COMMENTARY

Understanding Decision and Enabling Factors Influencing Clinical Trial Participation in Australia: A View Point

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Abstract

Understanding patient decision making with respect to clinical trial participation has the potential to improve both the efficiency of recruitment for clinical trials and their management. In this mini-review we consider 3 key factors influencing clinical trial recruitment outcomes that include; 1) patient personal characteristics, 2) enabling factors that involve patient centered attitudes or circumstances, and 3) aversion. These factors are explored across both Australian rural and urban settings and contrasted to reported outcomes from research across other countries. Australia has the lowest number of publications on rural clinical trial participation when compared to rural research in America and Canada. Across Australian urban areas where all 3 factors have been studied, trends are similar to those reported in other developed countries. In conclusion we suggest that trial participation could be improved if participants are better informed about a trial as this is a valuable factor to enable recruitment.

Keywords: Clinical trials - decision making - barriers - rural Australia

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Introduction

There are limited studies on patient factors that influence participation in Australian rural clinical trials. Personal characteristics, attitudes, enabling factors and barriers are examples of factors that have been implicated in the willingness of patients to participate in clinical trials. Reviewing factors in the literature that influence clinical trial participation in a rural context are important, as such reviews are likely to highlight areas where research data or policies are lacking.

From a practical standpoint understanding the motivations behind the participation or refusal to participate in clinical trials is vital to their success in terms of cost-effectiveness, speedy recruitment, statistical power and maintaining the motivation of clinical researchers to actively participate in ongoing and future clinical trials. By utilising studies on the motivations of participants and non-participants, clinical trials can be designed to maximise the number of approached candidates that agree to participate, hence minimising the economic cost and maximising the benefit of the trial.

Personal Characteristics Related to Clinical Trial Participation

Personal characteristics refer to inherent physical, psychological and socio-demographic attributes of the individual. There are conflicting reports of the importance of such factors in ascertaining the likelihood of an individual participating in a clinical trial. The personal characteristics most often implicated in determining patient motivations are age, health status and race.

Age can be a difficult factor to assess with respect to personal influence on clinical trial participation. This is because clinical trials are usually aimed at specific age groups rather than across a broad age range, and many conditions are seen predominantly in older people. This may be particularly the case in rural populations where age distribution is skewed towards aging and aged individuals. Some discrepancies exist in determining the impact of age on trial participation, although this may be dependent upon the condition being treated. Age trends may be affected by confounding factors; for example, younger people may attend different types of clinics compared to older individuals (Movsas et al. 2007). Recruiting older patients for clinical trials is further complicated by exclusions due to co-morbidities, and the potential for physicians to avoid enrolling their older patients due to a perceived risk of toxicities (Movsas et al, 2007). The potential for additional medical care and the ability to extend the scientific knowledge base are deemed important for all age groups, while for those aged under 65 years, financial concerns of out-of-pocket expenses/reimbursement and personal insurance coverage are additionally implicated (Baquet et al, 2006).

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Disease progression and severity are directly associated with wellbeing. Wellbeing is likely to influence the desire to participate within a clinical trial or a clinical intervention to improve outcomes. There is conflicting data regarding serious disease, in terms of whether patients with more or less advanced disease are more likely to participate (Diener-West et al, 2001). Patients often state they are either too sick or too well to participate in a clinical trial (Costenbader et al, 2005). The role of diagnosis-induced depression and anxiety in trial non-participation has been suggested, but is inconclusive to date (Daly et al, 2005). In cardiac patients following acute myocardial infarction there is a significant lack of participation and compliance in cardiac rehabilitation programs or trials (Daly et al, 2005).

