

Reasons behind the participation in biomedical research: a brief review

Motivações para participação em pesquisa biomédica: uma breve revisão

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ABSTRACT: *Introduction:* Clinical research is essential for the advancement of Medicine, especially regarding the development of new drugs. Understanding the reasons behind patients' decision of participating in these studies is critical for the recruitment and retention in the research. *Objectives:* To examine the decision-making of participants in biomedical research, taking into account different settings and environments where clinical research is performed. *Methods:* A critical review of the literature was performed through several databases using the keywords: "motivation", "decision", "reason", "biomedical research", "clinical research", "recruitment", "enrollment", "participation", "benefits", "altruism", "decline", "vulnerability" and "ethics", between August and November 2013, in English and in Portuguese. *Results:* The review pointed out that the reasons can be different according to some characteristics such as the disease being treated, study phase, prognoses and socioeconomic and cultural environment. Access to better health care, personal benefits, financial rewards and altruism are mentioned depending on the circumstances. *Conclusion:* Finding out more about individuals' reasons for taking part in the research will allow clinical investigators to design studies of greater benefit for the community and will probably help to remove undesirable barriers imposed to participation. Improving the information to health care professionals and patients on the benefits and risks of clinical trials is certainly a good start.

Keywords: Biomedical research. Clinical research. Research subjects. Healthy volunteers. Motivation. Vulnerability.

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RESUMO: *Introdução:* A pesquisa clínica é essencial para o avanço da Medicina, especialmente no que se refere ao desenvolvimento de novos medicamentos. Entender as razões que motivam pacientes a participarem dos estudos é fundamental para o recrutamento e retenção na pesquisa. *Objetivos:* Examinar o processo de decisão dos participantes em pesquisa biomédica, levando em consideração diferentes situações e ambientes onde a pesquisa clínica é conduzida. *Métodos:* Uma revisão crítica da literatura foi feita através de vários bancos de dados, buscando-se as seguintes palavras-chave: “motivação”, “decisão”, “razão”, “pesquisa biomédica”, “pesquisa clínica”, “recrutamento”, “inclusão”, “participação”, “benefícios”, “altruísmo”, “recusa”, “vulnerabilidade” e “ética”, entre agosto e novembro de 2013, em inglês e em português. *Resultados:* Essa revisão descreve que as razões que justificam a decisão podem ser diferentes de acordo com algumas características, como a doença em tratamento, fase do estudo, prognóstico e ambiente socioeconômico e cultural. Acesso a melhores cuidados de saúde, benefícios pessoais, recompensa financeira e altruísmo são mencionados dependendo das circunstâncias. *Conclusões:* Entender melhor as razões que movem os indivíduos a participarem de pesquisas permitirá aos pesquisadores clínicos desenhar estudos que tragam maior benefício à comunidade e provavelmente ajudarão a remover barreiras indesejáveis à participação. Melhorar a informação aos profissionais de saúde e pacientes sobre benefícios e riscos da pesquisa clínica é seguramente um bom começo. *Palavras-chave:* Pesquisa biomédica. Pesquisa clínica. Participantes de pesquisa. Voluntários sadios. Motivação. Vulnerabilidade.

INTRODUCTION

Clinical research depends on the successful recruitment and retention of participants. Understanding the reasons that move them can help in enrollment and ensure scientific validity to the research protocols.

In studies phase II to IV, patients who accept to be included in a clinical trial usually have some expectation regarding the benefits of their participation. However, results cannot be assured even having prior data suggesting it. At the same time, they are exposed to risk and some discomfort when they decide to participate in clinical research. These research participants with medical conditions to be treated are motivated to enter clinical trials as volunteers because they can benefit from the treatment or, in a worst scenario, at least better understand their disease. The motivations of healthy volunteers in phase I trials are probably different, since they don't have a disease to be treated^{1,2}.

OBJECTIVES

This exploratory study aimed to examine the decision-making of participants to enroll in biomedical research, taking into account different settings and environments where clinical research is performed. Specific objectives were: to review the literature, discuss the different reasons to participate in clinical research and, if possible, make proposals for methodological improvements.

