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Clinical Research

PERCEPTION OF CLINICAL RESEARCH AMONG HEALTHY VOLUNTEER STUDIES AND HUMAN CLINICAL PHARMACOLOGY-PHASE-I CLINICAL TRIALS

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ABSTRACT Purpose Clinical research relies on data from patients and volunteers, yet the target sample size is often not achieved. Here, we assessed the perception of clinical research among clinical trial participants to improve the recruitment process for future studies. The main aim of early volunteer studies should be evaluate all pharmacological properties of the drug in man so as to maximize its therapeutic impact. Having said this however, the objectives of volunteer studies must be seen in the general context of the complete development of the drug. The problems must not be considered in isolation. Observation made during this early phase will certainly influence the design of later phases and indeed should even provoke further animal experiments. Before dealing with the design of early volunteer studies it is necessary to consider who the clinical investigator (PI) should ideally be and to determine where exactly these volunteer studies should be performed. Healthy volunteers who reported financial motives had participated in more clinical trials. Consistent with great trust in medical staff and government research institutions, little concern was expressed about the misuse of personal data during the trial.

KEYWORDS : Clinical research · Treating physicians · Volunteer, Healthy patient, Acute mesuurement

INTRODUCTION

Healthy volunteers play a crucial role in Phase-I clinical trials by contributing to the development of safe drugs and biologics. They accept potential risks without anticipating direct health benefits from the investigational products. Generally, the incidence of serious adverse events in Phase 1 trials is low. Existing literature on healthy volunteer participation in Phase 1 trials has primarily focused on the ethics of financial compensation. Concerns have been raised about whether participation disproportionately attracts individuals with lower incomes and higher unemployment rates [1]. Evidence suggests that financial reward is a primary motivation for healthy volunteers participating in clinical trials. Some commentators express concerns about the socio-economic backgrounds of participants, labeling them as those who may be financially vulnerable. There is an emerging empirical literature that sheds light on the socio-demographics and enrollment preferences of healthy volunteers [2]. Previous studies have indicated that participants often have low incomes and high rates of unemployment. The study aims to examine socio-demographics, enrollment preferences, and decision-making processes of healthy volunteers. The analysis delves into how the type of study, study procedures, and potential side effects impact the willingness of healthy volunteers to participate in research. Many previous studies on this topic are dated, focused on specific geographic regions, or have small sample sizes. The current study seeks to address these limitations by surveying a large and diverse cohort of participants. In summary, your passage provides a comprehensive background on the motivations, concerns, and socio-demographic characteristics of healthy volunteers participating in Phase 1 clinical trials, with a focus on an ongoing survey of Pfizer trial participants in multiple countries. This research aims to contribute valuable insights into the decision-making processes of these volunteers and factors influencing their willingness to participate in such trials [3].

Selection Of Investigator And Site

The selection of investigator and of location are interlinked problems .the following facilities appear desirable and some of them are essential. To some extent they are dependent on the type of the study being done and the stage which it has reached. Instrument are necessary to collect the appropriate pharmacological data. A sufficient number of trained assistants, physicians, technicians and phlebotomist and nursing staff are necessary. They should be able not only to cope with routine collection of data but also able to deal with any emergency situation that might arise. Special investigation room are desirable. A clam quiet environment is important. Hospital records with their associated activity are not usually suitable for performing such studies. Some control over the room temperature is also important especially in pharmacodynamics (BA/BE) studies. The investigator should be able to observe the subject for the adequate period of time. The study must not have to stop at 5. Pm. There always danger when a new compound is given for the first time to man. The investigator must therefore have the ability and equipment to combat any untoward reaction. This means that at least the initial studies should be done in hospital environment. The expert opinion any other decision has allowed arguments of convenience or of finance to outweigh those of safety for the volunteer. The clinical investigator has to be both pharmacologist is immaterial. He must understand the details of the animal pharmacology and toxicology and be able to assess the level of confidence with which the prehumen pharmacological conclusions have been drawn. Otherwise he is not in position to fully understand the risk to which he is subjecting his volunteers. 'Doctor with no clinical pharmacological training or those who are not willing to collaborate with a clinical pharmacologist and adhere strictly to a protocol [4]. According to dangler (1974) 'very often underestimate the responsibility they are taking and are often of potential danger to the subject'. The professional clinical pharmacologist in a specialized hospital unit is the ideal investigator since he can function as physician yet be able to understand all the clinical pharmacological problem involved. From the results of his observations he may be able to suggest further animal experiments. Occasionally investigations are performed by a 'system specialist'. The danger of this is that undue attention may be focused on one system of the body to the determent of the others. Important clinical pharmacological points of therapeutic relevance may be missed.one is likely to find only what one looks for. If the individual has had training in clinical pharmacology, in addition to his specialist is usually found more helpful at later phase. There are many excellent clinical investigators in industry who have limited or no access to hospital facilities. This state of affairs must be changed clinical pharmacology and the need for further clinical pharmacologist has not resulted in the expected expression of the subject, mainly for economic reasons. If better facilities are to be provided then much of the funding will need to come from industry, at least for the next few years. The relationship between industry and academic units must be further improved. Secondment of individuals from industry to academic units and from academic units to industry needs to be encouraged. Such measures are consistent with opinion of the joint committee on higher medical training [5].

