Dropout reasons and associated factors with active dropout in Chinese healthy participants of bioequivalence studies

Hengyi Yu[1,2#], Yinian Fang[1,2#], Kaifu Wang[2], Qian Chen[1,2], Aihua Du[3], Xiuhua Ren[1,2*], Dong Liu[1,2*]

1. *Department of pharmacy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
2. *Phase I Clinical Trial Unit, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
3. *Department of Scientific Research Management, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*

Abstract: Maintaining participants in a trial ultimately without dropout helps keep a study on track, saving time, money, and resources. Since 2015, extensive bioequivalence (BE) studies have been carried out in China, while no research about dropout in healthy volunteers has been reported yet. In this retrospective study, 1078 healthy volunteers participating in 18 BE studies from March 2016 to February 2019 in one Chinese hospital were included. Information about the healthy participants and BE studies was recorded for analysis. In terms of the dropout reason, poor compliance, adverse event (AE), and loss of follow-up were found to be the three leading causes of dropout, accounting for 78.7% of all dropouts. In terms of associated factors with active dropout, smoking habit (OR = 5.790, $P < 0.001$) was significantly associated with increased risk of active dropout, while older age (OR = 0.940, $P = 0.042$) and AE except for SAE (OR = 0.321, $P = 0.004$) were significantly associated with a decreased risk of active dropout. Strengthening the education on younger participants and participants with a smoking habit, as well as emphasizing the possible adverse reactions and potential risks, might be strategies to reduce active dropout in healthy participants.

Keywords: Dropout; Healthy participant; Reason; Associated factor; Bioequivalence study

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1. Introduction

Owing to the generic consistency evaluation launched by China Food and Drug Administration in 2015[1], pharmaceutical companies are required to conduct new bioequivalence (BE) tests in healthy volunteers to improve the quality of Chinese generic drugs, and a significant rise in BE trial activities in China has started from then on[2].

It is well known that maintaining participants in a trial ultimately helps keep a study on track, saving time, money, and resources in the process, and the dropout of participants may be harmful to one study and the site as a whole[3]. However, to the best of our knowledge, studies about dropout in clinical trials or treatment have mainly focused on patients suffering from certain diseases, e.g. mental disorders[4–6], HIV[7], substance abuse[8,9], cancer[10,11], or patients receiving peritoneal dialysis[12,13], and there is no research about dropout in healthy volunteers. In the present work, we, for the first time, assessed the dropout in healthy participants of BE studies, and our findings might help deepen the understanding about dropout in healthy participants and yield strategies to reduce it.

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#Hengyi Yu and Yinian Fang contributed equally to this work.
*Corresponding author. Tel.: +86-27-69378207; +86-27-83663643
E-mail: 271052026@qq.com; ld2069@outlook.com

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2. Materials and methods

2.1. Data

Healthy volunteers participating in BE studies in Phase I Clinical Trial Unit of Tongji Hospital from March 2016 to February 2019 were included in this retrospective study. The protocol of every BE study has been approved by the Clinical Trial Ethnic Committee of Huazhong University of Science and Technology. Information on volunteers' informed consent and medical record was retrieved by two researchers (HY & YF) for analysis, including the demographic variables (gender, age, ethnicity, height, weight, body mass index, type of community, smoking habit, and drinking habit), information about BE studies (investigational product, financial reward, the administration under fasting or fed condition, period, duration, and administration route), adverse event (AE) and dropout.

2.2. Statistical analysis

The distribution of continuous data was tested with the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared by independent-sample *t*-test. Non-normally distributed ones were expressed as median (interquartile range, IQR) and compared through the Mann-Whitney U test. Categorical variables were reported as numbers and percentages (%), and the Chi-Square test or Fisher's exact test was used to detect differences between two groups. The unadjusted (univariable) and adjusted (multivariable) odd ratios (OR) both for variables above and dropouts were calculated using logistic regression models and presented as OR with their 95% confidence intervals (CI). All independent variables with P value < 0.1 for the association with the response variable at univariable analysis were tested in the multivariable model. For all tests, a P value < 0.05 was considered statistically significant. Analyses were performed by using IBM SPSS Statistics 23 (Armonk, NY IBM Corp).

