

Assessment of Patient Sociodemographic Variables in Clinical Trials— Can Patient Characteristics Make a Difference?

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Abstract

Introduction: The recruitment of patients into clinical trials is often thought to be a selective process whereby non-biological variables such as education, occupation, family/social support, and socioeconomic status are often found to be predictive of patient volunteers. This paper considers whether the susceptibility of trials to recruit non-representative patient populations may impair the extrapolation of results to diverse sociodemographic patient groups and/or hinder operational trial efficiency. **Method:** A review of the Embase and Medline databases was conducted using Subject Headings (clinical trial or randomised-controlled trial) combined with Keywords (sociodemographic, education, occupation or socioeconomic). References presenting patient sociodemographic characteristics in relation to trial recruitment or impact on measured trial data points were reviewed. **Results:** Both quantitative and qualitative reports suggest clinical trials are prone to recruit biased sociodemographic cohorts. This review suggests three trial cohort analyses that may enhance the interpretation of trial results and provide insight into the operational efficiency of clinical trials. Assessments include: (1) comparing recruited trial cohort with source population; (2) assessing trial data points across sociodemographic groupings irrespective of treatment; (3) assessment of patient dropouts based on sociodemographic characteristics. **Conclusion:** In view of the known sociodemographic disparities found in trial recruitment, a methodology is suggested which may provide valuable information regarding the external validity of trial results and/or assessing operational trial efficiency. The challenge to those undertaking clinical trials should be to firstly determine whether recruitment biases may exist, and secondly whether trial integrity may be compromised by the presence of such biases.

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Introduction

The pathway by which patients enter clinical trials can be a selective, non-random process. In order for patients to enter clinical trials, a set of circumstances must occur exclusive of having the disease being investigated and meeting clinical entry criteria. These factors include living in the region or country where clinical trials are conducted, having access to clinicians who are involved in clinical studies, being invited to participate in a clinical study, having the time and ability to participate and finally a willingness to participate. Following this constricting process, the patient then consents to enter the trial and is randomly allocated treatment.

Results obtained in clinical trials are generalising to real world populations with similar clinical features but not necessarily similar sociodemographic characteristics. Generalisability of trial results considers the clinical characteristics of trial participants compared to real world

populations and whether the treatment will be effective in these patient populations. This paper considers the generalisability of trial results, however focusing on whether the sociodemographic characteristics of patient volunteers in clinical trials compared with the social characteristics of real world populations may differ, and hence impair extrapolation of results. Furthermore, in view of the potential selective bias in clinical trials consideration will be given to whether a predictive nature exists between patient sociodemographic characteristics and measured trial data points [e.g. treatment compliance, trial dropout, adverse event (AE) reporting, resource utilisation] that may impair a trial's operational integrity and efficiency.

The underlying issues raised here regarding selective patient recruitment are the known inverse relationships which exists between morbidity and mortality in less socially privileged groups as well as variances in resource utilisation among different sociodemographic groups. The

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integration of these two fields of study can lead one to consider whether an imbalanced trial cohort's social make-up can undermine a trial's external validity.

Background

Sociodemographic Bias in Clinical Trials

Patient demographics such as age, sex and ethnicity are routinely collected in clinical studies for ensuring internal trial validity and, in many cases, to allow subgroup analysis in select patient cohorts. Demographic information can also be used to assess whether the recruited patient population is reflective of the broader population with the disease. Not surprisingly, clinical populations do not always represent the populations from which they were drawn as found in the United States where education, ethnicity, occupation, social support and socioeconomic status (SES), amongst other variables, are frequently found to indicate the likelihood of clinical trial participation.¹⁻¹⁰ While reports of selective recruitment are highly suggestive, it should be acknowledged that a review of this nature is problematic since the intent of clinical trials is not to assess the social characteristics of trial volunteers, hence trials do not regularly collect detailed social characteristics. In many respects, it is impossible to define a stereotypical sociodemographic recruitment profile due to the diversity of trials conducted in different regions, and across different therapeutic indications. It may be more appropriate to consider that all trials have some degree of sociodemographic imperfection, with the relevant question being whether the presence of such bias will impair trial integrity and external validity.