METHODS

A critical review of the literature was performed by looking for papers addressing the motivations and reasons why patients and health volunteers decide to participate in biomedical research. Besides “motivation”, “decision”, “reason”, “biomedical research” and “clinical research”, the terms “recruitment”, “enrollment”, “participation”, “benefits”, “altruism”, “decline”, “vulnerability” and “ethics” were also used as keywords. The search was done through several web tools, between August and November 2013, in English but also in Portuguese, in order to find publications made in local language, which otherwise could not be identified. Based on the globalization of clinical trials, which has been responsible for the inclusion of non-classical countries in multicenter international protocols, reports from developing countries had priority in the selection. The objective was not to extensively cover data available about the subject, but only to make a preliminary recognition of the main aspects related to motivation in clinical research.

RESULTS

It is known that several (and different) reasons can motivate an individual to participate in (different) clinical studies¹. Altruism is certainly one of them, helping other patients with the progress obtained through the clinical research. Being part of the discovery of new drugs and/or new procedures may also contribute to the decision for participating in clinical trials, either for their own benefit or for the benefit of others, or the society as a whole. Other reasons are certainly involved, such as better care and attention to their own health and access to new treatments before they become widely available. It is worth to mention that volunteers, by definition, do not expect any benefit from their work. They are motivated by a cause and therefore have a reason to accept the risks of their decision, but not necessarily additional associated risks².

REASONS FOR ACCEPTING OR DECLINING PARTICIPATION

A systematic review, published by Stunkel and Grady assessed the motivations of healthy volunteers in clinical research, usually involved in phase I studies of new drugs or, more recently, in bioequivalence/bioavailability studies¹. The perception coming from previous studies was that these volunteers agreed to participate in research only for financial reasons^{1,3,4}. However, financial motivation does not necessarily exclude other reasons and considerations. In this systematic review, the authors assessed data from clinical studies that measured self-reported motivation and decision processes that lead healthy volunteers to participate in research that would not bring direct benefits to them. Thirteen studies (published before March 2010) involving more than 2,000 volunteers were included. Six of them were conducted in the United States, six in Europe and one in Malawi, which was the only study identified in a

developing country that met the inclusion criteria of this systematic review. Financial reward was one of the main motivations to participate in twelve of thirteen studies included and was the main reason in eight studies. Access to health care was the main motivation in the study conducted in Malawi⁷. The same had been observed among elderly volunteers in a study by Van Gelderen et al., published in 1993⁶. Other reasons mentioned were: contributing to science and medicine, helping others, meeting people and making social contacts; desire to participate in something important, learn more about science and curiosity. While financial reward was the main motivation of these volunteers, other factors clearly influenced their decision and it does not necessarily mean that these individuals accept unreasonable risks or make decisions without proper information prior to participation. There are reports, however, that volunteers who participate in repeated clinical studies are more likely to reveal the possible risks or be motivated solely by financial reward⁷.

Berg et al., in a paper published in 2010, assessed the attitudes towards pharmacokinetic (phase I) studies in children with cancer, in the United States. The majority of subjects (72%) identified altruistic reasons for participation. Subjects who did not accept to participate mentioned extra time in the hospital and need for another IV catheter⁸.

In general, less than 5% of patients with cancer enroll in clinical trials⁹. On the other hand, progress has been observed in the recent years in pediatric cancers, and this would not have occurred without the commitment of the oncology community, which enrolls more than 70% of their pediatric patients with cancer on trials^{10,11}. Unfortunately, this emphatic pediatric participation is not a reality in several countries due to regulatory aspects, as well as lack of knowledge about clinical research benefits. Children are indeed a vulnerable population; however, pediatric research is a valuable activity to improve children's health and well-being. In the past, they have been disadvantaged by lack of research and data on which to base pediatric drug doses. Usually their parents are responsible for giving the consent to participate; therefore it is not clear if we can talk on "altruism" in the process for research with child subjects¹². A tailored approach is needed when discussing research participation with parents of eligible children with life-threatening illnesses. Adequate information about the alternatives and, of course, risks of research participation should be provided to these patients¹³.