3. Results

3.1. Dropout reasons in Chinese healthy participants of BE studies

Table 1 shows that 1078 healthy participants in 18 BE studies were included in this retrospective study. Among them, 61 participants (5.7%) did not finish their studies and dropped out. The dropout rate was between 0 to 14.7% in the 18 studies, and the average dropout rate was 5.4%.

According to the Declaration of Helsinki, volunteers have the right to refuse to participate in one study or to withdraw consent to participate at any time without reprisal. To explore why these participants chose to discontinue studies, we retrieved their medical records and summed up the dropout reasons.

As shown in Table 2, the primary reason for dropout in the 61 participants was poor compliance, endorsed by 36.1% of the whole dropouts, especially 'smoking during study' (n = 8, 13.1%), which may affect the process of drug metabolism and is often forbidden during BE studies. The second and third leading reasons for dropout were 'AE occurred' (n = 16, 26.2%) and 'loss of follow-up' (n = 10, 16.4%), respectively.

Among those participants, some withdrew studies for external or unavoidable reasons, such as AEs or family opposition, and we named this type of dropout as a passive dropout. However, the others withdrew studies due to personal or internal reasons, such as poor compliance or loss to follow-up, which were classified as an active dropout. Obviously, active dropout could be preventable and attracted more attention from researchers in BE studies.

Table 1. Information and dropout rates of the 18 BE studies.

Investigational medicine	Administration under fasting or fed condition	Administration route	Total participants	Participants dropped out	Dropout rate
Abiraterone	Fasting	Oral	36	1	2.8%
Adalimumab	Fasting	Intravenous	78	2	2.6%
Avanafil	Fasting and fed	Oral	109	16	14.7%
Dutasteride	Fasting and fed	Oral	98	4	4.1%
Entecavir	Fasting	Oral	30	1	3.3%
Imatinib[1]	Fasting and fed	Oral	56	1	1.8%
Imatinib[2]	Fasting and fed	Oral	48	3	6.3%
Indapamide (pilot trial)	Fasting and fed	Oral	16	0	0.0%
Isosorbide mononitrate	Fasting and fed	Oral	52	5	9.6%
Lenalidomide	Fasting and fed	Oral	57	5	8.8%
Minodronic acid	Fasting	Oral	69	2	2.9%
Mosapride	Fasting and fed	Oral	68	1	1.5%
Nifedipine	Fasting and fed	Oral	92	0	0
Olanzapine	Fasting and fed	Oral	64	1	1.6%
Pazopanib	Fasting	Oral	42	6	14.3%
Risperidone	Fasting and fed	Oral	63	7	11.1%
Rosuvastatin	Fasting and fed	Oral	80	5	6.3%
Tadalafil (pilot trial)	Fasting and fed	Oral	20	1	5.0%
Total			1078	61	5.7%
Average			60 ± 26	2 (1, 5)	5.4% ± 4.6%

1 and 2 are two imatinib generics made by two companies.

Table 2. Dropout reasons of the healthy participants in BE studies.

Total dropout (n = 61)	Dropout decided by researchers (n = 41)	Poor compliance (n = 22, 36.1%)	Leaving the ward without permission during the study (n = 1)	Active dropout
			Donating blood in the cleaning period (n = 1)	
			Active drug abuse test at the end of the cleaning period (n = 2)	
			Failing to complete a high-fat meal on time (n = 5)	
			Taking medication incorrectly (n = 2)	
			Smoking during the study (n = 8)	
			Taking other medication during the cleaning period (n = 3)	
		Experiencing adverse events (n = 16, 26.2%)	AE except for SAE (n = 14): Ongoing abnormal laboratory tests (n = 4)	Passive dropout
			AE except for SAE (n = 14): Fainting after acupuncture (n = 3)	
			AE except for SAE (n = 14): Abnormal heart rate or blood pressure (n = 4)	
			AE except for SAE (n = 14): Getting sickness (n = 3)	
			SAE (n = 2): Anaemia and hospitalization (n = 1)	Active dropout
			SAE (n = 2): Pregnancy during study (n = 1)	
		Others (n = 3, 4.9%)	Difficult to collect blood (n = 1)	Passive dropout
			Including participants by mistake (n = 1)	
			Dispensing incorrect medication by researchers (n = 1)	
	Dropout made by participants (n = 20)	Personal reason (n = 5, 8.2%)	Current study clashed with other work (n = 2)	Active dropout
			Screening only for free medical examination (n = 2)	
			Turning to another trial with higher payment (n = 1)	
		Family reason (n = 5, 8.2%)	Opposition from family (n = 4)	Passive dropout
			Family matters: taking care of family member (n = 1)	
		Loss of follow-up (n = 10, 16.4%)	Lost contact during the follow-up period (n = 10)	Active dropout

