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Healthy volunteers for bioequivalence trials: predictive factors for enrollment failures – a case-control study

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bioequivalence trials – healthy volunteers – predictive factors – enrollment failures

Abstract. Objective: To identify social predictors for enrollment failures of healthy volunteers (hv) in bioequivalence trials. Methods: Retrospective case-control study. Data was collected from clinical files of hv recruited in 13 bioequivalence trials approved by an independent IRB and local regulatory authority carried out between January and December 2009 at a Pharmacokinetic Unit in Buenos Aires, Argentina. All hv signed the Inform Consent Form. Only subjects who fulfilled all inclusion criteria required by the protocols were studied. Cases (enrollment failures): hv who fulfilled the protocols eligibility criteria but were not enrolled in the trials by their own decision. Controls: hv who fulfilled all the protocols eligibility criteria and were enrolled. Cases and controls were matched by demographic/ physical data and compared in relation to database contact, unemployment, alcoholic/ drug family environment, history of alcohol/ drug abuse, and other social variables. χ^2-test and t-test were used to compare data; variables presenting statistical difference were included in a logistic regression model. Results: A sample of 375 hv. was analyzed. Cases: 81/375(21.60%). Controls: 294/375 (78.40%). Cases did not differ from controls in relation to nationality, educational level, length of study and history of alcohol abuse. Statistical differences between cases and controls were found in non-database contact, unemployment, alcoholic environment, drug abuse environment and personal history of drug abuse. In a multivariate analysis only unemployment, (OR: 4.20, $p < 0.001$), non-database contact, (OR: 2.35, $p = 0.004$) and alcoholic environment, (OR: 1.94, $p = 0.045$) remained as predictive factors. Conclusion: In bioequivalence trials, an unemployment condition, and an alcoholic family environment were identified as negative predictors for effective enrollment in new healthy volunteers.

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Introduction

A determinant factor for the success of a clinical trial is the adequate selection of the study population which allows the recruitment and enrollment of subjects who fulfill protocol criteria [1]. A subject is considered to be recruited when he/she signs the Informed Consent Form document; then a subject is considered enrolled if he/she fulfills the eligibility criteria and is effectively included in the study.

An effective enrollment process is primarily related to the complexity of protocols eligibility criteria that are so tight that potential study subjects do not qualify for entry; however, other factors have also been reported to have a significant impact on this process [2, 3, 4].

In subjects contacted for participating in a new trial from an investigator database, high level of education, native nationality [2] and stable employment [3, 4], are more likely to be effectively enrolled. On the other hand: negative influence of the media, study designs with excessive visit schedules, physicians mistrust and poor personal motivation [1, 3], have been reported to produce a negative impact. Complex social and environmental factors such as a previous history of alcoholism or drug abuse, an alcoholic or drug abuse environment have been mentioned to affect the enrollment of healthy volunteers in Phase I studies [5, 6, 7].

Low enrollment rate has several negative implications in clinical trials, which results in longer duration, more effort from investigators staff and higher costs, since extra resources would have to be designated to the recruitment effort, and less statistical power for the study [1, 2, 3, 4].

Bioequivalence studies can also be affected by low enrollment rates. Enrollment of healthy individuals in these trials can be more difficult than in clinical trials involving patients, because healthy individuals might not

have a personal interest in the study topic and no therapeutic benefit is expected [8, 9]. There is emerging evidence that people who volunteer for Phase I studies are not always truthful with investigators about their social background during screening process [6, 7].

Additional effort is then required from the investigators for the adequate execution of this stage to achieve a successful process. No data has been reported in the literature in relation to the potential social and environmental factors affecting the enrollment of healthy volunteers in bioequivalence trials.

Objective

The objective of this study was to identify predictors for enrollment failures of healthy volunteers in bioequivalence studies.

Our hypothesis was that several social and environmental factors exist that significantly affect the participation of the healthy population in bioequivalence studies. The identification of these factors may help to improve the process of enrollment and hence the quality of results.

Methods

An observational retrospective case-control study was carried out. Data were collected from clinical files of the healthy volunteers recruited in 13 bioequivalence trials carried out between January and December 2009. Studies were performed at a Pharmacokinetic Clinical Unit in Buenos Aires, Argentina. All research protocols defined the bioequivalence assessment as final endpoint (new generic formulation vs. innovator dosage form) and followed the same design characteristics: single dose, open-label, randomized, two-way, cross-over, under fasting conditions. All studies were approved by an independent IRB and the local regulatory authority before being carried out.

