# Medical and Clinical Pathology Pre-Screening Visit and Enrolment Seasonal Variability in Healthy Volunteers

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**Abstract:** In the pharmaceutical industry, selection of healthy volunteers is one of the foundations in phase I clinical trials and is a difficult and costly process. The objectives of this study were to evaluate the seasonal variability in recruiting healthy volunteers and examine the value of utilizing a pre-screen visit for healthy volunteers to generate a database pool that will be used in the routine screening process of phase I clinical research studies. We retrospectively studied a total of 1115 male and female volunteers who were scheduled for a medical and clinical pathology pre-screen visit over a one year period. Written consents were obtained from all individuals who participated in the study. Medical pre-screen visit included a full medical history and examination and electrocardiogram and clinical pathology (clinical chemistry, hematology and urinalysis). There was apparent seasonal variability in the participation of individuals in the pre-screen visit. Increased values of clinical chemistry values such as alanine aminotransferase and aspartate aminotransferase accounted for the majority of the clinically relevant increased values. Increased values of WBC's and both platelets and mean corpuscular volume accounted for the lowest values. In urinalysis, the most prevalent abnormal values were increased WBC's and red blood cells. No apparent differences were seen between sexes. Conducting medical and clinical pathology pre-screening visit is important as a source for healthy volunteer database pool to participate in phase I trials.

**Keywords:** Clinical pathology, healthy volunteers, phase I trials, pre-screen.

## INTRODUCTION

In the pharmaceutical industry, selection of healthy volunteers is one of the foundations in phase I clinical trials and is a difficult and costly process. The objectives of single and multiple ascending dose studies in phase I clinical trials in healthy volunteers are to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of novel therapies in healthy subjects. Recruitment of enough number of healthy volunteers to be part of the phase I clinical research trials is critical to ensure the smooth operation in running a phase I clinical research unit and is an essential component of the drug development process. Low recruitment and insufficient sample size of healthy volunteers can result in significant delays in initiating these important trials and subsequent delays in later phases of drug development and delivering novel new medicines to patients. The difficulty in recruiting participants to clinical trials poses an ongoing obstacle for researchers, as well as for patients who are looking forward to seeing medical advances in delivering innovative medicine to cure debilitating diseases [1].

Before starting phase I clinical trials, selection of healthy volunteers is critical. Data quality and reliability of study results will depend on the healthy volunteer selection. Although the selection process is primarily clinical, it also relies on laboratory data as some diseases may be asymptomatic. The aim of the selection process is not to choose normal subjects, but to exclude volunteers with diseases or risk factors which could result in increased danger for themselves or confound the interpretation of study results. The success in reaching target recruitment will largely depend on being able to directly contact individuals who are assumed to be healthy volunteers through different recruitment modalities and the willingness of these individuals to participate in phase I trial. The lower than anticipated response rate and underdeveloped research infrastructure in some of phase I research trials makes recruitment more difficult, time-consuming, and costly. Healthy volunteers are generally more convenient to study than most patient populations and are often used because of their ability to participate in studies of rigorous protocol design. It is also desirable to exclude all other concomitant drugs and treatments to eliminate any variables that could produce some change in the disposition of the drug or some clinical or adverse effect that might be misinterpreted as being caused by the treatment variable itself.

The topic of using volunteers in clinical trials has been understudied in the national and international arenas [2]. Watson & Wild found that medical screening (including electrocardiogram, clinical chemistry and hematology in addition to urinalysis screens) of

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ISSN: 1814-8085 / E-ISSN: 1927-5129/14 

volunteers led to 28.5% of applications being rejected for various reasons of which 14% were rejected based on clinical grounds [3]. In another study by Joubert & Pannall, thirty four (34) healthy volunteers, 1653 biochemical and hematological tests were performed. The incidence of abnormal results was 11% [4]. Only 4 subjects had all tests within normal limits and when these repeated only 1 subject still had all results within normal limits. Therefore, the authors recommend that a stable volunteer pool, with regular physical examinations and blood tests, would provide a large, serial data base for use in subject selection for clinical trials.

Utilizing a pre-screen visit to create volunteers data pool of healthy volunteers for future phase I studies could offer many advantages in the routine screening process of phase I clinical research studies. There have been no studies to evaluate the value of a pre-screen visit to the recruiting process in phase I clinical research studies and no literature data describing factors that impact the recruitment rate of healthy volunteers to phase I clinical trials or features of those individuals enrolled in such clinical trial are available. This is the first study, to the best of our knowledge, which was undertaken to: 1) closely investigate if there is a seasonal variability in healthy volunteers participation, 2) examine if there is value in medical pre-screening to increase the speed and efficiency of screen visits section, and 3) examine the various laboratory reasons for rejection based on pre-screen visits testing.

