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RESEARCH ARTICLE

# Patients' perspectives on participation in clinical trials and subsequent ethical challenges in a hospital setting in Jordan

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## Abstract

*Background* The number of global clinical trials is increasing. Recruitment rate in clinical trials is a challenging task that affects sample size, power of the study, and adequate representation of the targeted population. An understanding of the worries and reasons why patients may refrain from participation in trials may lead to improved enrollment rates. *Objectives* To assess the rate of patients who are willing to participate in clinical trials, and aspects that might have an impact on the patients' willingness to participate. *Setting* Government tertiary hospital in Jordan. *Methods* This is a cross-sectional study. Patients were interviewed by pharmacists in different clinics in a tertiary hospital and information was collected using a data collection sheet. *Main outcome measure* Factors that might predict the inclination of a patient to participate in clinical trials, and the rate of willingness to participation in randomized controlled trials in cancer patients compared to non-cancer patients. *Results* A total of 1193 participants were enrolled in the study, one hundred and thirty-five participants (11.3%) had cancer and 80% of the participants had at least one chronic medical condition. Majority of patients (n = 882, 73.9%) believed that trials were safe and 1106 (92.7%) patients thought they were important. Age, education level, income, having cancer or any chronic medical condition, and degree of control of chronic diseases were statistically significant predictors of the willingness of patients to participate in trials. Patients with cancer had a higher rate of acceptance to participation in randomized controlled trials compared to non-cancer patients, 80.0% versus 62.4%, $p$ value $< 0.001$. *Conclusion* In general, almost two-thirds of patients were willing to participate in clinical trials, with a higher rate in cancer patients. Factors such as education level, income, and extent of control of medical conditions that might refrain patients from enrollment in trials will lower recruitment rate and must be addressed and taken into consideration before launching clinical trials.

**Keywords** Developing country · Ethics · Jordan · Perspectives · Randomized controlled trials (RCT)

## Impacts on Practice

- Cancer patients with a higher education are most likely to participate in clinical trials.
- The participation of women in trials in our country is often conditioned by the approval of the spouse.

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## Introduction

Randomized clinical trials are the golden standard for studying efficacy and safety of new medication, they constitute a major segment of medical research which is not possible without the recruitment of healthy subjects or patients. One review showed that only 31% of trials conducted in the UK achieved the required recruitment rate [1]. The rate of recruitment is an important factor in determining the final sample size of a study. Studies with a smaller sample size will not be powered enough to detect differences between groups and it will give false negative results [2]. Studies with two-group parallel design were not sufficiently powered, only 16% of the studies with dichotomous primary outcomes and 36% of the ones with continuous primary outcomes had sufficient statistical power (80%) [3].

Based on the previous facts, the rate of recruitment has been a considerable concern of several studies. In the United states, 24 of the trials attained 75% or more of their enrollment goals, eight between 25% and 74%, and six less than 25% [4]. Factors affecting recruitment are many, community awareness (both physician and public), active participation of the researchers, and patient attitudes are examples of these factors [5]. Patients' attitudes towards participation in research is paradoxical, some studies showed positive attitudes and showed interest in participation [6, 7], and others revealed that patients were not inclined to participate in clinical trials [8].

Exploring the patients' perspectives towards research and assessing their expectations, attitudes, and knowledge is imperative for improving enrollment rates. In addition, involving patients in certain aspects of research and viewing them as active participants rather than passengers would improve the quality of research [9]. Research that aims at identifying the best methods of engaging patients in research, its benefits and barriers has already started [10].

Efficacy and side effects of drugs are the result of an interplay between genetics, race, environmental conditions and the drug. This dictates that clinical trials should be conducted on an international level to provide proof of efficacy and safety in different ethnic groups. Additionally, the low cost of running trials in developing countries is another advantage of globalization of trials. This demands a thorough investigation of the willingness of patients to participate in clinical trials conducted in developing countries and examine factors that might impact their decision and address them appropriately.

