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SYMPOSIUM

Clinical Research: Comprehension of the Patient Information Leaflet and the Consent Form

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ABSTRACT

Informed consent process is an integral component of conducting clinical research ethically. Prior to giving an informed consent to participate in clinical research, it is important that the participant has fully understood all the components of a patient information leaflet and the consent form. The issue of comprehension of informed consent form and patient information leaflet has acquired particular importance in view of research being carried out in developing countries and in vulnerable population. The present review addresss this issue by discussing the need for addressing comprehension of research process by the participant, the tools for assessing the same and various ways in which these tools have been used.

Keywords: Informed consent, Comprehension, Clinical research.

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INTRODUCTION

One of the most important pillars of ethics of clinical research is autonomy, defined as the ability and right to make independent decisions. The application of this fundamental law of ethics is 'informed consent'. Informed consent has been an integral part of important codes of ethics in clinical research, such as Nuremberg Code (1947),[1] Belmont report (1974)[2] and Declaration of Helsinki (1964, latest revision 2008).[3] The Indian Council of Medical Research (ICMR) guidelines (1980, latest revision 2006)[4] also emphasize the need for informed consent in clinical research.

Although the informed consent process is of paramount importance in all types of clinical research, its importance is greater in certain special types of research such as nontherapeutic research involving healthy volunteers or patients or those conducted in vulnerable population. The salient characteristics of informed consent are disclosure, comprehension, voluntariness and competence. The indispensible component of informed consent process is an informed consent form (ICF) along with patient information leaflet (PIL). Role of the investigator is not merely confined to passing the information about research, or worse, just getting the signature of the participant. The investigator has to ensure that the contents of the information thus conveyed have been comprehended by the potential study participant. But how to do this is not an easy question to answer.

It is also generally believed that the informed consent process in developing countries is likely to be suboptimal because of various reasons one of which is the participants' inability of understand the consent form.

The present review aims at understanding various aspects of consent comprehension.

Factors determining comprehension are as follows:

Participant Centric

Educational Status

General perception is that patient's educational status is an important determinant of consent comprehension. In order to test this we evaluated factors influencing consent comprehension in two different studies—a phase III[5] trial in patients and a phase I study in healthy volunteers.[6] In both of these studies, after an initial briefing about the nature of the study in which the first statement was that we are asking them to take part in research, participants were given the PIL in a language they knew. In case of an illiterate patient, the PIL was read out by a third person. The participants were allowed to take the PIL and the ICF with them so that they could discuss it with their relatives or any other person. The signatures on ICF were obtained on a subsequent visit before which they were allowed to ask questions and remove any doubts.

Comprehension questionnaires (see below for more details) were developed for each of these studies and the participants were interviewed by a person not involved in obtaining the consent on a later date to obtain comprehension scores. In both these studies, the educational status was not found to be determinant of the comprehension scores. We concluded that the educational status of trial participants did not correlate with the comprehension score. One reason could be that educational opportunities are largely determined by the economic status of the participant and not his or her intellect.

Participants' Competence Related

Certain categories of patients, such as pediatric/adolescents, patients with mental illnesses may present a special situation. Often in addition to the patient, the patient's legal guardian is addressed to in these situations. An assent is taken in

addition to the guardian's consent in case of pediatric patients. It is important to recognize barriers to communication, such as stress due to the patient crying for attention, formal settings should be recognized and addressed. In case of patients with mental illnesses one should ensure that the legal guardian is authorized to decide for the patient. However, for illnesses which show only phasic response, one has to clarify that the patient's consent will also be sought when patient is understood to be competent by the treating physician. The language would need to be simplified. One can use pictorial presentations to explain the risk to children, e.g. pictorial visual analog scale may be used to explain the degree of pain the patient is likely to receive.

