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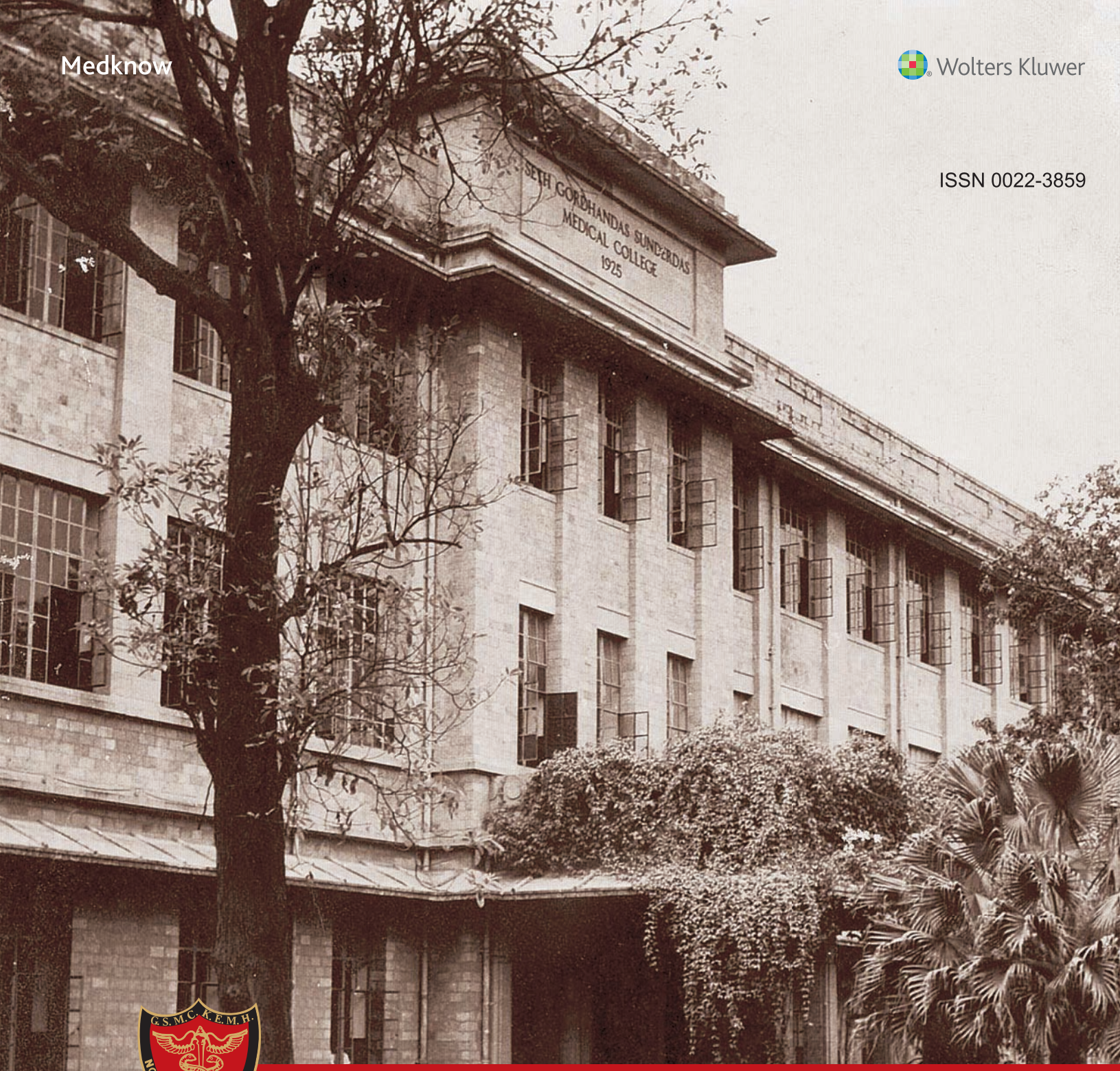

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An audit of consent refusals in clinical research at a tertiary care center in India