## Aim of the study

This main aim of the study was to assess the willingness of Jordanian patients to participate in clinical trials, measure differences in this rate between cancer and non-cancer patients and investigate possible predictors of patients' acceptance to participation. An additional objective of this study was to assess patients' attitudes, perceptions to research, and to evaluate their knowledge and other ethical challenges that accompany research.

## Ethics approval

Approval was obtained from the IRB committee in the Ministry of Health. Ethics approval letter number 19547.

## Methods

This cross-sectional study was conducted in Al Basheer Hospital, the biggest governmental hospital in Jordan. A convenient sample of patients was interviewed by pharmacists in different clinics throughout the period of 6 months (January–July, 2019), and information was documented using a data collection sheet, patients < 18 years of age were excluded.

Patients visiting the clinics were approached and invited to participate, patients that agreed on conducting the interview where asked to sign an informed consent, and informed consent was obtained from all individual participants included in the study. The pharmacists explained aspects that were ambiguous to patients.

### Attitudes to Randomized Trial Questionnaire (ARTQ)

The Attitudes to Randomized Trial Questionnaire (ARTQ) was part of the data collection sheet. The ARTQ, a questionnaire developed by Fallowfield et al. [11] to evaluate conceptions of patients of cancer clinical trials. It measures the negative and positive conception to medical research, readiness to participate in medical research, and inclination to participate in randomized trials. Subjects answer questions by "Yes", "No", and "Do not know". If they answer question number three by no, they proceed to questions 4, 5, 6, and finally after knowing the extra information they answer the last and seventh question. The ARTQ was provided to all patients to assess differences in attitudes between cancer patients and others.

### Statistical analysis

Data was analyzed using SPSS version 21. Categorical data was expressed as frequencies and percentages and continuous data as mean ± standard deviation. Differences between Categorical groups was assessed using Chi square. Predictors of the dependent dichotomous categorical variable were assessed using logistic regression. $p$ value < 0.05 was considered statistically significant.

## Results

A total of 1193 participants were enrolled in the study, with a mean age of 47.67 ± 14.77 (min = 18.00, max = 90.00), Table 1. Participants had several chronic medical conditions with an average of 1.59 ± 1.09 (min = 0, max = 6), and 80% of the participants had at least one chronic medical

**Table 1** General characteristics of participants, N = 1201

| | Frequency (%) | Frequency (%) | Frequency (%) |
|---|---|---|---|
| *Gender* | | *Clinics* | |
| Female | 831 (69.7) | Cardiology | 32 (2.7) |
| *Education level* | | Dermatology | 7 (0.6) |
| Less than high school | 478 (40.1) | Endocrine | 6 (0.5) |
| High school | 350 (29.3) | Gastrology | 8 (0.7) |
| Diploma | 188 (15.8) | Gynecology | 10(0.8) |
| BSC or higher | 177 (14.8) | Hematology | 6 (0.5) |
| *Income* | | Internal medicine | 675 (56.6) |
| < 400 JD | 830 (69.6) | Oncology | 122 (10.2) |
| 400–800 JD | 349 (29.3) | Orthopedic | 48 (4.0) |
| > 800 JD | 14 (1.2) | Rehabilitation | 43 (3.6) |
| *Social status* | | Rheumatology | 18 (1.5) |
| Single | 176 (14.8) | Respiratory | 45 (3.8) |
| Married | 871 (73.0) | Thalassemia | 90 (7.5) |
| Divorced | 28 (2.3) | Urology | 66 (5.5) |
| Widower | 118 (9.9) | Nephrology | 3 (0.3) |
| *Number of chronic medical conditions* | | Neurology | 13 (1.1) |
| None | 143 (12.0) | Ophthalmology | 1 (0.1) |
| 1 | 532 (44.6) | *Reason of the visit* | |
| 2 | 271 (22.7) | Follow up | 1082 (90.7) |
| 3 | 181 (15.2) | New visit | 111 (9.3) |
| 4 | 58 (4.9) | *Nationality* | |
| 5 | 4 (0.3) | Jordanian | 1166 (97.7) |
| 6 | 4 (0.3) | Non-Jordanian | 27 (2.3) |
| *Control of medical conditions* | | | |
| Good | 677 (56.7) | | |
| Neutral | 262 (22.0) | | |
| Bad | 254 (21.3) | | |

condition. One hundred and thirty-five participants (11.3%) had cancer, and 320 (26.8%) had diabetes, of which, 94 (29.4%) received insulin injections.

