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Abstract

Subject retention is one of the key factors that determine success of a clinical trial. Many researchers have focused on the issue of recruitment, and few have focused on retention. Subjects discontinue from clinical trials for variety of reasons. Sociodemographic characteristics such as age, gender, race, employment, and level of education have been implicated as the most common influencers for participation in clinical trials. This study evaluated the influence of these sociodemographic characteristics on the risk of subject discontinuation. There was little apparent difference in the sociodemographic characteristics among completers and discontinued subjects. Importantly, it was noticed that there is no common format for reporting clinical trial sociodemographic characteristics, thus leading to difficulties in the interpretation of the influence of such factors on subject retention. Suggestions are provided for future researchers that would greatly enhance the prediction of sociodemographic influences on subject discontinuation. Strategies to overcome such influences may be required.

Keywords

clinical trials, retention, dropouts, demographics, standardization

Introduction

Clinical trials are necessary to test new treatments. They may also be a valuable component in the treatment of patients suffering from many types of serious diseases.¹ A number of barriers, including those imposed by the physician, study trial, or the patients themselves, limit patient participation and retention in clinical trials. Successful conduct of a clinical trial depends on the enrollment of subjects as well their retention after the enrollment. A key factor for determining the success of a clinical trial is the recruitment and retention of the study population of an adequate sample size.²

Recruiting the right subjects in sufficient numbers to clinical trials is a well-recognized challenge, but a growing and equally critical challenge is keeping subjects in the studies.³ There is no value in recruiting the right subjects if they drop out before the clinical trial is completed.⁴ Recent clinical research conducted worldwide has been threatened by declining participation rates and misconceptions about the clinical research.⁵⁻⁷ It has been estimated by Center Watch that only about 70% of enrolled participants completed Phase 3 clinical trials.⁴ As the number of clinical trials increase, there is increased competition for a limited pool of available participants.

Much has been written on the recruitment issues in clinical trials; less emphasis has been placed on subject retention issues.

In any type of clinical research, but especially longitudinal studies, participant retention poses a major challenge and issues of dropouts and nonadherence can become frustrating. In weight loss and lifestyle change research, the average dropout rate is 32%, but this can be even higher depending on the participant population, the length of the study, and the demands of the protocol.⁸ In most clinical research, each participant represents a significant amount of time, effort, and resources, so high dropout rates are costly. High dropout/nonadherence rates not only are frustrating and costly but also pose a risk to the interpretation and validity of research findings.⁹

The importance of subject retention in clinical trials is well known.¹⁰ A few authors cite the influence of factors that influence retention.^{11,12} Reasons why a participant may withdraw from a clinical trial include moving from the study¹³ and randomization to a specific treatment group.¹⁴ Special retention

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issues are associated with studies in underserved communities,¹⁵ vulnerable families,¹⁶ family care givers,¹⁷ individuals with disabilities,¹⁸ runners,¹⁹ and nurses.²⁰ Retention issues with the hospitalized patients have been studied,^{21,22} but these investigators used longitudinal designs that were descriptive, correlational or comparative.

This analysis focuses on what specific sociodemographic characteristics may be associated with subjects who leave the clinical trials before completion. Some hypotheses have been developed by others.

Age

Studies have shown that the younger participants are at significantly higher risk of discontinuation in a clinical trial rather than the older participants.^{23,24} One hypothesis for this finding is that younger participants face numerous family demands and obligations that may not affect older people. Another cause may be that the older participants may experience declines in the health which might motivate them to continue in studies.

Gender

Women are more likely to discontinue from the clinical trials.^{24,25} Family and caretaking demands on women might make them more likely to discontinue from a clinical trial. However, others have reported that single participants²⁶ and fathers²⁷ have a higher dropout rate.

Minorities

Some studies have reported that minorities are also more likely to drop out from a clinical trial.²⁵ Socioeconomic status and increased life stress impact retention, but there may also be a lack of trust in the health care system amongst some minority groups.²⁸

Unemployment

Higher rates of discontinuation have been found in the subjects who are unemployed.²⁶ High stress levels in unemployed subjects may lead to increased discontinuation rates.

