Clinical Trial Pre-Screening Methods: A Meta-Analysis

A Two-step Pre-screening Process Before Site Referral Improves Efficiency and Reduces Costs

Executive Summary
Clinical trial recruitment involves three distinct phases: (1) Connecting with patients through advertising and outreach; (2) Engaging patients through pre-screening; and (3) Referring pre-screened patients to study sites. This paper focuses on how the second phase can be used to significantly reduce costs and increase trial efficiencies. While selecting the right patient for the right clinical trial can vary in terms of methodology, not all methods produce the same quality candidate in a time-efficient manner, or deliver the same cost-effectiveness.

A two-step screening process can reduce costs and improve screening rates

A meta-analysis involving four clinical trials that retained the services of MediciGlobal for their patient recruitment and pre-screening services revealed the following key insights:

- A multi-step pre-screening approach compared to a single-step (online) pre-screener increases on-site screening per 100 referrals by ~12 % [90 % confidence intervals of 2 % - 22 %]. This means that, on average, study sites will process 12 more screens for every 100 patients referred when using multi-step pre-screening, compared to using a single-step approach.
- A multi-step pre-screening approach provided quality referrals to study sites by removing a significant number of non-viable applicants and, conversely, adding applicants that might have otherwise not been referred to sites (due to incomplete pre-screening data) after follow-up by a nurse. Importantly, consistency of pre-screening against the inclusion/exclusion criteria was applied across the studies.

Furthermore, these analyses found that a multi-step pre-screening process can save sites considerable time and effort, whilst also potentially reducing recruitment-related costs.[1,2]

In addition to these findings, a previous meta-analysis by MediciGlobal found that randomised subjects that had been pre-screened were subsequently ~40 % more likely to remain in a clinical trial than those passively recruited from a site's database, irrespective of whether a multi-step or single-step pre-screening method was employed.[3] Collectively, these insights demonstrate that patients (or caregivers) who engage in single-step and multi-step pre-screening contribute to clinical trial efficiencies, reduced costs and improved retention rates.

Background

In a 2012 article published in BioMed Central Medical Research Methodology, Yu et al. discuss how a two-step screening approach can result in significant savings in randomised trials. The authors simulated a model to optimise cost-efficiency when designing randomised trials. They found that 8.9 % of total costs (including pre-screening, screening and intervention costs) can be saved by the use of a two-step pre-screening process compared to a single step. These savings are achieved by deselecting candidates who fail to meet initial protocol criteria from being referred to the study site, thereby reducing the number of unsuccessful (and more costly) on-site screens.[1]

It is well documented that the internet is a major source of health information. As a result, digital advertising is a cost-effective patient recruitment method for clinical trials.[2] A recent 2014 study showed that online patient recruitment offers greater precision in reaching and engaging the most relevant patients. The study further showed that internet-enrolled subjects have better response to treatment rates than subjects sourced by traditional print ads.[4]

A model by Yu *et al*. in 2012 found that two-stage pre-screening can save 8.9% of total costs.

At MediciGlobal, the majority of clinical trial recruitment projects involve digital advertising and employ two- to three-stage pre-screening strategies. These include an initial thorough online pre-screener, a follow-up "second level screening" (SLS) with a nurse by phone, and potentially the collection of patients' medical records. MediciGlobal's online pre-screener first matches patient applicants against the study protocol inclusion/exclusion criteria, and subsequent SLS follow-up phone call(s) to patients collect additional information to further determine potential clinical trial eligibility. The algorithm established for each pre-screener is metrics-based. Depending upon the specifications of the study protocol, SLS serves to reduce the number of questions asked online and allows for even greater detail about a patient's medical history to be gathered by shifting certain pre-screening questions to a nurse-patient conversation. SLS is also conducted when a study applicant's response to a pre-screener question triggers an alert that more in-depth data collection is required (such as if a respondent leaves important questions blank, or has a condition that may restrict them from entry in some cases).

Methodology

To investigate the full range of benefits resulting from multi-step pre-screening, multiple analyses have been conducted: A meta-analysis was conducted of four clinical trials that compared on-site screening rates of referrals that underwent single-step versus multi-step pre-screening conducted by MediciGlobal. Additional analyses were performed on time spent by MediciGlobal

nurses making calls to referrals that would otherwise have fallen to site staff, along with reasons for disqualifications to ascertain the 'quality' of patients referred, and how closely patient applicants met the criteria for the clinical trial.