## Awareness of clinical trials

Two hundred and fifty-eight patients (21.6%) knew about clinical trials, but only three patients (0.3%) were involved in trials. After patients were informed of the details of clinical trials and how they were conducted, 882 (73.9%) patients believed that trials were safe and 1106 (92.7%) patients thought they were important. On a scale from 1 to 10, participants rated the safety of clinical trials with $6.26 \pm 2.07$ and the importance of clinical trials with $7.85 \pm 1.74$.

The need for acquiring approval for participation from family members was different depending on gender. In the married participants (871), there were significant differences in the proportion of female and male patients who needed spousal approval before participation in trials, 494 (82.1%) of females stated that they needed their husbands' approval compared to 156 (58.0%) of males who thought that they needed their wives' approval, $p$ value $< 0.001$. However, among the unmarried (n = 322), consulting family members before participating in trials was not significantly different between females and males, 62.4% and 59.1% respectively with a p value of 0.581. Participants provided several reasons for considering participation in clinical trials, and why they might decline from participating in trials, Table 2.

## Attitudes toward physicians' participation

Almost half of patients 635 (53.2%) agreed that they would participate in clinical trials because it would provide them with more time with their physician. In addition, two-thirds of the patients 896 (75.1%) stated that the involvement of their physician would encourage them to enroll in trials. A similar proportion of patients 892 (74.8%) agreed that they believe that if their physician approached them for participation, they would expect it to be beneficial for them.

Attitudes to Randomized Trial Questionnaire (ARTQ) was presented to all patients to assess differences between patients with cancer and patients without cancer, Table 3.

**Table 2** Reasons for accepting or declining from participation in future clinical trials

| Reasons for participating | Frequency (%) |
|---|---|
| Religious | 469 (39.3) |
| My participation would help develop new medication | 635 (53.2) |
| It would provide me with better medical care | 724 (60.7) |
| I would participate if there is financial reimbursement | 426 (35.7) |
| My participation would help others | 721 (60.4) |
| My participation would contribute to science | 648 (54.3) |
| My participation would provide me an access to free medication | 524 (43.9) |
| My participation would provide me with free laboratory tests | 525 (44.0) |
| My participation will allow me to spend more time with my physician | 635 (53.2) |
| *Reasons for not participating* | |
| Clinical trials are not safe | 434 (36.4) |
| Clinical trials are not useful | 66 (5.5) |
| Clinical trials are do not provide me with any personal gain | 195 (16.3) |
| I have no time to participate in clinical trials | 454 (38.1) |
| *Other causes for not participating in trials provided by patients* | |
| Old age | 45 (3.8) |
| Trust issues | 13 (1.1) |
| Stable medical condition | 16 (1.3) |
| Too sick to participate | 30 (2.5) |
| Not interested in trials | 29 (2.4) |
| If my family objects to participation in trials | 38 (3.2) |
| If medication has adverse effects | 12 (1.0) |