3.2. Associated factors with active dropout in Chinese healthy participants of BE studies

To explore the factors associated with increased risk of active dropout, a case-control study was then carried out between the participants in active dropout and non-active dropout groups. Out of the 1078 healthy participants, 38 (3.5%) dropped out owing to personal or internal reasons and belonged to the active dropout group. The other 1040 (96.5%) belonged to the non-active dropout group, which consisted of participants in the follow-up group (n = 1017) and passive dropout group (n = 23). Table 3 shows the distribution of variables about individuals, studies, AEs, and their association with active dropout.

As shown in Table 3, there were no significant differences in gender, height, weight, BMI value, ethnicity, type of community, drinking habit, the administration under fasting or fed condition, administration route, study period, study duration, financial reward, and SAEs occurring between the active dropout and non-active dropout groups. However, compared with the participants in the non-active dropout group, participants in the active dropout group showed younger age (P = 0.04), a higher prevalence of smoking habit (P = 0.005), and a lower prevalence of AE except for SAE (P = 0.006).

Then, the binary logistic regression was used to analyze the association between the independent variable and active dropout. Using the univariate regression, smoking habit (OR = 5.779, P < 0.001) and SAE (OR = 14.027, P = 0.033) were found to be associated with the increased risk of active dropout, while older age (OR = 0.934, P = 0.020) and AE except for SAE (OR = 0.373, P = 0.008) were associated with a decreased risk of active dropout. Then, all independent variables showing a P < 0.1 at univariable analysis were tested in the multivariable model. Using the multivariate regression, smoking habit (OR = 5.790, P < 0.001) was still found to be associated with an increased risk of active dropout, while older age (OR = 0.940, P = 0.042) and AE except for SAE (OR = 0.321, P = 0.004) were associated with a decreased risk of active dropout.

4. Discussion

Healthy volunteers play very important roles in drug development[14]. Unlike patients who suffer from disease and may gain possible therapeutic benefits and free medical treatment in clinical research, healthy volunteers are exposed to risk and discomfort without any expectation of health benefits[15,16]. Currently, research about healthy volunteers has mainly focused on their participating motivations[15,17–19], but no research about the dropout in healthy volunteers has been conducted.

Multiple factors can play a role in one's decision to drop out, and each participant has their circumstances and motivations[20]. It is necessary to sum up common reasons for dropout in a clinical trial, e.g. inconvenient location, schedule conflicts, personal/family matters, physically unable, financial constraints, lack of appreciation, forgetting visits, fear, and anxiety, a condition not improving, side effects, refusal to comply, misunderstood expectations[3]. In this work, poor compliance, AE, and loss of follow-up were the three leading causes of dropout in healthy participants, accounting for 78.7% of total dropouts. Besides, the smoking habit was found to be associated with an increased risk of active dropout, while older age and AE except for SAE were associated with a decreased risk of active dropout.

Table 3. Variables of the participants in active dropout and non-active groups, and associations between each variable and the risk of active dropout.

