Screening and Enrolling Subjects in a Randomized Clinical Trial Involving Implant Dentures

Joanne N. Walton, DDS, Cert Pros, FRCD(C)[a]/Michael I. MacEntee, LDS (I), Dip Pros, PhD, FRCD(C)[a]

Purpose: When planning and budgeting for a clinical trial, researchers have few references to help them estimate how many volunteers will need to be screened, how long the screening process may take, and how much it may cost to enroll sufficient qualified subjects. The purpose of this study was to analyze the time and costs involved in recruiting, screening, and enrolling subjects for a randomized clinical trial examining patient satisfaction with mandibular dentures retained by 1 or 2 implants. ***Materials and Methods:*** Data collected included age and sex of volunteers, recruiting sources, length of time and costs of recruiting and screening volunteers, and reasons for inclusion or exclusion. Results were analyzed using Pearson chi-square tests. ***Results:*** We estimated that we would need to screen 180 volunteers over a period of 4 years at an estimated total cost of CAN$47,664.00 to enroll 86 subjects. Instead, we had to screen 220 volunteers at a direct cost of $63,324.81. We excluded 28% of volunteers, while 32% declined participation and 40% agreed to participate in the study. Volunteers were most commonly excluded because of technical problems with their existing dentures, while they were most likely to decline participation because of perceived surgical risks with implants. Those who agreed to participate most commonly cited anticipation of a more secure mandibular denture as their reason for enrolling. ***Conclusion:*** We had to screen more volunteers at a higher cost than anticipated, with only 40% of those screened meeting inclusion criteria and agreeing to participate in the trial. *Int J Prosthodont 2008;21:210–214.*

In an era of evidence-based dentistry in which evidence is ranked according to its strength,[1] randomized clinical trials are considered, along with systematic reviews, to be the highest level of evidence for clinical research.[2] Unfortunately, clinical trials with human subjects are expensive and time consuming,[3] and 2 factors that impact study costs and duration are recruiting suitable subjects and screening them to ensure that they meet inclusion criteria for the trial and wish to participate when they do qualify.

As part of the trial design, and before recruitment of volunteers to a clinical trial can begin, the minimum number of subjects required to detect a statistically significant difference in study outcomes must be estimated. Once the sample size estimation[4,5] is complete, researchers must estimate how many additional subjects will be required to allow for dropouts over the course of the study to ensure sufficient numbers remaining at the completion of the trial for valid statistical analysis of the results. This latter estimate is typically based on the experience of the researchers with previous similar research, as are estimates of the number of volunteers who will have to be screened and the length of time it will take to enroll the required number of subjects in the study.

Strategies for recruiting subjects to clinical trials have been reported,[6–8] but the challenge of actually enrolling subjects once they have been recruited has received scant attention. Similarly, while all subjects who are enrolled should be accounted for when reporting the results of the clinical trial, outcomes with volunteers prior to enrollment often remain a mystery. Given the costs and time involved in screening and enrolling those who have been recruited into a clinical trial, more information on the length of time, dollar costs, and reasons that volunteers either participate or do not could be important to researchers designing such trials and applying for funding.

[a]*Professor, Department of Oral Health Sciences, University of British Columbia, Vancouver, British Columbia, Canada.*

Correspondence to: *Dr Joanne N. Walton, Department of Oral Health Sciences, University of British Columbia, 2199 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 1Z3. Fax: 604 822 3562. E-mail: jnwalton@interchange.ubc.ca*

The aim of this study was to analyze the screening process for a randomized clinical trial, including *(1)* a comparison of volunteers recruited versus those enrolled, *(2)* the length of time and costs involved in screening volunteers, and *(3)* reasons they were excluded. We reported previously on the reasons given by the first cohort of volunteers for accepting or refusing an offer of free implants to retain their mandibular denture, including an analysis of factors more likely to predict those who will accept an offer of implant treatment. This paper is the next in a series reporting outcomes of this clinical trial, accounting for all 220 volunteers in the study.

