Post an Unforeseen Outcome of Serial Volunteering in Clinical Trials, What Does the Affected Community Want?

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Abstract

Background and Aims: A disturbing trend is largely seen in clinical trials that recruit healthy volunteers, where vulnerable low-income groups are over-volunteering, leading to adverse health outcomes. There is a need for an awareness study of the affected rural community that has witnessed an unforeseen outcome of clinical trial participation.

Method: Data on knowledge, attitude, practice and educational materials about clinical trial participation using a semi-structured interview schedule was collected from 192 heads of households from Nagampet Village in Telengana state, South India, that had been making headlines in the news because of the death of one of its residents due to adverse effects of repeated participation in clinical trials. Descriptive and Multivariate analysis of variance was used.

Results: 99% of heads of household were married men with 69.8% belonging to Lower Middle Class and 34.9% less than a primary education. Majority (86.5%) were not aware about clinical trial process. 68.8% opined that family members should reject the individual's voluntary decision about taking part in clinical trials because they fear the death of the only earning member of the family due to any ill-effects from clinical trial participation.

Conclusion: This study brings out what the people want in order to avert another death or another unforeseen event in their village due to clinical trial participation. They want a professional such as teacher, doctor or nurse to explain to them the crucial steps in clinical trial participation during gram sabha and special village gatherings. Well-informed decision-making in clinical trial participation through reliable sources would encourage them to take medical help when in need and not to be lured by middle-men or agents.

***Keywords*:** *Serial volunteering; Clinical Trial Participation; Awareness of Clinical Trial, KAP, Knowledge, Attitude, Awareness, MANOVA*

Introduction

Of recently, India's leading newspapers[1], local news channels and review journals[2] have brought to limelight that a growing number of low-income groups are over-volunteering for clinical trials to supplement for their income. Such serial volunteers are an especially vulnerable class of people because of their low levels of education, poverty and rural category[3,4].

Numerous studies, both quantitative[3,5,-10,] and qualitative [4,11,12], have explored the awareness, attitude and perception of general public and trial participants towards clinical research and the circumstances coercing the volunteers to partake in more than one clinical trial. Past studies conducted in North India were from urban and semi urban population and had contrasting results. Two studies[11,13] found majority knew nothing about clinical research while one KAP study[10] found that participants were aware of essential elements of clinical

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trials. Results of all these studies show that healthy volunteers with minimal primary school education, who had taken part in clinical trials atleast once in their lifetime, did not know which trial they had taken part and did not fully participate in informed consent process.

A Korean study[14] replicated the PARTAKE Survey[13] and found a higher percentage of responders from Korea have heard of clinical research compared to India, attributing to high use of internet, media and smart phone in Korea.

The meta-analysis of qualitative studies of Indian clinical trials[9], systematic review of all phase I studies[15], case study of a CRO in Hyderabad[2] and review article of trial compensation in Telengana state[16] reveal that poverty compels many from the marginalised sector to over-volunteer in clinical trials. Similar finding is observed from the qualitative accounts of individuals of a longitudinal study in US[12,15].

What is missing from the past studies is an awareness study of the affected rural community that has witnessed an unforeseen outcome of clinical trial participation. This study aims (1) to explore the knowledge, attitude and practices about participating in clinical trials from this rural community who might be at risk of being lured into clinical trials (2) to find out directly from the people the information/educational materials they would like to have to increase their awareness about clinical trial participation and (3) to find the association between knowledge and attitude about clinical trial participation with socio-demographic variables using multivariate analysis.

Method

Study setting

This specific research was conducted in Nagampet Village of Jammikunta mandal in Karimnagar district located in Telengana state, South India in June 2018. One of the residents had passed away due to adverse effects of repeated participation in clinical trials. This village had been making headlines in the news for the past one year as pharma companies from Hyderabad in Telengana, Bengaluru in Karnataka and other areas attract healthy volunteers from remote areas.

Study design

The study design was cross-sectional and has Institutional Ethics Approval.

Sampling and Participants

The unit of analysis was head of household. Sample size n=221 was calculated with a proportion of 73% people not aware or heard of clinical trials [taken from PARTAKE study[13]], effect size = 0.06 assuming overall knowledge of community people fluctuates between 6% points (ie. 67% and 79%), $Z_{0.05}$ at 95% confidence interval and 5% non-response rate.

The village panchayat office had the list of households N = 406, which formed the sampling frame. Circular systematic sampling methodology was used. The sampling interval k=N/n = 406/221 = 1.8 ≃ 2. Random start from random number table was r = 2. Of the every second household visited, 12 refused, 10 consented but withdrew in the middle of the survey, 5 absent and 2 abandoned households. Data was collected from 192 heads of households after taking informed consent.