Several explanations can be offered for biased clinical trial recruitment patterns, including logistic barriers (i.e. geographical barriers, lifestyle restrictions), protocol design (i.e. placebo run-in), and both explicit and implicit investigator selection/preferences. Additionally, there may be an element of a selective patient preference bias as suggested by both Gorelick and Mouton who reported that African Americans may be reluctant to enter clinical trials due to lack of trust of White investigators.^{11,12}

Additionally, potential relationships between sociodemographic characteristics and compliance, dropouts, or resource utilisation can be studied within the confines of clinical trials to assess operational trial efficiency. Previous studies have suggested that characteristic such as ethnicity and SES may be correlated with treatment compliance and dropouts in clinical trials.¹³⁻²² From the infrequency of such assessments in clinical trials, it is clear that this topic has yet to be justly treated. The issue is worthy of investigation, especially in cases where rigorous trial design may precipitate patient dropout and non-compliance independent of clinical circumstances

(i.e. AEs, lack of effect, side effects).

Influences of Sociodemographic Risk Factors

Cohort and observational based studies continuously point to a variety of sociodemographic risk factors known to be predictors of increased morbidity and mortality in both developed and developing countries.²³⁻²⁹ The inverse relationship which exists between low socially privileged classes and increased morbidity and mortality is found in virtually all major disease categories with some exceptions. The influences of patient sociodemographic characteristics on morbidity, mortality, as well as health care utilisation, are not considered in this review. However, what is considered here is whether the known influences of sociodemographic risk factors should be considered in clinical trials, especially in long-term chronic diseases where these factors can potentially impact trial outcomes.

One aspect likely to influence morbidity and mortality is the way in which different social classes utilise health care, and the influence of one's social environment on health. Once again, cohort studies provide insight into how non-biological sociodemographic variables influence individual health seeking behaviour. For instance, factors such as insurance status, available support (e.g. spouse, children, carer), and SES are known to influence health care utilisation and impact on clinical outcomes.³⁰⁻⁴¹ The direct and indirect implications of these findings, when applied to a biased clinical trial population, may highlight the importance of assessing the social characteristics of trial volunteers.

Current practise in clinical trials is to routinely collect basic patient characteristics such as age, sex and ethnicity. Studies where more detailed patient characteristics have been collected generally consider equity issues of patient access to trials rather than the potential impact on interpretation of trials results. However, two references have been identified where variations in clinical outcome were noted between different sociodemographic groups within a trial population. In a review of 8 cancer studies conducted through the Cancer and Leukemia Group B (CALGB), Cella et al⁴² reported that patients, enrolled in clinical trials, with lower education and annual incomes had reduced survival relative to higher SES groups. These statistically significant survival differences were noted after controlling for age and all clinical variables. Similarly, Gorkin et al⁴³ noted the influence of perceived social support on mortality for patients randomised to placebo in the Cardiac Arrhythmia Suppression Trial. Amongst patients receiving placebo, social support was a significantly independent risk factor after adjusting for clinical variables. These 2 studies serve to highlight the potential importance of sociodemographic imbalances in clinical

trials and the influence on trial outcome measures and external validity.

Discussion

This review considers whether clinical trial results obtained from biased trial cohorts in terms of social characteristics can impair extrapolation of results to populations with broader social characteristics. Similar extrapolative arguments have been put forward by Nattinger and colleagues⁴⁴ in relation to the Surveillance, Epidemiology, End Results Registry (SEER), whereby cancer incidence data collected from unrepresentative centres, particularly in regard to SES, is generalised to a broader population (also see Bergstrand⁴⁵). This paper broaches a similar issue in that clinical trial results generated in unrepresentative trial cohorts may show variation when extrapolated to diverse sociodemographic groups.