Materials and Methods

Volunteers were recruited to the Vancouver Implant Prosthesis study, a randomized clinical trial designed to compare patient satisfaction with implant-retained mandibular dentures and approved by the Clinical Research Ethics Board of the University of British Columbia (UBC). We used our primary research hypothesis that there would be no difference in patient satisfaction with mandibular dentures retained by either 1 or 2 implants to determine the required number of trial subjects. To provide 80% power, alpha of .05, and beta of .2, we calculated that a minimum of 75 subjects would be needed. Based on our experience with similar research,[9] we added 11 subjects to allow for possible dropouts over the planned 5-year study period, meaning that 86 subjects would need to be enrolled. We also estimated that we would need to screen approximately 180 volunteers to find 86 subjects who would qualify and wish to participate, and that it would take up to 4 years to enroll all 86 subjects at a rate of 16 in year 1, 30 in each of years 2 and 3, and 10 in year 4.

We estimated total costs for recruiting and screening at CAN$47,664.00 (CAN$1= $0.953 USD), based on honoraria paid to volunteers, fees and salary paid to clinical staff (prosthodontist and certified dental assistant), and fees paid to use the clinic space. We paid each volunteer an honorarium of $25.00 CAD to complete the screening process, and we paid a certified specialist in prosthodontics a fee of $100.00 CAD per subject screened. A certified dental assistant was paid for screening based on annual salary plus benefits divided by the estimated number of subjects per day and number of days estimated to screen 180 volunteers; this was calculated to be ~CAN$127.00 per volunteer. Further, as part of a partial cost-recovery philosophy to defray the costs of conducting clinical research in a patient-care and teaching facility, the UBC Clinic charges clinical trials a fee of CAN$125.00 per day. We therefore estimated clinic use costs at CAN$2,250.00 for 18 days to screen 10 volunteers per day.

We advertised the clinical trial first to patients who had attended the UBC Faculty of Dentistry undergraduate clinic to have complete dentures made, and then to local dentists, denturists, elders' organizations, and libraries in the greater Vancouver area. Our advertisement sought volunteers who were wearing complete maxillary and mandibular dentures to come to UBC for an examination and to complete a questionnaire about their dentures, noting that they may qualify to participate in a study comparing patient satisfaction with a mandibular denture retained by either 1 or 2 implants, all at no cost to them.

All recruited volunteers were grouped into 1 of 3 categories after screening: *(1)* those who did not meet inclusion criteria or who met at least 1 of the exclusion criteria, described elsewhere[10]; *(2)* those who met inclusion criteria and consented to participate in the clinical trial; and *(3)* those who met inclusion criteria but declined to participate in the trial.

Those who met the inclusion criteria were asked to indicate whether they wished to participate in the study and receive, at no charge, 1 or 2 (randomly assigned) mandibular implant(s) with stud attachment(s), followed by a reline of their existing mandibular denture. They were then asked to specify their reason(s) for accepting or refusing the offer of treatment. They were given a detailed consent form to be signed and witnessed to participate in the trial. We also recorded the age and sex of each volunteer.

Data were analyzed using Pearson chi-square tests to identify bivariate associations between age groups, sex, or recruitment source with the likelihood of volunteers being included or excluded or of qualified volunteers agreeing or declining to participate in the study. Age was made dichotomous by using a median split to compare those who were the same age or younger than the median with those who were older.

Results

The numbers and sources of volunteers who were screened and enrolled are shown in Table 1. Over a quarter (28%) of those screened did not meet the inclusion criteria, while almost three quarters (72%) qualified to participate in the study. However, only 40% of the total volunteers screened met the inclusion criteria and agreed to participate, while 32% qualified but declined to participate.

The majority of those screened previously had complete dentures fabricated in the UBC undergraduate dental clinic, and 77% of these UBC volunteers met the inclusion criteria for the study, accounting for 57% of the final study population. UBC and non-UBC volunteers who met the inclusion criteria were equally likely to agree to participate in the study ($P = .41$) and equally

Table 1 Volunteers Recruited, Screened, and Enrolled in the Study

		Recruitment source						
		Referral			Advertisement			
Status	UBC Clinic	Dentists	Denturists	Friends	Senior centers	Newspapers	Other	Total
Screened	121	17	13	1	23	36	9	220
Did not meet criteria	29*	9	1	1	6	11	5	62*
Declined participation	42*	1	5	0	8	14	0	70*
Enrolled	50*	7	7	0	9	11*	4	88*

*A total of 4 volunteers who had been screened died. The 2 who had been enrolled did not receive any treatment before they died.

