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Healthy subjects volunteering for Phase I studies: Influence of curiosity, exploratory tendencies and perceived self-efficacy

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Key words
Phase I studies – healthy volunteers – personality – curiosity – self-efficacy

Abstract. Objective: To test the hypothesis that trait-curiosity and perceived self-efficacy influence the willingness of healthy subjects to volunteer for participation in Phase I studies. Materials and methods: A group of healthy subjects who had never participated in clinical studies ("index group") were invited to participate in a Phase I study. They were assessed with regard to trait curiosity (Curiosity and Exploration Inventory; CEI-T) and perceived self-efficacy (Self-Efficacy Scale; SES) and subjects who accepted the invitation to participate were compared with those who refused and with a group of healthy subjects who had previously participated in clinical studies ("validation group"). Results: A significant positive correlation was found between the willingness to participate and the CEI-T total score ($R = 0.28$; $p < 0.01$), exploratory tendencies ($R = 0.34$; $p < 0.001$), SES total score ($R = 0.30$, $p < 0.01$), initiative and persistence ($R = 0.29$, $p < 0.01$), planning/goal setting ($R = 0.19$, $p < 0.05$) and social self-efficacy ($R = 0.29$; $p < 0.01$). The "index group" subjects who accepted the invitation to participate showed significantly greater CEI-T exploratory tendencies ($Z = -3.334$, $p = 0.001$, Mann-Whitney test) and total scores ($Z = -2.703$, $p < 0.01$) and greater SES total score ($Z = -3.131$, $p < 0.01$), initiative and persistence ($Z = -3.065$, $p < 0.01$), planning/goal setting ($Z = -2.173$, $p < 0.05$) and social self-efficacy ($Z = -2.954$, $p < 0.01$) than subjects who refused. No differences were found between the subjects in the "index group" who accepted the invitation and subjects in the "validation group". Using a logistic regression model, both CEI-T exploratory tendencies and SES initiative/persistence were significant predictors of participation. Conclusion: Subjects higher in curiosity/exploration and in perceived initiative/persistence are more willing to volunteer for Phase I studies. The impact of these self-selection biases on Phase I study results is unknown but deserves further evaluation.

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Introduction

There are several reasons against participation in a Phase I clinical trial: participation often requires frequent blood drawings and other inconvenient procedures, implies confinement for several days, and sometimes causes adverse effects; on the other hand, subjects are healthy and it is not expected that they will directly benefit from participating in such studies. Therefore, one could ask why a healthy subject is willing to volunteer.

The population samples in Phase I studies can be considered self-selected because participation depends on informed consent. Self-selection may complicate the interpretation of the results and represent a threat to their generalizability. However, limited attention has been given to potential self-selection biases in volunteer enrolment and few studies have examined whether the characteristics of healthy subjects who volunteer to participate in clinical trials are different from their peers who decline participation [Tishler and Bartholomae 2002].

Prior investigations of volunteer motivation concluded that the financial incentive is usually the main motive of whether or not to participate [Almeida et al. 2007a, Bigorra and

Baños 1990, Hassar et al. 1977, Van Gelderen et al. 1993, Vrlovac et al. 1990]. Other commonly self-reported motivations for volunteering for Phase I studies include opportunities for free clinical check-ups, and contributing to scientific advances to help others, and "curiosity" [Almeida et al. 2007a, Bigorra and Baños 1990, Farre et al. 1995, Van Gelderen et al. 1993]. However, it was not clear whether curiosity corresponded just to a "curiosity-state" (which is largely based on individual interests, expectations and prior knowledge) or would represent a "curiosity-trait" (personality characteristic of whom has the propensity to more readily enter in novel and challenging experiences).

It has been reported that personality traits such as altruism [Newton 1982], self-control, self-confidence, emotional stability [Meyer et al. 1995], and extraversion [Pieters et al. 1992] may increase subject's likelihood of participation. In our study, we were interested in two particular personality traits that might differentiate people who volunteer for clinical trials and those who refuse: curiosity and self-efficacy. Since both of these traits are related to psychological, physical, and social well-being [Kashdan 2004, Kashdan and Steger 2007, Maddux 1995, Silvia 2006], if volunteers for clinical trials differ from the rest of the population on these traits, potential problems might arise in the interpretation of findings including limits to their generalizability.

