REVIEW ARTICLE

Participation of healthy volunteers in clinical trials - motives, barriers, and ethical issues

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ABSTRACT

Recruitment of an adequate number of healthy volunteers is vital for the success of clinical trials but there is limited research on factors motivating the healthy volunteers to participate in clinical trials, especially in developing countries. Pakistani researchers also faced problems in enrollment of enough healthy volunteers during the COVID-19 pandemic when a number of clinical trials began in Pakistan. Around 117 research proposals were processed by the National Bioethics Committee of Pakistan in the last 2 years. A major proportion of these clinical research studies target healthy populations as primary research subjects or as controls. Numerous studies have investigated factors such as motives, barriers, risks, benefits, and ethical values affecting the recruitment and participation of healthy volunteers in clinical trials. We have reviewed the literature to learn about factors that motivate or prevent healthy persons to volunteer along with the pertaining ethical issues. The financial incentive is the principal motive for healthy volunteers to participate in clinical trials along with altruism, contribution to sciences, research and other people's health, desire to take part in something important, learning more about science and medicine, access to healthcare and free medical checkup, and prospects of one's social network expansion whereas time inconvenience, confidentiality, possible side effects and route of administration of drug, and fear of contacting the disease were identified as important barriers. The application of knowledge of these motives and barriers will help Pakistani researchers to enroll an adequate number of healthy volunteers for their clinical trials.

Keywords: Healthy volunteers, motives, barriers, risks, benefits, clinical trials.

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Introduction

Pakistan is a developing country located in South Asia exhibiting the highest growth rate of 2.4% in the region with a population of about 207.7 million comprising 51% males, 49% females, and 0.01% transgenders. Around 63.6% and 36.4% of the general population lives in rural and urban areas, respectively. Punjab is the most populous province harboring more than half of the national population (53%) followed by Sindh (23%), Khyber-Pakhtunkhwa (15%), and Baluchistan (6%). Although Pakistan has a national literacy rate of 58.9%, there are only 185 universities in the country. The total educated population consists of 5.26% graduates and 2.80% postgraduates[1] elaborating that Pakistan is lagging behind most developing and developed countries. There are only 175 students per 100,000 population enrolled in higher education whereas there are 217, 2,000, and 3,700 students enrolled per 100,000 population in India, Canada, and USA, respectively.[2] Pakistani Academia is actively involved in clinical research and trials despite deficient resources. State of art clinical trial units have been established in a number of hospitals and universities to enhance the quality of research. A continuous increase in the number of clinical trials is being observed in the country since the conduction of the first clinical trial in September 1992. Approximately 508 clinical trials were conducted in Pakistan from September 1992 to February 2019 whereas as maximum trials (13%) were conducted in the year 2018. Sindh remains the most common site for research hosting 53% of clinical trials whereas interventional clinical trials were more common than observational trials.[3] Around 2,962 Pakistani clinical trials are registered in the International Clinical Trials Registry Platform maintained by World Health Organization conducted from November 1999 to May 2023. Healthy volunteers were involved only in 11 clinical trials out of 2,387 registered Pakistani clinical trials in ClinicalTrials.gov database.[4,5] Similarly only one clinical

trial steered in Pakistan out of 11 and 1,085 planned and ongoing phase I studies conducted in South Asia and around the globe, respectively, from 2014 to 2016 as reported by ClinicalTrials.gov database whereas no Pakistani clinical trial was registered in trialTrove database during the same time period.[6] Despite prevailing trends in the execution of clinical trials characterized by the shift from advanced countries to developing nations, the potential of Pakistan for contribution to clinical trials remains untapped. A hefty pool of qualified and experienced physicians, low operative cost, and a high-volume healthcare system are negated by the non-existent government-led research platform and professional consortia. This situation is further complicated by a lack of research training, funding and financial incentive, massive paper work, and complex regulatory mechanism.[7] However, COVID-19 pandemic advances the conduction of clinical trials by devising innovative strategies like use of home-based testing, monitoring devices and telehealth, and engagement of courier services for pick-up and delivery of samples and investigational products.[8] National Bioethics Committee (NBC) of Pakistan played its role by adopting rapid turn around review of research proposals to facilitate the ethical clinical research in the country. Around 117 research proposals were processed by the NBC in last 2 years related to COVID-19. Out of which, 100 were approved, 1 was abandoned, 5 were not allowed, 2 were withdrawn by principal investigators, and the remaining were in processing.[9]

The use of healthy volunteers in research has many advantages as they are physically stronger and may tolerate the potential side effects and adverse events in a better way. An ample supply of healthy subjects makes the trial possible more quickly and at a less cost.[10]