Table 2 Comparison of Estimated and Actual Volunteer Screening, Subject Enrollment, and Costs*

	Estimated			Actual		
	Volunteers screened	Subjects enrolled	Costs	Volunteers screened	Subjects enrolled	Costs
Year 1	30	16	$8,944.00	110	36	$28,913.47
Year 2	70	30	$19,536.00	42	18	$12,689.94
Year 3	70	30	$17,536.00	30	11	$10,293.33
Year 4	10	10	$1,648.00	38	21	$11,428.07
Total	180	86	$47,664.00	220	86	$63,324.81

* Shown in Canadian dollars.

likely to be excluded from the study ($P = .08$), although only 24% of UBC volunteers were excluded compared to 33% of those recruited from outside UBC.

A total of 220 volunteers were screened—128 women and 92 men with a median age of 68.2 years (range: 34 to 100 years)—to enroll 86 subjects in the clinical trial. There were no significant differences in age among those who met inclusion criteria and those who were excluded ($P = .15$), or between those who agreed to participate and those who refused ($P = .38$). Likewise, men and women were equally likely to meet inclusion criteria ($P = .15$) or to accept a place in the study if it was offered ($P = .13$).

The number of subjects enrolled each year and costs, estimated and actual, are summarized in Table 2. Based on experience with previous clinical trials, we had predicted that we would enroll about half of those screened in the first year of the trial, but we were only able to enroll about a third. The percentage of those screened who were accepted went up by the fourth year of the study to 55%, but that too was less than the 100% enrollment that we had anticipated. It was estimated that it would cost ~CAN$265.00 per volunteer to enroll 86 subjects, but the actual cost per volunteer was ~CAN$288.00, making the total costs incurred when enrolling 86 subjects 33% higher than estimated.

Volunteers were most frequently excluded from the study because of technically unsatisfactory dentures.[10] Reasons for excluding volunteers are summarized in Fig 1. We also encountered 25 volunteers who were initially excluded and subsequently reapplied after addressing the reasons for their exclusion, most commonly by having had faulty dentures corrected or remade, or by having a medical concern resolved. Twenty-two of the 25 were able to meet inclusion criteria and were offered a place in the study, with 7 declining the offer and 15 enrolling.

Of the 88 volunteers who ultimately met inclusion criteria and agreed to participate in the study, the most common and highly rated reason given for accepting the offer of treatment was the belief that their mandibular denture would be more stable or secure when retained by 1 or 2 implants (Fig 2). This was in accordance with results reported in our previous study.[10]

There were 70 volunteers who met the inclusion criteria for the trial but who chose not to participate. We reported previously[10] on the reasons given by 38 of the first 101 study volunteers for refusing the offer of free treatment; there were an additional 32 of the remaining 119 subjects screened who declined to participate in the study despite meeting inclusion criteria. Their most strongly held reason for refusing the offer of free implant(s) was consistent with the first 101 subjects screened, ie, the concern about surgical risks (Fig 3).

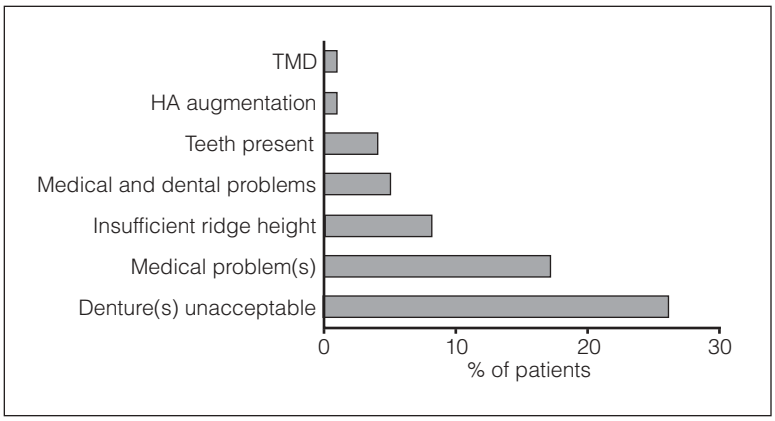

Fig 1 Reasons for excluding subjects from the study (n = 62). TMD = temporomandibular disorder; HA = hydroxyapatite.