Curiosity can be defined as the recognition, pursuit, and self-regulation of novel and challenging opportunities, often reflecting intrinsic values and interests [Kashdan et al. 2004]. Trait curiosity refers to a predisposition toward feelings of interest and curiosity and the resulting exploration of novel, puzzling, and uncertain situations [Kashdan and Fincham 2004]. A person high in "trait curiosity" prefers novelty, complexity, uncertainty and conflict and shows a preference for situations that are a match or slightly exceed their skills and derive satisfaction from the process of learning and discovery. Task or "state curiosity" is a transitory psychological state evoked by a specific interesting object or activity. We hypothesized that normal healthy subjects with greater trait curiosity, who are more exploratory by definition, are more likely to volunteer for clinical trials and subjects with less trait curiosity are more likely to view these situations as undesirable.

Another personality trait related to a wide range of health-related outcomes is self-efficacy [Bandura 1977]. Perceived self-efficacy is defined as beliefs about one's capacity to self-generate behaviors to obtain desired outcomes even when confronted with barriers and obstacles. People with high perceived self-efficacy choose to perform more challenging tasks, invest more effort and persist longer than those who are low in self-efficacy; people with low self-efficacy, doubting their capabilities, avoid or abort difficult tasks and often view them as personal threats (as opposed to challenges) [Bandura 1994]. In terms of the willingness to perform difficult tasks, self-efficacy has been consistently shown to be a more important determinant than anticipatory anxiety or the amount of prior task-relevant experience [Arch 1992, Bandura 1997]. We hypothesized that normal healthy subjects possessing the qualities inherent to self-efficacy would be more likely to volunteer for clinical trials whereas the relative absence of self-efficacy would lead to avoidance responses even in the face of valued contingencies such as financial incentives.

The primary objective of this study was to evaluate the influence of trait curiosity (assessed by the Curiosity and Exploration Inventory – Trait, CEI-T [Kashdan et al. 2004, http://mason.gmu.edu/~tkashdan/curiostywork.html/]) and perceived self-efficacy (assessed by the Self-Efficacy Scale, SES [Sherer et al. 1982]) on subjects' willingness to volunteer in a group of normal healthy subjects already enrolled in Phase I drug studies ("validation group") and in a group of healthy subjects who had never participated ("index group") and were invited to participate in a Phase I study. Since there is a possibility of overlap between curiosity and perceived self-efficacy, we also examined the relative independent contribution of each of these personality characteristics (and their lower-facet dimensions) on the prediction of participation.

Methods

Study populations

At the time of their participation in Phase I clinical trials with new chemical entities cur-

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

Variable		Index group (IG)		Validation group
		Accepted (n = 51)	Refused (n = 59)	(n = 216)
Gender	Male/Female	47.1%/52.9%	42.4%/57.6%	45.8%/54.2%
Age	Mean ± SD (years)	26.3 ± 6.6	26.6 ± 7.3	26.1 ± 5.3
	Median (years)	25	24	25
	Range (years)	18 – 45	18 – 45	18 – 45
Ethnicity	Caucasian/Other	92.2%/7.8%	98.3%/1.7%	95.8%/4.2%
Occupation	Student	56.0%	55.9%	57.3%
	Employed	38.0%	32.2%	36.7%
	Unemployed	6.0%	11.9%	6.0%
Monthly net income in relation to the mean national net salary in the industry and services sector*	< 25%	30.0%	28.6%	27.3%
	25 – 50%	35.0%	24.5%	28.5%
	51 – 100%	25.0%	28.6%	29.7%
	101 – 150%	10.0%	12.2%	9.9%
	> 150%	0.0%	4.1%	4.7%
Civil status	Single	72.5%	67.2%	77.9%
	Married/living together	23.5%	27.6%	17.1%
	Divorced	3.9%	5.2%	5.0%
School degree completed	4 years	2.0%	6.8%	0.0%
	6 years	3.9%	3.4%	1.0%
	9 years	9.8%	5.1%	7.0%
	12 years	60.8%	55.9%	63.8%
	Bachelor	5.9%	6.8%	7.5%
	Licensed	15.7%	20.3%	17.6%
	Mastership	2.0%	1.7%	3.0%

*approximately € 1,000/month, net.

rently in clinical development as new putative medicines for the treatment of neurological diseases conducted at the Human Pharmacology Unit of BIAL (Portela & Co. SA, S Mamede do Coronado, Portugal), a group of healthy volunteers (n = 216) were invited to participate in the current study. In accordance with the current regulatory requirements, their participation in the phase I studies had been preceded by standard informed consent procedures, including full information regarding the risks and inconveniences of study participation. All phase I participants who were invited to participate in the current study accepted the invitation.