Subjects

All healthy volunteers who signed the Inform Consent Form (ICF) to participate in bioequivalence trials and fulfilled all inclusion criteria required by the protocols were included in the analysis.

Subjects who signed the ICF and presented one or more protocols of the exclusion criteria were restricted from this study.

Inclusion/exclusion protocol criteria were those that are common for bioequivalence studies as defined by the Food and Drug Administration [10]. Inclusion criteria: men and women 21 – 55 years of age, body mass index (BMI) between 18 and 30 kg/m^2, supine blood pressure between 90 and 140 mmHg and women surgically sterile, abstinent, or if sexually active, be practicing an effective method of birth control. Exclusion criteria: history of/ or current clinically significant illness, clinically significant abnormal values in safety laboratory, history of alcohol/drug abuse in the last two years, drug and/or food allergies, use of any medication within 14 days before the first dose of the study drug, previous participation in a trial or donation of blood within three months of screening.

Cases (enrollment failures): Healthy volunteers who fulfilled all the eligibility protocol criteria, but were not finally enrolled because of their own decision.

Controls (effectively enrolled): Healthy volunteers who fulfilled all the eligibility protocol criteria and were finally enrolled in the trials.

Matching: Cases were matched with controls by age, gender, weight (kg), height (cm) and body mass index (BMI) (kg/m^2), Caucasian race, married as marital status and location of the site in a different area of residence, using an approximate ratio 1 : 4.

Variables of study: The following eight variables were compared between cases and controls: 1) Source of subject contact (investigator database: personal data previously filled in an investigator database/ non-database contact: subject was referred to the study from a previous participant and no personal data was filled in an investigator database), 2) Employment condition (stable employment/ unemployment), 3) Nationality (native/foreign), 4) Level of education (Completed/ uncompleted High School degree) , 5) Length of study visits (= 1 month/ < 1 month), 6) Presence/absence of an alcoholic family environment, 7) Presence/absence of a drug abuse family environment, 8) Personal history of alcohol or drug abuser (not in the last two years). Categorical data was reported by pro-

Table 1. Cases and controls matching criteria.

Demographic and physical data	Controls (n = 294)	Cases (n = 81)	p	OR	95% CI
Age (years), mean ± SD	35.46 ± 9.29	33.74 ± 8.76	0.13	–	Controls: 31.75 – 35.73 Cases: 34.39 – 35.73
Male, n (%)	185 (62.93)	51 (62.96)	0.95	0.99	0.57 – 1.70
Caucasian, n (%)	288 (97.96)	80 (98.77)	0.63	1.66	0.19 – 14.05
Married, n (%)	120 (40.82)	32 (39.50)	0.96	1.05	0.62 – 1.08
Location of the site in a different area, n (%)	190 (64.62)	46 (56.79)	0.18	1.40	0.82 – 2.38
Height (mts), mean ± SD	1.69 ± 0.8	1.71 ± 0.77	0.13	–	Controls: 1.68 – 1.70 Cases: 1.68 – 1.73
Weight (kg), mean ± SD	70.92 ± 9.82	71.75 ± 8.9	0.58	–	Controls: 69.80 – 72.06 Cases: 69.15 – 74.34
BMI (kg/m^2), mean ± SD	24.70 ± 2.23	24.66 ± .95	0.90	–	Controls: 24.44 – 24.96 Cases: 24.09 – 25.23

Table 2. Comparative data between cases and controls.

Variables of study	Controls (n = 294) (%)	Cases (n = 81) (%)	p	OR	95% CI
Non-investigator database contact	142 (48.30)	60 (74.07)	< 0.001	3.06	1.72 – 5.56
Unemployment	104 (35.37)	59 (72.84)	< 0.001	4.89	2.76 – 8.86
Native nationality	261 (88.78)	72 (88.88)	0.57	1.01	0.44 – 2.51
Uncompleted high school degree	162 (55.10)	46 (49.38)	0.44	1.07	0.63 – 1.81
Study visits ≥ 1 month	134 (45.57)	40 (49.38)	0.31	1.16	0.69 – 1.96
Alcoholic family environment	38 (12.93)	23 (28.40)	< 0.001	2.67	1.40 – 4.99
Drug abuse family environment	34 (11.56)	25 (30.86)	< 0.001	3.41	1.70 – 6.40
History of alcohol abuser	17 (5.78)	4 (4.94)	0.76	084	0.20 – 2.70
History of drug abuser	26 (8.87)	14 (17.28)	0.03	2.10	0.97 – 4.50

portions and continuous data by mean ± standard deviation (sd).