Participants could provide more than one answer

**Table 3** Proportion of participants who responded Yes to Attitudes to Randomized Trial Questionnaire (ARTQ)

| | Non-cancer patients N = 1058 | Cancer patients N = 135 | *p* value |
|---|---|---|---|
| *Perceptions of clinical trials* | | | |
| Q1—Do you think that patients should be asked to take part in medical research? | 966 (91.3%) | 125 (92.6%) | 0.614 |
| Q2—Suppose that you were asked to take part in a research study comparing two treatments, both of which were suitable for your illness. Would you be prepared to take part in a study comparing different treatments? | 651 (61.5%) | 97 (71.9%) | 0.02 |
| Q3—Usually the only scientific way to compare one treatment with another is for the choice between the two to be made randomly, rather like tossing a coin. Would you be prepared to take part in a study where treatment was chosen at random? | 544 (51.4%) | 96 (71.1%) | < 0.001 |
| Q4—If you answered "No" or "DK" to Question 3, we would now like to ask you a bit more about this. In a randomized study a choice would be made between two treatments, either of which would be suitable for you. Your doctor and experts in the field do not know for sure if one treatment is better than the other, or if they are both the same. That's why they want to do the study. Would knowing that encourage you to take part? | 637 (60.2%) | 104 (77.0%) | < 0.001 |
| Q5—In a random choice study, if the treatment you were receiving did not suit you for any reason you could leave the study. Your doctor would then give you whatever treatment might be appropriate for you. Would that encourage you to take part? | 658 (62.2%) | 107 (79.3%) | < 0.001 |
| Q6—Before you agreed to enter a random choice study the doctor would tell you all about the two treatments being compared, before you were allocated to one or the other. Would that encourage you to take part? | 657 (62.1%) | 107 (79.3%) | < 0.001 |
| *Intention/willingness to participate in a clinical trial* | | | |
| Q7—If you knew all the following things were taken in account, would you change your mind and agree to take part in the study? Both treatments were completely suitable. You could leave the study if the treatment did not suit you. There is plenty of information before the random choice was made | 660 (62.4%) | 108 (80.0%) | < 0.001 |

In the non-cancer group of patients, 514 (48.6%) respondents were not willing to participate in randomized trials (answered ARTQ 3 with "No") but after providing further information almost 116 (22.6%) of these participants changed their attitudes (answered ARTQ 7 with "Yes"). Cancer patients had lower number of patients that showed no interest in participation in randomized trials (answered ARTQ 3 with "No") 39 respondents (28.9%), and a higher percentage of these participants changed their opinion after obtaining further additional knowledge, 12 patients 30.8% (answered ARTQ 7 with "Yes"). Several characteristics were assessed as possible predictors of willingness to participation in clinical trials. Age, education level, income, having cancer or any chronic medical condition, and degree of control of chronic diseases were statistically significant, Table 4.

## Discussion

The reasons for participation in clinical trials presented by patients in our study were personal and altruistic, this is similar to results revealed by other studies [12, 13]. It is interesting that the religious motive for participants was lower than that shown in a similar study conducted in Saudi Arabia, 39.3% compared to 42.8% [8]. Personal gain is an important motive since patients with the preconception that they will gain certain benefits as a result of trial enrollment were more likely to participate in clinical trials [12].

Involvement of physicians in clinical trials is crucial, in many instances it is the first step in approaching patients for enrollment. Our study results showed that patients trust their physicians, and they would be more willing to participate if their physicians were part of the trial. The relationship between these two parties will reflect on an improvement in recruitment rate, the positive effect of physician's recommendation on the rate of participation was found to be the most influential factor in the patients' willingness to participate [14]. In addition, patients expected that if they participate, they would be seen more frequently by their physicians. This positive attitude is susceptible to change after the actual experience, where patients felt that the checkups for follow up information was performed by others and it was unsatisfactory [4]. Furthermore, the involvement of physicians in trials face many obstacles including hesitation of physicians to include their patients in trials and many logistical difficulties [15]. The expectations of participants of a better medical care when enrolled in a trial is ethically acceptable since even if they might not benefit directly from the new drug or placebo, they would have the advantage of regular visits and tests. Participants in developing countries also have the