Results and Discussion

The advantages of utilising a multi-step pre-screening process includes higher numbers of screens per 100 referrals sent to sites, as well as higher-quality referrals (defined as those more serious about study participation and those more likely to qualify for the study). This results in improved efficiency (the ability to screen more patient referrals), leading ultimately to reductions in recruitment costs and staff time.

A meta-analysis of four studies found multi-step pre-screening increases the proportion of referrals screened at sites by 12%

Improved Screening Levels

In the analysis of four studies that utilised MediciGlobal's services for recruitment, data shows that patient applicants that underwent a multi-step pre-screening process were 12 % more likely to be screened on-site than those that underwent a one-step (online) pre-screener process only (2 %-25 % to 90 % confidence intervals), as

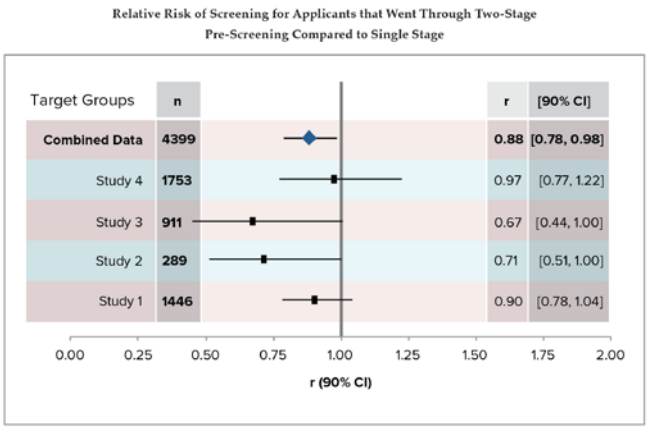


Figure 1 Data from four studies shows improved screening levels of 12% for multi-step pre-screening processes. [Relative risk 0.88 to 90% confidence intervals 0.98-0.78]

shown in Figure 1.

Follow-up calls to applicants eliminate unqualified referrals

It is important to note that other factors in addition to the multi-step pre-screening processes can affect screening levels. The four study meta-analysis (shown in Figure 1) indicated that heterogeneity testing resulted in a 99.96 % chance that project differences between screening levels are at least partially due to other factors such as protocol or disease idiosyncrasies. One reason a multi-step pre-screening process improves the percentage of referrals screening at sites, is because follow-up calls to applicants generate further 'filtering', resulting in the elimination of unqualified referrals due to factors related to protocol design, but also due to other factors such as a change of heart, logistics or unavailability. Notwithstanding the multi-step pre-screening process, some patient applicants (albeit few) were referred to study sites for discretionary review by the physician investigator to ascertain eligibility, as shown below.

Removal of Uninterested/Unavailable Applicants

Referrals were less likely to be disqualified from the site for non-medical reasons by an average of 17%

Importantly, the multi-step pre-screening process filtered out applicants not fully engaged in the clinical trial process. Since the pre-screening process requires an investment of time, those not fully engaged/not interested or unable to attend study visits are removed through the multi-step process. The success of the multi-step pre-screening process in extricating applicants from being referred to study sites due to non-medical reasons, such as lack of study commitment, transportation, or time availability to attend study visits, was decreased by

Site-Based Disqualification Rate for Generic (non-project specific) Reasons				
Project	Indications	Two-Step Pre-screen	One-Step Pre-screen	Less likely to be Disqualified by the Medical Site
Study 1	Alzheimer's	36%	44%	20%
Study 2	Ménière's	43%	44%	4%
Study 3	Interstitial Cystitis	50%	63%	26%
Study 4	Gout	No data collected		
Average		**43%**	**50%**	**17%**

Table 1 Rates at which sites disqualified referrals based on the one-step and two-step pre-screening process for non-protocol (medical) reasons (logistics, time availability, study commitment)

an average of 17 % across three of the studies (ranging from 4 % to 26 %).

The end-of-study retention percentages were calculated by applying the observed drop-out 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 the historical data. P values were calculated using the Poisson test for individual studies, and 95 % confidence intervals were calculated.

High-quality Medical Applicants

The impact of second-stage pre-screening on the percentage of patients disqualified for medical reasons at study sites depends greatly on the strategy used. For example, when a two-step pre-screening process is applied to 100 % of patients before being referred to sites, the percentage of patients disqualified at site for medical reasons will be reduced, as shown in Table 2, Study 2. In this project, single-step pre-screening was changed in favour of two-step pre-screening eight weeks through the project, and as a result on-site medical disqualifications decreased by 62 % . Importantly, since the two-step pre-screening was introduced partway through the project, the impact of this pre-screening intervention could be effectively benchmarked against a one-step pre-screening method.