## MATERIALS AND METHODS

### Pre-Screen Visit Participation and Seasonality

In this retrospective study, a total of 1272 individuals were anticipated to have a pre-screen visit and a total of 1115 male and female volunteers were scheduled for a pre-screen visit over a one year period (Table **1**). Written consents were obtained from all individuals who participated in the study. These 1272 individuals were to undergo a pre-screen screen visit and those who passed the screen were to be included in a database pool for potential healthy volunteers that are to participate in future phase I studies. The recruitment process for these individuals included: local newspaper and radio and television advertisements. A general phone questioner included male and female individuals that are between the ages of 18 to 55 years who are willing to participate in future clinical phase I study. The term healthy volunteer is a subject who is free from disease or risk factors likely to increase the risk for himself/herself or interfere with interpretation of the phase I study results. For each month starting from January until December, the percentage of individuals that were anticipated (individuals who showed interest, came for an orientation about the Clinical Research Unit (CRU), and have an appointment for physical examination), scheduled, attended, did not show up, cancelled, and rescheduled and the seasonal variability in pre-screen visit participation were investigated (Table **1**).

**Table 1: Pre-Screen Visit Individual Participation and Seasonal Variability**

| Month | Anticipated No. (% of total) | Scheduled No. (% of total) | Attended No. (% of sched) | No show No. (% of sched) | Cancelled No. (% of sched) | Rescheduled No. (% of sched) |
|---|---|---|---|---|---|---|
| Jan | 135 (11%) | 112 (10%) | 67 (60%) | 33 (29%) | 4 (4%) | 8 (7%) |
| Feb | 82 (6%) | 84 (8%) | 54 (64%) | 15 (18%) | 4 (5%) | 11 (13%) |
| March | 136 (11%) | 163 (15%) | 90 (55%) | 36 (22%) | 23 (14%) | 14 (9%) |
| April | 107 (8%) | 103 (9%) | 58 (56%) | 28 (27%) | 7 (7%) | 10 (10%) |
| May | 115 (9%) | 121 (11%) | 86 (71%) | 14 (12%) | 16 (13%) | 5 (4%) |
| June | 122 (10%) | 77 (7%) | 46 (60%) | 22 (29%) | 4 (5%) | 5 (6%) |
| July | 100 (8%) | 78 (7%) | 36 (46%) | 32 (41%) | 6 (8%) | 4 (5%) |
| Aug | 118 (9%) | 61 (5%) | 37 (61%) | 10 (16%) | 11 (18%) | 3 (5%) |
| Sep | 90 (7%) | 73 (6%) | 49 (67%) | 14 (19%) | 6 (8%) | 4 (6%) |
| Oct | 90 (7%) | 106 (10%) | 61 (57%) | 36 (34%) | 4 (4%) | 5 (5%) |
| Nov | 117 (9%) | 92 (8%) | 49 (53%) | 30 (33%) | 5 (5%) | 8 (9%) |
| Dec | 60 (5%) | 45 (4%) | 22 (49%) | 19 (42%) | 3 (7%) | 1 (2%) |
| Total | 1272 (100%) | 1115 (100%) | 655 (59%) | 289 (26%) | 93 (8%) | 78 (7%) |

To be considered "healthy", volunteers participating in the pre-screen visits had to comply with the following inclusion/exclusion criteria:

1) males and females ages between 18 and 55 years, 2) body mass index between 18 to 30, 3) no heavy smokers (non-smoker or fewer than five cigarettes per day), 4) no heavy alcohol drinkers (non-drinker or less than 14 drinks per week for male and less than 7 drinks per week for females), 5) no high calorie, high sugar or other special diet (e.g., vegetarian), 6) no concomitant or previous disease likely to interfere with the Study, 7) no abnormality at physical examination, 8) not on regular medication, 9) no previous history of significant drug/food or anaphylactic allergic reaction, and 10) no consumption of recreational drugs.

**Pre-Screening Criteria**

Individuals that are found to meet the above pre-screen general questioner criteria were scheduled for a pre-screen visit in the clinical research unit. The pre-screening process is usually conducted by a physician and a practicing nurse. All participants are required to undergo a thorough medical prescreening process to be included in a pool of potential future healthy volunteers' database. The pre-screening visit consisted of the following stages: 1) medical history and examination, 2) cardiac investigation with a computerized 12 lead ECG, 3) laboratory investigation that includes clinical biochemistry, liver function test, and thyroid function test, 4) clinical hematology including complete blood count (CBC) with differentials, and 5) urinalysis. Laboratory hematology values were classified as within historical reference range for normal healthy adults, critical (at least 2 to 3-fold higher than historical reference range), high (outside historical reference range) low (below historical reference range). Abnormal urinalysis values (outside historical reference range) is also included. The values that were not within the normal historical reference range, resulted in exclusion of participants, and were clinically relevant were closely examined (Tables **2** and **3**).