As discussed in the Introduction, entry into clinical trials is often found to be a demographically selective process.^{1-10,46} The presence of socially unrepresentative patient cohorts at trial entry cannot be resolved by randomisation. Randomisation is used to control for both known and unknown patient confounding variables, ensuring that potential cofounders are randomly distributed amongst treatment groups. However, randomisation cannot correct biased patient entry and alleviate whether the trial cohort is reflective of the broader patient population.

The relationship between patient sociodemographic characteristics and trial data points such as compliance, dropout, and health care utilisation can be tested in clinical trials to assess operational trial efficiencies. As previously discussed, cohort studies indicate that sociodemographic characteristics such as insurance status, social support, and SES can influence patient health care treatment decisions and treatment compliance. Intuitively one may consider whether the social make-up of a trial cohort may have both direct and/or indirect effects on a trials operation and internal validity. For example, the implications of a highly educated, high SES clinical trial cohort may result in increased resource utilisation and/or more effective doctor-patient communication resulting in higher proportions of AEs reported. Alternatively, a low SES trial cohort may result in low treatment compliance, high dropout rates, or ineffective doctor-patient communication. These hypothetical examples are provided as an impetus for discussion and may be worthy of further consideration in designing future clinical trials.

Sociodemographic Trial Design and Assessment

Prospective assessment of sociodemographics in clinical trials should be considered in trials where patient characteristics are thought to influence the external validity of results or to assess various components of a trials

operational efficiency. Sociodemographic assessments are likely to be most beneficial in long-term chronic disease studies where individual patient characteristics have been shown to influence health status. Three analyses are suggested for assessing sociodemographics in clinical trials (Fig. 1).

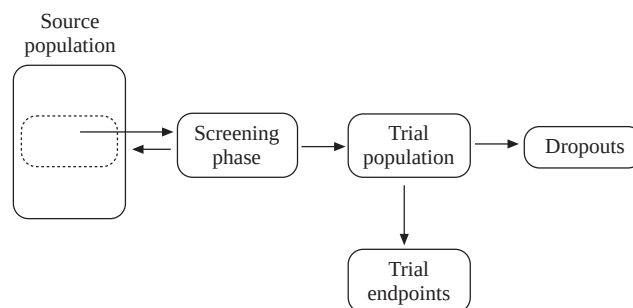


Fig. 1. Sociodemographic screening model in clinical trials. The “source population” is defined as all individuals having the disease within an arbitrary but pre-defined population area. The source population area can either be expanded or restricted based on geographic boundaries or other arbitrary measures. The “source population” also represents the target population in whom the drug will eventually be used. The dashed box within the “source population” suggests that a non-representative trial cohort is likely to be recruited to make-up the “trial population”. For the purposes of this diagram the sociodemographic representation of these two populations would be unknown.

- Comparison of “trial population” relative to “source population”

The most common assessment conducted in clinical trials is comparing sociodemographic characteristics between the recruited “trial population” and the “source population”. As discussed earlier, studies suggest that patients recruited to the “trial population” are potentially sociodemographically biased samples drawn from the “source population”. In many cases, it may be prudent for clinical scientists and investigators to consider the potential for sociodemographic influences on trial design and/or trial outcome measurements before commencement of the trial. Variables to consider will be dependent on the indication being studied and the patient characteristics that are likely to be recruited from regions where investigational sites are located. It is also important to consider that a comparative evaluation requires either quantitative data or qualitative sociodemographic knowledge from the source population in order to draw meaningful conclusions. Furthermore, consideration needs to be given to epidemiological correlations with disease status that may be suggestive of selective sociodemographic recruitment patterns.

- Assessment of protocol specific data points with patients stratified by sociodemographic characteristics

A variety of assessments can be conducted to determine

whether a relationship exists between patient non-biological characteristics and protocol specific data points (e.g. clinical endpoints, AE reporting, treatment compliance, resource utilisation) irrespective of treatment allocation. The broad implications of biased trial cohorts may be that the clinical results (i.e. clinical endpoints) from trials may be diminished or enhanced when applied to different settings due to sociodemographic interactions. For example, consider the response of a drug studied in a cohort of high SES patients with ample social support, and having received a lifetime of high standard health care. Compare this to a drug studied in a trial cohort of lower socioeconomic patients having received a lifetime of reduced standards of health care. In many cases, assessing trial data points across sociodemographic groupings may not retain the power to make statistical claims, however the findings may be suggestive enough to be considered in future trials.

