British Journal of Bio-Medical Research Vol.02, Issue 04, Pg.504-511, July-August 2018

Available Online at http://www.bjbmr.org

BRITISH JOURNAL OF BIO-MEDICAL RESEARCH

Cross Ref DOI: https://doi.org/10.24942/bjbmr.2018.234 Volume 02, Issue 04, July-August 2018

ISSN:2456-9739

Research Article

A Survey Of Understanding The Reasons For Possible Refusal To Participate In Phase I Clinical Trials Among Adults Of 18 Years And Above Living In Gurugram District, Haryana, India

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ARTICLE INFO

Article History:
Received on 11th July 2018
Peer Reviewed on 25th July 2018
Revised on 13th August 2018
Published on 29th August 2018

Keywords:
Phase I trials, Subjects, Adverse effects, Food and Drug Administration

ABSTRACT

Background: It's always a major setback for biomedical research that needs human participants when none or suitable amount is enrolled. The issue of humans not agreeing to participate in research has been consistent even with the set down rules and regulations to ensure their safety and enhance efficacy. The problem of Phase I studies is a special case because it's being conducted mostly on healthy subjects. Many studies have investigated the reasons why people participate in biomedical research. However, there have been less research and little attention specifically on reasons why people can say no to participation when it comes to biomedical research and clinical trials.

Objective: This study incorporated the collection of data based on a designed questionnaire in order to understand why the adult inhabitants of Gurugram district that are knowledgeable about clinical trials can choose not to participate in Phase I studies.

Method: A descriptive cross-sectional study was conducted from January to March 2018, among inhabitants living in Gurgaon district, Haryana, India. The participants were 177 (96 males and 81 females) in total.

Findings:

- A large number of undocumented inhabitants of the city knows nothing about clinical trials.
- 53.7% of the participants stated clearly that their reason for refusal can be lack of time availability.
- 36.2% of the participants accepted that they don't have access to clinical trials.
- 22.6% opted that "lack of study benefits" can be their reason for not participating in a phase I trial.
- Additional reasons given by 7 of the participants include; Less monetary benefits, Fear of Adverse effects and Poor accountability by Pharmaceutical Companies.

Conclusion: Time constraint is the most obvious reason that holds inhabitants of Gurgaon district, Haryana India from participating in Phase 1 clinical trials.

INTRODUCTION:

Phase I trials are conducted to determine the safety and maximum tolerated dose of investigational products. This is majorly determined by keeping account of all the related and unrelated adverse events that occurred throughout the study. Only the related adverse events assured to be caused by the administration of a dose of an Investigational Product are counted as "dose-limiting". Such adverse events are used to define MTD. It is highly essential to attribute any adverse event accurately so as to ensure the integrity of the safety data collected by any phase I studies[1]. The foundation of a successful clinical trial process depends upon Phase 1 trials because it represents the first administration or application of a study drug or combination of such to humans. The fate the clinical development of a drug depends solely on its early phase, so a careful and thoughtful approach is necessary in design of the phase I trial.

There are many components of a Phase I clinical trial design. Some of which include; starting dose, dose escalation method, dose increment, dose level, number of patients per dose level, specifications for dose-limiting toxicity (DLT), Moderate limiting toxicity, target toxicity level and maximum tolerated dose definition[2].