First Time Participants

Therapeutic misconception, i.e. inability to distinguish between practice and research is common in settings like ours. Though clinical research is not new to India, GCP-compliant research is relatively recent due to which there may be a certain lack of experience. While earlier paternalistic attitude of the investigators was fairly common practice, it is only now that increasing number of investigators have got indoctrined in the ethical principles governing clinical research. It is following this only that a learning portal about clinical research represented by clinical investigators is reaching increasing number of participant pools. It is only obvious that a person staying in an environment where his fellow beings are participating in clinical research or a person who has himself previously participated is more likely to comprehend the research.

PIL Centric

This is certainly the most researched factor in the comprehension of informed consent. The generally, prescribed norm for making the patient information leaflet is that it should be simple enough for a primary grader to understand it with ease. This is easier said than done. Of the topics in patient information leaflet which are commonly difficult for patient to understand are those relating to study design particularly terms like randomization and blinding, confidentiality, investigator, sponsor. Other barriers of comprehension include content presentation[7] and length of the PIL. For example, in one study investigators randomized the subjects to a concise and standard length consents and noted that subjects using concise consent forms scored as well as those using standard length consents in measures of comprehension (7 *vs* 7, p = 0.79 and 20 *vs* 21, p = 0.13), however, the trend was for the concise consent group to report feeling better informed. Both groups thought there the length and detail of the consent form were appropriate.[8]

An important issue is finding appropriate terminology when the consent form is translated into the vernacular language. Often, in order to maintain the validity of translation, the terms used are difficult to comprehend. For instance, if the title of a hypothetical study is: 'A double-blind study to assess safety and efficacy of ABC in patients with hypertension', its literal Hindi translation would be: 'Ek dohra agyaat waas adhyayan-ABC Aushadhi ke labhdayak ewam hanikarak prabhavon, un rogiyon mein jin me raktchaap ki vriddhi hui ho' losing the whole purpose of translation.

Using the concept of 'user testing' which is commonly used in developing PIL which come as package insert may be employed to improve participant information leaflet for clinical trials. This approach involves identifying key points of research and designing a leaflet based on this. A sample representative of research participants is interviewed and problem areas of the leaflet are identified. This information is used to redesign the PIL. This concept has been evaluated in a research setting and has been found to be useful.[9] In one study, the investigators tested the original patient information sheet (PIS) on people in the target group for the trial. Three rounds of testing were undertaken and the information was revised according to its performance after each of the first 2 rounds. The revised PIS was compared with the original in a parallel groups randomized controlled trial. Sixty-six percent of participants who read the revised PIS were able to show understanding of all aspects of the trial compared with 15% of those reading the original version and 87.1% participants chose the revised sheet.

METHODS FOR ASSESSMENT OF COMPREHENSION

In recent times the idea of objective assessment of comprehension assessment has been taken up by investigators. Various formats for assessment have been used. Questionnaires with a yes/no format or multiple choice questions or quizzes have been used by a different investigators. Not only have the format for comprehension assessment been different, the purpose for which these methods have been used are also different.

For a phase III drug trial of a new chemical entity we administered a set of multiple choice questions. The questions were categorized into broad categories on background details for the study, design of the study, rights of the patients and miscellaneous aspects pertinent to the clinical trial. The questionnaire comprised of 24 items and each correct answer was assigned a score of 1. Total comprehension score (CS) was obtained by summing all the scores. The participants in the study were from diverse socioeconomic and educational backgrounds.

The mean ± SD, CS achieved by the participants was 13.4 ± 2.9; median 14 (6-20). The highest correct responses were obtained for questions on background details (38%). For most of the categories the mean CS was more than 50%. Aspects related to design were the found to be the most difficult to comprehend. On receiving requests for fellow researchers and readers we published the set of questions to enable its use by other researchers.[10] However, the researchers would need to tailor the questions according to the study they are undertaking.