A group of normal healthy subjects (n = 119) who had never participated in a clinical trial was constituted ("index group"). Since it is known that healthy subject's socio-economic level [Viens 2001], income [Tishler and Bartholomae 2002], educational level and age [Van Gelderen et al. 1993] may influence the willingness to volunteer for Phase I participation, efforts were made to assure that the "index group" would match the Phase I participants sample in terms of main demographic (age, gender, ethnicity and occupation) and socio-economic (monthly income, civil status and school degree completed) characteristics.

Subjects of the "index group" were also provided with the typical informed consent information prepared for a real Phase I study and invited to participate. Among the 110

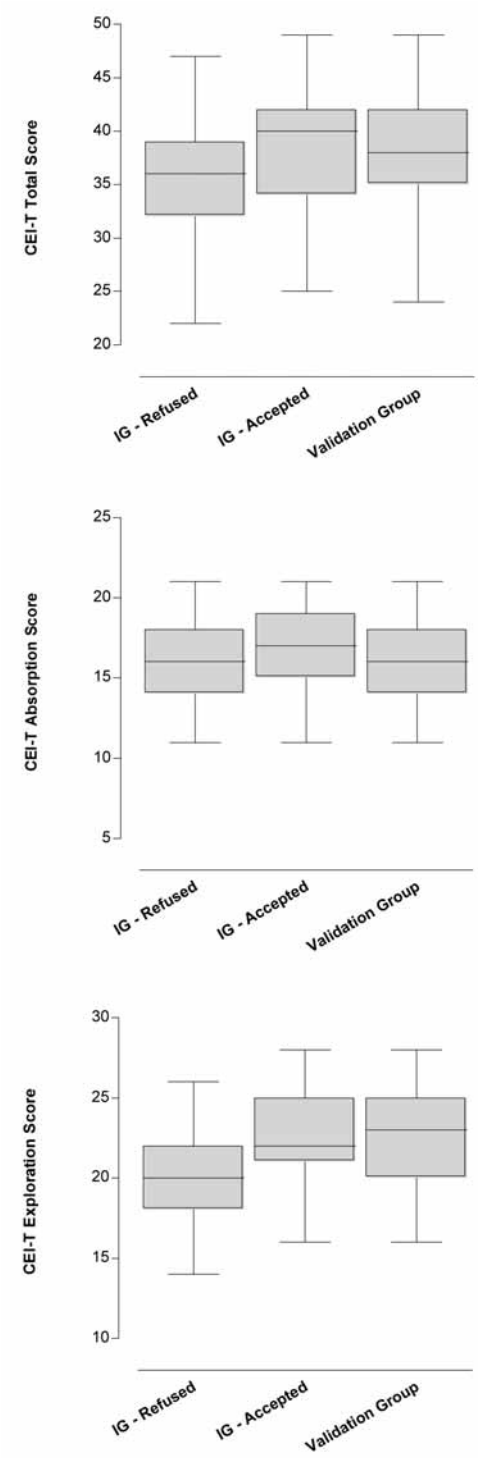

Figure 1. CEI-T scores in the "index group" (IG) subsets of subjects who "refused" and who "accepted" the invitation for participation in a Phase I study, and in the "validation group" (previous participants in Phase I studies): Box-and-whiskers plot showing median, quartiles and range values.

subjects who answered the invitation, 51 (46.4%) subjects declared that they would be willing to participate and 59 (53.6%) individuals refused participation in such Phase I study, and two subgroups ("accepted" and "refused") were constituted accordingly. Main demographic and socio-economic characteristics of the study populations are presented in Table 1.

Self-report measures

Subjects of both groups were invited to complete Portuguese adaptations of the CEI-T [Kashdan et al. 2004], to operationalize trait curiosity and exploratory tendencies, and the SES [Ribeiro 1995], to operationalize trait self-efficacy.