A survey from 2011, with adult patients and parents of pediatric patients participating in phase I to III cancer clinical trials, assessed why they agreed to enroll in the studies¹⁴. Among 253 subjects (205 adults and 48 parents of children), 47% reported that altruistic motivations were 'very important' to their decisions to enroll. Phase I trial participants least often identified altruism as a 'very important' motivation for enrolling when compared to phase III patients. Thirty-three respondents (13%) reported being motivated primarily by altruism; participants with poor prognoses (defined as an expected 5-year disease-free survival of $\leq 10\%$) reported altruism as their primary motivation less often than those with better prognoses. This data is derived from academic medical centers in one city (Toronto, Canada), and the study sample reflects limited sociodemographic diversity, thereby limiting generalization to other settings. Although cancer trial participants commonly report that

altruism contributed to their decision to enroll, it is rarely their primary motivation for study participation. Participants in early phase trials and those with poor prognoses are least often motivated by altruism. This fact could also be observed in another study conducted with cancer patients in phase I trials, published by Catt et al. in 2011¹⁵. The main reasons for trial entry were: hope of medical benefit and trial as the best available option (21% each), keep hope (15%) and help with the research (13%). The desire of helping others or contribute with science does not lead a volunteer to participate in a study, unless a personal benefit is also perceived. This behavior was described as “weak altruism” by Canvin and Jacob and as “conditional altruism” by McCann et al.^{16,17}.

Brintnall et al. performed screening telephone interviews, in Maryland (USA), with 965 potential research subjects for inclusion in mental disease trials (between 1999 and 2007) who, despite being eligible for the studies, declined participation¹⁸. Reasons for declining fell into five categories: protocol issues (36%), inconvenience and lifestyle issues (33%), other reasons not mentioned (26%), financial reasons (3%) and lastly, decision to participate in other trial (2%).

In another study, face to face interviews with 14 subjects in a HIV vaccine study, performed in 2007 and 2008, in Tanzania, assessed the reasons to decline. Fear of possible (negative) outcome and resistance from “significant others” (usually parents and close friends) were the main obstacles. These findings call attention to the importance of expanding clinical trial education and its benefit to general population¹⁹.

A qualitative study (Masiye, 2008) performed through focus groups assessed 81 participants in malaria research: 39 participants from an urban setting and 42 from a rural setting, both in Malawi²⁰. These places were selected because they have been served as locations for several large-scale clinical research projects. Most participants reported that they chose to participate as a way of accessing better quality medical care. Some wanted to benefit from the material and monetary incentives given (soap, peanut butter, napkins, and mosquito nets). There was also a sense of trust in health workers who asked them to participate.

Wright et al. conducted, in Canada, between 2000 and 2001, a series of focus groups with cancer patients (189), their physicians (28) and clinical research monitors (12) in order to identify independent predictors of a cancer patient’s decision to enter a randomized clinical trial. Patients’ perception of personal benefit was the best predictor of clinical trial entry. The author suggests that strategies that clarify the potential benefits of clinical research may result in improved accrual¹⁰.

A meta-analysis, published by Zammar et al. in 2010, assessed the reasons why Brazilian patients accepted to be involved in clinical research, and compared the results with another survey of Indian patients, conducted earlier by the same group of researchers²¹. The main findings of the study were: (i) the major motivation of Brazilian patients is altruism (can benefit other patients and/or opportunity to help science), present in 55% of responses; 48% of patients in India reported that the biggest motivation to participate in clinical trials is personal benefits, (ii) financial reimbursement is the least important factor for these patients (6% of participants), (iii) the personal health-related benefits are the motivation for 30% of them (included here a possibility for consultation with a specialist, learn more about their disease, free tests and

examinations), (iv) the convenience is cited by 11% of participants (not having to wait for a long time for the service, providing free medicines and tests). Additionally, the biggest barrier for Brazilian patients to participate in research is the fear of side effects. In this study, patients from Brazil seemed to be more likely to participate in clinical trials than patients from India.

