Available online at www.sciencedirect.com
ScienceDirect
Contemporary Clinical Trials 28 (2007) 288–294
Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

Factors associated with loss to follow-up in a large tuberculosis treatment trial (TBTC Study 22)

Donna Sepulveda Conwell [a,*], Ann Mosher [b], Awal Khan [c], Jan Tapy [d], Laurie Sandman [e], Andrew Vernon [c], C. Robert Horsburgh Jr. [f]
the Tuberculosis Trials Consortium (TBTC)

[a] *Veterans Affairs Medical Center, Washington, DC, USA*
[b] *Veterans Affairs Medical Center and Duke University Medical Center, Durham, NC, USA*
[c] *Centers for Disease Control and Prevention, Atlanta, GA, USA*
[d] *Department of Public Health, Denver Health and Hospitals, Denver, CO, USA*
[e] *Bellevue Hospital, NYU School of Medicine, New York, NY, USA*
[f] *Boston University School of Public Health, Boston, MA, USA*

Received 23 February 2005; accepted 21 September 2006

Abstract

Introduction: Loss to follow-up in clinical trials compromises achievement of study goals. We evaluated factors associated with loss to follow-up after completion of treatment phase in a large tuberculosis treatment trial (TBTC/USPHS Study 22) in the U.S. and Canada.
Methods: Patients who were lost to follow-up were compared to those who reached a study end-point or successfully completed follow-up. A generalized estimating equation model was used to combine patient-specific and site-specific factors.
Results: Of 1075 patients enrolled, 965 (89.8%) reached a study end-point, died, or completed the 2 year post-treatment follow-up phase, and 110 (10.2%) did not. Multivariate analysis showed the following factors to be independently associated with loss to follow-up: birth outside USA/Canada (OR 2.07, 95% CI 1.25–3.40, $p=0.005$), history of homelessness (OR 1.94, 95% CI 1.00–3.80, $p=0.05$), enrollment at a health department (OR 2.71, 95% CI 1.27–5.79, $p=0.010$), and use of any kind of incentive (cash/cash equivalent) during treatment phase (OR 3.04, 95% CI 1.73–5.33 $p=0.0001$).
Conclusions: Cultural or linguistic factors and lack of stable housing contribute to loss to follow-up. Attention to these factors could improve long-term retention in clinical trials. Enrollment at a health department and use of incentives during treatment phase may be markers for other factors leading to loss to follow-up.

Keywords: Loss to follow-up; Tuberculosis; Retention in clinical trials; Attrition in clinical trials

1. Background

Successful completion of clinical trials depends on satisfactory recruitment and retention of study participants. Even with successful recruitment and treatment adherence, retention of an adequate number of participants to the end of

* Corresponding author. Infectious Diseases Section (151B), Veterans Affairs Medical Center, 50 Irving Street, NW, Washington, DC 20422, USA.
E-mail address: donna.sepulveda@med.va.gov (D.S. Conwell).

1551-7144/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.cct.2006.09.003

study follow-up is essential for generation of valid results. Participant attrition at any stage of a clinical trial has the potential to compromise the achievement of study goals [1–3]. It threatens the internal validity and representativeness of study results [3,4]. More importantly, attrition is a potential source of bias in clinical trials [2,5,6]. Lost participants may be different from those retained with respect to the outcomes being studied. The greater the loss to follow-up, the less certain one can be that the study outcomes are representative of the entire study population. The bias this introduces can work in two directions [7]. Lost participants may be either sicker or healthier than those retained for follow-up. The effect of such a bias would be to spuriously increase or decrease the frequency of negative study outcomes.

In addition, the duration of a trial may need to be extended if there is substantial loss to follow-up to achieve the sample size needed for statistical power. Thus, responding to participant loss can consume considerable effort, time and money [8,9]. It is vital that factors which act as barriers to study completion be identified early. Appropriate interventions can then be developed to prevent loss of participants.

Published literature places greater emphasis on recruitment and adherence with study treatment than on retention, even in clinical trials with extended follow-up periods after participants have completed treatment. However, long term studies are more likely to lose participants [1,2]. Among reported barriers to participant retention are work and family demands, lack of transportation or distance to the clinic, frequent study visits, negative staff attitudes, other medical conditions, fear of study drug risks or side effects, lack of knowledge about the study, younger age, weak relationship with study staff, and life events [1,3,4,10–17]. There is a lack of research that focuses on retaining clinical trial participants after they have completed treatment and until they have completed the follow-up phase of the study. Additional studies that focus on retention in both the treatment and follow-up phases of clinical trials are needed.

Retention strategies from a broad range of studies included family involvement, incentives, and shorter office visits. Retention rates were reported to be higher in participants who felt they were helping others to "find a cure," or had a commitment to or "bonding" with the study [1,11–13,18]. The relationship between the study staff and participant was also thought to be significant. Other characteristics or actions reportedly associated with retention included efforts and communication by research staff with participants, spending time with the participant, and consistent contact with study personnel [1,11,12,14]. To identify factors associated with loss to follow-up, we studied the post-treatment phase of a large tuberculosis treatment trial in North America. In part, this was done using the framework of Ickovics and Meisler [19], who proposed that factors affecting adherence and retention in AIDS clinical trials could be placed in the following categories: (1) patient characteristics, (2) treatment regimen, (3) patient–provider relationship, (4) clinical setting, and (5) disease severity.

2. Methods

The Tuberculosis Trials Consortium (TBTC) recently concluded TBTC/USPHS Study 22. Our retrospective analysis looked at factors affecting retention in this multi-center, randomized, open label Phase III clinical trial that compared the efficacy and safety of once-weekly directly observed therapy (DOT) using rifapentine and isoniazid (INH) with those of standard twice-weekly DOT using rifampin (RIF) and INH, during the last 4 months of a six-month tuberculosis treatment regimen. Eligibility for Study 22 included successful completion of a standard 2 month induction regimen. Once enrolled, subjects were followed for 4 months of study phase therapy plus 24 months of follow-up phase.

Trial methods have been reported elsewhere [20]. In brief, between April 1995 and November 1998, Study 22 enrolled 1075 patients (1004 HIV negative and 71 HIV positive). At study entry, information was collected on patient demographic and other characteristics. Patients were seen monthly during the four-month treatment phase. They were seen during follow-up phase at months 3, 6, 9, 12, 18 and 24 following completion of treatment. Study 22 included subjects from diverse populations throughout the United States and Canada. The primary study endpoints were failure (evidence of recurrent tuberculosis disease during treatment), or relapse after treatment.

In August 2000, a questionnaire was distributed to 26 of the 29 sites that had participated in Study 22. Three sites were not queried (they were no longer part of the TBTC and had only 2% of total enrollment). The questionnaire collected data on: (1) clinical setting characteristics (e.g., medical care services, waiting time for DOT, treatment and follow-up visits, parking availability, type and frequency of patient/staff contact); (2) patient–provider characteristics (e.g., consistency of staff responsible for study visits, time spent at visits, provision of other assistance, availability of bilingual staff and social workers); and (3) use of incentives/enablers (e.g., cash incentives, vouchers, and completion bonuses). Responses to the clinical setting and patient–provider characteristics were assessed on a 5-point Likert Scale.