Indian Journal of Hygiene and Public Health
Publication of All India Institute of Hygiene & Public Health, Kolkata.
ISSN : 2455-1813

Short Communication

Methodological Lacunae in Recruitment of HIV Positive Persons in Randomized Controlled Trials

Arun Kr. Sharma, Vikas Meena, O. P. Rajoura, Kuldeep Kumar

Background

Recruitment of patients in a Randomized controlled trial (RCT) is crucial to the success of the trial. The sample selection and sample size estimation is based on previously reported research studies. An RCT was conducted to assess the effectiveness of mobile text messaging in improving adherence to highly active anti-retroviral therapy in an ART unit of a tertiary care hospital. In this paper we examined the impact of recruitment process and sampling on the outcome of the trial.

Methods

The required sample size for recruitment in the RCT was calculated based on a reported defaulter of 27% in a previous Indian study. In order to attain an effect size of 0.3 for 1 degree of freedom, the required sample size in each arm was 44. We recruited 60 persons in each arm taking into account 20% drop out and 15% mortality rate.

Results

Analysis of data showed that the initial assumptions were not matching. Loss to follow up due to death and attrition were 4.1% and 6.6% respectively. Using person months of observation, corresponding loss was only 2.6% and 1.2% respectively. Default rates in the intervention and control arms were 1.6% and 2.3% respectively (not significant).

Conclusion

The default rates were much lower than the a priori hypothesized values. The study suggests that selection of cases based on data from a different center may result in wrong estimation of

*** Director Professor, * Ex. Junior Resident, * Associate Professor**
Department of Community Medicine, University College of Medical Sciences, Delhi
*** Associate Professor, Department of Medicine, University College of Medical Sciences, Delhi**
Corresponding Author: Arun Kr. Sharma, Email: arsharma62@gmail.com

sample size.

Key Words: Randomized Controlled Trial, recruitment, HIV/AIDS, defaulter

Introduction

Anti Retroviral Therapy (ART) has improved survival in HIV/AIDS patients. Sustained adherence to ART is critical for durable viral suppression to reduce AIDS related mortality and morbidity.[1,2] Studies from India have shown adherence ranging between 57% and 94%.[3,4] However for ART to have maximum effect, greater than 95% adherence has been suggested. Thus there is a need to improve ART adherence. Mobile information technology is widely being used to improve health service delivery. In India, telecommunication industry is the world's fastest growing industry with 904.5 million mobile phone subscribers as of 31 October 2013.[5] Mobile phones are now being used to deliver automated SMS to remind patients to take their medicines in chronic diseases like hypertension[6], Tuberculosis[7], HIV infection[8], and diabetes mellitus.[9] So far only one study by Rodrigues et al showed that SMS text messaging improved adherence to ART in Bangalore.[8] Therefore, we considered it pertinent to examine the role of SMS text messaging in improving adherence to ART in a tertiary care hospital in Delhi, India. The findings of our study have been reported in a dissertation for MD degree submitted by Meena.[10] Randomized controlled trials are the gold standard of intervention research. It provides best evidence for the outcome of an intervention as compared to other study designs. Conventionally the RCT is designed and methodology is developed based on the available published research in the domain of the health condition and the intervention in question. However, in this paper, our objectives were to examine the limitations and lacunae of assembling the cohort for the RCT study and its impact on the results.

Materials and Methods

An open label randomized controlled trial design was used. Adult HIV positive persons attending the ART clinic at a tertiary care hospital in Delhi were the study subjects.

The inclusion criteria were

1. Diagnosed with HIV infection and currently on ART for more than one month.
2. Have a cell phone of their own.
3. Familiar with usage of SMS text messaging.
4. Ability to read and interpret SMS text messaging.

The exclusion criteria were

1. Pregnant and on ART only due to pregnancy (i.e., will no longer be prescribed ART after delivery)
2. Unable to provide assent or consent
3. Critically ill
4. Residence outside NCR of Delhi
5. Shared mobile phone

Sample size:Assuming an effect size of 0.3, for 1 degree of freedom, and a priori fixing of type I error at 5% and type II error at 20%, the total sample size required for testing the null hypothesis "SMS based text messaging system does not improve adherence to ART", is 88. Adding a loss to follow up of 20% (18) and a mortality of another 15% (14) (worst case scenario), initially 120 patients were recruited. Sixty patients were allocated to each of the intervention and control arm using random allocation technique. Randomization was carried out by generating random number table using SPSS 17.0 after entering registration number of patients in the spreadsheet. Investigator did not ask from respondents about receiving their SMS during the study period. The study was conducted from December 2011 to January 2013.

