REPORTING ON PARTICIPANT DISPOSITION IN CLINICAL TRIALS

Dennis C. Turk, Ph.D.[1]
University of Washington School of Medicine

Running head: Patient Disposition

[1]Preparation of this manuscript was supported in part by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR/AI44724, AR47298), the National Institute of Child Health and Human Development/National Center for Medical Rehabilitation Research (HD33989), and the Fetzer Institute. Portions of this paper were summarized at the second meeting of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT-II) meeting held in Washington, DC, May 2003.

Address all correspondence to: Dennis C. Turk, Ph.D., Department of Anesthesiology, Box 356540, University of Washington, Seattle, Washington 98195

Hundreds of clinical outcome studies are published each year. Detailed and specific information is required to evaluate the validity of the conclusions that can be drawn from a clinical trial. Often, however, the reporting of clinical trials is incomplete (Altman et al., 2001). A group of clinical investigators meet to respond to the problem and creating a set of standards and recommendation, published as the CONSORT statement (Begg et al., 1996, CONSORT statement: http://www.consort-statement.org). The authors of the CONSORT Statement acknowledged that the process was an evolving one and expected that revisions and extensions would routinely be prepared (Altman et al., 2001). To date a number of a number of some of the most well respected medical journals have adopted the CONSORT Statement and require the recommendations be adhered to in all submissions (Altman et al., 2001).

Table 1 contains the checklist of items that are recommended in the CONSORT Statement for inclusion in all clinical trials. The progression of participants in these trials is of particular interest as little attention has been given to this area, yet the determination of participants in these studies throughout the course of the trial will greatly influence the validity and generalizability of the results. Table 2 depicts the critical stages that need to be reported in clinical trials as suggested in the CONSORT Statement.

There are a number of important questions to ask in evaluating the validity of the results of any clinical trial. In addition to the design, methodology, data analyses, and interpretation, a fundamental issues if that of participant disposition. Participant disposition relates to enrollment, adherence, attrition, and loss to follow up. In particular important questions that should be considered include:

- How are participants recruited?
- Are participants who are included representative of the population of interest?

- What inclusion and exclusion criteria were used in selection of participants?
- What percentage of potential participants evaluated and invited to enroll refuse and why?
- What are the relative percentages of patients randomized into the comparisons groups who adhere to the treatment protocol?
- What were the reasons for failure to adhere to the treatment protocol for each group included in the clinical trial?
- What percentage of patients withdraw from each of the groups included in the protocol and why?
- What number of patients in each of the groups are lost to follow-ups and why?

Methods of Recruitment: who is included in clinical trials?

There are a number of ways to recruit participants for clinical trials and the methods may interact with the outcomes. Some trials recruit participants from referral of patients being treated by health care providers and others rely on the media. We can reasonable ask about the comparability of participants recruited by these two methods. When referrals are from the practices of health care providers these are people who have sought out treatment for a disease, symptom, or syndrome. There are many people in the community who may have comparable medical conditions but who do not seek treatment. Thus, those enrolled from health care provider referrals may differ those recruited through the media. For example, a higher percentage of patient with fibromyalgia syndrome (FMS) seen in clinics display symptoms of depressed mood compared to community samples who meet criteria for but who are not seeking treatment (Prescott et al., 1993; Aaron et al., 1996). Moreover, the sex ratio for treatment seeking and community samples of people with FMS differ from 8 to 1 to 3 to 1, respectively (Wolfe et al., 1995). Here we can see that although participants might meet the diagnostic criteria for FMS,

they may differ on other important characteristics depending upon which method of recruitment was used.

Another point to consider about recruitment of participants from clinical practitioners relates to whether there is any selection filter used by the referral agent. That is, are all patients who meet the criteria of the study referred or does the health care provider select some patients for referral (e.g, those who are likely to be cooperative, those with the most severe symptoms, those who they do not believe would be annoyed by being referred). The alternative would be for every patient in a health care providers practice who meets the inclusion criteria of the trial to be informed about the study and invited to enroll. In this approach it would be important to determine whether the volunteers were comparable to those who did not wish to participate.

When participants are recruited from the community through various media sources, it is difficult to know how comparable they are to others in the community who meet the inclusion criteria but chose not to participate. Little is known about the incentive for community volunteers to enroll in a clinical trial. For some it may be a hoped for improvement in their symptoms or even cure, for others in my be the financial incentive offered, and still other altruism to contribute to science. It is possible that participant enrolled with different motivations might behave differently in the trial (e.g., greater expectations and enthusiasm, more adherent to the protocol).