"Someone with no known significant health problems who participates in research to test a new drug, device, or intervention" is considered a healthy volunteer as defined by the National Institute of Health. Traditionally, phase I clinical studies are conducted on healthy volunteers for new drugs which are under investigation usually involving 20-80 subjects.[11] Participation of healthy volunteers in the phase I trial help to recognize and document the adverse effect of these investigational drugs and precise knowledge of these side effects is vital for prescribing physicians,[12] whereas research risk to study participants must be adequately curtailed against benefits or amount of scientific facts to be generated.[13] Healthy volunteer aid to state the normal limits during the development of new techniques like a blood test or imaging device and also engaged to work as the control for the patient to match the various characteristics like age, gender, etc.[14] Healthy volunteers also take part in controlled human infection or volunteer infection studies in which they are intentionally infected or challenge with a pathological agent. These volunteer infection studies are meant for the study of disease pathogenesis or to expedite vaccine/treatment testing.[15]

Numerous studies have investigated factors such as motives, barriers, risks, benefits, and ethical values affecting the recruitment and participation of healthy volunteers in clinical trials. We have reviewed the literature to learn about factors that motivate or prevent healthy persons to volunteer.

Methods

A domain-focused, systematic literature review was conducted to learn about factors that motivate or prevent healthy persons to participate in clinical trials along with the pertaining ethical issues. A thorough and comprehensive search for studies relevant to the research theme was performed in recommended electronic databases, i.e., PubMed Central, Google Scholar, Wiley Online Library, and SpringerLink. More than two databases were used to avoid biased outcomes owing to the scope of the selected database.

The search keywords were developed by appraising academic papers, documents, and medical subject headings followed by brainstorming sessions with subject matter experts. The search terms used were "clinical trials, healthy volunteers, motives for healthy volunteers, barriers for healthy volunteers, risks for healthy volunteers, benefits for healthy volunteers, and ethical issues in clinical trials." Boolean operators (e.g., AND, OR) were used to develop the string of search keywords (e.g., "Healthy Volunteer" AND "Clinical Trials"). Different spellings were considered, when appropriate, to capture both American and British spelling variants.

Both review and original articles written in English encompassing quantitative, qualitative, and mixed methods studies were included in the review whereas books, book reviews, commentaries, letters to the editor, newspapers, dissertations, and conference proceedings were excluded.

Discussion

Motives for healthy volunteer

There is limited research on factors motivating healthy volunteers to participate in clinical trials especially in developing countries although significant work is being done on community engagement and research ethics.[16] Key elements that healthy volunteers take into consideration while making enrolment decisions are risk, time, financial incentive, contribution to medical knowledge, and competence of research staff.[17] Participation of health volunteers in a research study is also influenced by their personal characteristics including some personality traits;

however, financial incentive remains a significant motivator, especially for research subjects with low monthly income and lower educational status.[18]

Although the monetary reward is the principal motivation for healthy volunteers to participate in clinical trials, their motivations are not limited to this. Personal interests in objectives of study, curiosity, relaxing, contribution to sciences and other people's health, meeting with people, desire to take part in something important, learning more about science and medicine, access to healthcare, and additional healthcare benefits also play important role elaborating that motivation of healthy volunteers is complex and multi-dimensional phenomena.[19] Along with the motivation, the decision of healthy people to participate voluntarily in research may be influenced by age, gender, ethnicity, income, education, and societal traditions.[20] A study conducted in China reported, to help more people, to contribute to scientific research, and to obtain money as the main motivations to volunteer in clinical trials.[21] Financial remuneration was also stated as the most common motivation by a healthy volunteer in a survey conducted in South Korea whereas they categorically found that the motivations of patients participants is different from healthy participants.[22] Similarly, a recent study involving Korean healthy volunteers reported that they are driven by diverse motivations and gave due deliberation to research programs, processes, and protection along with financial incentives while constructing their enrollment decision.[23] A qualitative study in Australia concluded money, altruism, and the opportunity for self-development as prime motivations for healthy volunteers. Opportunity for self-development encompasses participation in a valuable learning and life experience and prospects of one's social network expansion.[24] Financial interest was also described as a major reason by Indian volunteers followed by the advancement in scientific knowledge, social cause, and free medical checkup. Young fellows (29-38 years), men, married, urban slum residents, and people earning less than 5,000 Indian rupees per month were more attracted to participate in clinical trials solely for financial benefits.[25] These complexities of healthy volunteer participation in research across different nations may be better understood with the of relevant ethnographic research.[16] However, an international study involving groups of healthy volunteers from United States, Singapore, and Belgium demonstrated that healthy volunteers have clear-cut choices about type of research studies they want to join in based on the risk and awareness. Their preferences tell us that they are thinking above and beyond the financial reason as their enrolment decision is further guided by other factors such as risk, possibility to reverse the potential side effects, invasive nature of procedure, type of the study intervention, and type of investigational drug.[26]

Barriers for healthy volunteer

Enrollment of healthy volunteers in research is a challenging and time-consuming process that is usually managed by potential participant facilitation, internet advertisement, and direct email solicitation.[27]

Time inconvenience, confidentiality, possible side effects and route of administration of a drug, and advertisement sources are important barriers to healthy volunteers' participation.[21] Fear of contacting the disease was elaborated as a prominent barrier by healthy volunteers in a study focusing on HIV/AIDS clinical trials.[28] Unavailability during the proposed time and failure to spare time from official commitment also restrict their participation in research trials.[29] Type of study procedure also impacts the enrolment decision of healthy volunteer as many are reluctant to join a trial that includes lumbar puncture.[30]

