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Contents

Editorial
Antibiotic resistance: Unless we act soon!
Bavdekar SB ...................................................................................................................................... 107

Original Article
Recruitment of subjects for clinical trials after informed consent: Does gender and educational status make a difference?
Gitanjali B, Raveendran R, Pandian DG, Sujindra S .......................................................................... 109

Brief Reports
Human immunodeficiency virus type 1 infection in patients with severe falciparum malaria in urban India
Khasnis AA, Karnad DR ..................................................................................................................... 114
Antimicrobial-induced endotoxaemia in patients with sepsis in the field of acute pyelonephritis
Giamarellos-Bourboulis EJ, Perdios J, Gargalianos P, Kosmidis J, Giamarello H .................................. 118
A comparison of intravenous ketoprofen versus pethidine on peri-operative analgesia and post-operative nausea and vomiting in paediatric vitreoretinal surgery
Subramaniam R, Ghai B, Khetarpal M, Subramanyam MS .................................................................. 123
Extended interval between enzyme therapy infusions for adult patients with Gaucher’s disease type 1
Umbilical hernia in adults: Day case local anaesthetic repair
Menon VS, Brown TH ........................................................................................................................ 132

Special Articles
Tuberculosis: Looking beyond BCG vaccines
Mustafa Abu S, Al-Attiyah Raja ...................................................................................................... 134
Smallpox: Clinical highlights and considerations for vaccination
Mahoney MC, Symons AB, Kimmel SR ............................................................................................. 141

Case Reports
Laparoscopic bilateral nephroureterectomy and bladder cuff excision for native renal pelvic and ueteral transitional cell carcinoma after renal transplantation
Chen CH, Huan SK, Lin JT, Chiu AW ............................................................................................. 148
Meckel’s diverticulum: An alternative conduit for the Mitrofanoff procedure
Prabhakaran K, Patankar JZ, Mali V ................................................................................................. 151
Prenatal diagnosis of partial trisomy 21 associated with maternal balanced translocation 46,XX der 21 t(21q;22q) with pericentric inversion of chromosome 9
Parmar RC, Sira P .......................................................................................................................... 154
Colonic adenocarcinoma presenting as a cutaneous metastasis in an old operative scar
Wright PK, Jha MK, Barrett PD, Bain IM ......................................................................................... 157

Ethics-Forum
Ethics of patient care by trainee-doctors in teaching hospitals
Sethuraman KR .................................................................................................................................. 159
E-Medicine
The role of informatics in continuing professional development and quality improvement in primary care
de Lusignan S, Lahbani M, Chan T ................................................................. 163

Grand Round Case
A young man with sore throat, acute abdomen and respiratory failure
Isaac A, Baker N, Wood MJ .................................................................................. 166

Clinical Signs
Romberg’s test
Khasnis A, Gokula RM .................................................................................... 169

Images in Medicine
Holoprosencephaly
Thomas N, Cherian A, Sridhar S ................................................................. 173

Images in Pathology
Gonadoblastoma with distinctly unusual pattern of yolk sac tumour overgrowth
Madiwale CV, Fernandes GC, Pandit AA, Kane SV ........................................... 175

Images in Radiology
MRI in sleep apnoea
Maheshwari PR, Nagar AM, Shah JR, Patkar DP ............................................. 177

Review Articles
Role of left cardiac sympathetic denervation in the management of congenital long QT syndrome
Wang LX ................................................................................................................ 179

Brain natriuretic peptide in diagnosis and treatment of heart failure
Bhatia V, Nayyar R, Dhindsa S ......................................................................... 182

Letter to Editor
Bradyarrhythmia associated with ophthalmic beta-blockers ........................... 186
Unusual life-threatening adverse drug effects with chloroquine in a young girl .................................................. 187
Post operative abdominal wall mucormycosis mimicking bacterial necrotising fasciitis ........................................ 187
Endotracheal intubation related massive subcutaneous emphysema and tension pneumomediatinum resulting in cardiac arrest .................................................. 188

Looking Back
The life of Robert Koch ..................................................................................... 190

Subscription Details ......................................................................................... 192
Recruitment of Subjects for Clinical Trials after Informed Consent: Does Gender and Educational Status Make a Difference?