A recent survey conducted in Brazil through the internet, between 2009 and 2010, with major players in clinical research (investigators, members of Ethics Committees, sponsors and patients), included some questions aiming to assess the motivation of research participants²². Looking at the responses provided by the group of patients, personal benefit and altruism were the main motivators: 96% of patients rated as “very important” in the decision to seek better health care and medical attention and 94% of them also pointed out as “very important” to contribute with the development of science. However, putting together all groups interviewed (58 researchers, 124 members of ECs and 24 sponsors, besides the 54 patients), altruism appeared in last position: for the group as a whole, the greatest motivation for patients to participate in clinical research was the search for better medical care and attention to their health, followed by access to alternative treatment for their disease. Interesting to point that patients gave less importance to the risks of a new and experimental treatment than other players participating in the survey. For them, the potential benefits of the study were more important than the risks.

Almeida et al. developed a qualitative study in a rural area of Minas Gerais, in Brazil, to investigate the decision to participate in biomedical research²³. Nine subjects of a phase I study of a hookworm infection vaccine participated. The main motivation to participate in the research, where the individual benefit was not evident, was the opportunity to gain access to health care. Some testimonies of the volunteers also showed in their decision characteristics of altruism: (i) “Through the research, I felt that something better would occur to us. It will be beneficial for people’s health”; (ii) “It will be good. I decided to participate because up to now it was a good thing. The researchers bring a lot of good things for us (...) if this is an experiment, it can be useful for health in the future”; (iii) “The major motivation for me was that the vaccine would be good for the Brazilian population and the entire world”. The authors emphasize that the decision of participating in biomedical research is marked by psychosocial characteristics of the population and their socio-economic vulnerability.

Menequin et al. also conducted a research in Brazil with 80 subjects participating in clinical trials for hypertension and/or coronary disease, from Jan/2002 to Dec/2006²⁴. Regarding the motivation to participate in the studies, 66% attributed it to their own benefit, 42.5% for the sake of science and 25% answering to a request of their physicians.

A quali-quantitative research carried out in Brazil with 80 volunteers of phase I and III clinical studies, published by Nappo et al. in 2013, concluded that study participants are primarily motivated by personal benefits, basically financial gain and therapeutic alternative. When present as motivator, altruism was observed as a secondary reason to participate²⁵.

A survey from 2010 showed that the most effective way to motivate participation in biomedical research is offering a treatment that represents an improvement, followed by the convenience of the trial site, the possibility of receiving a free medication, the number of visits and the short

trial duration. One trial manager interviewed noted that, in urban settings, compensation was a motivating factor, but in rural settings, altruism is a driving force among people who are willing to better understand a disease or do something to give back²⁶. “Recruitment managers will make better decisions if they have a solid understanding of the patients’s demographic features and needs,” the report adds. Compensating for travel is certainly a benefit, but it doesn’t appear as a high motivator. The same was observed with monetary compensation, which didn’t rank high as a way to motivate people, at least in this survey. The more chronic and discomforting the medical condition is, the less money motivate the participant.

Aiming to understand why people with cystic fibrosis, in the UK, take part in research, Lowton found that an opportunity to improve personal health through access to new treatments or experts has motivated people with different diseases or conditions. Many people believe that taking part in clinical research allows them to have access to new treatments or modes of care that they would not normally have. Be treated by specialists and receive extra time in their appointments also count as motivation. Trust in the research site and wish to “give back” to others are also fundamental in their decision²⁷.

DISCUSSION

Participation in research is essential for the progress of science. Some ideas and strategies from previous experiences could be incorporated to manage the issue of recruitment & retention in biomedical research^{17,28}. A modest increase in participation of 2 – 3% could have a major impact on the recruitment and hence in the completion of the studies.

Our review identified different reasons behind the decision of participating in a clinical study, as well as for declining, which also adds useful information. The inclusion of studies performed in developing countries endorsed some of the findings from the developed world, but also enlarged and deepened the insights and perspectives through different eyes. Even though, the study has limitations as it was not an extensive or systematic review.

