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CLINICAL TRIAL

Who volunteers for phase I clinical trials? Influences of anxiety, social anxiety and depressive symptoms on self-selection and the reporting of adverse events

Luis Almeida · Todd B. Kashdan · Teresa Nunes · Rui Coelho · António Albino-Teixeira · Patrício Soares-da-Silva

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Abstract
Objective To investigate the influence of anxiety, social anxiety and depressive symptoms on the willingness of healthy subjects to volunteer for phase I studies and to report adverse events.
Materials and methods A group of healthy subjects who had never participated in a clinical trial ("Naïve Subjects") were invited to participate in a phase I study. All subjects were assessed for trait anxiety (State-Trait Anxiety Inventory, STAI-T), social anxiety (Social Avoidance and Distress, SAD, and Fear of Negative Evaluation, FNE) and depressive symptomatology (Beck Depression Inventory, BDI-II). Subjects who accepted the invitation to participate were compared with those who refused. The personality traits of a group of "Actual Participants" were examined, and the relation of these traits to adverse events reported during participation was evaluated.
Results A significant inverse correlation was found between the STAI-T ($R=-0.203$, $p<0.05$) and SAD ($R=-0.204$, $p<0.05$) scores and the willingness to participate. Naïve Subjects who refused the invitation to participate showed higher scores on STAI-T ($Z=-2.600$, $p<0.01$) and SAD ($Z=-2.524$, $p<0.05$) inventories. Logistic regression using BDI-II, STAI-T, SAD and FNE as covariates also showed that the only unique predictors of participation were the STAI-T ($p<0.05$) and SAD ($p<0.01$) scores. Significant positive correlations were found between trait anxiety and reporting of adverse events.
Conclusion Participants in phase I studies are a self-selected sample defined by low trait-anxiety and social avoidance behaviors. This self-selection bias may affect the study results because less anxious subjects tend to report fewer adverse events. The characterization of a participant's personality traits may be important in phase I studies.

Keywords Adverse events · Anxiety · Depressive symptoms · Healthy volunteers · Phase I studies · Social anxiety

L. Almeida (✉) · T. Nunes · P. Soares-da-Silva
Department of Research and Development,
BIAL (Portela & Co, SA),
A Av. da Siderurgia Nacional,
4745–457 S Mamede do Coronado, Portugal
e-mail: luis.almeida@bial.com

L. Almeida · A. Albino-Teixeira · P. Soares-da-Silva
Institute of Pharmacology and Therapeutics, Faculty of Medicine,
University of Porto,
Alameda Professor Hernâni Monteiro,
Porto, Portugal

T. B. Kashdan
Department of Psychology, George Mason University,
Fairfax, VA, USA

R. Coelho
Service of Psychiatry and Mental Health, Faculty of Medicine,
University of Porto,
Rua do Campo Alegre,
Porto, Portugal

A. Albino-Teixeira
Institute for Molecular and Cell Biology (IBMC),
University of Porto,
Alameda Professor Hernâni Monteiro,
Porto, Portugal

Introduction

Participation in phase I studies implies (1) subjection to unaccustomed procedures, some of which are relatively invasive and painful, such as venous catheterization, (2) the risk of occurrence of expected or unexpected drug adverse

events and (3) close social interactions with the research staff and often confinement for several days in research facilities with other participants. Consequently, participation in phase I studies can be perceived as a challenging event and that a number of personality characteristics will most likely have an effect on the subject's willingness to volunteer.

Although anxiety can manifest in a number of different ways, participation in a phase I study appears to support the investigation of two types of anxiety—trait anxiety and social anxiety. For example, potential adverse effects or painful procedures may be considered especially threatening by anxious people. Additionally, the close interaction with previously unknown people, such as clinical staff and other study participants, and confinement to an open-space ward with minimal privacy are conditions that can be perceived as threatening by people with elevated social anxiety. Preliminary results by our group [1] also indicated that subjects with elevated depressive symptoms tend to self-exclude from phase I participation. Based on these results, we hypothesized that people reporting elevated trait anxiety, social anxiety and depressive symptoms would be less willing to expose themselves to the risks, discomfort and interpersonal interactions required by participation in a phase I study. The primary objective of this study was, therefore, to evaluate the influence of these personality dimensions on the willingness of subjects to volunteer for participation in phase I studies. Since there is conceptual overlap between these personality constructs [2–5], we examined the independent contribution of each of them on the subject's willingness to volunteer in phase I studies.