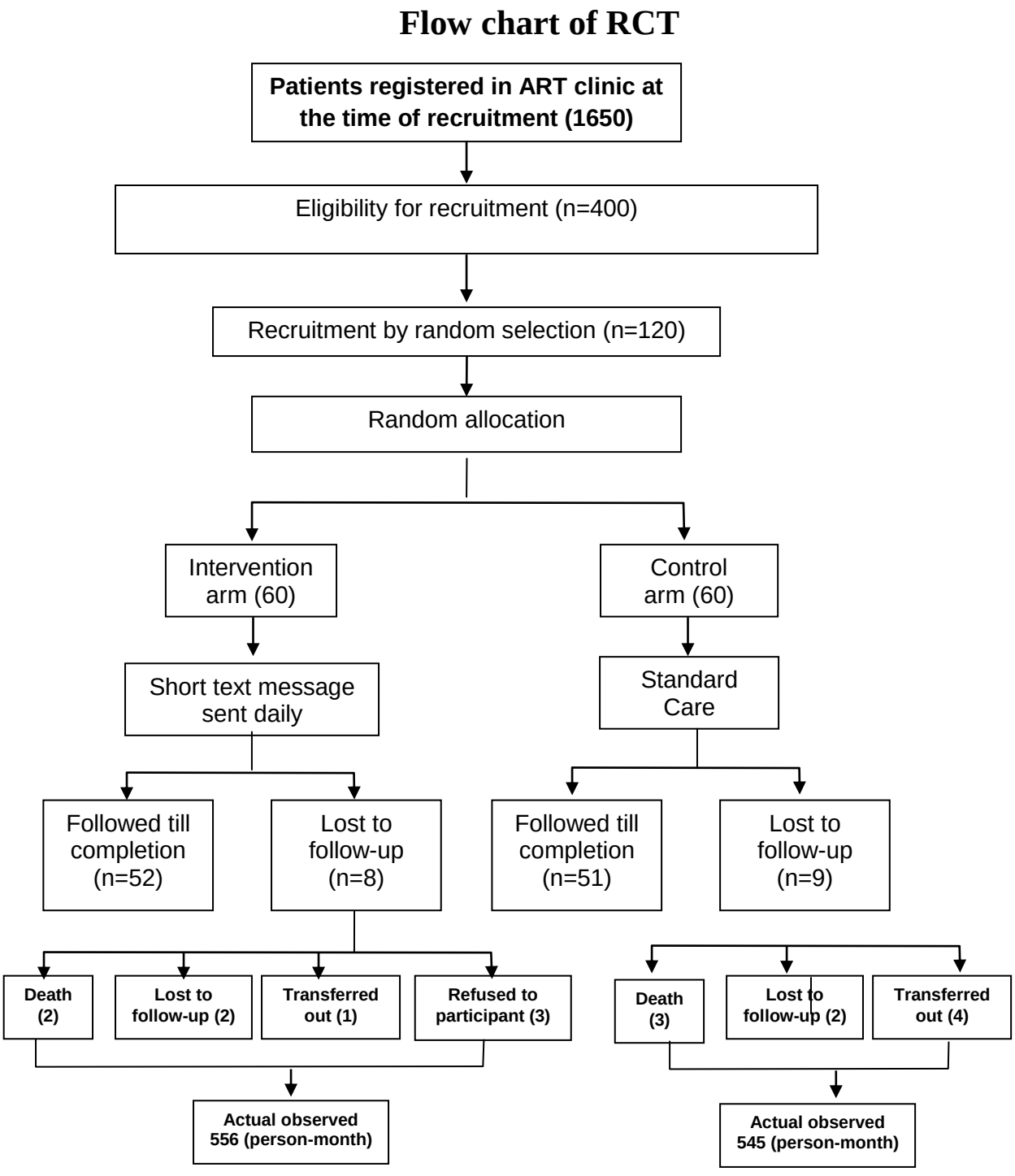
Informed consent: All eligible patients were individually given an initial verbal description of the proposed study by the investigator. Interested individuals were then presented with a written informed consent form. Consent was obtained by the investigator, who was not involved in the routine clinical care of the patient.