Education Level

Higher rates of clinical trial discontinuation have been found in participants with less formal education.²⁹ Lack of understanding the study protocol, procedures, and the importance of their participation might affect study continuation.

Method

The published literature was searched for topics concerning discontinuation of enrolled subjects in clinical studies. Some

of the findings with regard to the characteristics of the discontinued subjects were tested for their predictive value for other randomly selected published clinical trials. The database for health sciences EBSCOhost[®] was used for literature search. Key search words such as subject retention, sociodemographics, and clinical trials were used to retrieve available literature. Retrieved literature satisfying all search criteria yielded 12 publications, among which 6 are drug intervention trials (Tables 1 and 2) and 6 are non-drug intervention trials (Tables 3 and 4).

Authors use various delimiters to quantify subject characteristics. This review examines differences between completers and discontinued subjects based on the categories defined by the authors. Common trends and characteristics of the dropouts were examined. A mean of the means was calculated for all trials having data suitable for analysis. Earlier hypotheses were compared to the sociodemographic characteristics of the discontinued subjects in each set of these trials. After obtaining the results for drug studies, the results obtained compared to the non-drug studies.

Results

Drug Intervention Trials

Age

The mean age of the subjects who completed is 40.2 (± 4.8) while the mean age of the subjects who discontinued is 36.1 (± 3.4) (Tables 1 and 2).

Gender

Of the males, 52% (± 6.2) discontinued in this set of trials, as against 51.5% of the females (± 4.6) (Tables 1 and 2).

Race

Data analysis with regard to race was unable to be performed because of the paucity of data of the clinical trial subjects collected from the drug intervention trials.

Unemployment

Unemployment percentage among the individuals who completed the clinical trials was 20.6% and among those who discontinued from the clinical trials was 24.3% (Tables 1 and 2). The percentage of the employed individuals who discontinued from the clinical trials is much (75.7%) higher than the percentage of unemployed individuals who discontinued from the clinical trials (24.3%).

Education Level

There was a higher percentage of highly educated individuals who discontinued from participation in clinical trials (70.2%) compared to the percentage of the highly educated individuals

Table 1. Sociodemographic characteristics of completers in drug intervention clinical trials.

Reference	Number of subjects	Age (Mean and SD)	Sex (%)		Race (%)			Employment Status (%)		
			Male	Female	Caucasian	African American	Hispanic	Education (%)	Employed	Unemployed
30	417	≥40 = 14.4% ^a	N/A	N/A	0	0	100 ^a	67.60	86.60	13.40
31	198	34.7 (SD = 0.7)	44	56	90 ^a	N/A	N/A	N/A	N/A	N/A
32	83	42.1 (SD = 9.0)	45	55	N/A	N/A	N/A	N/A	N/A	N/A
33	199	43.8 (SD = 15.6)	N/A	N/A	N/A	N/A	N/A	N/A	70.4	29.6
34	412	>60 = 48.1% ^a	40.80	45.20	N/A	N/A	N/A	47.80	N/A	N/A
35	26,124	N/A	51.40	48.60	N/A	N/A	N/A	83.10	81.30	18.70
Total trials (n = 6)	27,433	40.2 (SD = 4.8)	45.3 (SD = 4.4)	51.2 (SD = 5.17)				66.17 (SD = 17.6)	79.43 (SD = 8.26)	20.57 (SD = 8.26)

a. Data not used for analysis.

Table 2. Sociodemographic characteristics of discontinued subjects in drug intervention clinical trials.

Reference	Number of subjects	Age (Mean and SD)	Sex (%)		Race (%)			Employment Status (%)		
			Male	Female	Caucasian	African American	Hispanic	Education (%)	Employed	Unemployed
30	53	≥40 ^a	N/A	N/A	0	0	100 ^a	66	84.90	15.10
31	62	32.4 (SD = 1.5)	44	56	92 ^a	N/A	N/A	N/A	N/A	N/A
32	36	36.6 (SD = 11.7)	52	48	N/A	N/A	N/A	N/A	N/A	N/A
33	197	39.2 (SD = 15.9)	N/A	N/A	N/A	N/A	N/A	N/A	58.70	41.30
34	533	>60 = 51.9 ^a	59.20	54.80	N/A	N/A	N/A	52.20	N/A	N/A
35	3801	N/A	53.00	47.00	N/A	N/A	N/A	92.40	83.50	16.50
Total trials (n = 6)	4682	36.06 (SD = 3.43)	52.05 (SD = 6.24)	51.45 (SD = 4.6)				70.2 (SD = 20.4)	75.7 (SD = 14.7)	24.3 (SD = 14.7)

a. Data not used for analysis.

