



Clinical Trial Retention Meta-analysis

How Patient Recruitment Methods Directly Relate to the Retention of Subjects

Patient recruitment methods can have a significant effect on the retention of subjects in clinical trials; these effects can result in considerable cost implications. Subjects that actively sought clinical trial involvement through an online pre-screener (in response to online clinical trial advertising) using the MediciGlobal model, showed 38% lower relative risk of dropout across four studies compared to those who were recruited by sites [95% confidence interval (CI) 19%–53%], with divergence across visits in all four studies. Since increasing sample size is typically associated with an increase in the statistical power of the study, the loss of subjects over the course of a trial can result in missed endpoints, and negatively impact the outcome of the study. Engaging subjects that actively seek clinical trial participation results in a reduction of study withdrawals or patient dropout rates; the effect of which eliminates the need for over-enrolment of patients to offset expected retention loss. Increased retention rates accelerate enrolment timelines and result in saving time and money.

Rationale: Enrolling subjects into clinical trials is, needless to say, crucial to the development of new medicines and new treatment indications. But keeping subjects enrolled is also critical to ensure that the statistical power of the study is achieved, particularly for ‘intent to treat’ analyses. Overlooking patient retention issues at the beginning of a study can lead to costly implications later, either in failing to achieve endpoints, or the potential for re-opening recruitment to offset higher-than-expected attrition rates.

Recruitment for clinical trials is performed in various ways; site databases, insurance claims data, pharmacy databases, digital and social media marketing, targeted mailings, traditional media, patient advocacy and other methods. Digital techniques such as web-based screening have been documented to increase recruitment efficiency rates in several studies.^{1–4} However, it is not well understood what effect, if any, these different routes to enrolment have on retention rates amongst subjects. A 2009 study by Raynor et al. evaluating recruitment methods across two paediatric obesity trials reported higher retention rates amongst subjects that had initiated their own enrolment, by responding to advertising when compared to those that had been reached out to by the site.⁵

To further investigate this question, a meta-analysis of four studies has been performed comparing attrition rates for subjects that took an active role in their recruitment to those that were passively approached. The aim of the analysis is to determine whether the route of entry has an effect on the probability of dropout.

During the course of the recruitment process, many factors vary which could alter the attrition rates of subjects, including method of first contact – whether the subject is approached for trial inclusion, or whether they sought out inclusion in the trial independently. In addition, the length and methodology of pre-screening procedures vary. For example, some subjects may undergo automated phone-based screening, compared to others that undergo a two-step process of online pre-screening combined with nurse follow-up — a ‘second level’ of pre-screening before the patient is referred to a research site for an initial screening visit.

Hypothesis, Objective and Outcome Measures

It is arguable that a passively approached patient (not actively seeking a clinical trial and invited by a medical professional to participate) may differ in their motivation to join a trial compared to a patient that proactively seeks trial inclusion. Proactive versus passive methods to clinical trial enrolment may impact subject retention. The objective of this meta-analysis is to quantify the end of study difference in attrition levels between randomised subjects that actively sought out clinical trial participation versus those that were approached passively.

The primary outcome measure was retention rates of subjects that enter trials by actively seeking them out, compared to subjects that enter by being approached by a medical professional. A secondary outcome was retention rates across all study visits, to determine divergence patterns between the two groups. **Patients not actively seeking clinical trial participation may differ in their motivation to join a clinical trial compared to a patient that proactively seeks trial inclusion.**

The study populations were subjects of randomised controlled clinical trials, which showed two clearly identifiable and distinct subject groups. Group A entered the trials through MediciGlobal’s recruitment model of advertising coupled with intensive online pre-screening for study inclusion/exclusion criteria, with further phone follow-up by a nurse for secondary pre-screening prior to being referred to a study site. Group B were recruited by medical professionals at study sites, with many subjects being offered study participation through referral by their healthcare professional, or contacted as a result of a database review. In such cases, patients played no active role in initiating the recruitment process. However, it should be noted that a small portion of group B played an active part in their recruitment by responding to site advertising. In total, early termination data from 2849 subjects was assessed for a minimum of seven months across four studies.

Search Strategy

Using PRISMA guidelines, systematic searches of MEDLINE, the Cochrane Library and the Educational Resources information centre were performed. These included studies from the past five years and produced 714 results, of which two compared the role of active and passive recruitment strategies to retention rates, underlining the lack of information and need for further research in this area.

Search terms included clinical trial retention, recruitment strategies, and attrition. See Table 1 for the full list of search terms. In order to be included, studies were required to have at least six months of retention data, specifying which subjects terminated early from the study, from the point of first randomisation. Neither of the two studies identified as relevant were found to have sufficient dropout data to be included in the analysis. The MediciGlobal database of past studies since 2009 was also searched for suitable studies, with four studies meeting the inclusion criteria.

In three out of four of the studies, data were available to show dropout rates at every study visit until the final visit. The fourth longer-term study is ongoing with final visit data yet to be collected.