Differences in the personality characteristics of healthy volunteers in comparison with those of their counterparts in the normal population does not necessarily mean that they are clinically meaningful. There are suggestions, however, that some personality traits or psychological states may influence the pharmacokinetics[6–9], pharmacodynamics [10–12] and probability of presenting clinical complaints [10]. However, results from systematic research in this field are still missing, and the impact of the self-selection bias on study results is largely unknown[7]. The secondary aim of our study was, therefore, to investigate correlations between the reported personality traits of a group of participants and the reporting of adverse events, a common endpoint in phase I clinical trials.

Material and methods

Populations

The subjects of this study comprised a group of actual participants in phase I drug clinical trials ("Actual Participants") and a group of healthy subjects who had never participated in a phase I clinical trial ("Naïve Subjects") and who matched the actual participants in terms of demographic and socio-economic characteristics. A total of 200 subjects in the Actual Participants group and 100 subjects in the Naïve Subjects group were estimated to provide a power of 80% to detect a difference of 2.5 in mean scales scores, at a significance level of 0.05. The subjects did not receive any financial compensation for participating in this study.

Actual Participants This group consisted of 198 consecutive normal healthy volunteers who participated in phase I clinical trials conducted at the Human Pharmacology Unit of BIAL (S Mamede do Coronado, Portugal). These trials were pharmacokinetic studies of new oral anti-epileptic and antiparkinsonian drugs and involved confinement for 3–14 days and frequent blood drawings. Before consenting to participate, participants received oral and written information on the study design, procedures, inconvenience, discomfort, precautions, possible adverse events and financial compensation. The financial compensation policy for participation in the phase I studies was similar in all studies.

Naïve Subjects This group consisted of normal healthy subjects who never had participated in a clinical trial. Members of the Naïve Subjects group were selected using the same method of recruitment as that for phase I participants to maximize similarities with the Actual Participants. Naïve Subjects (n=117) were provided with written information relative to a phase I clinical trial and invited to participate. That clinical trial implied procedures, confinement and residence at the clinical research facility that were similar to those required of participants in the Actual Participants group; financial compensation was also similar. Two subgroups were created among those who responded to the invitation to participate (n=110): "Accepted" (n=51) and "Refused" (n=59).

Procedures and self-report measures

Trait anxiety, social anxiety and depressive symptoms were measured by Portuguese adaptations of the trait anxiety portion of the State-Trait Anxiety Inventory (STAI)[13], the Social Avoidance and Distress (SAD) and Fear of Negative Evaluation (FNE) scales[14] and the Beck Depression Inventory II (BDI-II) [15].

Trait anxiety The STAI is the most widely used self-administered instrument for measuring anxiety in adults [16]. It consists of two separate scales: "state anxiety" (STAI-S), which refers to a transitory emotional state

characterized by subjective feelings of tension that vary in intensity over time, and "trait anxiety" (STAI-T), which refers to a relatively stable and long-standing disposition to respond to stress with elevated anxiety and a tendency to perceive a wide range of situations as personally threatening [13]. Each scale consists of 20 statements, and scores vary from a minimum of 20 to a maximum of 80. We used the STAI-T sub-scale in our study. High scores reflect greater trait anxiety. Prior research has shown that the STAI-T has strong internal reliability and construct validity [17].

Social anxiety Social anxiety is defined as "a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others" [18]. Commonly endorsed fears include public speaking, performance, speaking to strangers and meeting new people. Two scales were used here to measure the behavioral and cognitive components of social anxiety. The SAD consists of 28 true–false items assessing social anxiety and fear-motivated avoidance derived from potential or actual social interactions [19]. High SAD scores reflect a greater likelihood of avoiding potentially stressful social interactions. The FNE consists of 30 true–false items assessing the expectation and fear of being evaluated negatively by other people and catastrophic responses to mildly negative social events [20, 21]. Scores can vary from a minimum of 0 to a maximum of 28 (SAD) and 30 (FNE). Prior research has shown that both the SAD and FNE possess good psychometric properties in clinical and non-clinical populations [22]. Application of the SAD and FNE to the Portuguese population showed results similar to those found in studies performed in other countries [23]. Hofman [24] recently found problems in the original scoring instructions of the SAD; consequently, we used his corrected scoring system in our study.