Within cardiac clinical trials patient personal factors may not be the only contributing factor influencing clinical trial participation but also the personal characteristics of the treating doctors. The Chronic Heart-failure Assistance by Telephone (CHAT) study was an Australian national randomised controlled cluster-design trial that aimed to create a support service for general practitioners (GPs) and their patients (Yallop et al, 2006). Despite clear evidence of high rates of heart failure in Australia and a large group of 250 GPs enrolled to recruit patients, only 320 patients were recruited after 2 years (Abhayaratna et al, 2006). The lack of GP influence in patient clinical trial recruitment may reflect insufficient time available to screen patients during the recruitment phase. Doctors may be reluctant to recommend their patients for clinical trials, as has been demonstrated among Australian breast cancer specialists, despite recommendations that trials should be considered in early stage breast cancer management (Ellis et al, 1999).

With respect to the personal characteristic of race there has been the difficulty of recruiting patients from minority groups, particularly racially-determined groups. Racial minority groups are at higher risk of developing certain conditions at a higher incidence rate than the general population, whether due to genetic or environmental factors. While American studies tend to describe issues pertaining to the recruitment of African-Americans, in Australia a similar epidemiological situation can be identified, with a higher burden of disease in the Aboriginal population than in the non-Aboriginal population (Zhao et al, 2004). Despite evidence of ill-health and reduced quality of life in the Aboriginal population, often due to preventable diseases, recruitment studies have not been adequately conducted for this demographic (Dawson, 2004). Due to variation across populations, the response to treatments for various diseases is likely to vary for different ethnic groups; thus it is essential that racial minorities are at least proportionately represented in clinical studies (Corbie-Smith et al, 2003). To ensure results can be generalised to diverse populations, the National Institutes of Health in America formed the Revitalization Act of 1993, which requires that women and members of minority groups are included in all research projects unless a "clear and compelling" reason can be given for their under-representation (Corbie-Smith et al, 2003). No such legislation has been enacted in Australia to encourage equity in recruitment to clinical trials.

Enabling Factors

Enabling factors describe those attitudes and circumstances which make potential recruits more likely to participate in clinical trials. Perceived health benefit influences the decision to participate in clinical trials. Patients are more likely to be recruited if they believe the treatment they receive in the study will be better than the treatment currently available to them (Verheggen et al, 1998). This perceived benefit may be negated in some cases by the dislike of randomisation or other barriers to participation (Harrison et al, 2007). The concept of health benefit is also related to the patient's level of satisfaction with their current treatment regime, as satisfied patients are less willing to alter their treatment (Verheggen et al, 1998). On the other hand, some patients may overestimate the benefits of their current treatment and hence be reluctant to enter a trial (Sawka and Pritchard, 2001).

The provision of appropriate information about the clinical trial can be the stimulus for patient enrolment (Verheggen et al, 1998). Potential clinical trial participants desire to be well informed about the clinical trial process and what is involved during their participation. Individuals with greater knowledge of the specific clinical trials process that pertains to their condition are more likely to participate in clinical trial studies (Ellis et al, 2001). The means by which pre-trial information is provided may also influence the decision of the patient whether or not to participate within a clinical trial (e.g. use of audio-visual and interactive media contrasted against conventional methods of communication such as verbal or written information), although it remains unclear which communication tools are most effective (Verheggen et al, 1998; Sawka and Pritchard, 2001).

Physicians have a major role in patient accrual to clinical trials. Patients are more likely to enrol if they are directly referred to and informed about the trial by their physician (Corbie-Smith et al, 2003; Baquet et al, 2006). The patient may refuse to enter the clinical trial if they feel it might compromise the relationship they have with their current treating physician (Mills et al, 2006). A number of studies suggest that the recruiting doctor has the greatest influence on patient participation, and that it is important for patients to have confidence in the physicians and also to have an affinity with them (Ross et al, 1999). Regardless of other enabling factors, a patient will rarely enter a clinical trial unless their physician actively recommends it (Verheggen et al, 1998).