Methodology

For all four studies conducted by MediciGlobal, study visit attendance data was counted from the point of randomisation, through to the final visit (or in the case of the ongoing study, to visit 9 out of 10). The number and percentage of dropouts at each visit were calculated for each group, as shown in Table 2. The data included interim patients who had neither dropped from nor finished the study. These subjects had their visit attendance counted, but did not appear in the dropout counts, therefore the percentage dropout rate at each study visit only included discontinued patients.

the historical data. P values were calculated using the Poisson test for individual studies, and 95 % confidence intervals were calculated.

Relative risk was calculated to show the difference in risk of dropout between group A and B, and then data sets were combined to give overall relative risk of dropout across all studies. Heterogeneity or “non-combinability” was tested for using chi square statistic of Cochran’s Q (defined as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being the number of subjects in each group of each study, as used in the pooling method).

Study 4	Baseline	Visit 3 week 2	Visit 4 week 6	Visit 5 week 13	Visit 6 week 26	Visit 7 week 39	Visit 8 Week 52	Total ET
Number of dropouts (last visit attended) - Group A	3	2	4	5	4	2	0	20
Number of dropouts (last visit attended) - Group B	24	29	47	58	20	9	4	191
Group A randomisations that attended visit	112	109	107	92	89	78	60	
Group B randomisations that attended visit	777	753	724	677	502	301	173	
Group A dropout rate	3%	2%	4%	5%	4%	3%	0%	
Group B dropout rate	3%	4%	6.5%	9%	4%	3%	2%	

Table 2 Visit attendance and early dropout counts for study 4

End of Study Retention Projection	Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Total ET (%)	Difference	Poisson test (p value)
Group A Dropout rate	3%	2%	4%	5%	4%	3%	0%				
100 Group A Randomisations	100	97.3	95.5	92.0	87.0	83.1	80.9	80.9	19.1	31%	u=28, x=19
Group B Dropout rate	3%	4%	6.5%	9%	4%	3%	2%				
100 Group B Randomisations	100	96.9	93.2	87.1	79.7	76.5	74.2	72.5	27.5		0.02

Table 3 Comparing attrition rates for study 4

The end of study retention percentages were calculated by applying the observed dropout percentages for each group at each visit, as shown in Table 3. This accounted for the interim nature of the data by assuming that a percentage of subjects that neither discontinued nor completed the study would drop out in line with

Results and Discussion

When plotting actual early terminations from groups A and B and disregarding subjects that are yet to complete the study, all four studies display a lower relative risk of dropout by the end of data collection for subjects that played an active role in seeking out trial

inclusion compared with passive recruitment. This ranged from a relative risk of 0.72 (28% less likely to drop out) to a relative risk of 0.52 (48% less likely to drop out). One was found to be statistically significant when the studies are considered alone, as shown in Figure 1, in which three out of four of the studies have 95% confidence intervals which cross the “no-effect” line. However, combining the data from all four studies shows a statistically significant reduction in risk of dropout of 38% for the active group overall. It is also 95% certain that the true reduction in risk lies between 19% and 53%.

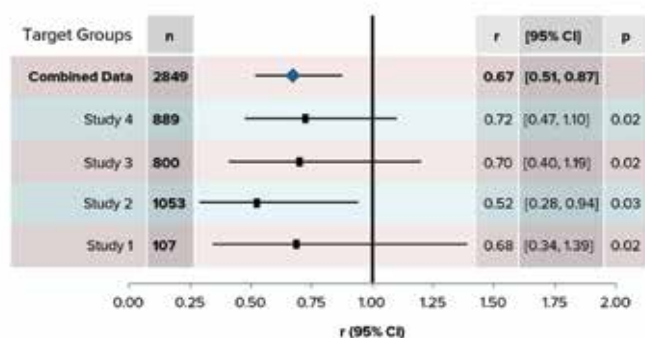


Figure 1 Relative risk of dropout of patients who played an active role in their recruitment as opposed to passive. Subjects actively seeking enrolment show 38% lower risk of dropout than those approached for enrolment [95% CI 19%–53%]

Despite the clear improvement in retention rates for actively seeking subjects, there was found to be an 89% chance of heterogeneity, meaning it is highly likely that recruitment method A or B is not the only factor affecting the retention levels within these studies. This limits the combinability of the results and brings into question what other factors may be at play. Compounding factors include trial design, intervention and therapy area. Future studies could improve on this analysis by controlling for these factors where possible, for example, combining the results from studies within the same therapeutic area.

The retention differences between groups A and B increase with time across all four studies, as shown in Figure 2. Group A — those taking an active role in their own recruitment through a MediciGlobal recruitment model showed superior retention rates in each case compared to those subjects recruited by sites. Interim study visits are accounted for by applying the actual dropout percentage at each visit to the whole group. The difference in retention rates between groups A and B by the end of study vary from 31%, as shown in study 4, to 41%, as shown in study 2. When counted across studies, group A shows lower dropout percentages than group B at 16 out of 26 visits (62%), equal dropout levels at five visits (19%) and greater dropout levels at five visits (19%).