Depressive symptoms The BDI is one of the most widely used instruments for assessing depressive symptoms. The most recent version (BDI-II) [25] corresponds to diagnostic criteria for major depressive disorder in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [18]. The BDI-II is a 21-item self-report scale for assessing cognitive, affective and somatic symptoms of depression during the previous 2 weeks. Each of the 21 items is summed into a single score. Scores can vary from a minimum of 0 to a maximum of 63. Higher total scores indicate more severe depressive symptoms. A meta-analysis [26] suggested evidence of excellent construct validity in clinical and non-clinical samples.

Adverse events Adverse events reported by the Actual Participants group were recorded during their participation in phase I clinical trials. In accordance with current regulatory standards, an adverse event was defined as any undesirable event occurring to a subject during the study, following the administration of an investigational product, irregardless of whether or not the event was considered to be drug-related. The possibility of a causal relationship between the adverse event and study drug was assessed by the investigator, following pre-specified rules similar to those issued by the World Health Organization (www.who-umc.org). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). For cross-over studies, each study period was considered to be one "test". The following variables were derived: percentage of tests with adverse events; percentage of tests with drug-related adverse events; number of adverse events/test; number of drug-related adverse events/test; number of adverse events/day of test; number of drug-related adverse events/day of test; number of central nervous system (CNS)-related adverse events/test; number of CNS-related adverse events/day of test.

Analyses

The first set of analyses compared the results of each scale between the "Accepted" and "Refused" sub-groups of the Naïve Subjects group; as internal validation, the Naïve Subjects "Accepted" subgroup was compared with the Actual Participants group. Tests for normality were performed using the Shapiro–Wilk test. When the dependent variable showed a non-normal distribution, the Wilcoxon–Mann–Whitney rank sum test was used for comparison; when it showed a normal distribution, *t* tests were used. For the BDI-II, the following cutoffs for depressive symptoms severity were considered, as suggested by the authors of the BDI-II [25]: 0–13=minimal; 14–19=mild; 20–28=moderate; 29–63=severe. Groups were compared on the distribution of subjects by severity degree with chi-square tests or Fisher's exact tests. In addition to these univariate analyses, the independent contribution of the STAI-T, SAD, FNE and BDI-II on the prediction of study participation was tested using multivariate logistic regression. Spearman's rho correlations were calculated between scales scores and (1) willingness to participate and (2) variables of adverse events.

Statistical analyses were performed with the *Statistical Package for Social Sciences* ver. 11.5 (SPSS, Chicago, IL).

Ethics

The current study was approved by an Independent Ethics Committee (Comissão de Ética Independente da UFH, S Mamede do Coronado, Portugal).

Results

Table 1 presents the demographic and socio-economic characteristics of study populations. The Naïve Subject and Actual Participant groups were similar in terms of relevant demographic and socio-economic characteristics such as age, gender, ethnic origin, monthly income and education. However, a few differences were apparent when the Naïve Subjects Accepted and Refused groups were compared: subjects who accepted the invitation to participate in a clinical trial showed a higher preference for exercising/sports than those who refused, and, surprisingly, the rate of refusal to participate was higher among unemployed than among employed subjects.

STAI-T, SAD, FNE and BDI-II univariate analysis

Figure 1 shows the median, quartiles and range scores on the STAI-T, SAD, FNE and BDI-II scales.