Variables	Total (n = 1078)	Active dropout group (n = 38)	Non-active dropout group (n = 1040)	Statistics	P value	Univariate analysis		Multivariate analysis	
						OR (95%)	P value	OR (95%)	P value
Gender				c^2 = 0.150	0.698				
Male	877 (81.4%)	30 (79.8%)	847 (81.4%)			1			
Female	201 (18.6%)	8 (21.1%)	193 (18.6%)			1.170 (0.528–2.593)	0.698		
Age (y)	27 (22, 31)	24 (22, 29)	27 (22, 31)	Z = 2.057	0.040*	0.934 (0.881–0.989)	0.020*	0.940 (0.885–0.998)	0.042*
Height (m)	1.69 (1.64, 1.73)	1.70 (1.64, 1.74)	1.69 (1.64, 1.73)	Z = –0.257	0.797	0.797 (0.007–85.966)	0.924		
Weight (kg)	61.7 (56.8, 67.6)	62.0 (57.2, 68.8)	61.7 (56.7, 67.6)	Z = –0.282	0.778	0.997 (0.957–1.038)	0.883		
BMI (kg/m^2)	21.8 (20.3, 23.6)	21.3 (19.9, 24.2)	21.8 (20.3, 23.6)	Z = –0.449	0.653	0.979 (0.840–1.141)	0.785		
Ethnicity				c^2 = 0.000	1.000				
Ethnic Han	1048 (97.2%)	37 (97.4%)	1011 (97.2%)			1			
Ethnic minorities	30 (2.8%)	1 (2.6%)	29 (2.8%)			0.942 (0.125–7.105)	0.954		
Type of community				c^2 = 0.154	0.965				
Rural	752 (69.8%)	28 (73.7%)	724 (69.6%)			1.215 (0.524–2.821)	0.650		
Small town	99 (9.2%)	3 (7.9%)	96 (9.2%)			0.982 (0.249–3.879)	0.979		
Urban	227 (21.1%)	7 (18.4%)	220 (21.2%)			1			
Smoking habit				c^2 = 20.064	< 0.001*				
No	1016 (94.2%)	29 (76.3%)	987 (94.9%)			1		1	
Yes	62 (5.8%)	9 (23.7%)	53 (5.1%)			5.779 (2.604–12.828)	< 0.001*	5.790 (2.554–13.127)	< 0.001*
Drinking habit					1.000				
No	1065 (98.8%)	38 (100%)	1027 (98.8%)			1			
Yes	13 (1.2%)	0 (0%)	13 (1.2%)			0.000	0.999		
Administration under fasting or fed condition				c^2 = 0.255	0.613				
Fasting	554 (51.4%)	18 (47.4%)	536 (51.5%)			1			
Fed	524 (48.6%)	20 (52.6%)	504 (48.5%)			1.182 (0.618–2.260)	0.614		
Administration route				c^2 = 0.635	0.426				
Oral	1000 (92.8%)	37 (97.4%)	963 (92.6%)			1			
Intravenous	78 (7.2%)	1 (2.6%)	77 (7.4%)			0.338 (0.046–2.497)	0.288		
Study period	2 (2, 2)	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	Z = –0.215	0.830	1.055 (0.643–1.731)	0.832		
Study duration (d)	18 (10, 23)	14.5 (10, 20.8)	18 (10, 32)	Z = –1.336	0.181	0.986 (0.966–1.006)	0.166		
Financial reward (¥)	6000 (6000, 8000)	6000 (6000, 7000)	6000 (6000, 8000)	Z = –0.344	0.731	1.000 (1.000–1.000)	0.442		
AE except SAE occurred				c^2 = 9.230	0.002*				
No	562 (52.1%)	29 (76.3%)	533 (51.2%)			1		1	
Yes	516 (47.9%)	9 (23.7%)	507 (48.8%)			0.326 (0.153–0.696)	0.004*	0.321 (0.149–0.692)	0.004*
SAE occurred					0.102				
No	1075 (99.7%)	37 (97.4%)	1038 (99.8%)			1			
Yes	3 (0.3%)	1 (2.6%)	2 (0.2%)			14.027 (1.244–158.180)	0.033*		NS

*P < 0.05, #P < 0.1, NS means no statistical significance.