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ABSTRACT

Background and Rationale: Ensuring research participants' autonomy is one of the core ethical obligations of researchers. This fundamental principle confers on every participant the right to refuse to take part in clinical research, and the measure of the number of consent refusals could be an important metric to evaluate the quality of the informed consent process. This audit examined consent refusals among Indian participants in clinical studies done at our center. **Materials and Methods:** The number of consent refusals and their reasons in 10 studies done at our center over a 5-year period were assessed. The studies were classified by the authors according to the type of participant (healthy vs patients), type of sponsor (investigator-initiated vs pharmaceutical industry), type of study (observational vs interventional), level of risk [based on the Indian Council of Medical Research (ICMR) "Ethical Guidelines for Biomedical Research on Human Participants"], available knowledge of the intervention being studied, and each patient's disease condition. **Results:** The overall consent refusal rate was 21%. This rate was higher among patient participants [23.8% vs. healthy people (14.9%); $P = 0.002$], in interventional studies [33.6% vs observational studies (7.5%); $P < 0.0001$], in pharmaceutical industry-sponsored studies [34.7% vs investigator-initiated studies (7.2%); $P < 0.0001$], and in studies with greater risk ($P < 0.0001$). The most common reasons for consent refusals were multiple blood collections (28%), inability to comply with the study protocol (20%), and the risks involved (20%). **Conclusion:** Our audit suggests the adequacy and reasonable quality of the informed consent process using consent refusals as a metric.

KEY WORDS: Autonomy, consent, India, reason, refusal, risk

Introduction

The ethical principle that every individual has the right to decide what can and cannot be done with his or her own body is the essence of the practice of medicine and clinical research. This principle, also called autonomy, represents freedom of choice and is an integral part of several national and international ethics codes including the Declaration of Helsinki.[1] However, the ethnography of individual autonomy varies across the world as the concept is rooted within customs, traditions, and practices that reflect family and societal obligations.[2] Critics have challenged the concept of a participant being a solitary, rational-thinking person who is able to exercise his autonomy through the process of informed consent (putative autonomy). Rather, they propose the concept of "relational" autonomy, wherein social context plays a key role in decision-making. Sometimes it would be appropriate for an individual to make personal decisions only after the involvement of others from his/her family, friends, spouse, or members of the community.[3,4]

The potential participant exerts his/her autonomy through the informed consent process, and the three components of an appropriate informed consent process include adequate disclosure, comprehension, and voluntariness.[5] While enrolling

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participants, researchers must convey to them in simple language the purpose of the study, the study design, the concept of randomization and blinding (wherever applicable), the nature of the intervention/s, the study methodology, their rights and responsibilities as participants, and potential risks and benefits. Despite the efforts expended by the researcher in obtaining and documenting informed consent, the comprehension of study information varies among participants.[6]

In such a scenario, assuming adequate disclosure of the study procedures, the validity of the informed consent process could be assessed by looking at the element of exertion of autonomy. As the benefits of participation in clinical research are uncertain and unproven, refusal to give consent may prove a rational choice made to protect one's well-being.[5] Although various tools developed to assess the quality of the informed consent process can measure the exertion of autonomy,[7] the number of refusals of consent could also act as indirect evidence and one of the metrics to assess the quality and adequacy of the informed consent process; hence this study.

Materials and Methods

Ethics

The institutional ethics committee gave approval for the study and a consent waiver was granted.

Characteristics of included studies

A total of 10 studies done over a 5-year period (2010-14) were included for the analysis. The nature of the studies is summarized in Table 1. The counseling registers (anonymized with respect to the identity of the participants) of these studies were examined and the number of consent refusals identified. The reason for refusal was also noted. Subgroup analysis was performed of consent refusals between patients and healthy volunteers, between investigator-initiated and pharmaceutical industry-sponsored studies, and between observational and interventional studies.[8]

In addition, each of these studies was classified as not more than minimal- or more than minimal-risk based on the Indian Council of Medical Research (ICMR) "Ethical Guidelines for Biomedical Research on Human Participants" (2006).[9] Studies that had the probability and magnitude of harm or discomfort not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests were categorized as minimal-risk studies, whereas risk greater than these situations qualified them for more than minimal risk.[10] The categorization was done to assess whether consent refusals actually differ between these two categories.

We also ranked the studies relative to one another on a risk scale of 1 to 10, with 1 representing minimal risk and 10 representing the highest risk. This classification was based on available knowledge of the intervention being studied (as per the investigator's brochure and product insert), published literature on the intervention, and the patients' disease condition (susceptibility to become vulnerable)).[11] A panel of three authors individually ranked all the studies. The rank assigned to each study was accepted if at least two of the three authors agreed on it. In case of any disagreement, the resolution and final rank assignment was done on the basis of arbitration by the fourth author. The study that we assigned the highest risk (rank 10) was the first-in-human (FIH) study of antirabies monoclonal antibody (mAb) in healthy participants where no clinical data were available. In addition, the study procedure involved intramuscular injections of the investigational product and multiple blood collections. However, the selected population was normal and had no direct benefit in participation. Meanwhile, the study we ranked the lowest (involving the least risk) focused on proteomic markers of malaria in healthy participants, which involved only a single 5-mL blood collection.