Phase I trials are mostly conducted at hospitals or in-patient clinics which serve as the sites. The subjects are kept for a full examination, mostly till the half-life of the trial drug is past. Normally, the number of subjects required is between 20 and 80 in number. Dose escalation is often implemented in this trial in order to determine the appropriate dose for the IP's therapeutic effect. The range of doses tested must be less than the dose that caused any form of toxicity to the animals during the pre-clinical testing. Most often, healthy volunteers are used. In fewer cases, patients with the disease being studied are used. This is due to the lack of other treatment options and the disease being at its end stage. Most trials of Oncology and HIV are conducted on patients with such ailments. Apart from assessing the safety of the study drug, tolerability, pharmacokinetics and pharmacodynamics are also studied[3]. The primary purpose of conducting phase I trials is not to ascertain the efficacy of the drug, so homogenous population is not required. For oncology trials, measurement of tumours is not mandatory though both factors are included in the trial protocols. In the United States, understanding the emphasis of safety in conducting phase I trials requires a proper understanding of the drug development history and this is why the Food and Drug Administration (FDA) is concerned with establishing efficacy only after safety is assured[4]. Primarily, the doses administered in phase I trials are meant to establish the level of safety or toxicity, with the aim of determining the dose of an IP to take into the next stage. Torneau and his colleagues stated that the principle guiding the dose escalation in phase I clinical trials is avoiding exposing many subjects to sub-therapeutic doses while preserving safety and maintaining amassment[5]. A typical phase I trial is a human pharmacology trial. The risks of harming subjects in phase I trials must be fully accessed. The sponsor of such trial must present the pre-clinical data/reports to experts with technical, scientific and clinical background for review. The sponsor's designated experts must scrutinize all aspects of the test article; class, novelty, specificity of species, potency, mode of action, dose, concentration, route of administration, safety, efficacy and toxicity[6]. Examples of specific end points for phase I trials include the Dose Limiting Toxicity (DLT) and the Maximum Tolerable dose (MTD). A DLT occurring in a subject show that an unacceptable adverse event which is presumably related to the drug has been experienced. These set of adverse events are pre-specified and classified accordingly in the protocol. They differ from trial to trial. Even though the sole aim of Phase I trials is not efficacy, Physicians commonly monitor the subjects for any activity showing effectiveness from the IP. Phase I trials mostly involve the study drug alone, while Phase I b trials combines the study drug with another agent by running a single trial in different arms. Typical example is the oncology trials[7]

trials. Leading to asking the research question; why do people refuse to participate?

Background

It's always a major setback for biomedical research that needs human participants when none or suitable amount is enrolled. The issue of humans not agreeing to participate in research has been consistent even with the set down rules and regulations to ensure their safety and enhance efficacy. The problem of Phase I studies is a special case because it's being conducted mostly on healthy subjects. Many studies have investigated the reasons why people participate in biomedical research. However, there have been less research and little attention specifically on reasons why people can say no to participation when it comes to biomedical research and clinical trials. Some of the data available on refusals is centred on non-response to postal questionnaires from different surveys[13]. For a clinical trial to be accepted, a reasonable amount of subject has to be enrolled. Recently there have been a huge drop in the enrolment of participants for phase I clinical

Aim

The aim of this study was to understand the reasons adults living in Gurugram district Haryana, India opt for "No" when called to participate in phase I clinical trials and also educate the reader about the important aspects of a phase I Investigational product research.

Objectives

- To deduce the major and minor reasons adults of Gurugram district Haryana can refuse to participate in a phase I clinical trial.
- To obtain any other non-pre specified personal reason if included.
- To educate the participants and the general public about the components and importance of a phase I trial in facilitating drug development.

Research Questions

- Why would an adult living in Gurugram district Haryana, who is knowledgeable about phase I clinical trials still refuse to participate in any?
- How versatile in knowledge are these adults about Phase I clinical trials.

MATERIALS AND METHODS

A descriptive cross-sectional study was conducted from January to March 2018, among inhabitants living in Gurgaon district, Haryana, India. The participants were 177 (96 males and 81 females) in total. Using the background and in-depth literature review, common questions regarding the refusal of humans to participate in clinical trials were outlined and properly arranged. A structured pre-tested questionnaire was developed with the questions related to these above options for refusal ranging from; lack of time availability, lack of understanding of the objectives of phase 1 trials, fear of breach of confidentiality and others. Based on these questions, the questionnaire was designed strictly for those who have a knowledge about clinical trials. The type of sampling used was simple random sampling, with the age of participants; 18 and above. Data entry and statistical analysis were carried out using SPSS 21 version. Descriptive statistics (mean, mode, median, standard deviation, range and variance) were used to summarize the quantitative and qualitative variables. The individual Student's t-test was used to compare the mean values of the continuous variables across the levels (2 and 3) of categorical variables.

Ethical Considerations

Pre-notification and information about the survey was discussed with the participants in-person and/or telephonic contact. During survey visits, the study coordinators introduced themselves and explained to the participants, the aim and objectives of the study and all procedures to be followed in filling the questionnaires. Semi-literate participants were interpreted to in Hindi. Subject number was given to each of the participants and the names were recorded as initials to maximize privacy. Although signatures were taking to ensure differences in identification. All other personal information was removed before data entry into the database.