Comprehension assessment has also been used as criteria for enrolment. Investigators of a study in HIV patients in Botswana assessed comprehension of ICF using a 20-question true/false quiz administered in 6-month intervals.[11] Quizzes were offered in both Setswana and English. To enrol in the trial, participants were required to have ≥16/20 correct responses. The authors examined concepts understood and the degree to which understanding changed over 3 years. They analyzed 5,555 quizzes from 1,835 participants. The participants' highest education levels ranged from no education to the tertiary education level. Eighty percent of participants passed the enrolment quiz on their first attempt and the remainder passed on their second attempt. Those having higher than primary education and those who took the quiz in English were more likely to receive a passing score on their first attempt [adjusted odds ratios and 95% confidence intervals, 3.1 (2.4-4.0) and 1.5 (1.2, 1.9) respectively]. The trial's purpose or procedures were understood by 90 to 100% of participants, while 44 to 77% understood randomization, placebos or risks.

Some investigators have gone a step further by using an educational intervention to improve actual informed consent understanding. New enrolees in the Adult AIDS Clinical Trial Group (AACTG) were administered to assess their baseline understanding on eight elements of informed consent associated with AIDS clinical trials.[12] Enrollees who scored 85% or less were randomly assigned to in-person, targeted education (intervention) or delayed education (control). Two follow-up assessments were administered. Repeated measures ANOVA was performed to determine intervention effectiveness in improving actual informed consent understanding overtime.

Actual understanding improved at the immediate post-intervention time point. This was one time intervention for which the effects were shown to last for a week at least. However, since trial participation could stretch overmonths, it is also important to see if this learning is retained throughout the course of the trial.

Rapid assessments, involving focus-group discussions and in-depth interviews have been used for improving the concept comprehension in the third world countries. In one such study,[13] discussions were conducted with podoconiosis patients and nonpatients in the community, fieldworkers, researchers, staff of the local nongovernmental organization (NGO), working on prevention and treatment of podoconiosis and community leaders. The extent of use of everyday language, the degree to which expectations of potential participants were addressed, and the techniques of presentation of information had considerable impact on comprehension of information provided about research. Moreover, in such research involving the local community level workers may enhance the comprehension by the community.

CONCLUSION

Ensuring comprehension of the information provided in the participant information leaflet is as essential as providing the information itself. In order to achieve reasonable understanding several approaches may need to be adopted. This may start from the stage of interacting with the prospective participants to designing the form and to communicating the information in a manner which is most suitable for the research and the clinical trial setting.

Keeping the above facts in mind, the following recommendations may be made:

Box-Steps for ensuring comprehension in the consent process of clinical studies are as follows:

1. Have a plan for consent process.
2. Write down the consent form yourself or refer to a template (an example may be seen)[14] and keep the following points in mind:
   - Keep the language simple such that a primary grader can understand.
   - Keep it structured with each heading addressing important issue about the study. It may even be in a question form, e.g. background of the study could be titled, 'why are we conducting the study.'
   - For translation in the vernacular language, keep words which are in local use, e.g. blood pressure is more commonly understood by Hindi speaking people than 'rakt chaap.' We suggest writing in Devanagari.
   - Any terminology which is technical should be explained in the subsequent line in a sentence format, e.g. placebo should be explained as a substance which has no action of its own but resembles the study drug.
   - Keep it grammatically correct.
   - Some risks should be detailed. The frequency may be given in form of simile besides giving 1 in 1000 (etc.) format. For example, the risk is same as that you have while driving on a busy road.
   - Use short sentences.
3. Pilot run it in some representatives of the target population. Identify the key problem areas and revise the form.
4. Give a person-to-person or person-to-group briefing before giving the PIS and give sufficient time to the participant to read it.

Contd.

Contd.

5. Administer the comprehension tool. The format of the same may be predecided.
6. Address the areas which have not been understood by the participant.
7. Keep a record of time spent on consent process, key areas of difficulty, action taken, participant's final decision and if available the reason for the decision.
8. Get the consent form signed and sign yourself. In case of an illiterate participant, ask an impartial witness to witness the informed consent process and then get his or her signature as well.
9. Give a copy of the signed consent form to the participant.

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