Ethical consideration: Participation was purely voluntary. Since intervention did not involve medication, there was no risk of side effects, hence there was no question of stopping the trial midway. The trial was not to result in any additional expenditure on the part of the patient. The study was approved by the institutional ethical committee for research on human beings. This was a parallel group study design to assess the effects of adding daily SMS text messages through mobile phone as reminder for taking ART. ART clinic attendees were screened initially to identify eligibility. The ART clinic registration no. of these patients was used for selection, randomization and allocation to study and control arm. The registration numbers were entered into SPSS and a table of random numbers was generated using the same software.

There was no blinding of researcher or patient in this study, however, data collection tool did not have any identifier to show whether the patient belonged to intervention or the control arm and the interviewer did not ask if the patient received any SMS. The intervention arm consisted of usual care and SMS text message and control arm consisted of usual care.

After initial screening, base line data of all eligible persons were recorded on a structured interview schedule. It contained information regarding name, age, sex, phone number, address. Socio-demographic factors likes surrounding environment, standard of living etc. Information was collected regarding knowledge about the importance of adherence to ART therapy and their adherence level by asking about the missing dose of medication in last one month, reasons for poor adherence. After obtaining baseline information, patients were assigned to intervention or control arm. Patients of the intervention arm were sent text message through SMS once daily. Each participant was contacted once every one month for a period of ten months to assess the adherence to ART.

Figure 1 shows the flow chart of the RCT:



Results

At the time of developing the study design, based on a previous research conducted in Mumbai reporting 27% default rate[11], we expected that out of 1650 patients on ART at the ART clinic of the tertiary care hospital; will have more than 400 defaulting patients. But once we started recruiting patients for the study we found that only about 400 patients fitted the inclusion criteria as a large number of patients were either illiterate or were not having mobile phone or simply refused to participate in study. Out of these 400, only 37 patients reported defaulting in medication during the recruitment period, therefore we decided to include some patients with regular adherence assuming that default may happen subsequently. In all, 120 patients were recruited for the study and randomized into intervention (n=60) and control (n=60) arms. The proportion of non adherence was similar in intervention and control arm ($p > 0.05$). Potentially, each of the 120 patients if followed for 10 months would have given a total of 1200 person-months of observation. But due to death, transfer out, loss to follow up and voluntary withdrawal by 5, 5, 4 and 3 patients respectively at different stages of the study, effectively only 1101 person-months follow up was possible, The total observed periods in intervention and control arm were 545 and 556 person-months respectively. A total of 14194 messages related to reminder about ART were delivered to all the recruited patients of intervention arm, but no messages were sent to the patients in control arm, however all the patients continued to get the usual support from the ART clinic as per protocol. Month wise status of defaulter is given in the Table 1. Table 2 shows the number of days of default, that the patients cumulated prior to recruitment in the study.

Table -1. Status of defaulter in each month

Defaulter	**May 2012**	**June 2012**	**July 2012**	**Aug. 2012**	**Sept. 2012**	**Oct. 2012**	**Nov. 2012**	**Dec. 2012**	**Jan. 2013**	**Feb. 2013.**
Intervention (60)	1	1	0	4	2	1	0	0	0	0
Control (60)	4	3	2	1	0	1	2	1	0	0

Table-2.Numbers of days of defaulter in patients who had history of default before recruitment.

Group	No. of patients	No. of days of default
Intervention (n=60)	18	24
Control (n=60)	19	64

Table 3 shows the default rate calculated per hundred person months. No statistically significant difference was observed in default rate among intervention and control arms (p>0.05).

Table-3. Default rate per hundred person-months in both intervention and control arms.

Arm	Expected person-months	Actual person-months (%)	Actual default person-months (%)	Default Per hundred person-months
Intervention	600	556 (92.6)	10 (1.6)	1.79
Control	600	545 (90.8)	14 (2.3)	2.56

Chi squared: 0.447, two tailed p value: 0.5037

Discussion

Following observations emerged from the results of this study.

1. Defaulter rates vary from centre to centre and hence using default rates from one centre may give incorrect estimate of the required sample size.

2. During data collection, we observed that treatment adherence was higher among the patients because of additional efforts made by the medical officer, counsellor and support staff at the centre in explaining the importance of treatment adherence to the patients.

3. Since patients recruited into the study were those having a mobile phone, having adequate knowledge of English language to read and understand text messages and a willingness to participate in research work (thus better educated), these patients were more likely to be conscious about need for regular drug intake and hence the baseline default rate was much lower in the recruited group.