Trait anxiety Naïve Subjects expressing a willingness to participate in a phase I clinical trial ("Accepted" subgroup) showed significantly lower scores on the STAI-T ($Z=-2.600$, $p<0.01$; Wilcoxon–Mann–Whitney test) compared with Naïve Subjects who denied participation ("Refused" subgroup). No significant differences were found between Naïve "Accepted" respondents and the Participants Group ($Z=-0.985$, $p>0.05$). Significant differences were found when the full Naïve Subjects group was compared with Actual Participants ($Z=-3.718$, $p<0.001$). Using Spearman's *rho*, we found a statistically significant inverse relation between STAI-T scores and the willingness to participate in a phase I clinical trial ($R=-0.203$; $p<0.05$). Taken together, the results showed that subjects high in trait anxiety tend to self-exclude from participation in phase I studies.

Social anxiety Statistically significant lower SAD scores ($Z=-2.524$, $p<0.05$) were found in the "Accepted" subgroup compared with the "Refused" subgroup of the Naïve Subjects. Significantly higher SAD scores were found in the "Accepted" subgroup of Naïve Subjects compared with the Actual Participants group ($Z=-2.435$, $p<0.05$) and when the entire Naïve Subjects group was compared with Actual Participants ($Z=-5.038$, $p<0.001$). Using Spearman's *rho*, we found an

Table 1 Main demographic and socio-economic characteristics of the study cohorts

Parameter	Variable	Actual Participants ($n=198$)	Naïve Subjects	
			Accepted ($n=51$)	Refused ($n=59$)
Gender (%)	Male/female	47.5/52.5	47.1/52.9	42.4/57.6
Age (years)	Mean ± SD	26.4±5.5	26.3±6.6	26.6±7.3
	Median	25	25	24
	Range	18–45	18–45	18–45
Ethnic origin (%)	Caucasian/other	95.5/4.5	92.2/7.8	98.3/1.7
Occupation (%)	Student	55.7	56.0	55.9
	Employed	38.9	38.0	32.2
	Unemployed	5.4	6.0	11.9
Monthly net income in relation to the mean national net salary in the industry and services sector[a] (%)	<25%	25.2	30.0	28.6
	25-50%	27.7	35.0	24.5
	51-100%	31.4	25.0	28.6
	101-150%	10.7	10.0	12.2
	>150%	5.0	0.0	4.1
Civil status (%)	Single	76.2	72.5	67.2
	Married/living together	17.8	23.5	27.6
	Divorced	5.9	3.9	5.2
School degree completed (%)	4 years	0.0	2.0	6.8
	6 years	1.0	3.9	3.4
	9 years	7.0	9.8	5.1
	12 years	63.8	60.8	55.9
	Bachelor	7.5	5.9	6.8
	Licensed	17.6	15.7	20.3
	Masters	3.0	2.0	1.7
Smoking (%)	≥1 cigarette/day	34.9	21.6	27.1
Coffee drinking (%)	≥1 cup/day	67.6	58.8	66.1
Exercising/sports (%)	≥1 session/week	62.5	72.5	47.5
Alcohol consumption (%)	≥1 occasion/week	49.5	52.9	44.1

All values for all parameters, with the exception of "Age", are given as a percentage of that study cohort