**Table 4** Predictors of Intention/willingness to participate in a clinical trial (total number of patients who answered yes to ARTQ number 7)

| Variables | Univariate logistic regression | | | Multivariate logistic regression | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *p* value | Odds ratio | 95% CI | *p* value |
| **Age** | 0.976 | 0.968–0.984 | < 0.001 | 0.969 | 0.959–0.979 | < 0.001 |
| **Gender** | | | | | | |
| Females (reference) | | | | | | |
| Males | 1.129 | 0.871–1.464 | 0.360 | 1.170 | 0.885–1.549 | 0.271 |
| **Education level** | | | 0.003 | | | 0.005 |
| < High school (reference) | | | | | | |
| High school | 0.802 | 0.604–1.064 | 0.126 | 0.572 | 0.418–0.784 | 0.001 |
| Diploma | 1.153 | 0.807–1.647 | 0.435 | 0.821 | 0.559–1.207 | 0.317 |
| BSC or higher | 1.664 | 1.131–2.448 | 0.010 | 0.870 | 0.551–1.374 | 0.551 |
| **Income** | | | 0.001 | | | 0.023 |
| < 400 JD (reference) | | | | | | |
| 400–800 JD | 1.586 | 1.210–2.080 | 0.001 | 1.455 | 1.076–1.968 | 0.015 |
| > 800 JD | 3.822 | 0.85–17.190 | 0.080 | 3.272 | 0.691–15.499 | 0.135 |
| **Does the Patient have cancer?** | | | | | | |
| Yes | 2.412 | 1.554–3.744 | < 0.001 | 3.240 | 1.991–5.272 | < 0.001 |
| **Married** | | | | | | |
| Yes | 1.043 | 0.799–1.361 | 0.755 | 1.265 | 0.946–1.693 | 0.113 |
| **Chronic medical condition** | | | | | | |
| Yes | 1.037 | 0.721–1.492 | 0.844 | 1.999 | 1.320–3.028 | 0.001 |
| **Control of disease** | | | < 0.001 | | | < 0.001 |
| Neutral (reference) | | | | | | |
| Good | 1.846 | 1.373–2.481 | < 0.001 | 1.701 | 1.245–2.324 | 0.001 |
| Bad | 0.861 | 0.608–1.218 | 0.397 | 0.992 | 0.689–1.428 | 0.966 |

right to the best standard of medical care similar to those in developed countries [16].

The percentage of participants who knew about clinical trials was low, but it was higher than 9.1% which was reported in Saudi Arabia [17], and lower than that reported in Oman 31.3% [18]. Limited knowledge of clinical trials, among other factors, is a cause for low recruitment rates [19]. The ratio of participants who were involved in trials was much lower than that of the neighboring countries, 7.3% in Saudi Arabia [8], 6.5% in Oman [18]. Recruitment is a very important aspect in site feasibility when considering a country as a candidate for conducting clinical trials [20]. The number of clinical trials conducted in developing countries in the last decade have increased and will probably continue to grow. Yet, the contribution of the Middle East/Northern Africa (MENA) region (which includes Jordan) to the global sites of clinical trials is very low [21].

The ratio of married women who required the approval of their spouses was significantly higher than that of married men. This conditional participation interferes with the women's right to make decisions and echoes the lack of autonomy, which is an important ethical consideration in research. The perception of women's autonomy in Western countries is different than that in other parts of the world. This demonstrates the cross-cultural disparities when considering ethical requirements [22].

Reasons for participation such as helping others, developing new medications, and getting best medical care were also shared by patients in Saudi Arabia [8, 17]. Most of participants believed that trials were safe, which is one of the ethical requirements of RCTs [16]. Furthermore, most of the participants considered them important.

Similar to other studies, transportation and worries from adverse effects were considered as possible reasons for declining participation in trials [23]. Appropriate financial reimbursement for the travel expenses and inconvenience is ethically acceptable, but the amount is disputable. The payment should not influence patient's consent, and it is the role of the IRB committee to decide and guarantee that it is fair, suitable, and not overestimated [24].

Patients with low education, low income, without cancer or any chronic medical condition were less willing to participate in clinical trials. Conversely, patients with an education higher than high school, moderate income, with cancer or a chronic medical condition, and with a good control of their medical status, were more willing to be enrolled in a trial. Patients with higher income compared to those with low income were more likely to participate (OR 1.455, $p = 0.015$), similar results were demonstrated by a study that showed that cancer patients with higher income were more likely to participate in cancer research, this might be caused by costs of participation that can be resolved, as mentioned previously, by financial reimbursements [25]. Older age might lead to low participation in clinical trials, although small OR but statistically significant, OR 0.976, $p$ value $< 0.001$. Age related willingness was seen in a study conducted in cancer patients where patients $\geq 70$ years less likely to accept participation in trials [26]. This may affect the recruitment rate of the elderly, reduces their representation in trials, and consequently deprive them from the opportunity to study safety and efficacy of medications in their age group.