4. Follow up and monthly reminder for collection of drugs by the ART clinic for defaulting patients as a routine activity also improved treatment adherence.

5. In such settings, role of SMS text messaging may not be very important in improving treatment adherence.

Conclusion

1. Sample size estimation is more accurate if based on data from the study site itself
2. A pilot study or examination of the treatment adherence pattern should be carried out prior to embarking on a new intervention.
3. Heterogeneity in treatment adherence rates in different centres suggested that, the intervention should be contextual and evidence based and not empirically planned.

References

1. Ickovics JR, Cameron A, Zackin R, Bassett R, Chesney M, Johnson VA, Kuritzkes DR; Adult AIDS Clinical Trials Group 370 Protocol Team. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. AntivirTher 2002;7(3):185-93.
2. Lima VD, Harrigan R, Bangsberg DR, Hogg RS, Gross R, Yip B et al. The combined effect of modern highly active antiretroviraltherapy regimens and adherence on mortality over time. J Acquir Immune DeficSyndr 2009; 50(5): 529-36.
3. Naik E, Casanas B, Pazare A, Wabale G, Sinnott J, Salihu H. Cost of treatment: The single biggest obstacle to HIV/AIDS treatment adherence in lower-middle class patients in Mumbai, India. Indian J Sex Transm Dis. 2009;30:23–7.
4. Sarna A, Pujari S, Sengar AK, Garg R, Gupta I, Dam J. Adherence to antiretroviral therapy and its determinants amongst HIV patients in India. Indian J Med Res. 2008;127:28–36.
5. India's telecom subscriber base rises to 933 million. The Times of India. Retrieved 15 May 2014. Retrieved from http://timesofindia.indiatimes.com/tech/tech-news/Indias-telecom-subscriberbase-rises-to-933-million/articleshow/35024488.cms (accessed on 15/08/2015)
6. Bobrow K**,** Brennan T**,** Springer D**,** Levitt NS**, R**ayner**,** Namane M**,** Yu LM**,** Tarassenko L, Farmer A. Efficacy of a text messaging (SMS) based intervention for adults with hypertension: protocol for the StAR (SMS Text-message Adherence suppoRt trial) randomised controlled trial. *BMC Public Health* 2014, **14**:28 doi:10.1186/1471-2458-14-28

7. Nglazi MD**,** Bekker LG**,** Wood R**,** Hussey GD, Wiysonge CS.Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review. *BMC Infectious Diseases* 2013, **13**:566 doi:10.1186/1471-2334-13-566.
8. Rodrigues R, Shet A,Antony J, Sidney K, Arumugam K, Krishnamurthy S, D'Souza G, DeCosta A. Supporting Adherence to Antiretroviral Therapy with mobile phone reminders: Results from a cohort in South India. PLoS One. 2012; 7(8): e40723.Published online 2012 August 27. doi: 10.1371/journal.pone.0040723
9. Riaz T, Riaz H, Hussain SA, Kherani D. SMS Reminders-future in self care management of diabetes mellitus. DiabetolMetabSyndr. 2012; 4: 31. Published online 2012 July 4. doi: 10.1186/1758-5996-4-31.http://www.dmsjournal.com/content/4/1/31 accessed on 23 January 2013.
10. Meena VK. Effectiveness of mobile text messaging in improving adherence to highly active anti-retroviral therapy: A Randomized Controlled Trial. Thesis for the degree of Doctor of Medicine (Community Medicine). University of Delhi 2013.
11. Shah B, Walshe L, Saple DG, Mehta SH, Ramnani JP, Kharkar RD et al. Adherence to antiretroviral therapy and virologic suppression among HIV-infected persons receiving care in private clinics in Mumbai, India. Clin Infect Dis 2007; 44(9): 1235-44.