RESULTS

Table 1: Gender of the Participants

S.No	Sex	Frequency	Percent	Valid Percent	Cumulative Percent
1	Male	96	54.2	54.2	54.2
2	Female	81	45.8	45.8	100
	Total	177	100	100	

Table 2: Descriptive statistics for the age of the participants

N	Valid	177
	Missing	0
Mean		24.5424
Std. Error of Mean		0.38875
Median		23
Mode		23
Std. Deviation		5.172
Variance		26.75
Range		29
Minimum		18
Maximum		47

Figure 1: Bar Chart representing the occupation of the participants

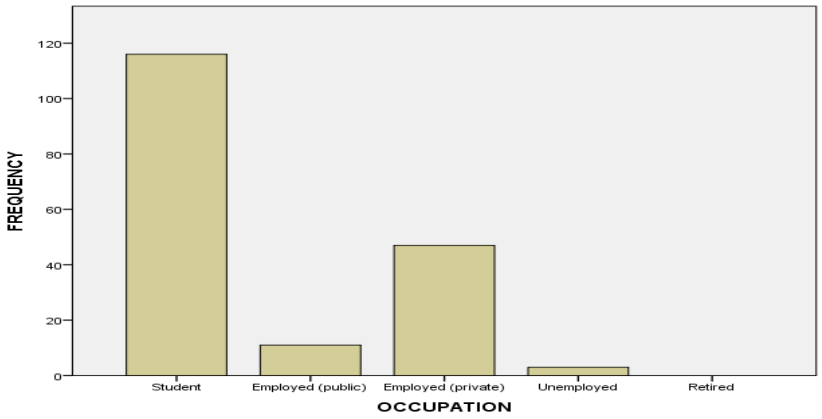

Table 3: Frequency distribution of Age of the participants

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	18	10	5.6	5.6	5.6
	19	16	9	9	14.7
	20	15	8.5	8.5	23.2
	21	16	9	9	32.2
	22	9	5.1	5.1	37.3
	23	25	14.1	14.1	51.4
	24	11	6.2	6.2	57.6
	25	18	10.2	10.2	67.8
	26	7	4	4	71.8
	27	13	7.3	7.3	79.1
	28	6	3.4	3.4	82.5
	29	5	2.8	2.8	85.3
	30	5	2.8	2.8	88.1
	31	2	1.1	1.1	89.3
	32	2	1.1	1.1	90.4
	33	5	2.8	2.8	93.2
	35	6	3.4	3.4	96.6
	36	2	1.1	1.1	97.7
	37	1	0.6	0.6	98.3
	42	2	1.1	1.1	99.4
	47	1	0.6	0.6	100
	Total	177	100	100	

Table 4: Response to Time Constraint (Lack of Time Availability)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	95	53.7	53.7	53.7
	No	82	46.3	46.3	100
	Total	177	100	100	

Table 5: Response to Fear of Breach of Confidentiality

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	57	32.2	32.2	32.2
	No	120	67.8	67.8	100
	Total	177	100	100	

Table 6: Response to Ignorance about the procedure of giving informed consent

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	42	23.7	23.7	23.7
	No	135	76.3	76.3	100
	Total	177	100	100	

Table 7: Response to Lack of Understanding the objectives of Clinical Trials

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	78	44.1	44.1	44.1
	No	99	55.9	55.9	100
	Total	177	100	100	

Table 8: Response to previous bad experiences from old volunteers

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	35	19.8	19.8	19.8
	No	142	80.2	80.2	100
	Total	177	100	100	

Table 9: Response to lack of will to participate

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	64	36.2	36.2	36.2
	No	113	63.8	63.8	100
	Total	177	100	100	

Table 10: Response to financial constraints to travel

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	32	18.1	18.1	18.1
	No	145	81.9	81.9	100
	Total	177	100	100	

Table 11: Response to superstitious/religious beliefs

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	17	9.6	9.6	9.6
	No	160	90.4	90.4	100
	Total	177	100	100	

Table 12: Response to lack of study benefits

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	40	22.6	22.6	22.6
	No	137	77.4	77.4	100
	Total	177	100	100	

Table 13: Response to fear of strangers

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	38	21.5	21.5	21.5
	No	139	78.5	78.5	100
	Total	177	100	100	

Table 14: Response to lack of access to clinical trials

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	64	36.2	36.2	36.2
	No	113	63.8	63.8	100
	Total	177	100	100	

Table 15: Correlation of Educational Status and Lack of Understanding of Clinical Trial Objectives.