Financial reward can be the most relevant motive in surveys and in phase I studies with healthy volunteers (but not in Oncology, where usually pre-treated patients are included), mainly if repeated participation is observed. On the other hand, access to (better) health care appears to be the main motivator in studies conducted with the elderly or about diseases with poor prognosis. The same can be observed in research carried on with economically or educationally disadvantaged population, where the participation offers a treatment opportunity that the patient would not have otherwise.

Altruistic reasons (helping others or contributing with science) are mentioned in several situations, but it is not rare to see the so-called “weak” or “conditional” altruism, where the wish to help does exist but it is not enough to motivate a patient, unless a personal benefit is also identified. This was observed in several papers found in this review, including the ones carried out in Brazil²¹⁻²⁴. Trust in health care professionals and agreeing with a request from their doctors are also reasons described as motivators.

In this regard, a brief comment on the vulnerability of research participants should be added. It is not rare to find publications mentioning the vulnerability of subjects, especially when the research is carried out in less developed countries. The word comes from Latin *vulnerare*, “to wound”. In clinical research the term is usually applied to define individuals who are unable to give informed consent or who are susceptible to coercion. The term “vulnerable populations” suggests that the characteristic of vulnerability is fixed and immutable. Almost everyone, however, will face poor health or disability at some point in life^{29,30}. According to Goodin, the vulnerability of other human beings is the source of our special responsibilities to them³¹. The term has been defined in such different ways that almost every research subject could be labeled vulnerable. In fact, we should regard every research subject as vulnerable until proved otherwise on an individual basis³².

In order to determine an appropriate risk-benefit ratio for clinical studies and to reduce vulnerability, the principal investigator and the Ethics Committee have the responsibility to evaluate the protocol before inclusion of any patient in the study. In this sense, the ethics committees play a key role on approval of research protocols, putting in place the four principles of bioethics: respect for autonomy, justice, beneficence and non maleficence. More progress can be made by improving methods of communicating study findings and facilitating informed consent process, rather than excluding these groups from research^{29,33}. Important to remember that, once admitted to a clinical protocol, the participant has the right to withdraw anytime.

In the debate about the need of improving communication related to clinical research participation, it is also necessary to find a balance between promoting the possibility of personal benefit during a clinical study and the need to understand the larger social purpose of clinical research, which is to optimize future patient care, bringing new therapies based on strong scientific evidence^{10,34}. An open discussion will help build on respect and trust between researchers and participants and will add value to the ethical considerations on individual interests and possible decision bias.

When it comes to health, hope plays an important role. Being connected with others who share the same disease generates personal identification, breaking the feeling of loneliness. Solidarity is also seen in social networks on the Internet created with this purpose, such as PatientsLikeMe, Inspire, CureTogether³⁵. Probably, these feelings can also be found behind the decision to participate in clinical research.

FINAL REMARKS

Reports on patient motivation are usually limited to English-language journals, which imposes a bias in the review process and, more important, in the assessment of the genuine reasons for their participation. In this short review, we tried to include some reports from developing countries, looking for additional insights and experiences.

Understanding what motivates patients to participate in clinical trials is critical if we really intend to increase their participation in research protocols. Different motivations for participation in clinical research exist and depend on the study phase, the disease, the prognosis and the environment. Access to health care and personal benefit seems to be an important motivator in studies with the elderly or patients with poor prognosis, as well as in economically disadvantaged populations. Altruism does exist but usually comes with other reasons. Conversely, in early phases of clinical research such as phase I, bioequivalence/bioavailability studies or surveys, monetary incentives usually play a relevant role. Taking these differences into account, needless to say that clinical research enrollment and completion can benefit from careful considerations by the investigator (and sponsor when applicable), on the specific participants' characteristics.

Expand the information to health care professionals and patients about benefits, risks, and the importance of volunteering is a strategy that could improve the recruitment.

Finding out more about individuals' reasons for taking part in research will enable researchers to design studies of greater benefit for the community as well as to remove unnecessary barriers to participation. Proper communication is key and will bring quality to clinical investigation, which will potentially benefit patients, researchers and the society.

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