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Factors influencing recruitment and retention of participants in clinical studies conducted at a tertiary referral center: A five-year audit

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Abstract

Introduction: A key determinant of the success of any study is the recruitment and subsequent retention of participants. Screen failure and dropouts impact both the scientific validity and financial viability of any study. We carried out this audit with the objective of evaluating the recruitment and retention of participants in clinical studies conducted over the last five years at our center.

Methods: Studies completed between 2014 and 2018 at our center were included. Screening ledgers and study trackers were hand searched for screen failures and dropouts. Four pre-identified predictors were evaluated – risk as per the classification of Indian Council of Medical Research 2017 Ethical Guideline, nature of funding, study design, and nature of participants. Association of the predictors with screen failures and dropouts was determined using crude odds ratios along with 95% confidence intervals. All analyses were done at 5% significance using Microsoft Excel 2016.

Results: A total of $n = 19$ completed studies had $n = 2567$ screened and $n = 2442$ enrolled participants with a screen failure and dropout rate of 5% and 4%, respectively. We found 59% screen failures due to abnormal laboratory values. The main reasons for dropouts were lost to follow-up 86 (88%). High-risk and interventional studies were the predictors for both screen failures and dropouts, but pharmaceutical industry-funded studies and healthy participants were predictors for only screen failures.

Conclusion: Risk, funding, study design, and nature of participants are important to be considered while planning studies to minimize screen failures and dropouts.

Keywords: Dropouts, healthy participants, high-risk studies, pharmaceutical industry-funded studies, screen failures

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INTRODUCTION

A key determinant of the success of any study (academic or regulatory) is the recruitment and retention of participants. Successful recruitment and retention enables fulfillment of requirements of the calculated sample size and helps the study hypothesis to be tested. This is, however, one of the most challenging aspects of any study.[1] Low rates of recruitment and retention are known to have a detrimental

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effect on the scientific validity and financial viability of studies.[2] Screen failure rates of 20%–30% and dropout rates of 15%–40% in clinical trials are known, and 86% of all clinical studies in the United States fail to recruit the required number of participants in a timely manner as per a CenterWatch report.[3,4] A systematic review on the subject also shows that approximately 30% of investigators have suboptimal enrollment in clinical studies.[5] The consequences of low recruitment and retention include delay in study completion, lowering of statistical power, delay in bringing the investigational product to the market and thus delaying patient access, pressure on funding agencies, and in extreme cases, study termination.[6]

Literature on this subject is largely restricted to studies conducted in developed countries, and this literature also includes strategies to strengthen recruitment and minimize attrition.[7] The present study was thus envisaged as a five-year audit of recruitment and retention of participants in completed clinical studies at a tertiary referral center.

METHODS

Ethics

The Institutional Ethics Committee approved the study (EC/OA-65/2018) with a consent waiver. The authors anonymized the data using unique identifiers prior to the analysis.

Study design, selection criteria, and study sample

The audit included all clinical studies (both academic and regulatory) which were conducted and completed at our department over a five-year period (2014–2018).

Methodology

We hand searched both screening ledgers and study trackers for (1) the number of participants screened, (2) number of screen failures, and (3) reasons for screen failures. Clinical study reports were evaluated to assess (1) the number of participants finally enrolled, (2) number of dropouts, and (3) reasons for dropouts (if they could be ascertained). We also identified the phase of drug development and the therapeutic area of the study.

The studies were subsequently classified as per four pre-identified predictors. These were (1) study risk based on the classification of the Indian Council of Medical Research 2017 Guideline for Biomedical and Health Research Involving Human Participants (less than minimal risk, minimal risk, slightly above minimal risk, and high risk),[8] (2) nature of funding (whether industry-funded or investigator-initiated studies [IISs]), (3) study design (interventional or observational), and (4) nature of the participants (healthy participants vs. patients).

Outcome measures

These were (1) number of participants screened and finally enrolled and (2) number of dropouts and the reasons for the same.

Statistical analysis

Both descriptive and inferential statistics were applied. Quantitative data were described using median (interquartile range), while categorical data were expressed as proportions. The association between the four pre-identified predictors (nature of risk, nature of funding, study design, and nature of participants) and the two outcome variables (screen failures and dropouts) were evaluated using crude odds ratio (cOR) along with 95% confidence intervals (CIs). Chi-square test was used for calculating statistical significance and, $P < 5\%$ was considered as statistically significant. All analyses were done using Microsoft Excel version 16.