Statistical analysis: Univariate analysis was performed. χ^2-test was used to compare categorical data reporting odds ratios (ORs) with 95% binominal approximation confidence intervals and p values for each variable. For continuous variables, differences in the means of control subjects versus the means of cases were compared using Student-t-test. Point estimates of the differences in case and control means were calculated as well as 95% confidence limits. To avoid the spurious effect of confounding factors, all variables with statistical difference between groups ($p < 0.05$) were included in a logistic regression model to identify risk factors reporting odds ratios with a 95 % confidence interval. Logistic regression was used since the outcome was a categorical variable: enrollment failures vs. effectively enrolled. The model was employed to predict the probability of the occurrence of the outcome, as a function of the independent variables of the study, and for reporting OR associated with each predictor value [11, 12]. Selection bias was minimized by matching both groups with demographic and physical data. Software: Stata v09.

Results

A total of 382 healthy volunteers were recruited for bioequivalence studies. Seven subjects were restricted from the analysis since they presented one or more exclusion protocol criteria.

Table 3. Multivariate analysis (logistic regression) for predictive factors.

Predictive factors	OR	SE (*)	p	95% CI
Unemployment	4.20	1.27	< 0.001	2.32 – 7.61
Non-investigator database contact	2.35	0.70	0.004	1.30 – 4.07
Alcoholic family environment	1.94	0.64	0.046	1.01 – 3.71
History of ex-drug abuse	2.36	1.03	0.052	0.99 – 5.58
Drug abuse family environment	1.85	0.64	0.081	0.92 – 3.67

(*) Standard error.

A final sample of 375 healthy volunteers who fulfilled the eligibility criteria were analyzed. Cases: 81/ 375 (21.60%) and controls: 294/ 375 (78.40%).

No statistical differences were found when cases were matched with controls at any category. Cases and controls matching criteria is summarized in Table 1.

In the univariate analysis, five factors were more prevalent among cases than controls with statistical significance. Cases were more likely to be unemployed, to be a non-database contact, to report an alcoholic family environment, to report drug abuse family environment and personal history of drug abuse. However, cases did not differ from controls in relation to native nationality, uncompleted high school degree, length of study visits more than one month and personal history of alcohol abuse. Data is summarized in Table 2.

Of the hypothesized predictors that were positively associated with enrollment failures, three of five remained significantly associated in the multivariate logistic-regression model: Unemployment, OR = 4.20 (2.32 – 7.61), $p < 0.001$, non-database contact, OR = 2.35 (1.30 – 4.25), $p = 0.004$ and alcoholic environment, OR = 1.94 (1.01 – 3.71), $p = 0.045$ (Table 3).

Discussion

Several factors have been reported in the literature affecting the effective enrollment of clinical trials [1, 2, 3, 4, 5, 6, 7, 8, 9]. In this study, we demonstrated that social and environmental factors significantly affect the participation of the healthy subjects who volunteer for bioequivalence studies. We found an unemployment condition, non-investigator database contact and an alcohol family environment as predictive factors for the lack of enrollment of healthy volunteers.

A stable employment condition has been described as a positive predictor for effective enrollment in special populations [8, 13]. In our study, the unemployment condition was shown to be the most significant predictor for enrollment failures in bioequivalence studies (OR = 4.20, $p < 0.001$). Healthy volunteers who were enrollment failures referred an unemployment condition in 72.84% (59/ 81) of cases in contrast with the enrolled subjects: 35.37% (104/294). This could be partially explained because the lack of a stable employment increases the risks of personal uncertainty, generates a lower self confidence and lower compliance with programmed schedules [3, 13]. Moreover, social self-efficacy has been demonstrated to be associated to willingness to participate in healthy volunteers for Phase I studies [14]. In a previous study, volunteers tending to change jobs more frequently and moving to new locations to take up these jobs represented a potential barrier for enrollment [15]. Financial reward is also described as a motivator for participation of normal healthy volunteers in Phase I studies [8, 9], however, we did not analyze the real impact of financial reward due to the design of this study, but we did find that employment conditions and their social circumstances has to be taken into consideration during the recruitment phase of healthy volunteers for bioequivalence studies in our population to avoid potential high rates of enrollment failures.