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Abstract:

CONTEXT: Researchers and investigators have argued that getting fully informed written consent may not be possible in the developing countries where illiteracy is widespread. AIMS: To determine the percentage of patients who agree to participate in a trial after receiving either complete or partial information regarding a trial and to find out whether there were gender or educational status-related differences. To assess reasons for consenting or refusing and their depth of understanding of informed consent. SETTINGS AND DESIGN: A simulated clinical trial in two tertiary health care facilities on in-patients. METHODS AND MATERIAL: An informed consent form for a mock clinical trial of a drug was prepared. The detailed / partial procedure was explained to a purposive sample of selected in-patients and their consent was asked for. Patients were asked to free list the reasons for giving or withholding consent. Their depth of understanding was assessed using a questionnaire. Chi-square test was used for statistical analyses. RESULTS: The percentages of those consenting after full disclosure 29/102 (30%) and after partial disclosure 15/50 (30%) were the same. There was a significant (p=0.043) gender difference with a lesser percentage of females (30%) consenting to participation in a trial. Educational status did not alter this percentage. Most patients withheld consent because they did not want to give blood or take a new drug. Understanding of informed consent was poor in those who consented. CONCLUSIONS: The fact that only one-third of subjects are likely to give consent to participate in a trial needs to be considered while planning clinical trials with a large sample size. Gender but not educational status influences the number of subjects consenting for a study. Poor understanding of the elements of informed consent in patients necessitates evolving better methods of implementing consent procedures in India. (J Postgrad Med 2003;49:110-113)

Key Words: Clinical trials, informed consent, gender, educational status

Scientific investigators have an ethical, legal and moral responsibility to ensure that patients and subjects understand their participation in research. The ICMR ethical guidelines for conducting research in human subjects’ makes it mandatory for investigators in India to seek written informed consent from subjects volunteering for medical research. These norms have been broken in the past soliciting a great amount of negative publicity. Investigators have felt that getting fully informed written consent may not be possible in developing countries, where illiteracy is widespread and explaining the nuances of a clinical trial may not be feasible. It has been shown that even when care has been taken to get proper informed consent, participants may have a very limited understanding of their basic rights concerning a clinical trial. However, excluding illiterate people from trials would limit the generalisability of the conclusions.

In India, getting fully informed written consent from subjects may not be easy, given the large number of languages and dialects spoken, migration of people from one state to another, etc. These difficulties have led to many investigators resorting to getting partial consent, at times only verbally, and by downplaying the adverse effects and actual implications of randomisation, and use of controls, etc. These researchers believe that while the actual process of consent may not be in keeping with the international requirements and spirit of informed consent, it is a good trade-off between the two. This has led to an international denunciation of the ethics of the trials concerned.

A study from Italy has shown that there is a strong aversion among potential subjects to participate in trials involving drug administration with fewer than 60 out of a 1000 potential participants available for a hypothetical trial. It also showed that there was no difference in the percentage consenting between those who are highly educated and those with a low educational background. India is being projected as a fertile place to conduct clinical trials due to the vast number of potential subjects, availability of good healthcare facilities and the en-
thatism of the medical fraternity to be involved in introducing novel therapies. In order to protect the interests of participants in these trials and see that they are enrolled in an informed, voluntary manner we must know how well they would understand the process of an informed consent. Hence, we decided to find out what percentage of hospitalized patients would agree to volunteer in a clinical study when they are given full disclosure regarding a study and to see whether educational status and gender would alter this percentage. We also wanted to find out whether more people would consent to enroll in a study if only partial information regarding the study-details were to be given to them and their reasons for agreeing to participate or refusing consent. We also wanted to test the depth of understanding of those subjects who had consented to participate after full disclosure.

Subjects and Methods
The study was conducted in the wards of Jawaharlal Institute of Postgraduate Medical Education & Research, a tertiary care teaching hospital and at Nallam Hospital, a private hospital, both situated in Pondicherry, South India during the months of May and June 2001. One hundred and two adult in-patients of either sex who were hospitalized were chosen as subjects. Children, pregnant women, mentally ill patients and those who were admitted for emergency conditions were excluded, as were patients who were acutely and seriously ill. An informed consent form for a mock trial was prepared and this was explained to the subjects by authors DGP and SS who introduced themselves as members of a research team from the Dept. of Pharmacology. The subjects were not informed that this was only a mock trial. The “proposed” study consisted of administering a “new” drug orally, single dose for the particular condition of the patient and withdrawing samples of blood (eight 5 ml samples every hour) for eight hours and collecting over night sample of urine for estimating the drug levels in blood and urine respectively. The consent form also included some rare adverse effects of an indwelling IV cannula and the fake drug. The adverse effects listed were the same for all patients. It was also explained that the subjects could withdraw from the study at any time. The primary end-point was taken as giving/refusing consent. Since the study aimed at looking at gender and educational status, equal number of males and females as well as literate and illiterate subjects were chosen. Those subjects who had studied up to the tenth standard and above were labelled “literate” and the rest “illiterate” for the purpose of this study. In order to assess whether a subject has understood the main implications of having given consent for a trial, five questions (Table 1) were asked to all those who had consented for the trial and each correct answer was given one point. The subjects were asked these questions the next day by the same investigators.