Statistical analysis

Descriptive statistics were used. Categorical variables were compared using the chi-square test. A crude odds ratio and its 95% confidence interval (CI) were calculated. For assessing the effect of increasing risk on consent refusals, the chi-square test for trend was used. All analyses were done using EpiInfo 7.0 developed by Centers for Disease Control & Prevention and GraphPad Instat 3.0 developed by GraphPad Software, Inc. for Windows at 5% significance.

Results

Profile of the studies

There were three observational and seven interventional studies that involved counseling of 976 individuals. Of these 10 studies, six were pharmaceutical industry-sponsored and four were investigator-initiated.

Analysis of consent refusals

Of the 976 individuals counseled (296 healthy individuals and 680 patients), overall, 206 (21%) refused consent ranging from 0-64%. Of the 296 healthy individuals counseled, 44 (14.86%) refused consent, while 162/680 (23.82%) patients refused consent [Table 2]. The crude OR for the consent refusals between patients and healthy individuals was 1.79, indicating a greater likelihood of patients declining consent relative to healthy participants [95% CI 1.24, 2.58]. This difference was significant ($P = 0.002$).

Analysis of consent refusals based on study design and sponsor

There was a greater number of consent refusals in interventional (171/509, 33.6%) versus observational studies (35/467, 7.5%); [$P < 0.0001$, crude OR 6.22, 95% CI (4.23, 9.23)] Consent refusals were also seen more in pharmaceutical industry-sponsored (171/493; 34.82%) studies as compared to investigator-initiated studies (35/483; 7.2%) [$P < 0.0001$, crude OR 6.8, 95% CI (4.6, 10.05)].

Analysis of consent refusals based on risk stratification

The 10 studies were further divided on the basis of risk as described above. Three studies ($n = 467$ counseled) were no more than minimal-risk and the rest were more than minimal-risk ($n = 509$ counseled) studies. There were 35/467 (7.5%)

Table 1: Consent refusals in various phases of clinical trials conducted in the department

Scientific title of the study	CTRI Reg. No.	Ethics committee approval number	Type of the study	Sponsor	Consent refusals (n/Total counseled) (%)	Reason/s for consent refusal	Number of consent refusals *n* (%)
Pharmacokinetics of colistin, after intravenous administration of colistimethate sodium in subjects with nosocomial infections caused by multidrug resistant, gram negative bacilli	CTRI/2009/091/000252	EC/PHARMA-38/2008	Interventional (Phase IV)	Investigator-initiated	0/16	NA	NA
Open-label, randomized, dose escalation Phase I study in healthy adult volunteers to evaluate the safety and pharmacokinetics of a human monoclonal antibody to rabies (SII RMab) in comparison to human rabies immune globulin administered in conjunction with rabies vaccine (RABIVAX®)	CTRI/2009/091/000465	EC/Pharma-35/2008	Interventional (Phase I)	Pharmaceutical-sponsored	16/162 (9.88)	Not ready to come for the follow-up visits	16(9.88)
Three way, three period, cross over bioequivalence study of single oral dose of three brands of 300 mg phenytoin sodium tablets marketed in India, on healthy Indian human volunteers	CTRI/2011/05/001709	EC/Pharma-42/2010	Interventional (Phase IV)	Pharmaceutical-sponsored	2/24 (8.33)	Not ready to come for the follow-up visits	2 (8.33)
A prospective study to assess the correlation between genotype, phenotype and *Prakriti* of an individual on phenytoin monotherapy	CTRI/2011/06/0011782	EC/152/2010	Observational	Investigator-initiated	35/337 (10.38)	Extra blood draw	35 (10.38)
A randomized, double blind, multicentric, placebo controlled, Phase II study assessing the safety and efficacy of intraarticular *ex-vivo* cultured adult allogeneic mesenchymal stem cells in patients with osteoarthritis of knee	CTRI/2011/07/001891	EC/Pharma-25/2011	Interventional (Phase II)	Pharmaceutical-sponsored	0/11 (0)	NA	NA
A phase III, open label, randomized, parallel group, multicentric trial comparing the safety and efficacy of fixed dose combination tablets of arterolane maleate and piperaquine phosphate (PQP) with chloroquine tablets in patients with acute uncomplicated Plasmodium vivax malaria	CTRI/2011/11/002129	EC/Pharma-26/2011	Interventional (Phase III)	Pharmaceutical-sponsored	93/145 (64.14)	Not ready for hospital admission	67 (46.21)
						Multiple blood collections	22 (15.17)
						Not ready to come for the follow up-visits	4 (2.76)
A Phase II/III, randomized, multi-centric, comparator-controlled study of the safety and neutralizing activity of a human Monoclonal antibody to rabies (SII RMAb) Administered in conjunction with rabies vaccine for post-exposure prophylaxis in patients following potential rabies exposure	CTRI/2012/05/002709	EC/Pharma-11/2011	Interventional (Phase II/III)	Pharmaceutical-sponsored	34/91 (37.36)	Safety concerns about the investigational product	20 (21.97)
						Objection for participation from family members	2 (2.20)
						Not ready to come for the follow-ups	12 (13.19)
Evaluation of host immune responses and parasite proteome in healthy volunteers	CTRI/2013/08/003876	EC/Govt-8/2012	Observational	Investigator-initiated	0/50 (Healthy volunteers)	NA	NA
Evaluation of host immune responses and parasite proteome in patients with severe/complicated malaria	CTRI/2013/08/003876	EC/Govt-8/2012	Observational	Investigator-initiated	0/80 (Sever malaria patients)	NA	NA
A Phase 1, prospective, randomized, two-arm, active controlled, double-blind study to evaluate the safety and tolerability of Serum Institute of India's 10-valent pneumococcal conjugate vaccine (SIILPCV10) in Healthy Indian young adults	CTRI/2013/ 09/003961	EC/Pharma-8/2013	Interventional (Phase I)	Pharmaceutical-sponsored	26/60 (43.33)	Safety concerns about the investigational product	20 (33.33)
						Not ready to come for the follow up-visits	6 (10)