The 7-item CEI-T assesses two relatively independent dimensions of curiosity: (1) *Exploration* – general strivings to seek out novelty, challenge, uncertainty, and intriguing experiences (4 items; e.g., "Everywhere I go, I am out looking for new things or experiences") and (2) *Absorption or Flow* – the propensity to be deeply absorbed in the interesting target of one's attention (3 items; e.g., "When I am participating in an activity, I tend to get so involved that I lose track of time") [Kashdan 2002]. The 2-dimensional approach of the CEI-T focuses on the defining features of curiosity rather than different objects that induce curiosity [Kashdan 2002]. Respondents rate the items according to a 7-point Likert-type scale that indicate agreement with the statements provided from "Strongly Disagree" to "Strongly Agree".

The original English version of the CEI-T has good psychometric properties, is relatively unaffected by socially desirable responding, and is relatively independent from positive affect [Kashdan et al. 2004]. The Portuguese CEI-T version was submitted to confirmatory factor analysis and also showed good psychometric properties. A model comparison procedure introduced by Bollen [1980] was used to test whether the 2-factor model with *Exploration* and *Absorption* as separate, but correlated components of curiosity provided a better fit to the data than a one-factor model. The hypothesized 2-factor model was compared to a model where the zero order association between the two dimensions of curiosity was constrained. The models could be directly compared by interpreting the change in the χ^2 (per change in *df*). The 2-factor model with *Exploration* and *Ab-*

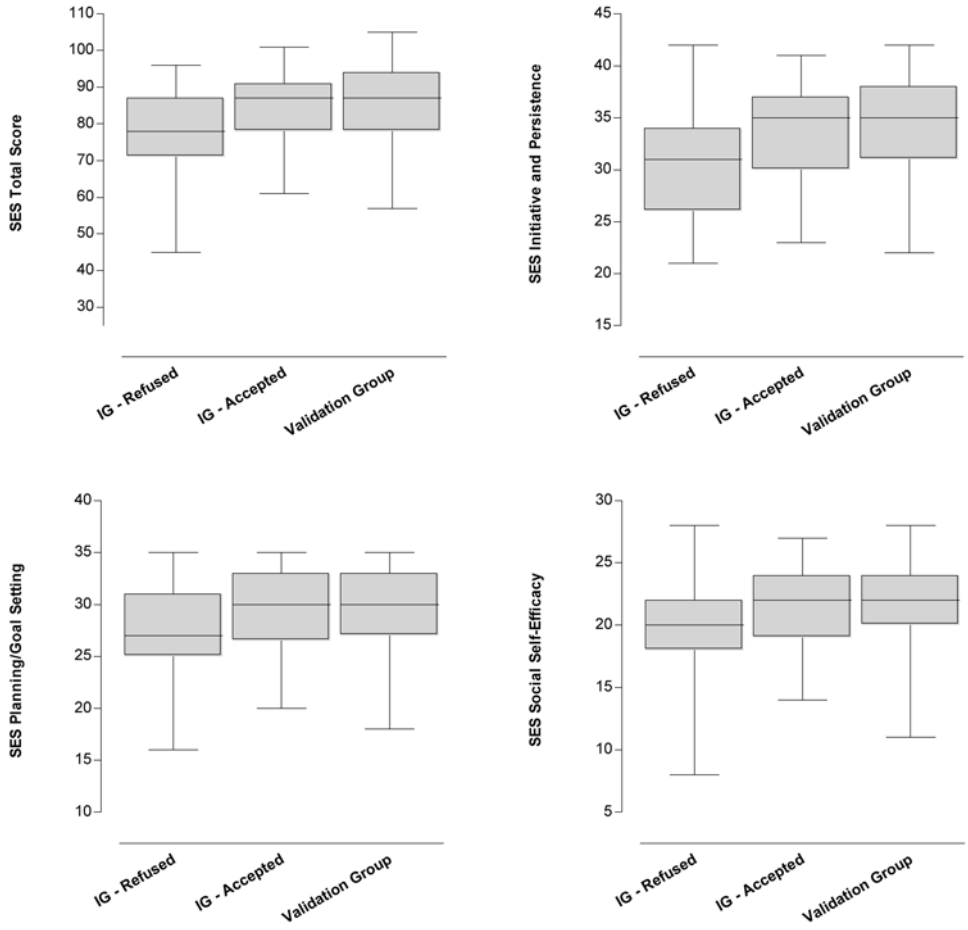

Figure 2. SES scores in the "index group" (IG) subsets of subjects who "refused" and who "accepted" the invitation for participation in a Phase I study, and in the "validation group" (previous participants in Phase I studies): Box-and-whiskers plot showing median, quartiles and range values.