**RESULTS**

There was apparent seasonal variability in the participation of individuals in the pre-screen visit (Table **1**). The highest percentage of anticipated individuals who attended occurred in May followed by September (71% and 67%, respectively), while the lowest percentage occurred in July followed by December (46% and 49%, respectively). The percentage range of attendance for other months of the year ranged from 53% to 64%. In some months (February, March, May, and October), the percentage of scheduled individuals were higher than those anticipated because some individuals from previous months schedules reschedule for the following month. A large percentage (41 and 42%) of participants did not show up in the month of July and December. Most cancellations (18%) occurred in August, while lower percentage (4% to 14%) of cancellations occurred in other months of the year (Table **1**).

In our sample of 1115 volunteers who were scheduled for a medical pre-screen visit to qualify for a healthy volunteers database for future phase I trials, a total of six hundred and fifty five (59%) volunteered attended the visit over a one year period, two hundred and ninety two (26%) did not show for their visit, one hundred and nineteen (8%) cancelled and seventy eight (7%) rescheduled (Table **1**).

Volunteers' selection is mainly a clinical process but a laboratory screening is essential because some diseases are asymptomatic. In our study, a random sample of 587 of volunteers with 471 males (80%) and 116 (20%) females were chosen for a medical pre-screen visit which included a full medical history and examination, electrocardiogram, clinical chemistry, hematology and urinalysis. Only a total of 44 (9%) and 23 (20%) hematology values in males and females respectively were within the reference range and 427 (91%), 93 (80%) males and females, respectively, had values that were outside reference range (Table **2**). Based on the pre-screen criteria, a higher percentage (%) of participants had high values of hematology parameters. A total of 345 (73%) and 71 (61%) urinalysis values in males and females respectively were within reference range and 126 (27%), 45 (39%) males and females respectively were outside the reference range (Table **2**). The most prevalent abnormal values were increased white blood cells (WBC's) and red blood cells (RBC's). No apparent differences were seen between sexes (Table **3**).

High values of certain clinical chemistry values such as alanine aminotransferase (ALT) (26%) and aspartate aminotransferase (AST) (26%) accounted for the majority of the clinically relevant high values in males. High values of WBC's (46%) in females and both platelets (PLT) (47%) and mean corpuscular volume (MCV) (33%) accounted for the lowest values among the males and females, respectively (Table **3**).

**Table 2: Hematology and Urinalysis Values of Pre-Screen Visit Participants**

| Total participants = 587 | | Male participants = 471 (80%) | Female participants = 116 (20%) |
|---|---|---|---|
| Hematology Values | | | |
| Within reference range | | 44 (9%) | 23 (20%) |
| Outside reference rage | | 427 (91%) | 93 (80%) |
| | High | 269 (63%) | 52 (56%) |
| | Low | 158 (37%) | 41 (44%) |
| Urinalysis values | | | |
| Within reference range | | 345 (73%) | 71 (61%) |
| Outside reference range | | 126 (27%) | 45 (39%) |

**Table 3: Clinically Relevant Values of Male and Female Participants at Pre-Screen Visit**

| Total participants = 587 | | Male participants = 471 (80%) | | Female participants =116 (20%) | |
|---|---|---|---|---|---|
| Outside reference rage = 520 (100%) | | Males = 427 (91%) | | Females = 93 (80%) | |
| Total participants with clinically relevant values =166 (32%) | | Males with clinically relevant values =130 (30%) | | Females with clinically relevant values =36 (39%) | |
| Total participants with clinically relevant blood values | | Males = 95 | | Females = 17 | |
| High | Lab value | Lab value range | n (%) | Lab value range | n (%) |
| | | | 78 (82%) | | 11 (65%) |
| | ALT (U/L) | 269-90 | 20 (26%) | 132-100 | 2 (18%) |
| | AST (U/L) | 335-103 | 20 (26%) | 112-79 | 3 (27%) |
| | WBC (10e3/uL) | 15.2-11 | 13 (17%) | 12.6-11 | 5 (46%) |
| | TSH (mIU/L) | 21.8-8.26 | 6 (8%) | ≥6.5 | 0% |
| | Creatinine (mg/dL) | 1.5-1.3 | 6 (8%) | ≥1.3 | 1 (9%) |
| | HGB (g/dL) | 18.5-18.1 | 4 (5%) | ≥18.1 | 0% |
| | T. Bill (mg/dL) | 4.6-2.1 | 3 (4%) | ≥2.1 | 0% |
| | Glucose (mg/dL) | 300-38 | 2 (2%) | 300-38 | 0% |
| | BUN (mg/dL) | ≥30 | 1 (1%) | ≥30 | 0% |
| | MCV (fL) | ≥101 | 1 (1%) | ≥101 | 0% |
| | K (mmol/L) | ≥5.5 | 1 (1%) | ≥5.5 | 0% |
| | Na (mmol/L) | ≥149 | 1 (1%) | ≥149 | 0% |
| Low | Lab value | Lab value range | n (%) | Lab value range | n (%) |
| | | | 17 (18%) | | 6 (35%) |
| | PLT (10e3/uL) | 148-114 | 8 (47%) | ≤150 | 1 (17%) |
| | MCV (fL) | 69.7-58.8 | 5 (29%) | 65.5-65.2 | 2 (33%) |
| | TSH (mIU/L) | 0.16-0.2 | 4 (24%) | ≤0.3 | 0 |
| | HGB (g/dL) | ≤10 | 0 | 10.5-10.1 | 2 (33%) |
| | WBC (10e3/uL) | ≤2.5 | 0 | ≤2.5 | 1 (17%) |