RESULTS

Demographics

Screening

A total of $n = 19$ studies were included where $n = 2567$ participants were screened and finally $n = 2442/2567$ (95%) participants were enrolled giving a screen failure rate of 5%. Of the $n = 125$ participants who were screen failures, 74/125 (59%) were due to abnormal laboratory values, followed by 31/125 (25%) due to consent withdrawal post-screening. Of the $n = 31$ participants who withdrew consent, 25/31 (81%) were normal, healthy participants.

Dropouts

A total of 98/2442 (4%) participants were dropouts. The reasons were lost to follow-up (86/98; 87.75%), nonadherence to protocol (05/98; 5.1%), and consent withdrawal and adverse events (01/98 each or 1%).

Analysis of studies based on study design and therapeutic areas

A total of 14/19 (74%) studies were interventional and 05/19 (26%) were observational. Among the interventional studies, a little over one-third of the studies 05/14 (36%) were either Phase II or Phase III studies, which tested either vaccines or drugs. Similarly, 05/14 (36%) studies pertained to pharmacokinetics. Two of 14 (14%) studies were first in human vaccine studies. Among the 05 observational studies, 60% (3/5) were on proteomics, whereas the remainder $n = 02/05$ (40%) were in the area of pharmacogenetics.

Classification of studies based on pre-identified predictors

1. Risk – A total of *n* = 12/19 (63%) studies were classified as high risk and the remainder 07/19 (37%) studies were low risk. There were no studies that were minimal risk and less than minimal risk
2. Funding –A total of 09/19 (47%) studies were funded by the pharmaceutical industry and 10/19 (53%) were investigator – initiated
3. Design – A total of 14/19 (74%) studies were interventional and 05/19 (26%) were observational
4. Nature of participants – More than half of the studies (10, 53%) recruited healthy participants and 07 (37%) studies enrolled patients, whereas 02 studies (10%) recruited both healthy participants and patients.

Association of predictors with screen failures

Participants screened for high-risk studies had almost 39 times the odds of being screen failures relative to the participants screened for low-risk studies (cOR – 39.4, 95% CI [17.3, 89.9]; $P < 0.0001$). Similarly, participants screened for pharmaceutical industry-funded studies had 27 times the odds of being screen failures relative to the participants screened for IIS (cOR – 27.3, 95% CI [17.4, 42.7]; $P < 0.0001$). With regard to study design, participants screened for interventional studies had 237 times the odds of being screen failures relative to the participants screened for observational studies (cOR – 237.6, 95% CI [33.2, 1702]; $P < 0.0001$) and healthy participants had almost 20 times the odds of being screen failures relative to the patient participants (cOR – 19.5, 95% CI [12.4, 30.4]; $P < 0.0001$).

Association of predictors with dropouts

Participants enrolled in high-risk studies had almost thrice the odds of being dropouts relative to the participants enrolled in low-risk studies (cOR – 2.6, 95% CI [1.7, 3.9]; $P < 0.0001$). Participants enrolled in interventional studies had almost three times the odds of being dropouts relative to those enrolled in observational studies (cOR – 2.5, 95% CI [1.6, 3.7]; $P < 0.0001$). We did not find an association between nature of funding and nature of the participants on the dropout rate.

Table 1 depicts association of predictors with screen failures and dropouts.

Table 1: Impact of pre-identified predictors on screen failures and dropouts

Variables	Variables	*P**	cOR (95% CI)
Screen failures			
High risk	Low risk	<0.001≠	39.4 (17.3-89.9)
Industry funded	IIS	<0.001≠	27.3 (17.4-42.7)
Interventional	Observational	<0.001≠	237.6 (33.2-1702)
Healthy participants	Patients	<0.001≠	19.5 (11.4-27.5)
Dropouts			
High risk	Low risk	<0.001≠	2.6 (1.7-3.9)
Industry-funded	IIS	0.26	1.4 (0.82-2.46)
Interventional	Observational	<0.001≠	2.5 (1.6-3.7)
Healthy participants	Patients	0.36	1.3 (0.7-2.5)

≠Chi-square test used for statistical significance, *$P<0.05$ was considered as significant. CI=Confidence interval, cOR=Crude odds ratio, IIS=Investigator-initiated study

DISCUSSION

Our study was a five-year audit of completed studies and found a 5% screen failure rate and 4% dropout rate among the participants. The screen failure rates of interventional studies were as high as 12.8% compared no screen failure in observational studies. But, the dropout rates among the interventional studies were 6.5% compared to 2.7% among the observational studies. It also identified that high-risk and interventional studies to be associated with a greater likelihood of both screen failures and dropouts. However, nature of funding and the type of participant were associated only with screen failures but not dropouts. The considerably low rate of both screen failures and dropouts relative to the world literature is likely to be due to the fact that the center is dedicated to clinical research and has trained staff, with both experience and expertise in the area.