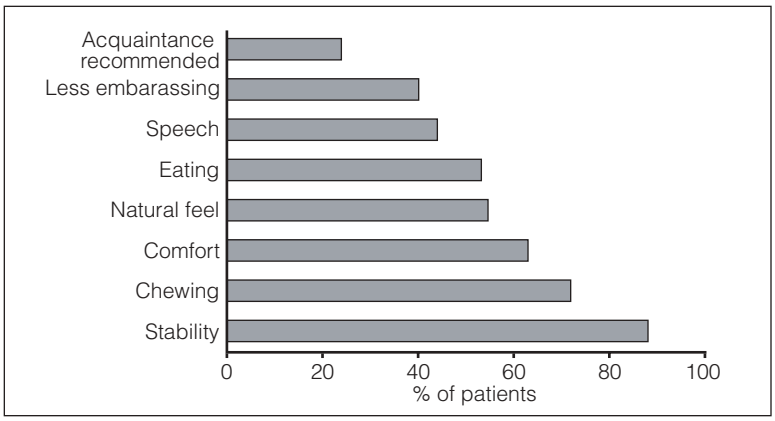

Fig 2 Reasons given by subjects for participating in the study (n = 88).

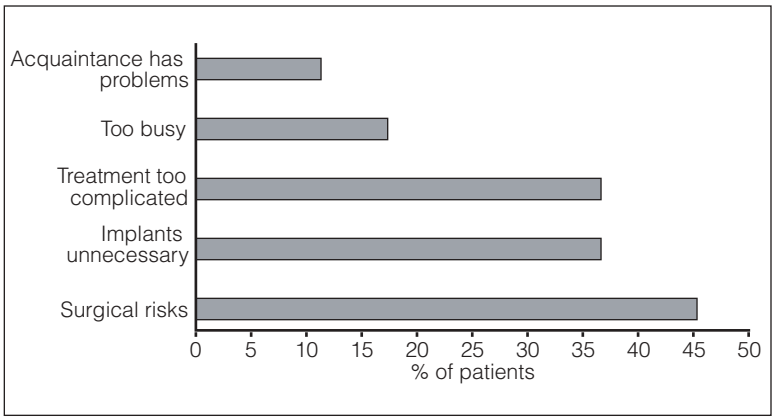

Fig 3 Reasons given by subjects for declining to participate in the study (n = 70).

Discussion

The sample size in this randomized clinical trial (86) was larger than that seen in many implant studies reported in the literature, and this increased size had an impact on the time and costs to complete the study. Our sample size estimation was based on testing the null hypothesis that there is no difference in patient satisfaction with mandibular dentures retained by 1 or 2 implants, and we were concerned that it might be possible to infer no difference if there were not enough subjects enrolled to detect a difference. Thus, although the costs of a sample size sufficient to detect a significant difference (or conclude that there is no difference) are greater, so should be the reliability of the conclusions that may be reported from this trial.

Given the large number of patients in our clinical database who had received complete dentures at UBC, it is not surprising that the majority of volunteers and subjects came from UBC. Existing UBC patients were also the first responders, and we were surprised by the large number (46%) of those who qualified for the

study but declined to participate. We discovered that many of the patients whose dentures had been fabricated in our undergraduate clinic did not see the value in "risking" a surgical procedure when they were already satisfied with their conventional dentures.

Since the main reason for excluding volunteers was technically unacceptable dentures,[10] the greater tendency for volunteers from outside UBC to be rejected for not meeting inclusion criteria may be explained by the strict quality control of denture fabrication in our undergraduate clinic.

Although the estimates of how many volunteers could be screened in the early years of the trial were low, predictions as to how many of those screened could be enrolled were overly optimistic. The unexpectedly high ratio of volunteers screened to those enrolled caused our year-by-year budget estimates to be off considerably, especially in year 1 of the study. It is likely that our enrollment rate increased from a low of 33% in year 1 to a high of 55% in year 4 because we became more efficient and effective in our initial telephone screening of applicants. Clearly, our ability to anticipate and provide effective answers to inquiries improved with time. Nevertheless, the need for a larger than anticipated pool of volunteers strained both our budget and our time, leading us to be 33% over budget for screening and behind the anticipated start time of the study. Along with the budgetary impact of increased screening costs, the cost of completing the study later than planned was substantial. Since each subject in this study must complete at least 1 year with their modified mandibular dentures, the end of the study and the commencement of final data analysis have been delayed by approximately 1 year.