**(Table 3). Continued.**

| **Total participants = 587** | **Male participants = 471 (80%)** | | **Female participants =116 (20%)** | |
|---|---|---|---|---|
| Total participants with clinically relevant urinalysis (UA) vales | Males = 35 (100%) | | Females = 19 (100%) | |
| Lab value | Lab value range | n (%) | Lab value range | n (%) |
| UA WBC (/HPF) | >50-15 | 18 (51%) | 29-15 | 11 (58%) |
| UA RBC (/HPF) | 29-15 | 11 (32%) | ≥50-15 | 8 (42%) |
| UA Protein (mg/dL) | 30-10 | 5 (14%) | + | 0 |
| UA Glucose (mg/dL) | ≥1000 | 1 (3%) | + | 0 |

## DISCUSSION

The availability of a volunteer pool data based on pre-screen visit, with regular physical examination and blood tests provides a large, serial database for future use in subject selection in future clinical trials. It also minimizes cancellation, rescheduling, seasonal variation in enrollment rates seen during the initial recruiting process, and maximizing the overall enrolment of healthy volunteers in upcoming phase I research trials. There was apparent seasonal variability in the participation of individuals in the pre-screen visit. While there is no clear reasoning behind the monthly variation, maximizing the efforts for recruiting during those months of higher yield would overall generate better recruiting rate.

Pre-screen visit is designed to identify clinical conditions and clinically relevant lab tests that could disqualify a volunteer from participating or subject him or her to unnecessary risk. It is considered a buffer zone that allows time to gather more clinical information about each volunteer to maximize the recruiting effort for upcoming studies. According to Singh and Williams in a sample of 1293 subjects who volunteered to participate in medical research studies, the prevalence of medical conditions was 10.9% [5]. The most common undiagnosed medical conditions were cardiovascular disease, liver diseases, anemia, hyperlipidaemia, excess alcohol consumption, and thyroid dysfunction. These conditions accounted for approximately 80% of the abnormalities detected. Therefore, performing a pre-screen visit would identify these major medical conditions to exclude volunteers early and save time and speed the efficiency of performing phase I clinical trials.

Normal ranges for laboratory tests customarily represent 95% confidence limits for a supposedly normal population. This immediately suggests that 5% of tests, i.e., 1 in 20 in normal individuals will be abnormal in that they are outside this range. Volunteer populations may differ markedly from populations used for establishing normal ranges with regards to factors such as age, ethnic composition, physical activity, diet and occupation which all has been reviewed as part of the prescreen visit during the initial history and physical exam. In our random sample of 587 volunteers, only 9% and 23% hematology values in males and females, respectively, were within reference range. Based on the pre-screen criteria, a higher percentage of participants had high values of blood parameters with ALT and AST which accounted for the majority of the clinically relevant high values in males and WBC in females and both platelets and MCV accounted for the lowest values among the males and females, respectively. Therefore, both hepatic and hematologic conditions were among the main causes to exclude participants from future research studies in phase I units.

These results indicate that pre-screening for healthy volunteers before they participate in a screening process for a specific phase I trial is essential, both from health and safety prospective to ensure that the subject population studied is indeed composed of 'healthy volunteers' with no evidence of undiagnosed medical conditions that could put them at a higher risk. In conclusion, this study demonstrated the importance of performing medical and clinical pathology pre-screening visit to create a healthy volunteers database pool before volunteers are allowed to participate in phase I clinical trials.

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Received on 16-06-2014 Accepted on 01-09-2014 Published on 08-09-2014

http://dx.doi.org/10.6000/1927-5129.2014.10.55