After this study was completed an additional fifty subjects were selected and partial consent was sought. The methodology adopted was exactly the same as the first study except that this consent form did not list the exact amount of blood that would be drawn (“very small quantity of blood”) from the subjects and also did not mention any serious adverse effects. These subjects were not assessed for their understanding of the trial protocol. Statistical analysis was done using the Chi-square test and p<0.05 was considered significant.

Results
152 subjects were recruited for the study. Full disclosure was given to 102 while partial disclosure was given to 50 subjects. 44 out of the 152 (30%) agreed to participate in the study while 108 (70%) refused. The percentages of those consenting after full 29/102 (30%) and partial disclosure 15/50 (30%) were the same. More females refused to consent and fewer females agreed to participate when compared to males (Table 2). This significance is not evident for partial disclosure even though a trend may be noted.

The reasons for giving/refusing consent are given below in Table 3. Among those who gave fully informed consent, none scored all five points for understanding the elements of consent (Table 1) and only one patient scored four points. 17 patients scored three points while 10 scored 2. No patient scored one and one patient got all answers wrong.

Literacy does not appear to influence the number of subjects consenting to participate (Table 4).

Discussion
Despite the highly limited generalisability of our results due to

Table 1: Five point scale to assess comprehensibility of informed consent

<table>
<thead>
<tr>
<th>What is the drug given for?</th>
<th>How long (in days) will this study last?</th>
<th>What body fluids will we be collecting?</th>
<th>Can you opt out of the study before completion?</th>
<th>Why is this study being conducted?</th>
</tr>
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| Table 2: Gender distribution of subjects consenting and refusing after full and partial disclosure regarding study details |
|---|---|---|---|---|---|---|---|
| Consent given | Consent refused | Consent given | Consent refused | Consent given | Consent refused |
| Consent given | Consent refused | Consent given | Consent refused | Consent given | Consent refused |
| 29 (30%) | 73 (70%) | 15 (30%) | 35 (70%) | 20 | 9* |
| M F | M F | M F | M F | M F |
| 34 | 34* | 16 | 16 | 70% | 30% |
| 46% | 54% | 40% | 46% | 54% |

*denotes significant difference from males, p=0.043, chi square test.
the study-design used, we can state that in any clinical trial to be conducted on in-patients in India, we can probably expect 70% of the subjects approached, to refuse to participate. While this mock trial is of a fairly simple design necessitating no additional hospitalisation, no added cost to the patient, only one drug taken to be taken orally (once) and collection of blood with no other additional invasive investigations, other longer trials with more invasive investigations may possibly further decrease the percentage of recruitment.

This poor recruitment percentage may mean that studies requiring a large sample size will need to have a very large sampling frame to begin with. Investigators may have to find out whether such a large number of potentially recruitable subjects are available. These poor recruitment rates have also been seen in Italy,9 and the U.K.10 and it can be assumed that there does not seem to be a cultural difference in the outlook of patients who agree to participate in research. In our personal experience, even medical students (from our institute) in India, hesitate to volunteer for research if drugs are involved, whereas, in the developed countries many studies use student-volunteers. The problem of poor recruitment has been discussed before and it has been suggested that planning for recruitment should be a part of the overall trial design.11,12

Twenty subjects said they refused consent because they were not in a position to make independent decisions. The significant difference seen in the gender of subjects consenting and refusing may be directly linked to the fact that the women participating in this study were not in a position to make independent choices. However, this gender difference has been reported in another study in which similar results were obtained even if women were in a position to make independent decisions.10

Those who refused, did not want to subject themselves to any investigation which was not a part of their treatment. Many parents who consented to a physiological study on their infants to prevent Sudden Infant Death Syndrome in New Zealand did not understand the implications of the study,13 a scenario also described elsewhere.14 Five out of 29 subjects answered the question on freedom to opt out of the study correctly. This may be taken as a pointer that patients may not opt out of a study even if they want to, because they did not understand this aspect of informed consent. Other studies too have described similar situations.6,7 The absence of a difference in recruitment rates between full and partial disclosure is perhaps another indicator that patients did not actually understand what they were consenting to. The five questions used to test their understanding of consent did not include specific adverse effects. This was because we thought this question may be difficult for the patient and may test their memory (recall) more than the basic elements of the study and the actual elements of the informed consent.

The major lacuna of the study was that it was conducted at two centres (one a governmental hospital and the other a private hospital). The reason for including a private hospital was that the number of literate subjects available at JIPMER was very low and in order to make a comparison we needed to have an adequate number of literate subjects. The sample from the private hospital was too small to detect any inter-centre differences. Randomisation was not done due to logistic reasons and this contributed to the limited generalisability of the results. The other lacuna was that the consent was sought by doctors other than treating physicians.