Material

The study tool was a semi-structured interview schedule on Knowledge, Attitude, Practice and Educational/Informational materials about clinical trial participation. A pre-validated questionnaire by Burt et al., 2013methodological, and operational reasons. There are indications that the public is unaware or misinformed, and not sufficiently engaged in clinical research but studies on the topic are lacking. PARTAKE – Public Awareness of Research for Therapeutic Advancements through Knowledge and Empowerment is a program aimed at increasing public awareness and partnership in clinical research. The PARTAKE Survey is a component of the program. Objective To study public knowledge and perceptions of clinical research. Methods A 40-item questionnaire combining multiple-choice and open-ended questions was administered to 175 English- or Hindi-speaking individuals in 8 public locations representing various socioeconomic strata in New Delhi, India. Results Interviewees were 18–84 old (mean: 39.6, SD±16.6[13] was used. It was reviewed for completeness, supplemental questions added and checked if it matches with this study's objective. The questionnaire underwent translation and back-translation from English-Telugu-English. Uday Pareek's socioeconomic scale and Kuppuswamy's monthy family income[17] updated for 2017 was used to collect socio-demographic information.

Data analysis

SPSS 16 was used to analyse data. The KAP component in Objective 1 and Objective 2 was analysed using Descriptive analysis. For Objective 3, the association between following variables was conducted using two-way multivariate analysis of variance (MANOVA). $P < 0.05$ was considered a significant difference.

Dependent variable 1	**Total knowledge score**
Dependent variable 2	Total attitude score
Between-group independent variables	Education Occupation Monthly family income Socio-economic status Willingness to participate in clinical trials

Results

Descriptive analysis

99% of heads of household were married men. 69.8% were Hindus. Half of the respondents belonged to Lower caste (50.5%), followed by Artisan caste (17.2%), Schedule caste (17.2%), Agriculture caste (14.1%) and Prestige caste (1%). Only 10.9% were graduates, 54.2% studied upto Middle and High School, and 34.9% had less than a primary education. In terms of occupation, majority were labourers (42.7%) with monthly family income in the range Rs. 6214 – Rs. 10356 (53.6%). Totalling the scores obtained using Modified Kuppuswamy Socio-Economic Status Scale revealed that 69.8% were from Lower Middle Class and 30.2% were from Middle Class.

The mean knowledge score was 22.24 ± 3.291 SD (n=192). Majority (86.5%) were not aware about clinical trial process. Almost all of them (96.9%) expressed that financial gain was the reason for taking part in clinical trials, a means of additional source of income. In the event of any side-effects from taking medicines during clinical trial participation, it is surprising to see that there were respondents who did not consider it important to take medical help. There were five respondents who felt that the volunteers of such clinical trials should keep it discrete and not tell anyone, for the fear of being scolded, rejected by family or treated differently by society.

The mean attitude score was 8.45 ± 1.439 SD (n=192). Though a majority of respondents (91.7%) considered experiments on humans essential to developing new treatments, they (76%) did not favour such experiments on humans. Most respondents (98.4%) said it is important to keep family members informed about clinical trial participation. Contrastingly, more than half the respondents (68.8%) opined that family members should reject the individual's voluntary decision about taking part in clinical trials. 77.6% respondents remarked such experiments are harmful to society. When asked, "given an opportunity, would they take part in clinical trials?" Majority (81.8%) said 'no'.

Regarding materials that educated them about participation in clinical trials, majority preferred to have messages through TV (17.2%), brochure (15.8%), messages in mobile (10.4%) and other means. The respondents wanted local government support in the form of monetary compensation for victims' family (10.9%) and panchayat meetings addressing this issue through expert advice (9.4%).

Two-way MANOVA

Two-way MANOVA is used to find out if there is an interaction between independent variables and the two dependent variables.

Checking correlation

The Pearson correlation for the dependent variables was within acceptable limits for MANOVA outcomes (r=0.5).

Checking assumptions

Levene's Test for homogeneity of variance assumption for dependent variables indicated that there is no homegeniety of between-group variance for knowledge (p=0.001) and attitude scores (p= 0.008). The Box's M value of 66.374 had a non-significant association with a p-value of 0.099. The covariance matrices between the groups were assumed to be equal.

Multivariate outcome

MANOVA was conducted to test null hypothesis that group mean vectors are all equal to one another. Wilks' Lambda is chosen. As shown in Table 1, a significant multivariate effect is obtained for the combined dependent variables of knowledge and attitude in respect of:

Education: λ = 0.868, $F(4,280) = 5.15$, p=0.001, partial eta squared = 0.069. Power to detect the effect was 0.868.

Occupation: λ = 0.852, $F(10,280) = 2.33$, p=0.012, partial eta squared = 0.077. Power to detect the effect was 0.852.

Education*Occupation: λ = 0.842, $F(14,280) = 1.79$, p=0.039, partial eta squared = 0.082. Power to detect the effect was 0.842.

Monthly family income*Willingness to participate in clincal trials: λ = 0.954, $F(2,140) = 3.34$, p=0.038, partial eta squared = 0.046. Power to detect the effect was 0.954.