CTRI = Clinical Trials Registry — India

Table 2: Comparison of consent refusals between studies on the basis of study type, design, and the risk stratification and gradation

Scientific title of the study	Sponsor	Type of the study	Risk stratification of the study (As per ICMR guidelines)	Study rank as per risk gradation by the Investigator	Consent refusals (*n*/ Total counseled) (%)
Evaluation of host immune responses and parasite proteome in healthy participants	Investigator-initiated	Observational	Minimal risk	1	0/50
Evaluation of host immune responses and parasite proteome in patients with severe/complicated malaria	Investigator-initiated	Observational	Minimal risk	2	0/80
A prospective study to assess the correlation between genotype, phenotype and *Prakriti* of an individual on Phenytoin monotherapy	Investigator-initiated	Observational	Minimal risk	3	35/337 (10.38)
Three way, three period, cross over bioequivalence study of single oral dose of three brands of 300mg Phenytoin sodium tablets marketed in India, on healthy Indian human volunteers	Investigator-initiated	Interventional (Phase IV)	Minimal risk	4	2/24 (8.33)
A phase III, open label, randomized, parallel group, multicentric trial comparing the safety and efficacy of fixed dose combination tablets of arterolane maleate and piperaquine phosphate (PQP) with chloroquine tablets in patients with acute uncomplicated Plasmodium vivax malaria	Pharmaceutical-sponsored	Interventional (Phase III)	More than minimal risk	5	93/145 (64.14)
A randomized, double blind, multicentric, placebo controlled, phase II study assessing the safety and efficacy of intraarticular *ex-vivo* cultured adult allogeneic mesenchymal stem cells in patients with osteoarthritis of knee	Pharmaceutical-sponsored	Interventional (Phase II)	More than minimal risk	6	0/11 (0)
A phase II/III, randomized, multi-centric, comparator-controlled Study of the safety and neutralizing activity of a human monoclonal antibody to rabies (SII RMAb) administered in conjunction with rabies vaccine for post-exposure prophylaxis in patients following potential rabies exposure	Pharmaceutical-sponsored	Interventional (Phase II/III)	More than minimal risk	7	34/91 (37.36)
A phase 1, prospective, randomized, two-arm, active controlled, double-blind study to evaluate the safety and tolerability of Serum Institute of India's 10-valent pneumococcal conjugate vaccine (SIILPCV10) in healthy Indian young adults	Pharmaceutical-sponsored	Interventional (Phase I)	More than minimal risk	8	26/60 (43.33)
Pharmacokinetics of colistin, after intravenous administration of colistimethate sodium in subjects with nosocomial infections caused by multidrug resistant, gram negative bacilli	Pharmaceutical-sponsored	Interventional (Phase IV)	More than minimal risk	9	0/16 (0)
Open-label, randomized, dose escalation phase I study in healthy adult volunteers to evaluate the safety and pharmacokinetics of a human monoclonal antibody to rabies (SII RMab) in comparison to human rabies immune globulin administered in conjunction with rabies vaccine (RABIVAX®)	Pharmaceutical-sponsored	Interventional (Phase I)	More than minimal risk	10	16/162 (9.88)