The Selection Subjects

Volunteer subjects are usually recruited from industrial personnel or from laboratory staff. In academic units. Such sources may become exhausted fairly rapidly. There is a real need for volunteer from other sources. One answer would be to set up a Clinical Trial Registry (CTRI) of volunteer. The volunteer should not be in a position of subservience to the investigator. For this reason many academic and industry do not allow their personnel to volunteer for studies in academic clinical pharmacology units. Surely these doctors are adult enough to make such decision for themselves? They can avoid the problem by acting as volunteer at other institutions. The question of payment is difficult. Certainly the subject should not be 'out of pocket' for being public spirited, but neither should payment be so generous that it results in the 'professional' volunteer. It must not be so large as to be considered in any way a bribe. Once the subject has volunteered it is

important that he or she is given a through medical examination by an independent doctor and that the subject's liver and renal function is shown to be normal. it is wise to inform the general practitioner of the volunteer that the study is being done.it is important also that everyone talking part in Phase-I study is covered by adequately insurance. This applies to both the subject and the investigator [6].

Ethics

Written consent after full explanation of the protocol and procedure in the presence of LAR/Impartial witness is almost essential. Recently it has been suggested that verbal consent before the third party who confirms it in writing might be a satisfactory alternative to written consent nearly all research department have now to submit the details of the projected investigations to an independent ethics committee composed of both professional and lay members[7]. One effective system is that the protocol is sent to every member of the ethical committee. They then return this with either their individual approval or adverse comments to the secretory. Any query is directed immediately to the investigator or who can usually satisfy the ethical committee member on the point fairly quickly. A full ethical committee meeting is called only if a point of disagreement arises. This system causes little delay to the clinical research project yet the ethics are competently and fully dealt with [8].

Design of Clinical Investigation.

The design of the initial human investigation will be largely but not entirely dependent on the potential use of the drug; for instance , weather it is going to be used in cardiovascular, respiratory or psychiatric fields. Only generalizations about the design are therefore possible. Ideally, both pharmacokinetic and pharmacodynamics measurements will be made. Apparent pharmacokinetic and pharmacodynamics failure can be due to pharmacokinetic factors. If a drug lacks effect it essential to discover the reason, for it may simply have failed to reach the site of action. One of the objective of initials experiments is to determine whether the pharmacological finding in animal apply also to man. In addition, special attention should be paid to those variables were animal apply also to man. In addition, special attention should be paid to those variables where animal experimentation is unable to supply the answer for instance psychological testing [9].

Some of the more important factors influencing the design of volunteer studies are listed below:

The likely mechanism of action of the drug. If this is known from the animal experiments it is important to check whether the same conclusion apply for man. If the mechanism of action is known one can predict more accurately where and when the drug will be of clinical value and possibly be able to predict and avoid adverse reactions. The design of the investigation also is very much simplified. The predicted effect is likely to occur after a single dose or after repeated administration. In the latter case prolonged studies involving continuous administration may be necessary in phase-I or may be appropriate in Phase-II [10].

The predicted effect is likely to occur only in diseased subjects. This is not necessarily preclude volunteer studies. An example of where acute volunteer studies are of use is afforded by pharmacokinetic studies involving antimicrobial drugs. Checks can be made to ascertain whether or not an adequate drug concentration is achieved in plasma, urine or at other appropriate sites. The effect to be measured is the therapeutic effect itself or whether it is only beloved to correlate with it. These latter studies are never easy to design well and interpretation of results is often difficult. There are some situation where normal volunteers are not used for instance with cytotoxic drugs [11].