There is a problem of not knowing the “denominator” in the community that would permit determination of the percentage recruited from those available. The higher the percentage the less representativeness would be concerns. To illustrate, if the number of people with pain associated with diabetic neuropathy in a community were known then it would be possible to

determine what percent of the available people with painful diabetic neuropathy were included in a study.

Finally, people seek treatment for symptoms when they reach a certain threshold of bothersomeness or distress. Since many symptoms fluctuate in severity, it is reasonable to assume that those who volunteer to enroll in a clinical trial will enter when there symptoms are acute and the statistical concept of regression to the mean may play a significant role in the outcome of the trial. Appropriate randomization should at least control for the regression effects. Thus, it is important to know that the participants were randomized to treatment groups independent of the methods of recruitment.

Inclusion and exclusion criteria

There is a balance in conducting a clinical trail between including people who are representative of the population for which the treatment is to be applied but excluding people who have some characteristics (e.g., demographic, physical, co-morbid condition, consuming medication that might interact with treatment) that are believed to interfere with or interactive with the treatment under investigation. For example, we can consider a situation in which a high percentage of a people being treated for a specific disorder were depressed. If one of the exclusion criteria for a trial were depressed mood then a substantial percentage of patients would be eliminated from consideration that actually meet the diagnosis. Those who would meet the criteria and enroll in the trial would be a select sample with important characteristics that may not differ from the broader population and it would be inappropriate to attempt to generalize from the sample included to the population. Investigators must balance the two competing demands. It is incumbent on those who are writing up the results of clinical trials to describe the inclusion and exclusion criteria and provide a rationale for these criteria.

Refusal to enroll in a trial for which they are eligible

As noted above, some percentage of candidates for enrollment in a trail will be excluded based on the initial evaluation and the inclusion and exclusion criteria established for a trial. There is another subgroup to consider, this consists of those candidates for inclusion in a clinical trial who meet the inclusion criteria but who choose not to enroll. Candidates may withdraw from further involvement in a trial once they learn more details of the trials including logistical requirements, the nature of the treatments, or the randomization process. Studies of candidates offered treatment in rehabilitation programs for chronic pain have noted as many as 30% (Turk & Rudy, 1990) may refuse once they learn of the details involved with the treatment protocol. Those who agree to participate in a trial may differ substantially and in important ways from those who decline. It is possible that the benefits of the treatment will be inflated, as only those who had a positive expectation for the treatment might be included. Investigators should report not only on the number of candidates who refuse to continue following the provision of details of the study and if participants terminate involvement after randomization, the investigator should report on the reasons for termination from each comparison group.

Adherence to the treatment protocol and protocol violations

For a treatment to be effective in producing the desired outcomes, at least two things must occur. The active ingredient of the treatment must have some truly beneficial effect and the patient much adhere to the treatment as prescribed. Nonadherence is a significant problem with many treatment recommendations. There are some estimates that up to 20% of prescriptions for medication are never filled and a substantial minority of people prescribed medications will not take them in the recommended manner (Meichenbaum & Turk, 1986) some in a manner that will lead to significant adverse effects. Adverse reactions to drugs whether from inappropriate use or

the drug themselves are among the leading causes of hospitalization and death in the United States (Bates, 1998; Lazarou, Pomeranz, & Corey, 1998).

When attempting to conduct clinical trials, it is essential that some means be used to assess adherence. Patients who are nonadherent will not obtain the optimal benefit and patients who are adherent may differ from those who are nonadherent on some important variables that interact with the active treatment. When two groups are being compared in a trial, differential rates of adherence in the different group may influence the outcomes. There are a number of forms of nonadherence such as failing to follow the treatment as prescribed (e.g., too little, too much, different schedule), use of concomitant treatments, and failure to appear at scheduled appointments. Thus, not only the rates but also the reasons for nonadherence and nature of inappropriate behavior need to be ascertained and reported for each group.