[a] Approximately €1000/month, net

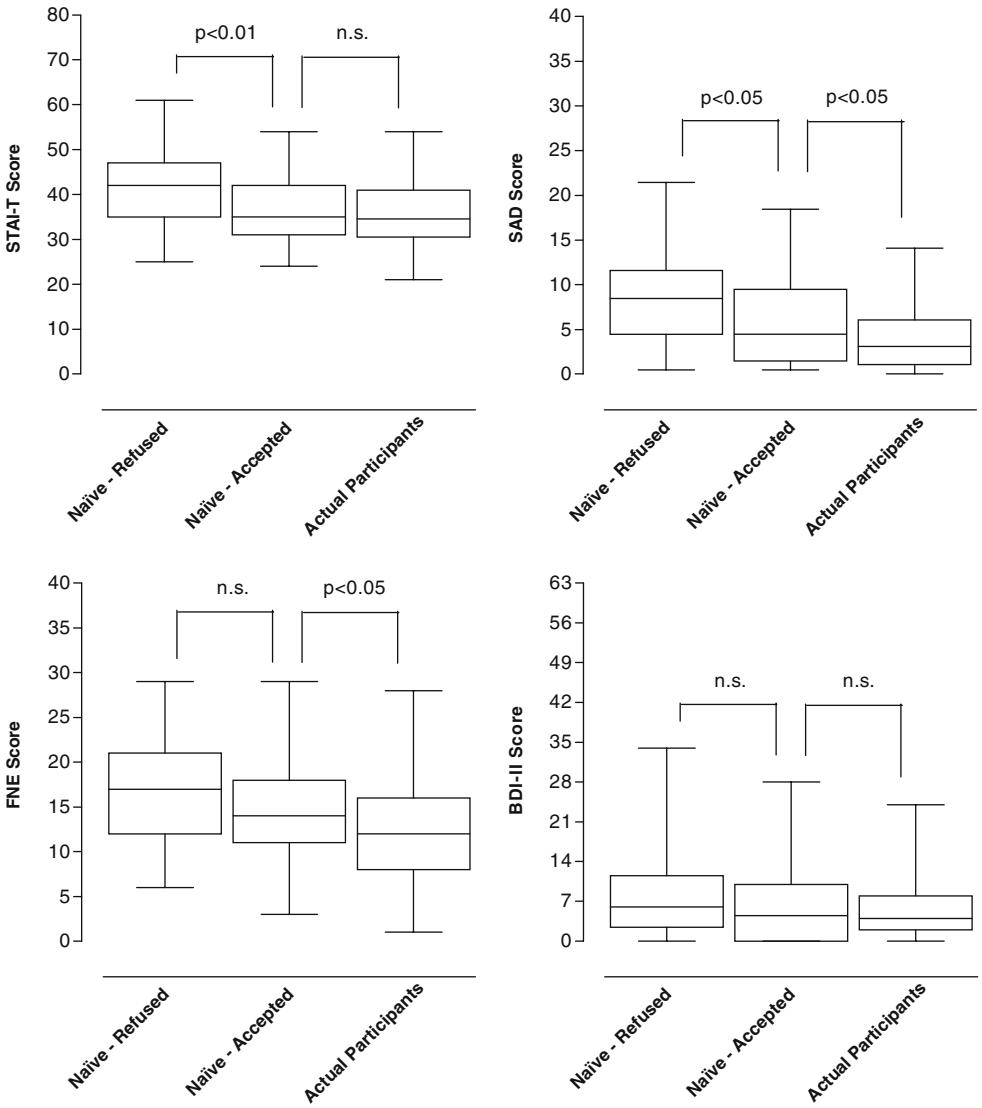

Fig. 1 STAI-T, SAD, FNE and BDI-II scores in the subsets of the Naïve Subjects who "Refused" and who "Accepted" the invitation to participate in a phase I clinical trial, and in the Actual Participants group. *Box-and-whiskers plot* showing median, quartiles and range values. For a description of the self-report measures, see the section Procedures and self-report measures

inverse relation between the SAD score and willingness to participate in a phase I clinical trial (R= −0.204, p<0.05). Taken together, the results indicate that people to whom social interactions cause distress tend to self-exclude from participation in phase I studies.

Significantly higher FNE scores were found in the "Accepted" subgroup of the Naïve Subjects than among the Actual Participants (Z=−2.439, p<0.05) or when the whole Naïve Subjects group was compared with the Actual Participants (Z=−4.298, p<0.001). Using Spearman's *rho*, we found no significant correlation between FNE scores and willingness to participate in a phase I clinical trial (R= −0.108, p>0.05). Overall, results suggest that the fear of negative evaluation does not substantially contribute to self-exclusion from study participation.

Depressive symptoms No statistically significant differences were found in BDI-II scores between the "Accepted" and "Refused" subsets of the Naïve Subjects (Z=−1.006, p>0.05) or between the "Accepted" subgroup of the Naïve Subjects and Actual Participants. Using Spearman's *rho*, we failed to find a significant relation between BDI-II scores and willingness to participate (R=−0.067, p>0.05). However, groups differed in the distribution of subjects into depressive severity categories: in Actual Participants, 5.1, 1.9 and 0.0% of the subjects presented mild, moderate and severe symptoms, respectively; in Naïve Subjects, the results were 7.8, 6.9 and 2.6%, respectively (chi-square=2.69, df = 3, p<0.01). Overall, the results suggest that subjects presenting moderate or severe depressive symptoms tend to self-exclude from participation in phase I studies.

