measures included: 1) symptom severity, 2) clinical global impression of the illness, 3) global functioning, 4) quality of life, and 5) patients’ satisfaction with service. We also performed a direct cost-effectiveness analysis.

In addition, we added an explanation to the “planned analysis” section as follows: We calculated all direct medical and non-medical costs of care from a societal point of view. To do that, total costs of care (not just out-of-pocket payments) were considered. Medical costs included costs of hospitalization, outpatient and community visits, family psychoeducation, social skills training, medicine, and complementary-alternative therapies in both groups and also all payments for providing specific healthcare of the interventions. Non-medical costs included
costs of transportation of patients, caregivers and healthcare teams (in the intervention group). We divided incremental direct costs (Costs in the intervention group minus control group) by incremental effects (based on primary and secondary outcomes) to calculate Incremental cost-effectiveness ratio (ICER).

• Comment: In general methods appear weak, e.g.: a) What is the rationale for the calculation of sample size (Cohen)?

• Response: We corrected the text in the sample size calculation as follows:

In a study on the efficacy of home care service [64], it was shown that the mean hospitalization days in the home care group was about a third of that in the treatment as usual group (14.5 vs. 41.7 days). Also in an unpublished study (Vandad Sharifi, Personal Communication), we found that mean hospital stay of patients with severe mental disorders equals to 45 days with the SD of 18 days. For the present study we aimed for a more conservative and still important difference. We hypothesized that the home care program leads to at least 10 days reduction in hospital stay (X1-X2=10, SD=18, Cohen's d=0.6). Sample size was estimated 45 per group; assuming about 30% losses to follow-up, sample size was calculated 60 per group (in total: 120). In one of the centers (Roozbeh hospital) the sample size was 80 per group (in total: 160), because the case load was higher than the other centers and we had more chance for recruiting more patients.

• b) The primary outcome is LOS and not a repeated measure and thus cannot be used in repeated measures analysis.

• Response: We corrected the text in “planned analysis” as follow:

LOS was assessed in each period of follow-up; we analyzed LOS both as the cumulative hospital stay (using t test) and as the stay in each follow-up period. The second analysis was performed by repeated measures analysis.

• c) I doubt that “qualitative” data can be compared by a chi square test.

• Response: We corrected the text on p. 15 as follows: We replaced “qualitative data” with “qualitative variables”.

• d) ICERs per se cannot be calculated from cost data alone, but express the relation between cost and outcome.

• Response: Modification was done. Please see the new paragraph in “planned analysis calculation”

• e) Be clear on the randomization procedure. It is not possible that “the patients were then divided… by the psychologist” (p. 10).

Response: The text was corrected and clarified.

• Comments: Writing is not acceptable. Just to give a few examples:
• a) “Therefore, aftercare setting … “(p. 2)

• b) “Aftercare services were included treatment …” (p. 2).

• c) “Those who did not consent… was conducted…” (p. 9).

• d) “… questionnaire … designed by research team.” (p. 11).

• e) “Also, the trial sought to understand…” (p.15: nothing has been understood yet)

• f) “Determining… will help policy makers in ministry of health for further planning.” (p. 15; you might want to address a wider audience)

• Response: All corrections were made accordingly. Also manuscript was edited for vocabulary and grammatical errors.

Reviewer 1:

• Comment: The rationale for not including medication delivery/supervision should be provided since a critical influence, at least for ACT, in preventing psychiatric hospitalizations

• Response: One of the roles of the general practitioner in the home care team was medication delivery/supervision. In each home visit he/she assessed the signs and symptoms of the illness and side effects. Then he/she reordered or changed the medication treatments as needed.

• Comment: An analysis plan based on three groups (less compliant and more compliant in the experimental arm) and the control group could be provided.

• Response: In this study home care and telephone follow-up were the components of a whole care program. Inside the intervention group patients received home care or telephone follow-up not randomly but based on their needs. We are going to test the effectiveness of a whole program (including different components) with a control group of usual care. According to the protocol the patients could cross from one intervention component to another one “inside” the aftercare group. In addition, the sample size has been calculated for the two main groups, intervention and control groups, and it is not enough for subgroup analysis.

• Comment: More recent references are available on assertive community treatment (ACT) and social skills training although they may not provide findings which differ from the earlier ones cited

Response: The results of a recent paper on ACT and social skills training were added to the text.

• Comment: The follow-up strategy for the study patients is strong, but data about refusals and “loss to follow-up” could be included relevant to reader
understanding of acceptability of the study and the final sample size.

• Response: At the present time the data of “loss to follow-up” is not available.