In addition to failing to take a prescribed medication, participants in clinical trials may violate the treatment protocol by using prohibited medication or modifying the protocol making unauthorized changes in prescribed regimen. For example, if one pill relieves pain by 25%, a participant may decide to up the dose to two pills in order to obtain greater relief. Conversely it taking a medication causes unacceptable side effects; the participants may decide to reduce the routine to once a day. Participants have observed their physicians engage in such titration and may view this behavior as reasonable and appropriate. Unless asked about such alterations and the inclusion on non-prescribed treatments, they investigator be unaware of these behaviors and their potential for affecting the treatment outcomes.

There are a number of strategies and methods to assess adherence to the protocol (e.g., interviews, self-reports, pill counts, tallies of refills, biochemical markers, record of appointment attendance, electronic monitoring of vial opening) (see Meichenbaum & Turk, 1986). There are a

number of possibly reasons for nonadherence – adverse reaction, inadequate relief, inconvenience or complexity of the protocol, forgetfulness, symptom improvement, misunderstanding of instructions.

There is often an assumption that nonadherence is attributable to characteristics of the participants. That is that their failure to follow the protocol results from personality characteristics, demographics (e.g., age, education level), forgetfulness, apathy, pessimism, and beliefs. None of these factors have been shown to predict nonadherence. In addition to the individual difference variables noted, other factors that may contribute to nonadhernce include disease or disorder variables (e.g., stability of symptoms), treatment variables (e.g., complexity of the treatment regimen, adequacy of instructions, size and taste of medication, adverse reactions), and relationship variables (e.g., interactions between investigators and participants). Identification of reasons for nonadherence may lead to improvements in the design of future studies. Because of the numerous factors that may influence participants' adherence with the treatment protocol, it is not only important to report the number or percentage of patients who are nonadherent but also the reasons why they chose not to adhere and the nature of the nonadherence behaviors.

Withdrawal from trial

Attrition from a clinical trial is a serious problem as it can bias the results, challenge the validity of conclusions, and interfere with the interpretation of the results and conclusions. Reports of clinical trails for fibromyalgia patients illustrate the problem. Goldenberg and colleagues (1996) reported the results from a randomized, double-blind crossover trial with amitriptyline and fluoxetine. Each patient in this study underwent 6-week trials of placebo, fluoxetine, amitriptyline, and combination of fuoxetine and amitriptyline. Comparisons with the baseline

levels revealed that the use of fluoxetine and amitriptyline was associated with improvements in pain, sleep, fatigue, and moods. Furthermore, the combination of two drugs yielded even better outcome than the use of either medication alone. However, the rate of drop out from the trial was 40% a figure that challenges interpretation of the results.

There are a number of reasons why a participant in a clinical trial may withdraw from the protocol. The reasons for withdrawing from a trial may have different implications for the treatment. For example, participants may withdraw from a study because they did not like the clinic staff, logistical requirements made it inconvenient to continue, a new medical problem may have appeared that is unrelated to the disease or syndrome being treated, some life events may have interfered with continuation (e.g., illness of a significant other). Investigators should not only report on the number who withdraw from each group but should attempt to determine the reasons for withdrawal. Intent-to-treat analyses are designed to take have been advocated as a way to control for attrition.

Attrition from a clinical trial is a problem as there loss from the study may bias the results towards those who were obtaining beneficial effects of the treatment. As a consequence the treatment may appear to be more effective. It would seem therefore that the reasons why participants dropout from each of the treatments should be reported.

Loss to follow-ups

Loss to follow-up creates the same issues noted for treatment dropout. Investigators should attempt to determine the reasons why participants are not available for follow-up. Some for example, may simply refuse to participate whereas other may not be able to be contacted (e.g., moved, disconnected telephone). The former may be dissatisfied with the treatment whereas the later may simply be unreachable.

The questions outlined are all related to the general classification of participant (patient) disposition. In short, who are included in clinical trials, are they representative samples, and what happen to candidates and actually participant who enroll in a trial throughout the course of the trial. Biases in the samples any point from recruitment to follow-up can undermine the internal and external validity of any clinical outcome study. Turk and Rudy (1990) noted that only about 10% of patients referred for treatment at a multidisciplinary pain center were available at follow-up. Drawing conclusions regarding the efficacy of treatment are limited if not invalid given the small percentage of patients who were available. What happens to participants in clinical trials – participant (patient) disposition is an important area that needs to be considered in evaluation of clinical trials, and hence the design of the study should plan on how this information will be obtained, reported, factored into the analyses, and reported.