Younger age has been reported to be linked to an increased probability of treatment dropout. Bukten et al. have found that dropout from opioid maintenance treatment within 18 months is associated with younger age[21]. Wang has found that the dropout rate in patients receiving mental health treatment is decreased with an increase in age[22]. Imanaka et al. have found that a high dropout rate of sublingual immunotherapy on Japanese cedar pollinosis patients is associated with younger generations[23]. In this work, older age (OR = 0.940, P = 0.042) was found to be associated with a decreased risk of active dropout, which was consistent with those in the literature. Accordingly, education on younger healthy participants at the time of informed consent and during studies should be strengthened, which might be useful to reduce active dropout.

AEs are a common reason for dropout in clinical trials and treatments. Jin et al. have found that AE accounts for 27.0% of dropouts in breast cancer drug clinical trials carried out in one Chinese hospital[10]. In this work, although AE was the second leading cause of dropout in healthy participants, AE except for SAE (OR = 0.321, P = 0.004) was found to be associated with a decreased risk of active dropout. This finding could be attributed to that AE except for SAE might raise participants' awareness of risk, which might help them keep in the trials and prevent active dropout. Emphasizing the possible AEs and potential risks to participants might be useful strategies to reduce active dropout.

Marcus et al. have found that smoking is significantly associated with the dropout in a lung cancer high-risk cohort[24]. In this work, smoking habit (OR = 5.790, P < 0.001) was found to be associated with an increased risk of active dropout in healthy participants, indicating that strengthening education on participants with smoking habit might be useful strategies to reduce active dropout.

Finally, there are some limitations in the present study. Firstly, the data were obtained from one center, and the study sample size was relatively small. Secondly, as a retrospective case-control study, some socio-demographic characteristics were not available in participant's informed consent or medical records, such as education, employment, marital status, children's situation, and psychological features, and the experimental design could be optimized in the future. Despite these limitations, we, for the first time, explored the dropout reasons and associated factors with active dropout in healthy participants, which might help us deepen the understanding of dropout in healthy participants and have the potential to yield strategies to reduce it.

Ethics approval and consent to participate

Protocols of the eighteen BE studies have been approved by the Clinical Trial Ethnic Committee of Huazhong University of Science and Technology. All subjects provided written informed consent.

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生物等效性试验中健康受试者的脱落原因及主动脱落相关因素分析

余恒毅[1,2#], 方一念[1,2#], 王开付[2], 陈倩[1,2], 杜艾桦[3], 任秀华[1,2*], 刘东[1,2*]

1. 华中科技大学 同济医学院附属同济医院 药学部, 湖北 武汉 430030
2. 华中科技大学 同济医学院附属同济医院 I期临床试验研究室, 湖北 武汉 430030
3. 华中科技大学 同济医学院附属同济医院 科研处, 湖北 武汉 430030

摘要: 避免参加临床试验的受试者脱落有助于临床试验的顺利开展, 同时节省时间、经费和其他资源。自2015年以来, 我国针对仿制药一致性评价工作开展了大量的生物等效性(BE)试验, 但尚无健康志愿者脱落相关的研究报道。本次回顾性研究中, 我们纳入了2016年3月至2019年2月间在我中心开展的18项BE试验的1078名健康志愿者, 通过记录每位受试者的人口学资料和临床试验信息, 对生物等效性试验中健康受试者的脱落原因及主动脱落相关因素进行分析。结果显示, 依从性差、发生不良事件和失访是受试者脱落的三大主要原因, 占全部脱落的78.7%; 吸烟习惯(OR = 5.790, $P < 0.001$)与受试者主动脱落的风险增加显著相关, 而年龄增长(OR = 0.940, $P = 0.042$)和非SAE的不良事件(OR = 0.321, $P = 0.004$)与受试者主动脱落的风险降低显著相关。加强对年轻受试者和有吸烟习惯受试者的教育, 并向受试者强调研究药物的潜在的不良反应和风险可能是减少健康受试者主动脱落的有效策略。

关键词: 脱落; 健康受试者; 原因; 相关因素; 生物等效性试验