Drug Administration

Acute Data

On the empirical ground it is usually regarded as satisfactory if the drug is administered for one to four weeks in animal before a single dose or series of doses on one occasion is to given man. It is usual to start with two per cent of the scaled dose that is effective in animal and to do double this until either the therapeutic effect occurs or the expected dose is reached. The route must be the same in animal and man. It is important note that a minute dose of the radioactive labeled drug may be all that is necessary for initial pharmacokinetic data. However, it is better to correlate pharmacodynamics with pharmacokinetic changes and this can only be done with an effective dose. If possible the dose of the drug should be titrated against the effect. Such studies give much more information than a single fixed dose study [12].

Chronic Data

Long term treatment in man must be preceded by three to twelve months of the toxicity testing in animals. this animal toxicity testing is designed to show the clinical pharmacologist or toxicologist what organ systems to monitor rather than to provide a testimonial for the drug .therefore , the clinical pharmacologist will want to ensure that inadequate does has been given to the animals[13].

With a single dose the rate of absorption as well as the fraction of drug absorbed from the dosage from can markedly influence the onset, intensity and duration of the response. With continuous administration on the other hand , the rate of absorption would have little effect on the plasma concentration and pharmacological effect achieved; in this case the major determinant of the steady state level would be the fraction of drug absorbed from the dosage from . The rout or major routes chosen for the study should be the ones by which it is intended that the drug should be given clinically. Variation in the route can result in surprising pharmacokinetic pharmacodynamics differences [14].

Measurements

The measurements that will be made depend largely on the drug and the disease for which it was developed. It is important to set the net wide to check whether the same features are found in man as in animals and to evaluate whether there are any new ones which did not show up in the animal experiment . Particularly important is the testing of variables which are difficult or impossible to do in animals, for instance psychological testing[15] Good simple measurements that are unlikely to go wrong are more useful than complicated ones which are often found to be unreliable. For example, intelligent use of blood pressure measurements, pulse rates before and after exercise can reveal a lot more information than single readings or complicated measurements of cardiac function. Electrocardiography, electroencephalography and the use of radioisotopes including the inert radioactive gases can however provide a great deal of information with relatively little trauma. Safety lies in good experimental design using techniques with which the investigators are happy. An attempt should be made to correlate pharmacodynamics data with pharmacokinetic data [16].

In acute studies, estimation of plasma concentration provides clues as to whether the drug or a metabolite is responsible for the pharmacological effect, and will reveal whether the drug disappearance obeys first or zero order kinetics. The volume of distribution and clearance will be obtained for most drugs. Possibly the dosage schedule can be decided at this stage. The chronic administration pharma kinetic data will serve as a check on initial impressions from the acute data and will allow more complicated pharmacokinetic systems to be revealed. If the kinetic data correlate well with the dynamic data there is strong presumptive evidence that the drug itself and not a breakdown product is responsible for the effect [17]. If a more active metabolites is identified, the possibility of developing that compound as the drug of choice should be considered.

During chronic administration to volunteers monitoring of the function of those organs most likely to be affected (according to animal data) should be performed. If a serious reaction occurs such as jaundice, which may or may not be due to the drug it is essential to investigate the patient and circumstances as thoroughly as possible. Future subjects may be put at hazard unnecessarily or a useful drug may be withdrawn unnecessarily for want of evidence which would have been available if the adverse reaction had been properly investigated at the time.

Although not often carried out during Phase-I, the problems of possible drug interaction can frequently be answered by good human investigation. It is also important to know whether the drug acts as an enzyme inducer before it is given to patients on any large scale. Complete records of all patients receiving the new drug must be kept. It is a good idea to design and print a preform so that no details are forgotten for an individual. Time spent on the design of such forms will be amply rewards during the stage of data analysis. Such information should be made available to workers investigating the drug in other centers.

I would like to repeat the plea of modell(1974) that the results of Phase-I studies be made available to everyone more quickly and specially when for some reason the drug is withdrawn. Knowledge will be more

quickly disseminated and advances in the field of clinical pharmacology hastened [18].

CONCLUSION

The main aim of early volunteer studies should be to evaluate all the pharmacological properties of the drug in man so as to mixture its therapeutic impact. In practice simple pharmacokinetic data such as half-life and the volume of distribution should be obtained initially, in addition to the principal pharmacodynamics effects. More sophisticated investigations should be left to later stage. Fuller collaboration of clinical pharmacologists in academic units, the health service, and the pharmaceutical industry will improve the speed, efficiency and safety with which such studies can be done.

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