STAI-T, SAD, FNE and BDI-II multivariate analysis on the prediction of study participation

To explore the unique contributions of trait anxiety, social avoidance and distress, fear of negative evaluation and

Table 2 Summary of logistic regression analysis of STAI-T, SAD, FNE and BDI-II scores as predictors of participation in a phase I clinical trial

Self-report measures[a]	β	Standard error	Exp(B)	95%CI for Exp(B)	Significance
STAI-T	-0.072	0.029	0.930	0.88, 0.99	$p<0.05$
SAD	-0.096	0.031	0.908	0.86, 0.97	$p<0.01$
FNE	-0.030	0.029	0.970	0.92, 1.03	n.s.
BDI-II	0.043	0.032	1.044	0.98, 1.11	n.s.
Constant	4.956	0.943	142.094		$p<0.001$

β , Regression coefficient; Exp(B), Odds ratios; CI, confidence interval; n.s., not statistically significant
[a] STAI, State-Trait Anxiety Inventory; SAD, the Social Avoidance and Distress scale ; FNE, Fear of Negative Evaluation (FNE) scale; BDI-II, Beck Depression Inventory II

depressive symptoms in predicting participation, we developed a logistic regression model. The results of the model are presented in Table 2. The only statistically significant predictors of participation were the STAI-T ($p<0.05$) and SAD ($p<0.01$) scores.

Correlation between STAI-T, SAD, FNE and BDI-II and the reporting of adverse events

Information regarding adverse events was available for 470 study periods ("tests"). Mean number of days per test was 10.0±9.0 (range 1–47). Adverse events (a total of 382) were reported in 57.2% of tests. Most adverse events were nervous system disorders or gastrointestinal disorders, according to the System Organ Class (SOC) classification of the MedDRA dictionary. Table 3 presents the most frequently reported adverse events, classified according to the MedDRA Lowest Level Term. The mean number of adverse events per test was 0.88±1.3 (range 0–7), of drug-related adverse events per test, 0.64±1.2 (range 0–7), of adverse events per day of test, 0.18±0.22 (range 0.0–1.0), of drug-related adverse events per day of test, 0.12±0.18 (range 0.0–0.9), of CNS-related adverse events per test, 0.42±0.82 (range 0.0–5.0) and of CNS-related adverse events per day of test, 0.08±0.14 (range 0.0–0.8).

Post-hoc evaluation showed a power of approximately 70% for the correlations between scales' scores and adverse event variables. No significant correlations were found between the BDI-II, SAD and FNE and adverse events. Significant positive correlations were found between STAI-T scores and each adverse event variable: percentage of tests with adverse events ($R=0.163$, $p<0.05$), percentage of tests with drug-related adverse events ($R=154$, $p<0.05$), number of adverse events per test ($R=0.193$, $p<0.05$), number of drug-related adverse events per test ($R=0.158$, $p<0.01$), number of adverse events per day of test ($R=0.188$, $p<0.01$), number of drug-related adverse events per day of test ($R=0.166$, $p<0.05$), number of CNS-related adverse events per test ($R=0.175$, $p<0.05$) and number of CNS-related adverse events per day of test ($R=0.173$, $p<0.01$). Overall, the results suggest that subjects with lower trait anxiety scores reported fewer adverse events.

Discussion

Participation in phase I clinical trials is based on free informed consent. Therefore, participants are a self-selected population of volunteers, and it is reasonable to assume that factors affecting the willingness to volunteer induce a self-selection bias that has a potential impact on study outcomes. The results of the current study show that more anxious, socially avoidant and depressed people are less

Table 3 Adverse events coded by the MedDRA Lowest Level Term (LLT) with a frequency of at least 1.0%