A study involving minorities reported mistrust, uncomfortable process, lack of information and awareness, time, and resource constraints as major obstacles to their participation in clinical trials.[31]

Risks and benefits

Phase I clinical trials are considered quite harmless as life-threatening events have occurred in exceptional cases only but healthy participants may experience temporary symptoms related to the gastrointestinal system and headache.[32] Typical example of serious adverse events is the tragic incident at Northwick Hospital of London that resulted in the hospitalization of six healthy volunteers in March 2006. They had systemic organ failure in a first-in-human trial involving TGN1412, a new monoclonal antibody despite the administration of a sub-clinical dose.[27] Death of Ellen Roche (2001) and Hoiyan Wan (1996) after inhalation of hexamethonium and administration of lidocaine, respectively, are also examples of serious harm to healthy volunteers.[33]

Healthy volunteers are usually not the direct beneficiaries of the therapeutic benefits of a clinical trial with the exception of an innovative vaccine trial where these healthy people may have access to the vaccine which is not available to the general public.[24] A study in the United States classified the benefits of the trial for healthy participants in three categories economic, non-economic personal, and societal. They further categorized the economic benefits further into two classes, i.e., a mechanism to stay afloat and an investment approach. Non-economic personal benefits consist of finding new friends, new life experiences, opportunities for behavior change, and affording a new lifestyle. These study benefits were defined by the healthy volunteers' own experiences.[34]

Ethical Issues

Most healthy volunteers are motivated by financial incentives, which might compromise the informed consent, especially

if it could fascinate the unprivileged segment of society to ignore the reasonable research risks or conceal the relevant health information to qualify for recruitment. Recent ethical discussion is more inclined to paying too much money rather than paying at all urging Institutional Review Boards for vigilant review of payment to avoid the undue influence. On the contrary, giving the meager amount of money could lead to the exploitation of the research subject and may make it difficult to achieve the recruitment goals which are necessary for the validity of the study.[35] Although monetary compensation of healthy volunteers is well-recognized practice question of right and reasonable payment is yet to be answered.[36]

An important ethical and moral challenge regarding the recruitment of healthy volunteers is the paucity of diversity. A homogenous population of healthy volunteers in a study may cause the result to be skewed and poor generalization whereas a diverse population is helpful in understanding the response to treatment among various ethnic and racial groups.[31]

Confinement for a certain period of time ranging from days to weeks is a distinctive feature of the phase I trial where healthy volunteers are kept under standardized conditions to generate valid results. Similarly, human volunteer challenge studies may also require the research participant to be retained in hospitals or research units to prevent the transmission of infection to other people.[37,38]

Healthy volunteers in developed countries are sometime literate university students enjoying a reasonable living standard as compared to developing countries where they may not even appreciate trial risks owing to their low literacy level and poor socioeconomic status. Financial gain from trials is valuable earning for them. This situation may be equated with “professional volunteers” in rich countries who also take part in trials solely to earn their livings. They have developed their skills and maneuvers to qualify for enrollment by hiding their medical conditions, substance abuse, and concomitant drugs use making them vulnerable to risks.[39] Masking of psychiatric disorders is easier than medical illnesses due to the absence of signs and lack of biomarkers.[40]

Deception by research participants is a dynamic ethical dilemma that may lead to flawed results and may harm the patient when applied in clinical practice. Concealment, fabrication, and collusion are in practice to varied degrees ranging from 03% to 25% among healthy volunteers in numerous studies.[41]

Reporting any physical or psychological changes being experienced by healthy volunteers in a clinical trial is their moral responsibility and may result in a poor understanding of the side effects of a marketed drug if they do not fulfill their obligation in this regard. It is estimated that 30% of research participants either delay or completely omit the recording of adverse events due to fear of removal from the trial, trouble expressing the body changes and forgetting. Precise knowledge of side effects is important for physicians to resolve their prescription preferences.[12]

Conclusion

The motivation of healthy volunteers to participate in research is complex and multi-dimensional phenomenon influenced by their age, gender, ethnicity, income, education, and societal traditions. Their preferences elaborate that they are thinking above and beyond the financial incentive which is identified as key persuasion. Time inconvenience, confidentiality, possible side effects, and route of administration of the drug are significant barriers identified in the literature.

Limitations of the Study

The review just offers an overview of the available literature and does not provide an answer to a specific research question. The articles in languages other than English and the paid articles without full texts could not be retrieved.

Further recommendations

Studies should be conducted in Pakistan to have a better understanding of the motives and barriers of local healthy volunteers.

List of Abbreviations

NBC National Bioethics Committee

Conflict of interest

None to declare.

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Authors’ contributions

RSA: Concept and design of the study, acquisition of data, drafting of the manuscript.
JS: Drafting of the manuscript.
MI: Critical revision with intellectual input.
ALL AUTHORS: Approval of the final version of the manuscript to be published.

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