Table 3. Sociodemographic characteristics of completers in non-drug intervention trials.

Reference	Number of subjects	Age (Mean and SD)	Sex (%)		Race (%)			Education (% or years)		Employment Status (%)	
			Male	Female	Caucasian	African American	Hispanic	Education (% or years)	Employed	Unemployed	
29	173	28.6 (SD = 5.1)	66.50	33.50	N/A	N/A	N/A	64.7% ^a	41.60	42.80	
36	N/A	40.9 (SD = 12.9)	82	18	63	31	6	14.5 (SD = 3.2)	68	32	
37	1226	74 (SD = 8.7)	35.80	64.20	86.50	9.30	3.10	13 (SD = 3.8)	N/A	N/A	
27	347	30 (SD = 8)	57	64	60	54	64	12.5 (SD = 4)	57	67	
38	117	64.1 (SD = 12.1)	17	73	75		25 ^a	14.0 (SD = 2.6)	32	68	
39	132	62.0 (SD = 12.1)	64	36	70		30 ^a	14.5 (SD = 3.3)	N/A	N/A	
Total trials (n = 6)	1995	49.93 (SD = 19.2)	53.7 (SD = 23.44)	48.11 (SD = 21.89)	70.9 (SD = 10.5)	31.4 (SD = 22.3)	24.3 (SD = 34.3)	13.7 (SD = 0.9)	49.65 (SD = 15.9)	52.45 (SD = 17.9)	

a. Data not used for analysis.

Table 4. Sociodemographic characteristics of discontinued subjects in non-drug intervention trials.

Reference	Number of subjects	Age (Mean and SD)	Sex (%)		Race (%)			Education (% or years)		Employment Status (%)	
			Male	Female	Caucasian	African American	Hispanic	Education (% or years)	Employed	Unemployed	
29	257	28.5 (SD = 4.5)	82.50	17.50	N/A	N/A	N/A	64.7% ^a	45.10	42.40	
36	NA	40.8 (SD = 10.7)	51	49	29	71	0	13.3 (SD = 2.4)	57	43	
37	276	73 (SD = 9.0)	33	67	85.10	8.30	5.40	12 (SD = 3.6)	N/A	N/A	
27	216	29 (SD = 9)	43	36	40	46	37	12.5 (SD = 3)	43	33	
38	14	60.6 (SD = 14.3)	14	86	79		21 ^a	12.9 (SD = 2.0)	21	79	
39	90	62.4 (SD = 14.4)	63	37	71		29 ^a	13.8 (SD = 3.0)	N/A	N/A	
Total trials (n = 6)	853	49.05 (SD = 18.8)	47.7 (SD = 23.7)	48.75 (SD = 24.4)	60.82 (SD = 24.8)	41.76 (SD = 31.5)	21.2 (SD = 22.3)	12.9 (SD = 0.69)	41.5 (SD = 15.0)	49.3 (SD = 20.2)	

a. Data not used for analysis.

who completed the participation in the clinical trials (66.2%) (Tables 1 and 2).

Non-Drug Intervention Trials

Age

The mean age for completers was 49.9 (± 19.3) and for the discontinued subjects it was 49 (± 18.9) (Tables 3 and 4).

Gender

The mean percentage of the males that discontinued from the non-drug intervention clinical trials was 47.75% (± 23.79), while the mean percentage of the female participants who discontinued from the same set of trials is at 48.75% (± 24.48) (Tables 3 and 4).

Race

The mean percentage of the Caucasian subjects who completed the trials is 70.9 (± 10.5); discontinued subjects were 60.82 (± 24.8) Caucasian. For African American subjects, the mean percentage of the completers is 31.4 (± 22.3) versus discontinued subjects at 41.7 (± 31.5). For Hispanic subjects, the mean percentage of the completers is 24.3 (± 34.3) versus discontinued subjects at 21.2 (± 22.3) (Tables 3 and 4).