Keeping in mind that social structure in India permits paternalistic attitudes to some extent and the limited understanding of a subject’s perception of a clinical trial,15 it may be argued that, conforming to universal guidelines by taking writ-
ten informed consent may be done only with the intent of prescribing to international pressure rather than any real effort on the part of investigators to assure themselves that the subjects were indeed well-informed and made a truly independent choice. For consent to be truly informed, the information imparted to potential participants "must clearly explain study procedures, distinguish research from treatment, realistically portray the potential for medical or other benefits from participation and the nature of potential benefit, carefully explain the potential for discomfort, toxicity, or other risks that may accompany participation in the research, and clearly delineate the participant’s rights and limits regarding confidentiality and withdrawal from participation".  

This would make one wonder whether all subjects participating in studies being conducted in India are "truly informed", a surmise both unfair and somewhat ahistorical to those investigators who have taken the time and trouble to inform their subjects on the trial concerned. The subjects found it difficult to understand the study described in this paper, which is of a fairly simple design. Therefore, we may be correct in assuming that more complex designs may not be understood by a large number of the patients hailing from similar educational and socioeconomic backgrounds. Hence, we need to explore whether consent is being taken to pay mere lip service to international ethical regulations or out of a genuine concern and respect for the rights of patients.  

A more focused standard of uncoerced and undeceived consent should perhaps replace the old standard of voluntary and informed consent. It is time researchers, ethicists, communication experts and policy makers came together to formulate a nationally acceptable template for describing trial designs and the rights of participating subjects to illiterate subjects, rather than using one which is obviously not adaptable and applicable to Indian culture. As has happened in the subject of compensation for organ donors, where there has been a discernible shift in the ethical attitudes of medical professionals, in this area too, the researchers, ethicists and the public will be looking at more practical ways of conducting research, protecting patient’s rights and publishing the work done. The paramount respect for individualism inherent in informed consent has been questioned recently regarding whether it is truly respectful of people of all cultures and whether it is right for some societies to insist that their ethical standards are applied elsewhere. Instead of applying the informed consent rule too rigidly, the quality of consent needs to be balanced against a backdrop of scientific, social and cultural needs.  

The study concludes that only 30% of patients are willing to participate in clinical trials when no inducements are offered in a tertiary care setting in Pondicherry, South India. The amount and quality of disclosure (full versus partial) does not increase recruitment numbers. Males gave consent more readily than females and literacy does not improve recruitment rates. This study raises important issues which must be borne in mind by investigators and ethics committees during the planning and conduct of a clinical trial in India in particular and developing countries in general.  

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Improving Informed Consent and Participation Rates in Clinical Trials

With globalisation comes several difficult questions. For clinical researchers, one of the more pressing questions of late has been whether ethical norms from a few developed nations ought to be applied strictly in international settings where cultural values and socioeconomic circumstances may differ considerably. Do the ethical arguments that suggest the need for truly informed consent in some nations apply equally in others?

In light of this mounting debate, the study by Gitanjali et al reported in this issue of the Journal is particularly timely. This study addresses patients’ willingness to participate in a generic clinical trial, and the potential for obtaining truly informed consent for such participation. Several conclusions merit further consideration.

First, the authors report that a modified consent procedure, in which the amount of blood to be withdrawn was described qualitatively rather than quantitatively, did not influence participation rates. In interpreting this finding, it is important to realise that patients were not randomised to receive one consent procedure or the other, and so it is possible that the patient samples differed in important ways such that the null finding is attributable to confounding.

Furthermore, even if the result is valid, its implications are uncertain. There is a wealth of evidence, from this study and others, that the most important features governing decisions regarding participation are the potential for personal benefit, the potential to benefit future patients, the hassles of participation, and the risks of adverse events from trial interventions. Thus, the finding that manipulating information disclosed about a relatively trivial feature such as phlebotomy does not shed much light on the more general question of whether modified informed consent procedures would influence participation. Regardless of the effect on participation, however, the more important question from an ethical standpoint is what effect such modified consent procedures have on the ability of patients to be adequately informed to make autonomous decisions.

Lastly, given the limited scope of the present study, and the tremendous importance of protecting the interests of those who would participate in clinical trials, it seems premature to draw any conclusions about the ability to obtain truly informed consent in India. The authors may be correct in suggesting that cultural features and socioeconomic circumstances make western standards for informed consent inapplicable in India. However, the fact that patients displayed poor understanding in this mock trial does not necessarily mean that the problem of patient understanding is insurmountable in India. Equally likely is that Indian investigators have yet to develop adequate methods for informing prospective research participants. In this regard, Indian investigators face similar challenges to those faced daily by their counterparts in countries such as the United States, where methods to augment the informed consent process remain a prominent area for investigation.

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