Whereas, socio-economic status (p=0.194), monthly family income (p=0.269), willingness to participate in clinical trials (p=0.324) were not significantly associated with knowledge and attitude towards clinical trial participation.

Univariate statistics

Both dependent variables differed significantly in knowledge about clinical trial participation in respect of independent variables [education $F(2,141) = 9.886$, p<0.001) and occupation $F(5,141) = 4.64$, p=0.001)]. But not so with repect to attitude score [education $F(2,141) = 0.087$, p=0.917) and occupation $F(5,141) = 4.501$, p=0.775)].

Similarly, both dependent variables differed significantly in knowledge about clinical trial participation in respect of education*occupation*monthly family income $F(1,141) = 5.52$, p=0.02). Both dependent variables differed significantly in attitude score in respect of education*occupation*willingness to partcipate in clinical trials $F(1,141) = 5.069$, p=0.026).

Post-hoc analysis

Education

Since there did not exist equal variances across independent variables, Games-Howell outcome for knowledge and attitude scores is referred to. It indicated that graduates or those heads of households with higher levels of education were more knowledgeable (p<0.001; mean difference between 'graduates & above' and 'primary & below' is 8.32, 95% CI [6.97,9.67] whereas mean difference between 'graduates & above' and 'middle & high school' is 6.5, 95% CI [5.12,7.89]) and had better attitude towards clinical trial participation (p<0.001; mean difference between 'graduates & above' and 'primary & below' is 1.76, 95% CI [0.98,2.55] whereas mean difference between 'graduates & above' and 'middle & high school' is 6.50, 95% CI [0.66, 2.10]).

Occupation

As the hierarchy of occupation increases from low-skilled to professional jobs, there is an increase in knowledge score about clinical trial participation. Those in the Service sector, such as teaching and hospital have better understanding about clinical trial process than labourers. Mean difference between 'service-oriented occupation' and 'labourer' is 1.89, 95% CI [0.86, 2.93]

Table 1: Results of Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Intercept	Wilks' Lambda	0.028	2.467	2	140	0.000	0.972
Education	Wilks' Lambda	0.868	5.154	4	280	0.001	0.069
Socio-economic status	Wilks' Lambda	0.977	1.659	2	140	0.194	0.023
Occupation	Wilks' Lambda	0.852	2.328	10	280	0.012	0.077
Monthly family income	Wilks' Lambda	0.964	1.304	4	280	0.269	0.018

Cont... **Table 1: Results of Multivariate Tests**

Willingness to participate in clinical trials	Wilks' Lambda	0.984	1.137	2	140	0.324	0.016
Education*Occupation	Wilks' Lambda	0.842	1.797	14	280	0.039	0.082
Monthly family income* Willingness to participate in clinical trials?	Wilks' Lambda	0.954	3.345	2	140	0.038	0.046

Discussion

While there had been studies in the past about awareness on clinical research with sampled population from general public and hospital patients who either had no knowledge[11,13,14] or some knowledge about clinical trial process[10], the very little knowledge that the heads of households of this study possessed about clinical trial participation is from the news that spread through the death of one of their residents in the neighbourhood who had secretly taken part in many clinical trials one after another, which made headlines in local news channels. With this, the villagers developed hatred towards pharma companies/CROs and felt that clinical trial volunteers are not taken care or treated properly by CROs.

This study brings out what the people want in order to avert another death or another unforeseen event in their village due to clinical trial participation. They want a professional such as teacher, doctor or nurse to explain to them the crucial steps in clinical trial participation such as informed consent, side effects, trial compensation, etc during gram sabha and special village gatherings. They would also like to have such information disseminated to them through radio, television and other means.

The multivariate analyses indicated that not all socio-demographic variables differed significantly in respect of a combination of knowledge and attitude towards clinical trial participation. Subsequent univariate analyses showed that there were significant effects for education and occupation in respect of knowledge and attitude scores. Games-Howell post hoc analyses suggested having educational qualification beyond high school and holding better jobs reflected in better knowledge and attitude about clinical trials process and participation.

Conclusion

The very few (13.5%) heads of households knew something about clinical trial process through word-of-mouth. They end up gathering wrongful information about clinical trials, developing negative attitude about it. This is reflected in victims fearing to take support from family or medics. One way to overcome this would be to disseminate the study findings to local village governance that will help in planning and conducting specific educational programs, tailored to appropriate cultural content and language and can be scaled to other rural settings in India with similar demographic and socio-economic characteristics.

Although the poor financial status of the family is the driving factor for the head of the household to discretely partake in clinical trials without his family's knowledge, it is not his socio-economic status that influences his awareness and perception about clinical trials but his education and occupational status. The educated masses from the community can be identified, training provided to them who in turn can educate the villagers, especially about making well-informed decision-making in clinical trial participation through reliable sources, encourage them to take medical help when in need and not to be lured by middle-men or agents.

Ethical Clearance: Expedited Ethics Review Committee approval from School of Public Health, SRM-IST

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Conflict of Interest: Nil

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