Unemployment

The mean percentage of the discontinued subjects who are employed in the non-drug intervention clinical trials is 41.5 (± 15.0), while the mean percentage of the discontinued subjects who are unemployed in the same set of trials is 49.4 (± 20.2) (Tables 3 and 4).

Level of Education

The mean years of education for subjects who completed the clinical trials is 13.7 (± 0.9), while the mean years of education for subjects who discontinued from the clinical trials is 12.9 (± 0.7) (Tables 3 and 4).

Discussion

Age

There is some difference in age (~ 4.0 years) between completers and discontinued subjects in drug intervention trials, while there seems to be no apparent difference in age among completers and discontinued subjects in non-drug intervention trials. Thus, older subjects discontinued from drug intervention trials at a higher rate, while there is no such difference in non-drug intervention trials.

Gender

Analysis of both drug intervention and non-drug intervention clinical trials failed to establish any influence of gender on the

discontinuation of subjects from clinical trials, thus contradicting a common assumption. The difference between completers and discontinued subjects in both sets is only about 1%.

Race

Racial intervention could not be done for drug intervention clinical trials because of a lack of available data. Analysis from non-drug intervention clinical trials showed that African American subjects discontinued at a higher rate compared to other races in the same set of trials. This finding seems to agree with the earlier assumptions.

Unemployment

There is high percentage of discontinued subjects who are employed when compared to unemployed subjects in drug intervention trials. However, data analysis for non-drug intervention clinical trials agreed with the assumption that the unemployed subjects discontinued more than the employed subjects.

Education Level

Analysis of both drug intervention clinical trials and non-drug intervention clinical trials revealed that lower level of education does not seem to have influence over the incidence of discontinuation from the clinical trials. The difference between completers and discontinued subjects is minimal.

To more accurately address the issues raised here, we suggest that all sources for clinical trial information should include and consistently document and report sociodemographic data for both completers and discontinued subjects. Data that are currently available are difficult to compare because of differences in the format of the data presented. For example, some of the trials presented the age for completers and discontinuers in the format of mean age and standard deviation, while some other trials presented in a format of some percentage above a particular age, for example, 40 or 50 years old.

The same difficulty was encountered for education. Some trials reported education in mean years and standard deviation, while others presented the percentage of highly educated subjects. Hence, one cannot accurately determine if real differences exist.

We recommend that all investigators adopt a common format in presenting the data. Investigators should include the marital status as single, married, or divorced/widowed. This characteristic might help to understand whether family obligations and child care would put study participants at a greater risk for discontinuation.

Socioeconomic status is recommended to be included in all reports. This characteristic may be the most important socio-demographic factor that influences discontinuation. Failure to

gather this information might lead to generalizations that some minorities are at a greater risk of discontinuation. Race may actually have much less influence than socioeconomic status. Every effort should be taken to employ a standardized format when reporting socioeconomic or income level. One suggested format is that researchers use variables such as low, mid, or high income levels based on the federal government guidelines. If every clinical trial used similar formats, the data could be interpreted across studies.

Efforts should be taken in all the future clinical trials to include the variables such as unemployed or full-time employment or part-time employment to accurately judge the influence of this characteristic. Stating simply employed or unemployed would not be a sufficient characteristic, as time spent in clinical trial participation is highly influenced by the amount of available time one has, which depends on one's full-time, part-time, or unemployed status.

Data obtained from future analyses might help researchers to identify groups at higher risk of discontinuation and therefore might necessitate increased enrollment of these groups or special attention to these participants to minimize attrition.

Conclusion

Sociodemographic characteristics such as age, gender, and education level do not seem to have an influence on the discontinuation rates of subjects in the clinical trials. African Americans do seem to be at a higher risk of discontinuation from clinical trials based on the available data, although this finding may be influenced by socioeconomic status. No conclusion may be made on the influence of unemployment, as contradictory results were observed in drug intervention and non-drug intervention clinical trials. These findings are merely preliminary. Further research and consistent methods of demographic documentation are necessary to more accurately predict clinical trial subject retention.

Declaration of Conflicting Interests

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