sorption as separate, but correlated components of curiosity, fit the data well, $\chi^2 = 24.56$, $p = 0.03$, $\chi^2/df = 1.89$, TLI = 0.97, CFI = 0.98, RMSEA = 0.05, SRMR = 0.03. Allowing *Exploration* and *Absorption* to covary freely in a 2-factor model resulted in a significant improvement in model fit, χ^2 (1) = 11.12, p = 0.001. Loadings on the *Exploration* factor ranged from 0.41 – 0.82, loadings on the *Absorption* factor ranged from 0.57 – 0.85, and the two factors correlated at 0.74. Thus, the 2-dimensional CEI-T is synonymous with the English version.

The 23-item SES [Sherer et al. 1982] focuses on the willingness to initiate behavior, willingness to expend effort in completing behavior, and persistence in the face of adversity. 6, 5 and 4 items compose the *Initiative/Persistence, Planning/Goal Setting,* and *Social Self-Efficacy* subscales, respectively. It has shown to be a valid predictor of academic and professional behavior [Ferrari et al. 1992, Sherer et al. 1982], self-esteem [Woodruff and Cashman 1993], and general adjustment [Martin et al. 1996, Sherer and Adams 1983]. In our study, we used a 15-item Portuguese validated adaptation of the original scale [Sherer et al. 1982], performed by Ribeiro [1995]. The Portuguese adapted scale shows good psychometric properties [Ribeiro 1995]. The items are rated on a 7-point Likert-type scale, ranging from 1 ("Fully Disagree") to 7 ("Fully Agree").

Statistical considerations

Statistical analyses were performed with the Statistical Package for Social Sciences version 11.5 (SPSS Inc., Chicago, IL, USA). The criterion for statistical significance was set at an α error of 5% ($p < 0.05$), 2-sided.

Table 2. Spearman's correlation between CEI-T and SES scores and interest into participation in a Phase I study.

Scales	Spearman's rank correlation	
CEI-T		
Total	*R* = 0.28	p = 0.004
Exploration	*R* = 0.34	p = 0.000
Absorption	*R* = 0.14	n.s.
SES		
Total	*R* = 0.30	p = 0.002
Initiative and Persistence	*R* = 0.29	p = 0.002
Planning/Goal Setting	*R* = 0.19	p = 0.048
Social Self-Efficacy	*R* = 0.29	p = 0.002

n.s. = not statistically significant.

Table 3. Statistical comparison (Wilcoxon-Mann-Whitney rank sum test) of CEI-T and SES scores between subjects of the "index group" (IC) who "accepted" the invitation to participate in a Phase I study versus those who "refused" (A), and versus the "validation group" (B).

Scales	(A) IC - Accepted vs. IC - Refused		(B) IC - Accepted vs. Validation group	
CEI-T				
Total	*Z* = –2.703	p = 0.007	*Z* = –1.247	n.s.
Exploration	*Z* = –3.334	p = 0.001	*Z* = –0.454	n.s.
Absorption	*Z* = –1.366	n.s.	*Z* = –1.839	n.s.
SES				
Total	*Z* = –3.131	p = 0.002	*Z* = –0.456	n.s.
Initiative and Persistence	*Z* = –3.065	p = 0.002	*Z* = –0.621	n.s.
Planning/Goal Setting	*Z* = –2.173	p = 0.030	*Z* = –0.164	n.s.
Social Self-Efficacy	*Z* = –2.954	p = 0.003	*Z* = –0.140	n.s.

n.s. = not statistically significant.