consent refusals in the no more than minimal-risk studies and 171/509 (33.6%) consent refusals in the more than minimal-risk category, the difference being statistically significant ($P = 0.0004$). The crude OR for the difference among consent refusals in more than minimal risk versus no more than minimal risk studies was 6.24 (95% CI 4.23, 9.23), with the likelihood of consent refusals being greater with higher risk.

When the studies were ranked [as listed in Table 2], the proteomics study in healthy participants received a rank of 1, and the Phase I antirabies mAb study received a rank of 10. It was seen that consent refusals increased with increasing risk and this was statistically significant ($P < 0.001$).

Of the total 206 consent refusals, 67 (32.5%) declined to participate, citing an unwillingness to undergo hospital admission and 57 (27.7%) declined, stating that they did not want to give blood multiple times. A total of 40 (19.4%) individuals expressed inability to follow up in compliance with the protocol, and another 40 (19.4%) had concerns regarding the risk associated with the intervention. Interestingly, four studies had no consent refusals. These were the studies on the use of colistin in patients with sepsis in the Intensive Care Unit and on the use of intraarticular stem cells in osteoarthritis, and two studies on assessing host immune responses in malaria.

Discussion

The ability of a research participant to decide whether to participate or refuse is in a way dependent on the adequacy of the informed consent process, which could be assessed using consent refusals as one of the metrics. Our study found an overall consent refusal rate of 21% (0-64%), Gatusso *et al.* (2006) from North America observed an overall refusal rate of 24% (6.7%, 46.7%) in 10 nursing and behavioral medicine studies.[12] Alei *et al.* (2013) observed a 27% refusal rate among the esophageal cancer patients who took part in their study to identify the etiology of the disease.[13] These add to the growing body of evidence on the topic of consent refusal.

The process of informed consent allows not just for the individual agreeing to participate but also applies equally to refusal to participate in clinical research.[14] Several factors have been described to influence the potential participant's decision to refuse participation in clinical research and these include concerns about the risks or of a placebo, lack of trust in the treating doctor or researcher, poor information about the consent process, complexity of the protocol, loss of confidentiality, lack of awareness about clinical research, and previous bad research experience.[15,16] In our study, the most common reason for consent refusal observed was inability to comply with the study protocol and multiple blood collections. Similar to our observations, Alaei *et al.* (2013) found that 34% of consent refusals in a study conducted to find the etiology of esophageal cancer were primarily due to fear of blood draws and unwillingness to comply with study processes.[13] Safety concerns regarding the investigational product was another common reason for consent refusal in our study, also reported in other studies.[17,18]

We observed a higher consent refusal rate among patient participants (24%) relative to healthy participants (15%). A meta-analysis of qualitative studies that identified reasons that Indian participants agreed to take part in a clinical study has described, among others, personal health benefits, altruism, trust in physicians, and a source of extra income as factors motivating individuals to take part in a clinical study.[18] In a previous study, we had found that the most common reason given by patients to consent to participate in nontherapeutic research was that the treating physician invited them to participate, while healthy participants said they did so for the financial reward.[19] The two patient studies (antirabies mAb, 37% and arterolone in malaria, 64%) that had very high refusals were protocols that required follow-ups and blood draws, both of which were the main reasons for declining consent. Healthy participants are less likely to refuse participation as they appear for counseling with the intent to participate, primarily for the financial compensation,[19] and it is of great importance that the amount of compensation for participation does not become undue inducement.[20] In the present study we found 43% consent refusals in a new vaccine study and 10% refusals in a FIH study of a monoclonal antibody. The most common reason for declining was concerns about the safety of the product, suggesting that although the amount of compensation was legitimate and approved by the Ethics Committee, participants did refuse consent on account of the risks. This emphasizes that the amount of compensation did not create undue inducement.