Although ARTQ was validated for cancer patients only, we decided to provide the survey for all patients since it contains questions that reflect the patient's opinion towards medical research, randomization, and willingness to participate after complete knowledge was provided to patients. The questions in the ARTQ were relevant to the scope of our study, so all participants were asked to respond to them. In this study, we wanted to compare the results of this survey between two groups of patients: cancer patients and non-cancer patients and test the assumption that those with cancer may have a different rate of willingness to participate in clinical trials.

Both cancer and non-cancer patients agreed equally that patients should be asked to participate in medical research. However, differences became significant when patients were asked to participate in randomized trials. This trend was seen in other studies, where patients were discouraged from involvement in randomized trials [26]. In our study, cancer patients showed a higher rate of approval compared to other studies, 71% compared to 28.7% [27]. This study revealed that, at every level of information, cancer patients had higher willingness to participate than non-cancer patients and that providing further information increased the rate of approval in both groups, but to different extents. Additionally, as mentioned earlier in the predictive model, cancer patients were three folds more likely to accept participation in clinical trials. This might be due to the aggressive nature of the disease and limited success of therapies that function as incentives for cancer patients to participate in randomized trials to explore new alternative medications.

The implications of the study reflect directly on trials' recruitment rates and generalizability of the results drawn from clinical trials. The findings from this study revealed that age, income, education level, presence of chronic medical conditions and level of control of these medical conditions were all factors that might influence whether a patient would participate in a clinical trial or not. Based on the previous results, patients with these characteristics might be under-represented in trials that test the efficacy and safety of drugs. Consequently, there will be a lot of missing information concerning the clinical effects of drugs in older patients, those who have poorly controlled medical conditions, and patients with certain lifestyle that is affected by income or level of education.

Moreover, married women needed the assent of their husbands before considering participation in trials. Females are poorly represented in clinical research all over the world, to address this issue in the United States, the National Institutes of Health Revitalization Act was passed in 1993. The act mandated the inclusion of women and minority groups in clinical trials to enhance their representation [28]. Despite many policy initiatives, female representation is still low. A recent study examined clinical research articles published in PubMed from 1966 to 2018 and records from ClinicalTrials.gov from 1999 to 2018. Eleven diseases were investigated in the studies that included diabetes, HIV/AIDS, neoplasms, and many others. The study results showed that women were underrepresented in 7 of the 11 diseases [29].

The representation of females in clinical trials is crucial, since many drug effects are affected by gender. A Cochrane meta-analyses revealed that 5% of the 162 randomized control trials investigated that enrolled both sexes, had a sex-treatment interaction that was statistically significant [30].

Limitations of our study include lack of certain data such as employment data, place of residency, distance traveled to the hospital, and type of insurance. The previous information was not included to make the questionnaire more practical and can be conducted in a reasonable time. Another limitation is the fact that this hospital is a governmental hospital (not private), this may have led to the enrollment of high percentage of low-income patients.

## Conclusion

Cancer patients were more willing to participate in clinical trials than non-cancer patients. Furthermore, patients with an education higher than high school and with a chronic medical condition which is controlled were more inclined to participate in trials. The participation of women in trials is conditioned by the approval of the spouse, this represents an important cultural aspect that must be considered when approaching women for enrollment in clinical trials.

In order to recruit enough patients in trials, further investigation should be conducted to assess the attitudes of patients towards participation and explore how they can be addressed in an ethically appropriate manner.

Future studies in developing countries should focus on vulnerable populations such as women and older patients. Considering factors that might impede the participation of these subgroups of patients can improve their representation in clinical trials.

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