There may be multiple factors resulting in the retention differences, such as the motivation of the subjects in each group, or study-specific reasons. Factors could include the process of vetting candidates, differences in access to healthcare between the two groups, personalities of people proactively researching their options or financial motivations. Further research in this area is needed to better understand the motivations of subjects entering research through various channels.

Firstly, in all of the studies included, the process of vetting candidates from the proactive group was sufficiently thorough that only high-quality, motivated candidates make it through to

randomisation. Such methods include a comprehensive online or telephone pre-screener (or both) during which the inclusion/exclusion criteria are applied, before the candidate is passed on to the site as a referral. In the mainly passive group, the candidate usually starts off being reached out to directly by the study site or healthcare professional.

As previously mentioned, Raynor *et al.* (2009) found that enrolled subjects responding to advertising, such as newspapers, internet and television ads) dropped out at a lower rate in comparison to those contacted by sites directly.⁵

Secondly, people come from a variety of backgrounds and have different levels of access to healthcare. One 2014 study on recruitment strategies by Maghera *et al.* published in the journal of BMC Medical Research Methodology found that recruitment strategy has an effect on the demographic profile of applications such as family income, university attendance and race.⁶

Those that were contacted passively, through their healthcare professional or other databases, have all had access to medical treatment at some point, and may be more likely than those who are seeking inclusion in clinical trials to still have access to healthcare. People who are unable to access healthcare may seek out clinical trials and be more committed to completing a study, and therefore drop out at a lower rate.

Thirdly, people vary in their behaviours when facing medical problems. Some proactively seek out information and options, whilst others take no action. It can be argued that those actively seeking inclusion in trials may contain a larger proportion of the proactive part of the behavioural spectrum than those who were approached. A 2002 study on cancer prevention programmes by Linnan *et al.* published in the Annals of Behavioural Medicine found that subjects who responded to recruitment advertising as opposed to being approached offered significantly higher “reach” within the study (such as giving permission to be called at home) than those who were approached (74.5% vs. 24.4%).⁷ In addition, those who are proactively researching their options are seeking to reach their own conclusion regarding whether to participate in a trial or not. This may also lead to firmer decisions being made, and lead to lower dropout levels.

In addition to the retention boost that an actively-initiated pre-screening process can produce, one 2012 study on cost efficiency in randomised trials by Yu *et al.* in the journal BMC Medical Research Methodology found that a two-stage screening procedure, including a pre-screening phase, significantly reduces costs.⁸

Conclusion

This analysis has shown that the method used for patient recruitment had a significant effect on patient retention rates in clinical trials. Subjects that actively sought out clinical trial involvement through MediciGlobal’s online recruitment model showed 38% lower relative risk of dropout across four studies compared to those who were recruited by sites — the majority of which played a passive role in initiating enrolment [95% CI 19%–53%]. The retention levels of the active and passive groups diverged across visits in all four studies. Higher retention levels of actively recruited subjects compared to those that were approached may be related to different motivations between the groups, and in part due to the comprehensive vetting procedures used on the active group. More research is needed to understand the cause of these differences.

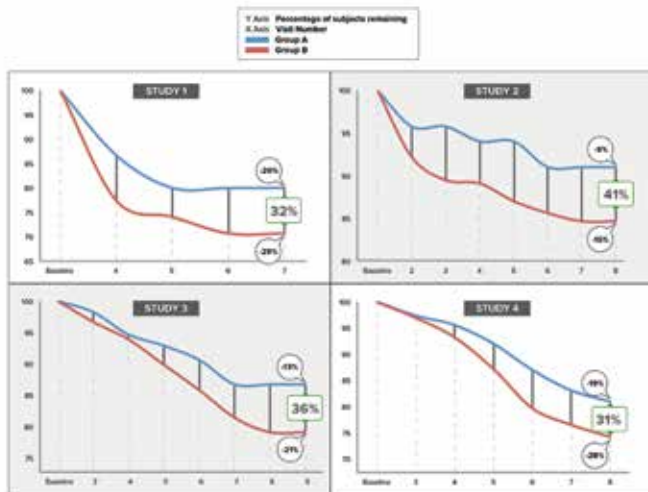


Figure 2 Retention percentages of studies by visit number

From a business and data perspective, retaining subjects is the most important aspect of maintaining data integrity and sustaining the statistical power of a study. The loss of too many subjects over the course of a trial, particularly those with data that will undergo intention to treat analyses, could jeopardise the drug approval process. If necessary, re-opening a study for enrolment is hugely costly and results in lost time. Recruiting subjects that are actively seeking clinical trial enrolment minimises the risk of dropout, and could make the difference between re-opening enrolment or not, saving significant time and money in the process.

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