Follow up strategy is customisable, and maintains or increases the medical quality of referrals

On the other hand, some clinical trials employ a strategy that follows up only some respondents before referring them to sites, with the rest being sent straight through to sites. In these cases, the pool of applicants that are followed up tend to be more likely to disqualify, either because they've missed out answering some questions online, or because they've indicated that in some way they may be outliers with regard to the inclusion/exclusion criteria and require further investigation. In these cases, despite follow-up calls removing the vast majority of applicants from the referral pool, the medical disqualification rate is higher for two-step screening applicants than it is for the single-step applicants. This can be seen by studies 1 and 3 in Table 2, with the two-step pre-screening groups disqualifying at 12-13 % higher. However, it is important to remember that without a two-step pre-screening process, the difficult choice about whether to remove these referrals from the referral pool (and subsequently losing a large number of randomised patients), or sending some or all of them through to sites without follow-up (and subsequently burdening sites) would need to be made. By employing a partial second-stage pre-screen process the subjects are neither lost, nor the sites over-burdened, maintaining recruitment efficiency and optimising marketing spend.

Site-Based Disqualification Rate for Medical Reasons				
Project	Indications	Two-Step Pre-screen	One-Step Pre-screen	Less likely to be Disqualified by the Medical Site
Study 1	Alzheimer's	33%	29%	12%
Study 2	Ménière's	20%	32%	-62%
Study 3	Interstitial Cystitis	19%	16%	13%
Study 4	Gout	No data collected		
Average		**24%**	**26%**	**-12%**

Table 2 Rates at which sites disqualify referrals from the one-step and two-step referral pool for medical reasons

Time Saved at Sites

Hundreds of hours of site time can be saved by a second stage of pre-screening

Time is a scarce commodity at study sites, and delays in following up with referrals can result in patient applicants losing interest. This can also slow the pace of enrolment. A multi-step pre-screening process can significantly reduce staff time at sites for patient referral follow-up, as shown in Table 3. Looking at study 1, it can be seen that 959 referrals were sent through to sites following follow up calls, with 200 hours being spent calling these referrals collecting further data to be passed on to sites, and 54 hours spent disqualifying non-suitable applicants. Study 4, on the other hand, sent 325 referrals through to sites following follow-up calls. Only 17 hours were spent confirming suitable referrals eligibility before referring to sites, and 149 hours were spent eliminating unsuitable applicants. This demonstrates the versatility of multi-stage pre-screening, as the call triggers and questions asked at each stage can be tailored to best suit the project. Each pre-screening step serves to remove applicants early

Project	Indications	Total calls	Referrals	Total Call Time (hours)	Call Time (referrals)	Call Time (Disqualified applicants)	Average Call Duration (mins)
Study 1	Alzheimer's	3102	959	254	200	54	13
Study 4	Gout	4594	325	166	17	149	3.2

Table 3 Rates at which sites disqualify referrals from the one-step and two-step referral pool for medical reasons

to ensure that only 'quality' patient referrals (those most likely to meet protocol criteria) were sent to study sites.

Case Studies

Study 1, an Alzheimer's study, applied both one-step and two-step pre-screening methods. The second step was applied only to applicants with borderline or incomplete answers to the online pre-screener. Of 1446 applicants, 34 % were referred directly to study sites based on information provided via the online pre-screener. The remaining 66 % underwent another level of pre-screening with nurses; 3100 outbound follow-up phone calls by nurses resulted in 959 patient referrals. These referrals screened at a rate of 30 %, compared with 28 % for those that underwent one level of pre-screening. Table 1 shows that the rate of disqualification for generic, non-medical reasons also decreased by 20 % for those that had been through the two-step process, but that two-step referrals were still 12 % more likely to disqualify for medical reasons, owing to the fact that some inclusion/exclusion criteria were open to the discretion of the investigator at the study site. It can be seen that 254 hours of MediciGlobal nurse time was spent following up with applicants – much of which time would have been passed to sites if the multi-step pre-screening process had not been used.

Study 2, a study for Ménière's disease, applied second-level pre-screening (SLS) to applicants whose answers designated them as 'probable' candidates and whereby additional information was required. This was modified to include 100 % of applicants at week 8. This decision was based on metrics showing a higher conversion rate of patients referred and screened via SLS. SLS calls to patients completing the first step of pre-screening improved screening rates by 29 %. One-step pre-screening had a pre-screen fail rate of 23 %, whereas the two-step pre-screening process disqualified 31 % of patients, thereby further qualifying applicants based on their medical histories and their match to the study's inclusion/exclusion criteria, before reaching the study sites. While non-medical disqualifications at the study site only decreased by 4 %, patients disqualified for medical reasons decreased by 62 %.