Research in cognitive psychology has tried to explain how people understand risks and how this influences decision-making. It has been said that this process is not always a rational and logical one and people often use shortcuts to simplify the decision-making process. Perception of the risks and benefits of clinical research also greatly differs among those who agree to take part in a clinical trial as compared to those who refuse to participate.[21,22] Studies have shown that in the positive decision-making process, participants always tend to overlook risks and overestimate benefits, and *vice versa*.[18,23] Barofsky and Sugarbaker (1989) reported that patients' beliefs about the effects of the treatments on their functional abilities and quality of life were the primary determinants of their decision to refuse enrolment or to withdraw from these trials, and that safety concerns were the primary reasons for refusals in our study as well as other studies.[17,24]

When we classified our studies according to the extent of risk involved and ranked them based on relative risks as perceived by the investigators, we found that the number of consent refusals increased with increasing risk. A higher rate of consent refusals was seen in pharmaceutical company-sponsored studies done in our department, which involved more than minimal risk, as compared to the investigator-initiated studies, and also in ininterventional studies as compared to observational studies with minimal risk. More interestingly, a trend toward increased consent refusals was seen when studies were ranked as per the investigator's risk perception about a particular study ($P < 0.001$).

It has also been said that estimation of risk may differ between the investigator and the participant.[21] Although we did not

assess the risk perception from a participant's point of view, it is noteworthy that it is not the only factor in deciding participation. This is reflected in the number of consent refusals (10%) in the FIH study of an antirabies mAb, ranked the highest risk by us, being lower than in the Phase I study assessing the safety and tolerability of a "me-too" decavalent pneumococcal vaccine ranked eighth by us on the risk scale (43%), although the most common reason cited was safety concerns about the new investigational product. There are increasing safety concerns among potential participants, especially healthy participants, and the refusals can be influenced by the negative press that clinical research has got in recent times in India.[25] Surprisingly we had no consent refusals in two interventional studies, which had been graded as high-risk by us (use of colistin in critically ill patients, rank 9, and allogenic mesenchymal stem cells in patients awaiting knee replacement surgery, rank 6). The colistin study was done in critically ill participants who were unable to give willful informed consent and therefore legally acceptable representatives (LARs) were approached. Colistin was the only treatment option left in these patients and the LARs would have agreed to avail the free treatment and ancillary care measures such as concomitant medications, free investigations, and ventilatory support, all of which was available through the research. In a study of adults who participated in several research projects over several years in Malawi, it was seen that the majority of the patients participated in research to receive treatment made available through the research, which was provided as ancillary care.[15] Shah *et al.* (2010) have mentioned that the expectation of personal health benefits is the most recurrent theme that has contributed to the decision to participate in clinical research in India.[18]

The other study (in our series) that had no consent refusals was one that examined the efficacy of allogenic mesenchymal stem cells in patients awaiting knee replacement surgery. Fear of surgery and lack of other medical options could have perhaps provided a strong impetus to give consent for such a study. As the investigational products in both these cases were offered by the treating physician/surgeon, potential therapeutic misconception among potential participants would have resulted in no consent refusals.[26] This has been reported by Doshi *et al.* (2013), who found that the main reason cited by the patients (87.5%) to take part in clinical research was, "My doctor asked me to." They also observed that those who said agreed to participate in clinical trials, 67% of healthy participants, and all patient participants had trust in the skills of clinical staff. This could also have contributed to our observed findings of lower number of refusals due to risks as compared to logistic reasons.[19]

Limitations

Our study was limited by the fact that there was heterogeneity among the studies we audited. This, however, could not be controlled. A larger proportion of the studies were interventional and the lack of information on the predictors of consent refusals such as age, gender, and socioeconomic strata prevented us from doing multivariate logistic regression analysis.

The use of consent refusals as a metric for assessing autonomy itself is new and deserves further discussion. Agreeing to participate and refusing to do so are both positive decisions, and both in equal measure reflect the exertion of autonomy.[27] Mandava *et al.* (2012) also suggest in their study that participants report different sources of pressure to say "yes" to participate in research, especially in developing countries. However, they are less likely to refuse or withdraw as compared to their counterparts in developed countries.[6]

Conclusion and Future Directions

We conclude that in a varied sociocultural framework such as India, focusing on consent refusals and its predictors would be important to better understand the decision-making process in informed consent. In summary, a 21% rate of consent refusals does indicate the adequacy and reasonable quality of the informed consent process at our center. However, a prospective study looking at consent refusals with predictors such as age, gender, socioeconomic strata, level of literacy, level of comprehension for the information given, perceived risk of the intervention, and complexity of the protocol (number of visits and visit-specific activities) is the need of the hour.

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Conflicts of interest

Author Gogtay NJ is the Editor of the Journal of Postgraduate Medicine.

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