Adverse event LLT	Frequency (%)
Dizziness	10.0
Somnolence	6.8
Nausea	4.2
Headache	3.9
Dysmenorrhoea	2.6
Pharyngitis	2.6
Myalgia of lower extremities	2.1
Increased levels of creatine phosphokinase	2.1
Rhinitis	2.1
Tremor of hands	1.8
Vomiting	1.8
Epistaxis	1.8
Frontal headache	1.6
Rhinorrhoea	1.6
Toothache	1.6
Ecchymosis	1.3
Heartburn	1.1
Lumbar pain	1.1
Catheter site phlebitis	1.1
Diarrhoea	1.1
Loose stools	1.1
Nasopharyngitis	1.1
Paraesthesia tongue	1.1
Sore throat	1.1

likely to volunteer for participation in phase I clinical trials. The results also suggest that phase I study participants with lower trait anxiety scores report relatively fewer adverse events when participating in phase I studies.

The Naïve Subject and Actual Participants groups showed similar demographic and socio-economic characteristics, and the Actual Participants group is representative of our historical database of participants in phase I studies [27]. Anxiety-trait, social anxiety and depressive symptoms scores in the Naïve Subjects group are relatively similar to those of healthy samples with similar demographic characteristics [15, 23, 29]. However, since reports of phase I studies usually do not include information on the socio-economic status of study participants [28], it is unclear whether our sample is representative of subject populations volunteering for phase I studies in other clinical pharmacology units. The median STAI-T score was 35 and 42 in the "Accepted" and "Refused" subgroups of the Naïve Subjects, respectively; this difference is statistically significant ($p<0.01$) and clinically meaningful [17]. In terms of social anxiety (SAD scores), the median score in the "Refused" subgroup was twofold higher than that in the "Accepted" subgroup (8 versus 4, respectively), which is also statistically significant ($p<0.05$) and clinically meaningful [14].

It is noteworthy that the scores for all scales were slightly higher for the Naïve Subjects "Accepted" subgroup than for the Actual Participants group. This may be due to the fact that Naïve Subjects "Accepted" subjects only expressed an "intention" regarding participation, and it may be speculated that at the decision-making moment, some subjects (most likely among those with high scores) would reverse their consent to participate.

There is conceptual overlap among the personality traits under study. Upon controlling for shared variance among the STAI-T, SAD, FNE and BDI-II, we found that the only unique predictors of participation were trait anxiety and social avoidance. These traits appear to be of particular importance in terms of understanding the willingness (and reluctance) to volunteer for phase I clinical trials. Participation in phase I clinical trials with drugs in clinical development involves discomfort and the risk of experiencing expected and unexpected adverse events. According to current good clinical practice and regulatory requirements, volunteers must be made aware of all such inconveniences and risks before consenting to participate. Since subjects with greater anxiety are more likely to perceive a wider range of situations as threatening[13], it seems reasonable that they are more likely to view a phase I clinical trial as an unappealing and stressful situation. Participation in a phase I clinical trial also requires relationships with unknown people and the ability to embrace socially challenging situations, such as living together with strangers in a ward with minimal privacy for several days. Therefore, it is reasonable to expect subjects with higher social avoidance to self-exclude from participation in such studies.

Although it is accepted that phase I study participants do not necessarily represent the general population, it is assumed that they should represent at least their age group [30]. However, our study corroborates data suggesting that participants in phase I clinical trials may differ from the population from which they are drawn [30]. That said, the self-selection bias will be important only if it interferes with study outcomes or conclusions. Overall, our results suggest that subjects lower in trait anxiety report fewer adverse events. Since study participants represent a self-selected population of less anxious subjects than the full population [31], it may be concluded that: (1) globally, the self-selection may cause a decrease in the likelihood of reporting adverse events during phase I clinical trials; (2) in case of parallel-group clinical trials in which tolerability is the main endpoint, between-group imbalances in trait anxiety may lead to biased results. As a prevention strategy, the assessment of the individual's anxiety level could be included in the volunteer's screening procedures and adequate stratification could be carried out during subject assignment to different study groups.

In conclusion, our study found that less anxious and less socially avoidant subjects are self-selected for participation in phase I clinical trials. The impact of these self-selection biases on the phase I clinical trial results has not been completely characterized, but there is a strong suggestion that subjects low in anxiety tend to report fewer adverse events. Therefore, the characterization of participant's anxiety levels may be important in phase I studies.

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