The assessment of non-endpoint data such as AE reporting, treatment compliance or resource utilisation is one way of evaluating a trials operational efficiency. For example, it is known that a patient's characteristics are likely to influence the manner in which medicines are used, health services are utilised and disease progression.³⁰⁻⁴¹ Therefore, for trials conducted in sociodemographically imbalanced trial populations, the trial data points may be skewed and lead to misinterpretation of findings or increased/decreased operational efficiency. This could be reflected in high or low background rates of AE reporting or skewed resource utilisation findings. Potential data collection imbalances would not arise from drug treatment effect, rather as a consequence of biased sociodemographic trial composition.

- “Trial population” compared to “dropouts” (based on non-clinical grounds)

The assessment of patient “dropouts” compared to those patients remaining in the “trial population” for non-clinical reasons is one area where gains in trial efficiencies are likely to be made. Those involved in the operation of clinical trials at the patient level are well aware of the challenges that patient volunteers face and why patients frequently withdraw from trials. Previous attempts to capture this information suggest there may be patient characteristics predictive of patient dropout.^{14,16,18,21} The value in obtaining data on patient dropouts will be in designing future trials to prevent dropout and in devising ways to retain patient volunteers.

A variety of benefits may be achieved by incorporating sociodemographic analysis into clinical trials, most important of which is in determining whether clinically significant results obtained in trials may be diminished or enhanced when applied in different patient groups. In many situations, sociodemographic assessment may be

useful in explaining variations in response to treatment between centres or in explaining problematic trial results. Benefits will also be obtained by gaining an understanding of the types of patients willing to volunteer for studies, and more importantly, those individuals not participating. This information would be valuable in formulating future recruitment methodologies and addressing the concerns and needs of patient volunteers. Furthermore, if a predictive relationship does exist between patient sociodemographic characteristics and trial data points (e.g. dropout, treatment compliance, AE reporting and resource utilisation), measures can then be taken to correct such anomalies.

Perhaps the important point to consider in this review is in generating an awareness that all clinical trials would be likely to contain some degree of bias if enough patient variables were evaluated. In fact, it should be expected that no two clinical trials would have the same sociodemographic composition due to a multitude of factors such as site selection and sociodemographic risk factors associated with disease. The reality of the issue should be in considering whether a particular biased variable is present in a trial and whether such a bias has the potential to impact trial integrity and extrapolation of results.

Conclusion

This review has raised the concern that since clinical trials are prone to recruit biased homogenous patient populations this may limit the generalisability of trial results and/or impair operational trial efficiency. The debate regarding whether trials should include homogenous or heterogeneous patient populations is frequently raised for understanding the magnitude and generalisability of treatment effect. Some would argue that trading off a degree of external validity in order to maintain high internal trial validity is justifiable in order to detect moderate treatment effects. This further suggests that responses generated in heterogeneous patient cohorts may not be generalisable to some patient groups. However, the issue raised in this review is that the majority of trials are oblivious to whether they are internally or externally valid in terms of the sociodemographic profile of trial cohorts. Hence, a prospective assessment of patient characteristics at trial outset may provide some indication regarding trial integrity and enhance the interpretation of trial data. The benefits of sociodemographic assessment in clinical trials may be in minimising sociodemographic selection bias, enhanced extrapolation of results and increasing trial efficiency.

A final consideration should be given to the fact that the papers discussed in this review measuring socio-demographic characteristics in clinical trials have been conducted in North American patient populations. It may be of interest to consider whether these same predictive

sociodemographic characteristics are found in different regions of the world conducting clinical trials.

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