The perception that clinical trial participation will lead to positive outcomes either for the individual or for society is a motivation for enrolment. Altruism, the performance of unselfish acts for the benefit of others, is a commonly quoted motivation for entering a clinical trial (Rosenbaum et al, 2005). Altruistic participants are also more likely to adhere to the study (Rosenbaum et al, 2005). Interestingly, patients with a history of volunteerism have a greater tendency to participate in clinical trials (Corbie-Smith et al, 2003). The participation of altruistic individuals in clinical trials presents an ethical imperative to report the results of all clinical research through a transparent reporting system (De Angelis et al, 2004). Additional

intrinsic motivations relating to positive rewards/ outcomes include the benefits of additional and follow-up care, however this is expected to be more relevant to individuals in the USA since the Australian health care system provides comparatively more equitable free access to health services (Baquet et al, 2006).

Barriers

Some enabling factors allude to barriers that prevent individuals from participating in clinical trials. The most commonly discussed barrier to participation in clinical trials is dislike of the research process. This aversion to the clinical trial protocol mostly arises from concerns with the process of randomization (Mills et al, 2006). The intrinsic uncertainty or "gamble" of the randomisation process is problematic for many people, thus it is important that recruiters do not emphasise these aspects in their explanation of randomization (Harrison et al, 2007). Additionally, barriers for patients to be involved within the clinical trial process include: an objection to being an experimental subject; difficulty understanding informed consent; complex or stringent protocols; preference for the other treatment; assignment to placebo or no-treatment group; and a general unease with the entire process (Sawka and Pritchard, 2001; Mills et al, 2006). These barriers to clinical trial participation may be reduced by ensuring potential recruits are adequately informed about the trial process.

In some cases, physicians may directly advise patients against participating in a trial (Corbie-Smith et al, 2003). Physicians may discourage trial participation for a variety of reasons including: excessive time commitment for the physician or the patient; intrusion into the doctor-patient relationship; complications of informed consent; imposed financial burden; dissatisfaction with trial protocol design; discomfort with discussing patient uncertainties regarding the trial; and feelings of potential responsibility if the patient's treatment suffers as a result (Lovato et al, 1997). It is therefore essential to ensure that the treating physicians fully understand the requirements and benefits of the trial in order that they might pass a positive sentiment about the trial onto their eligible patients. Improving the communication skills of the recruiters is also important, as patients are more likely to participate if the consent forms are verbally discussed in a supportive manner (Sawka and Pritchard, 2001).

While clinical trials aim to improve individual quality of life, patients often express concern that trial participation may reduce their quality of life (Ross et al, 1999). Some patients express anxiety about potential side effects of the treatment (Harrison et al, 2007). It is important for recruiters to alleviate the patient's concerns regarding perceived side effects by providing them with sufficient information regarding any actual unwanted effects, thus removing the element of speculation (Harrison et al, 2007).

An Australian Rural context

Australia has the lowest number of publications reporting on clinical trials carried out in rural areas across the main developing countries, when compared to the USA and Canada (McLean et al, 2007). The effect of rurality on clinical trial participation has been recently investigated in cancer trials in remote regions of Queensland. Participation rates in cancer trials of rural or remote patients living around Mt Isa compared to those living in Townsville (a regional city). There was no significant difference between willingness to participate and rurality. However, rural patients face unique challenges that could act as barriers to participation, particularly as they usually have to travel great distances to participate in these trials. This study found the most important barriers was the inconvenience, the cost of travel and the need for family members to accompany them (Sabesan et al, 2011). The likely most important aspect to rural clinical trial recruitment is that indeed few clinical trials are available within rural and remote areas. For example, a review of cancer clinical trials in rural USA New Hampshire and Vermont revealed that clinical trials were unavailable for 75% of patients living in these rural areas (Maurer et al, 2001).

Conclusions

One of the practical methods by which clinical recruitment can be enhanced is by ensuring potential participants are well informed. This will impact on individual participants and their personal factors. To date limited studies exist on the motivations of participants in Australian clinical trials, in particular within a rural context where particular barriers exist including specialised personal to assist in trials, travel, patients presenting late for treatment, and generally older population samples. Studying the motivations of Australian patients to participate in clinical trials within urban areas has the potential to assist in recruiting greater numbers of participants in the future, thus improving the efficiency, cost-effectiveness and equity of future clinical trials.

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