The first set of analyses consisted of comparing CEI-T and SES scores to examine if there were differences between those subjects in the "index group" who declared they would accept to participate and those who refused. An internal validation was performed by comparing the "index group" subset of subjects who declared they would accept to participate with the "validation group". Tests for normality were performed using the Shapiro-Wilk test. Since the dependent variables were not normally distributed, the Wilcoxon-Mann-Whitney rank sum test was used for the comparisons. In the "index group", Spearman's correlations between the CEI-T and SES scores and the answer to the invitation to participate were performed.

In addition to univariate analyses, the independent contribution of each CEI-T and SES sub-scale on the prediction of study participation in the "index group" was tested by using logistic regression.

Ethics

This study was approved by an Independent Ethics Committee (Comissão de Ética Independente da UFH, Porto, Portugal).

Results

CEI-T and SES univariate analysis

CEI-T and SES scores are displayed in Figures 1 and 2. The results of the Spearman's correlation between CEI-T and SES scores and interest into participation in the "index group" are presented in Table 2. Statistical comparison of CEI-T and SES scores between "index group" subjects who accepted the invitation for participation in a Phase I study versus those who refused participation, and versus those subjects who had previously participated ("validation group") are presented in Table 3.

Trait curiosity

Within the "index group", respondents who accepted the invitation for participating in a Phase I study showed significantly greater *Exploration* score ($Z = -3.334$, $p = 0.001$) and *Total Score* ($Z = -2.703$, $p < 0.01$) than those who refused; no significant difference was found in *Absorption*. No significant differences were found between those "index group" subjects who declared they would accept to participate and the "validation group". In the "index group", a significant positive linear correlation was found between the interest in participation and the CEI-T *Total*

Table 4. Summary of logistic regression analysis of CEI-T and SES scores as predictors of participation in a Phase I study.

Scales	β	SE	Exp(B)	95%CI for Exp(B)	
CEI-T					
Exploration	0.174	0.088	1.190	1.002, 1.413	p < 0.05
Absorption	–0.059	0.087	0.943	0.795, 1.119	n.s.
SES					
Initiative and Persistence	0.098	0.049	1.103	1.003, 1.214	p < 0.05
Planning/Goal Setting	–0.040	0.064	0.961	0.849, 1.089	n.s.
Social Self-Efficacy	0.081	0.073	1.085	0.940, 1.251	n.s.
Constant	*–6.629*	*1.928*	*0.001*		*p = 0.001*

β = regression coefficient; SE = standard error of the mean; Exp(B) = odds ratios; CI = confidence interval; n.s. = not statistically significant.

Score ($R = 0.28$, $p < 0.01$) and CEI *Exploration* ($R = 0.34$, $p < 0.001$).

Perceived self-efficacy

Within the "index group", respondents who accepted the invitation for participating in a Phase I study also showed significantly greater scores on all variables: *Total Score* ($Z = –3.131$, $p < 0.01$), *Initiative and Persistence* ($Z = –3.065$, $p < 0.01$), *Planning/Goal Setting* ($Z = –2.173$, $p < 0.05$) and *Social Self-Efficacy* ($Z = –2.954$, $p < 0.01$). No significant differences were found between those "index group" subjects who declared they would accept to participate and the "validation group". In the "index group", a significant positive linear correlation was found between the interest in participation and the SES *Total Score* ($R = 0.30$, $p < 0.01$), *Initiative and Persistence* ($R = 0.29$, $p < 0.01$), *Planning/Goal Setting* ($R = 0.19$, $p < 0.05$) and *Social Self-Efficacy* ($R = 0.29$, $p < 0.01$).

Multivariate analysis on the prediction of study participation

To explore the contributions of each CEI-T and SES component to the prediction of participation, a logistic regression model was composed in the "index group" using CEI-T *Exploration* and *Absorption*, and SES *Initiative and Persistence, Planning/Goal Setting* and *Social Self-Efficacy* as covariates. The results of the model are presented in Table 4. Both CEI-T *Exploration* ($p < 0.05$) and SES *Initiative and Persistence* ($p < 0.05$) were found to be statistically significant predictors of participation.