Conclusion

Participant disposition is not an outcome in clinical trials but rather refers to the process of recruitment and the progression of participants throughout a clinical trial. Details of participant disposition are essential for the adequate evaluation of the validity of conclusions regarding the efficacy of treatment in any clinical trial. The CONSORT Statement (Begg et al., 1996; Altman et al., 2001) describes the inclusion of information about participant flow throughout a clinical trial. However, the recommendations do not make any suggestions regarding the report of reasons for attrition and loss to follow-up. In this manuscript, I recommend that the CONSORT Statement be extended beyond simply reporting on the numbers of participants who withdraw and lost to follow-up for each group to the provision of information about the reasons for withdrawal and loss (see Table 3). In addition I suggest that additional information regarding participant disposition should be included that describes and reports on

- the recruitment process and percentages from each method if more than one
- the number of candidates who are excluded from participation and the reasons why
- the number of candidates who choose not to enter the trial and the reasons why (if this occurs after randomization, the number and reasons for each group should be reported)
- both the number and reasons for withdrawal from each treatment group in the trial
- rates, types, and reasons for nonadherence
- the number and reasons for loss to follow-up for each group should be reported.

In those instances where more than one treatment is included in a clinical trials, the investigator should report on whether there were any significant between group differences in the numbers that withdrew, were nonadherent, or were lost to follow-up.

References

Aaron LA, Bradley LA, Alarcon GS, et al. Psychiatric diagnoses in patients with fibromyalgia are related to health care-seeking behavior rather than to illness. Arthritis Rheum 1996; 39:436 45.

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Int Med 2001;134:663-694.

Bates DW, Drugs and adverse drug reaction: how worried should we be? JAMA 1998;279:1216-1217.

Begg C, Cho M, Eastwood S, Horton R, Moher D, Okin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA 1996;27:637-639.

CONSORT statement: http://www.consort-statement.org

Goldenberg, D., Mayskiy, M., Mossey, C., Ruthazer, R., & Schmid, C. (1996). A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheumat 1996; 39: 1852-1859.

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a metaanalysis of prospective studies. JAMA 1998;279:1200-1205.

Meichenbaum D, Turk DC. Facilitating treatment adherence: A practitioner's guidebook. New York: Plenum Press, 1987.

Moher D. CONSORT: an evolving tool to help improve the quality of reports of randomized clinical trials. Consolidated Standards on Reporting Trials. JAMA 1998;270:408-412.

Prescott E, Jacobsen S, Kjoller M, Bulow PM, Danneskiold-Samsoe B, Kamper Jorgesen J. Fibromyalgia in the adult Danish population: I. Prevalent study. Scand J Rheumatol 1993;22: 238-242.

Turk DC, Rudy TE. Neglected factors in chronic pain treatment outcome studies -- Referral patterns, failure to enter treatment, and attrition. Pain 1990;43:7-25.

Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995; 38:19-28.

Table 1

Checklist of Items to Include When Reporting a Randomized Trial

Title and Abstract

Introduction and Background

Methods

- Participants
- Interventions
- Objectives
- Outcomes
- Sample size
- Randomization
  - Sequence generation
  - Allocation concealment
  - Implementation
- Blinding
- Statistical methods

Results

- Patient flow
- Recruitment
- Baseline data
- Number analyzed
- Outcomes and estimation
- Ancillary analyses
- Adverse events

Discussion

- Interpretation
- Generalizability
- Overall evidence

Table 2

Participant Flow

Stage	Number Included	Number Not Included
1. Enrollment	# evaluated for enrollment	# did not meet inclusion criteria # met inclusion but declined
2. Randomization	# randomized	
3. Tx Allocation	# received tx. as allocated by group	# did not receive tx as allocated by group
4. Tx. Completion	# completed tx as allocated by group	# did not complete tx as allocated by group
5. Follow-up	# completed f/u as planned by group	# did not complete f/u as planned by group
6. Analyses	# included in main analysis by group	# excluded from main analysis by group

Table 3

Participant Disposition

Report:

1. Methods of recruitment and number obtained if multiple methods
2. Number excluded and reasons for exclusion
3. Number of candidates who refuse to enroll and reason(s) why (if after randomization from each treatment group)
4. Number of participants who withdraw from each treatment group and reasons why
5. Rate and nature of incidence of adherence with each treatment and reasons for nonadherence
6. Number lost to follow-up from each treatment group and reasons why