New healthy volunteers referred to the study from a previous participant source (not contacted by an investigator database) was the other predictive factor associated with healthy volunteers who were enrollment failures (OR = 2.35, $p = 0.004$). Enrollment failures coming from a previous participant source represented 74.04% (60/81) of cases while this accounted for 48.30% (142/294) in the enrolled subjects. Database contact represented 51.70% (152/294) in effective enrolled subjects vs. 25.92% (21/81) in enrollment failures. This reflects the importance of an accurate healthy volunteer database with updated contact information. Demographic and social characteristics of the target audience are identified using a primary database research to determine how best to reach the

study population for the requested study. Thus, this analysis can help to improve the enrollment rate to reach what can be expected in terms of enrollment success [1, 2, 3]. Family members, partners or friends of the previous participants were the primary source of new healthy volunteers. Despite the positive influence of the subjects with previous participation, new healthy volunteers seemed to have a different perception of the studies. Naive healthy volunteer's motivations and perceptions toward participation in Phase I studies are influenced by individual characteristics, including some personality traits as described in the literature [9, 14]. We could not investigate personality traits of the healthy subjects volunteering for bioequivalence due to the retrospective design of the study, but we found social factors such as unemployment to have an important negative influence in the enrollment of these new subjects. It has been demonstrated that recruiting new healthy volunteers for research participation via internet and social networks represent a valuable method [16]; however the lack of a personal computer in subject volunteers made this strategy difficult in our population and all new healthy volunteers came from a previous participant source.

An alcoholic family environment was another negative predictor for enrollment (OR 1.94, $p = 0.046$). Enrollment failures presented an alcoholic environment in 28.40% (23/81) while this accounted for 12.93% (38/294) in the effective enrolled volunteers. Although drug abuse environment and a personal history of drug abuse (not in the last two years) were statistically more frequent in the enrollment failures vs. the effectively enrolled volunteers: 30.86% (25/81) vs. 11.56% (34/294) and 17.28% (14/81) vs. 8.87% (26/294), respectively; they did not emerge as independent negative predictors for enrollment in the multivariate analysis since the probability of the occurrence of being enrollment failures as a function of these variables was not statistically significant ($p > 0.05$) as well as the range of the 95% Confidence Interval (CI) of the OR associated with each of these predictors values included the unity (1.0). The importance of assessing risk factors for alcoholism during the recruitment process of healthy volunteers [5] and benefits of urine drug tests during screening [6, 7] has been mentioned in the literature. However, very little data has been reported regarding the subject environment in relation to alcohol and drug abusers. Despite the difference in the alcoholic environment, enrolled subjects did not differ from enrollment failures in relation to a previous history of alcoholism (not in the last two years): 4.94% (4/81) vs. 5.78% (17/294), $p = 0.76$. This reflects the importance of questioning not only the personal alcohol/drug abuse background of the subject, but the environment as well to identify factors affecting the enrollment. Detecting a family member or a healthy volunteer's friend with a history of alcoholism could reflect a more complex social environment and demands a more exhaustive examination of the subject's social and psychological profile before deciding the enrollment despite the subject protocol eligibility criteria. Drug abusers in the subject environment as well as a previous history of drug abuse should call the investigator's attention to detect other factors related to the lack of enrollment such as alcoholism, environment or an unstable job condition.

It has been reported that protocol-related factors affecting enrollment in clinical trials such as lengthy study period and excessive visit schedules [1, 2, 3, 14, 17]. We found no statistical difference between the effectively enrolled and enrollment failures in relation to the length of the study visits (more than one month).

Several authors indicated both cultural issues and language as potential barriers for effective enrollment, though there has been controversial reports about this data [1, 2, 3, 4, 16, 17, 18, 19, 20]. No difference was found in relation to an uncompleted high school degree and native nationality between effective enrolled and enrollment failures: 55.10% (162/294) vs. 49.38% (46/81); 88.78% (261/294) vs. 88.88% (72/81); respectively. Foreign nationality accounted for only 11.20% in both groups, being from other Latin-American countries in all cases. Both native and foreign subjects spoke and understood the Spanish language well and all foreign volunteers had relatives or friends living in Argentina. Subjects with a different nationality and/or speaking a different language represented a small sample in this study,

therefore our analysis cannot be conclusive about this issue.

Since the occurrence of being an enrollment failure was not a rare event in our population, we believe the OR can be a good predictor for enrollment failures in bioequivalence trials; however we believe further prospective studies involving social and environmental variables, should be carried out in healthy subjects volunteering for bioequivalence studies to model strategies for an effective enrollment.

Conclusions

In bioequivalence trials, an unemployment condition, and an alcoholic family environment were identified as negative predictors for effective enrollment in new healthy volunteers.

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