Close to 60% screen failures were due to "abnormal" laboratory values. As a center that does several studies for the pharmaceutical industry, this could be attributed to many of these trials using a central laboratory, with its "normal ranges" being at variance with the population of participants we studied. For example, the hemoglobin reference range used at our site laboratory (9.3–16.5 g/dl; data on file) differs significantly from that which is used by many central laboratories (13.5–18 g/dl; data on file). In a first in human study done by us, a large number of exclusions of "normal" healthy participants due to "low" hemoglobin as defined by the central laboratory led to a dialog with the sponsor and a study amendment to lower the hemoglobin specified in the protocol to reflect the hemoglobin values seen in the population presenting to us.[9] In addition, screen failures could also be explained by the fact that some studies were multi-country and included "normal ranges" from a different ethnic population. Siblle and Vital Durand have emphasized that laboratory normal ranges should not be fixed but rather defined as a function of the population that is actually being studied.[10]

Twenty-five percent of screen failures were due to consent withdrawal and more than eighty percent of these were healthy participants. An earlier study done by us evaluating

screen failures has shown that consent withdrawal by healthy participants often occurs as many of them merely get screened to ensure "normality" of laboratory reports.[9] Yet, another reason could be peer pressure to withdraw after screening when "high risk" is discussed with the family or the family general practitioner.

Our study shows that almost 90% of the dropouts resulted from lost to follow-up. Two reasons included change of contact numbers and, therefore, inability to contact the participants and migration to another geographic area (as ascertained telephonically). International Conference on Harmonization E9 also describes lost to follow-up as the first reason for dropouts in clinical trials.[11] It is well-known that the participants who drop out have different characteristics from those who continue in the study,[12] and studies specific to India to identify these very patient characteristics would help minimize and address dropout rates.

All four predictors – the presence of intervention, (highest odds), high risk, funding by the pharmaceutical industry, and healthy participants – had greater likelihood of being associated with screen failures. Majority of these interventional studies were first in human, Phase II or Phase III studies which mandated rigorous eligibility criteria and multiple laboratory tests consequently leading to screen failures. Risk and pharmaceutical industry funding also indicate stringent screening to obtain a homogeneous population thus adding to problem of screen failures.

The identification of risk as a predictor for dropouts logically indicates that greater emphasis should be given on explaining the nature of the risk as well as risk mitigation strategies that will be followed at the site for participant risk mitigation which are also explained during the consent process. Important elements of the consent should also be reemphasized to the participants during their subsequent visits at the site especially for studies with high risk and a long duration of follow-up.

As strategies for mitigating screen failures and dropouts, we propose that sites develop and use their own normal ranges which can be utilized even in regulatory studies to avoid screen failures. This, however, means that laboratories should move toward accreditation, and the pharmaceutical industry could help study sites with this process. Second, greater emphasis should be given on explaining the risks and ensuring adequate participant comprehension during the pre-screening and informed consent process. Similarly, greater focus should be given on explaining the societal benefits of the study during the same processes, especially for low or minimal-risk studies to minimize dropouts. Finally, home-based follow-up visits can be conducted with the help of the research staff to reduce the need for hospital visits where the protocol permits.

Our study is limited by the number of completed studies included for the analysis and that too from a single center. All predictors that were identified *à priori* and were inter-correlated (for example, pharmaceutical industry-funded studies are almost always high-risk studies) and hence it is difficult to evaluate the impact of each predictor independently on the two outcome measures.

CONCLUSION

In summary, risk, funding, study design, and nature of the participants were found to be associated with both screen failures and/or dropouts in clinical studies. Greater care should be exercised when studies involve high risk, are pharmaceutical industry sponsored, are interventional in nature, and involve healthy participants.

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Conflicts of interest

There are no conflicts of interest.

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