		Educational Status	Lack of Understanding the Objectives of Clinical Trials
Educational Status	Pearson Correlation	1	.201**
	Sig. (1-tailed)		0.004
	N	177	177
Lack of Understanding the Objectives of Clinical Trials	Pearson Correlation	.201**	1
	Sig. (1-tailed)	0.004	
	N	177	177

***. Correlation is significant at the 0.01 level (1-tailed).*

Table 16: One-Sample Test for Question 1 to 6

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Time Constraint (Lack of Time Availability)	38.93	176	0	1.46328	1.3891	1.5375
Ignorance about the procedure of giving informed consent	54.969	176	0	1.76271	1.6994	1.826
Fear of Breach of Confidentiality	47.641	176	0	1.67797	1.6085	1.7475
Lack of Understanding the Objectives of Clinical Trials	41.668	176	0	1.55932	1.4855	1.6332
Previous Bad Experiences from Old Volunteers	60.03	176	0	1.80226	1.743	1.8615
Lack of Will to Participate	45.24	176	0	1.63842	1.5669	1.7099

Table 17: One Sample Test for Question 7 to 10

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Financial Constraints to travel	62.712	176	0	1.81921	1.762	1.8765
Superstitious/Religious Beliefs	85.724	176	0	1.90395	1.8601	1.9478
Lack of Study Benefits	56.272	176	0	1.77401	1.7118	1.8362
Fear of Strangers	57.683	176	0	1.78531	1.7242	1.8464
Lack of Access to Clinical Trials	45.24	176	0	1.63842	1.5669	1.7099

DISCUSSION

The major hiccup in getting participants to participate in this study is the broad and widespread lack of knowledge about Clinical trials. A 2013 survey conducted in India to study the public knowledge and perception about Clinical research showed that 26.3% of the respondents reported having heard and 72.6% reported having not heard of clinical research35. Evidence seems to be obvious in this study because even though the participants have knowledge about clinical trial, majority opted for no (80.2) when asked if “bad experience from old volunteers” can be their reasons for refusing to participate in a study. This asks another research question which is “how many people have they encountered that participated in a clinical trial”. Another significant reason for refusal is lack of time availability. 53.7% of the participants stated clearly that they are not willing to put in their time in any phase I clinical trial. Generally, phase II and III studies enrol patients suffering from the disease or disorder being researched upon. These subjects are more willing to partake in clinical trials in comparison with healthy subjects for phase I studies. Although from this survey, only 22.6% opted that “lack of study benefits” can be their reason for not participating in a phase I trial. Recently there are websites and other platforms that provides education and access for different types of CTs. The impact is not convincing seeing that 36.2% of the participants accepted that they don’t have access to clinical trials. This seems to be an issue of poor awareness, even at a big city like Gurgaon. Majority of the adults that understood what clinical trial is also know the process and need for giving informed consent. There is low degree of positive correlation when comparing the educational status and lack of understanding of clinical trial objectives. Seven of the participants gave additional reasons which can be their cause for saying no to Phase I Clinical Trials. They include; Less monetary benefits, Fear of Adverse effects and Poor accountability by Pharmaceutical Companies.

CONCLUSION

Time constraint is the most obvious reason that holds inhabitants of Gurgaon district, Haryana India from participating in phase 1 clinical trials. Other obvious reasons include; lack of understanding of the objectives of clinical trials, lack of will to participate and fear of breach of confidentiality. Unrelated observational information deduced during the conduct of this survey presented that even with higher level of education, many of the inhabitants have never heard of clinical trials.

RECOMMENDATIONS

- The Ministry of Health and other related authorities should educate the general public about the topic of clinical research and its importance in improving human health.
- Medical and Pharmaceutical professionals should assist in educating the public about the need for new drugs and the importance of humans participating in clinical trials to actualize the availability of these drugs in the market.
- Information should be spread throughout the media either by websites, TV and Radio; giving updates about availability of clinical trials on vaccines, most especially in public health cases like spread of diseases like Dengue fever, Chikungunya disease, Ebola virus, Zika Virus, etc.
- Ethics regarding the conduct of clinical trials should be monitored at all times by the constituted body to avoid any violation form hospitals, clinical research organizations and pharmaceutical companies.

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How to cite this article:

Udeh Chukwunonso Livinus & Pramod Singh Khatri. ***A Survey Of Understanding The Reasons For Possible Refusal To Participate In Phase I Clinical Trials Among Adults Of 18 years And Above Living In Gurugram District, Haryana, India.*** **Br J Bio Med Res , Vol.02, Issue 04, Pg.504-511, July-August 2018. ISSN:2456-9739 Cross Ref DOI : https://doi.org/10.24942/bjbmr.2018.234**

Source of Support: Nil **Conflict of Interest:** None declared.