While we were pleased that 25 subjects who had initially been excluded had the identified problem(s) addressed and returned to be reevaluated, the fact that only 15 of them proceeded to enroll may indicate that they believed they were expected to return for reassessment whether or not they planned to participate.

We found that almost as many subjects declined to participate (70) as agreed to enroll (88), probably because our recruiting advertisement sought denture-wearers for an oral examination without reference to implants. We wrote the advertisement in this way to reduce the likelihood of attracting volunteers who were very dissatisfied with their dentures. This finding may also reflect a more widespread satisfaction with conventional dentures than we expected in light of recent recommendations that 2-implant mandibular overdentures ought to be the standard of care for edentulous patients.[11] It certainly lends further support to the view that the first line of treatment for the edentulous mandible should be a conventional complete denture, leaving implant retention as a secondary option for those who are dissatisfied with their conventional dentures.

Conclusion

Volunteers who had previously had dentures made in our university-based dental clinic were more likely to apply and commit to this clinical trial of satisfaction with implant overdentures. For those who were excluded from participating, the most common reason was technically unacceptable dentures. When planning and budgeting for a clinical trial, researchers may wish to keep in mind that it took longer and cost more to recruit and screen volunteers for this clinical trial than was anticipated. Only 40% of the volunteers screened met inclusion criteria and agreed to participate, despite being offered free treatment and a small honorarium as incentives.

Acknowledgments

This study was supported by the Canadian Institutes of Health Research (Grant #58954), The ITI Foundation (Grant #222), and Straumann Canada.

References

1. Woolf SH, Battista RN, Anderson GM, Logan AG, Wang E. Assessing the clinical effectiveness of preventive maneuvers: Analytic principles and systematic methods in reviewing evidence and developing clinical practice recommendations. A report by the Canadian Task Force on the Periodic Health Examination. J Clin Epidemiol 1990;43:891–905.
2. Sutherland SE. Evidence-based dentistry: Part IV. Research design and levels of evidence. J Can Dent Assoc 2001;67:375–378.
3. Lader EW, Cannon CP, Ohman M, et al. The clinician as investigator. Participating in clinical trials in the practice setting. Appendix 1: Fundamentals of study design. Circulation 2004; 109:c302–c304.
4. Devore J, Peck R. Introductory Statistics. St Paul: West Publishing, 1990:240–241.
5. Lader EW, Cannon CP, Ohman M, et al. The clinician as investigator. Participating in clinical trials in the practice setting. Appendix 2: Statistical concepts in study design and analysis. Circulation 2004;109:c305–c307.
6. Sarkin JA, Marshall SJ, Larson KA, Calfas KJ, Sallis JF. A comparison of methods of recruitment to a health promotion program for university seniors. Prev Med 1998;27:562–571.
7. Treves TA, Verchovsky R, Klimovitsky S, Korczyn AD. Recruitment rate to drug trials for dementia of the Alzheimer type. Alzheimer Dis Assoc Disord 2000;14:209–211.
8. MacEntee MI, Wyatt C, Kiyak HA, et al. Response to direct and indirect recruitment for a randomized dental clinical trial in a multicultural population of elders. Community Dent Oral Epidemiol 2002;30:377–381.
9. Walton JN, MacEntee MI, Glick N. One year prosthetic outcomes with implant overdentures: A randomized clinical trial. Int J Oral Maxillofac Implants 2002;17:391–398.
10. Walton JN, MacEntee MI. Choosing or refusing oral implants: A prospective study of edentulous volunteers for a clinical trial. Int J Prosthodont 2005;18:483–488.
11. Feine JS, Carlsson GE, Awad MA, et al. The McGill consensus statement on overdentures. Mandibular two-implant overdentures as first choice standard of care for edentulous patients. Gerontology 2002;19:3–4.