Discussion

This study examined whether normal healthy subjects participating and willing to volunteer for Phase I clinical trials differ from those who do not take part, in terms of tendencies to be curious, exploratory, and self-efficacious. Supporting our hypotheses, subjects who were more curious and self-efficacious were more likely to volunteer for participation in Phase I studies. There is potential overlap between the personality traits of curiosity and self-efficacy, as people possessing these qualities are prone to view difficult situations as challenges rather than threats and they are more likely to engage in approach behavior even in the face of avoidance motives to prevent negative outcomes. Upon controlling for shared variance among the CEI-T and SES sub-scales, we found that the unique predictors of participation were CEI-T *Exploration* and SES *Initiative* and *Persistence*. Thus, these traits appear to be of particular importance in understanding the willingness (and reluctance) to volunteer for Phase I clinical trials.

The results are consistent with the theoretical framework. Participation in Phase I studies with drugs in clinical development may be perceived as a challenging situation because

it involves the discomfort, performance of unaccustomed procedures, close social interactions with the clinical staff and other participants, the risk of occurrence of expected and unexpected adverse events, and, according to current Good Clinical Practices and regulatory requirements, the volunteers must be made aware about all such inconveniences and risks before giving their informed consent. Since highly curious and self-efficacious subjects show a higher tendency to embrace and even thrive in challenging situations [Kashdan and Silvia (in press), Maddux 1995], it seems plausible that they are more likely to view a Phase I study as an appealing and satisfying situation.

During the clinical development process of a new medicine, normal healthy volunteers are utilized in Phase I clinical trials to provide pharmacokinetic, pharmacodynamic and tolerability information to help to determine the doses to be used in future Phase II and III clinical trials and, afterwards, in the target patient population. Ideally, samples of normal healthy volunteers selected for Phase I studies should be representative of the population for whom the drug is intended. However, pragmatic issues of convenience, practicability and cost prevent the recruitment of such an ideal population [Tishler et al. 2005]. Although it is accepted that healthy volunteers do not necessarily represent the target population, it is assumed that they should represent at least their age group [Pieters et al. 1992]. However, our study corroborates data from other studies [Meyer 2001] suggesting that participants in Phase I studies differ in important ways from the population from which they are drawn. For example, healthy people who volunteer for Phase I studies appear to show a greater tendency toward sensation-seeking and to be more extraverted and self-confident than normative samples [Ball et al. 1993, Cami et al. 1989, Farre et al. 1995, Pieters et al. 1992], and volunteers were also shown to be less socially anxious [Almeida et al. 2007b] and depressed [Almeida et al. 2007c] than controls.

The overarching aim of this line of research is to determine whether normal healthy subjects differ from the population of interest in a meaningful way [Tishler et al. 2005]. The self-selection bias will be important only if it interferes on the study outcomes or upon the interpretation of the studies. There is evidence that some personality characteristics may influence the pharmacodynamic response [Meyer 1992], objective pharmacokinetic data [Meyer 2001] and subjective tolerability information gathered from normal healthy volunteers [Meyer et al. 2000]. For instance, there are suggestions that extroverted personality characteristics influence the subjective tolerability and physiological response of normal healthy subjects to drug administration [Meyer 2001]. Also, there is some evidence that volunteer's type of personality may influence the subjective response to placebos, which are commonly used in Phase I clinical trials with new drugs, and therefore impair the evaluation of new drugs in such studies [Drici et al. 1995]. However, the variability in drug response and/or pharmacokinetics due to personality or psychological features is an overlooked topic, systematic research in this field is still missing, and the impact of the self-selection bias on the study results is largely unknown [Tishler et al. 2005]. Once known, the characterization of the volunteers' personality and psychological characteristics that actually may affect their subjective response and pharmacokinetic parameters could be addressed in the screening process for controlled Phase I studies, through the formation of balanced groups [Meyer et al. 2000], or in the statistical analysis [Tishler et al. 2005].

Conclusion

Results from our study, which to our knowledge was the first to use a control group, suggested that participants in Phase I studies show a preference to seek novel, uncertain, and complex situations (as shown by greater CEI-T *Exploration* scores) and are more willing to initiate behavior and to persist (as shown by greater SES *Initiative* and *Persistence* scores), compared with their control peers. Results were consistent across comparisons between subjects who had never participated in a Phase I study and who declared that they would consider participating versus those who declined invitation to participate (behavioral intentions), and between subjects who accepted the invitation versus a group of subjects who had previously participated.

These findings may have implications for interpreting threats to the generalizability of the results of Phase I studies. The impact of these self-selection biases on the Phase I study results is unknown but deserves further evaluation.

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