Figure 1: Flow chart of RCT

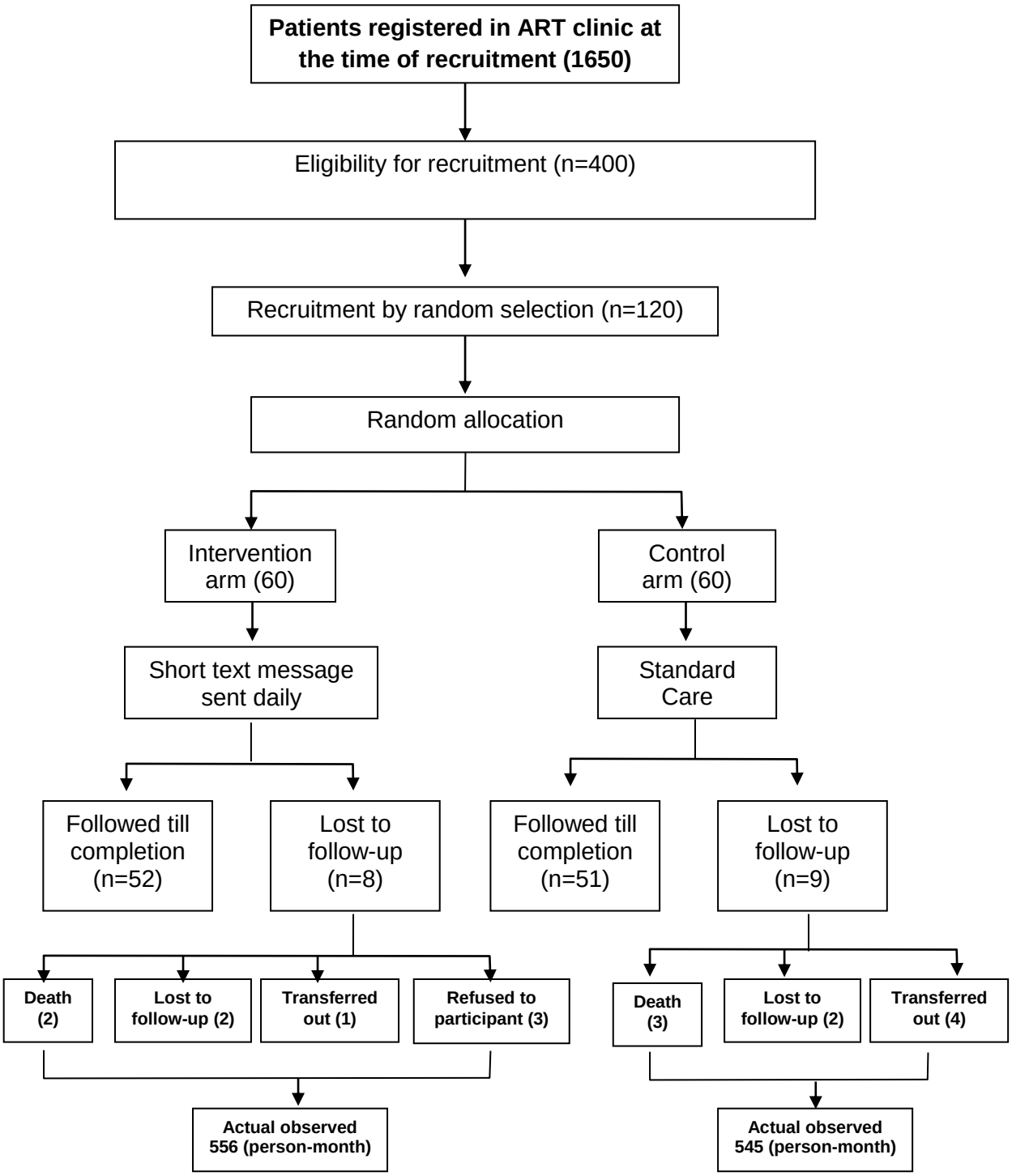


Table -1. Status of defaulter in each month

Defaulter	**May 2012**	**June 2012**	**July 2012**	**Aug. 2012**	**Sept. 2012**	**Oct. 2012**	**Nov. 2012**	**Dec. 2012**	**Jan. 2013**	**Feb. 2013.**
intervention (60)	1	1	0	4	2	1	0	0	0	0
control (60)	4	3	2	1	0	1	2	1	0	0

Table-2.Numbers of days of defaulter in patients who had history of default before recruitment.

Group	**No. of patients**	**No. of days of default**
Intervention (n=60)	18	24
Control (n=60)	19	64

Table-3. Default rate per hundred person-months in both intervention and control arms.

Arm	**Expected person-months**	**Actual person-months (%)**	**Actual default person-months (%)**	**Default Per hundred person-months**
Intervention	600	556 (92.6)	10 (1.6)	1.79
Control	600	545 (90.8)	14 (2.3)	2.56

Chi squared: 0.447, two tailed p value: 0.5037