Study 3, a study for interstitial cystitis, implemented a two-step pre-screening process after an analysis revealed a high disqualification rate amongst the initial referrals. This resulted in a 33 % improvement: one-step pre-screening (utilising online pre-screening alone) screened out 14 % of applicants compared to 20 % of patients who underwent a two-step pre-screening process.

More than four weeks (166 hours) of MediciGlobal

nurse time was spent following up with potential referrals in study 4, a clinical trial for gout. A two-step pre-screening process was applied to patients who provided responses to pre-screener questions that warranted additional insight. During the duration of the recruitment period, 1753 referrals were sent to study sites, of which 325 patients referred had been through the two-step process. Overall, 16 % of both the single-step pre-screened and multi-step pre-screened referrals were screened, demonstrating how SLS maintains referral quality. In this case, the second stage of pre-screening yielded 52 screens from a large pool of candidates with low-quality data from the online pre-screener. These referrals would otherwise have been lost from the study if not referred to sites, or would have required valuable site follow-up and screening time if they had been referred to sites.

Conclusion

A two-stage pre-screening process increases screens per 100 referrals, reduces marketing and onsite screening costs and makes more efficient use of site staff resources.

Clinical trial recruitment strategies that engage patients (and caregivers) through online, advocacy and traditional media campaigns would benefit from including multi-step pre-screening processes before patients are referred to study sites.

Sponsors that invest in pre-screening processes, including online pre-screening, nurse pre-screening by phone, and obtaining patients' medical records, will increase the quality of patients referred by an average of 12 %, as shown by increased site screening levels within the multi-step group. Applicants who are uninterested or unavailable for studies are removed before sites attempt to make contact, and the application of inclusion/exclusion criteria can be made more rigorous and consistent across the study.

From an overall clinical trial management perspective, a multi-step pre-screening process can reduce costs in multiple ways:

- Increased productivity; with more screens per 100 referrals sent to study sites;
- Potential reduction in marketing expenditures; since multi-step pre-screening allows referrals that might otherwise not have provided enough information to be viable with single-step pre-screening to be sent to sites;
- Reduction in the number of screen fails at study sites (due to screening of non-serious applicants or medical reasons);
- More efficient use of staff resources at the study sites, which enables sites to focus on recruiting more patients, thus allowing potentially faster enrolment speeds and preventing potential subjects from losing interest.

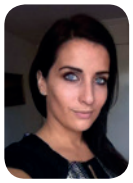
The cost-saving benefits to pharmaceutical sponsors can be combined with previous analyses by MediciGlobal that showed higher levels of engagement and, subsequently, higher retention rates amongst patients that underwent single-step and multi-step pre-screening. These analyses found that MediciGlobal referrals were retained at a combined 38 % higher rate compared with other referrals.[3]

The benefits of utilising MediciGlobal's online and metrics-driven recruitment methods combined with multi-step pre-screening are significant. The improved efficiencies result in time and cost savings, both of which are critical factors in accelerating recruitment and driving quality results.

References

1. Yu M, Wu J, Burns DS, Carpenter JS. Designing cost-efficient randomized trials by using flexible recruitment strategies. BMC Medical Research Methodology 2012 Jul 24;12:106.
2. Raynor HA, Osterholt KM, Hart CN, Jelalian E, Vivier P, Wing RR. Evaluation of active and passive recruitment methods used in randomized controlled trials targeting pediatric obesity. International Journal of Pediatric Obesity 2009;4(4):224-32.
3. Jackson C, Ozdemir U, Moench L. Clinical Trial Retention Meta-Analysis. Drug Information Association Global Forum 2015 June.
4. Carmi L, Zohan J. A comparison between print vs. internet methods for a clinical trial recruitment—A pan European OCD study. European Neuropsychopharmacology 2014;24(6):874-878.

Liz Moench, President and CEO of MediciGroup® Inc, has implemented innovative programs that have changed the pharmaceutical industry twice in her 30 year career. Her achievements include launching the industry's first direct-to-consumer advertising campaign (1983) for Boots-Ibuprofen, and pioneering the first direct-to-patient clinical trials recruitment for Taxotere (Rhone-Poulenc Rorer Pharmaceuticals, now Sanofi-Aventis) in 1991. Today her pioneering initiatives involve optimising digital strategies and social media for patient recruitment and engagement, including development and management of some of the largest online patient communities globally like Team Epilepsy, Gout Study and Lupus Team to promote clinical research.



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