Brief report

Introduction

Recruiting participants for research studies is a daunting, time consuming and laborious task. Phase 1 studies where the primary objective is safety and assessing the maximum tolerated dose without side effects are even more demanding than other studies in terms of recruitment as this involves participants accepting a certain amount of risk for no foreseeable benefit. While there is no standard accepted definition of a non patient volunteer, [1] a reasonable definition is "one who cannot be expected to derive therapeutic benefits from the proposed study, is not known to suffer from any significant illness relevant to the present study and whose mental state is such that he is able to understand and freely give valid consent for the study. [2] The definition of a "volunteer" is thus one who is fully informed about the compound, its benefits and risks, procedures to be undergone and the knowledge that he can withdraw from the study at any time without having to give reasons for doing so.

Whether an individual is "normal" and "healthy" is usually defined in Phase 1 studies both on history and laboratory parameters. The term "healthy" often remains imprecise particularly in the distinction between "statistically normal" and "healthy" since normal ranges usually represent 95% confidence limits within a specific population. The idea of laboratory screening is not so much to identify "statistically normal" subjects but rather to exclude those with subclinical illness who might be at increased risk of adverse events in the study and whose participation will adversely affect the interpretation of study results. [3, 4] Over a period of time, the number of laboratory tests has also considerably expanded and it is known that chance of finding abnormalities rises with the increase in number of tests. [5]

We present in this paper our experiences both on recruiting normal healthy participants for a Phase 1 study involving a humanized rabies monoclonal antibody as well as challenges in defining normality which affect recruitment and thus accrual. We also briefly attempt to address the issue of the nature of participants, their education level and why some may have declined consent.

Methods

The present study was an open label, dose escalation study conducted finally in 74 normal healthy volunteers, as against the planned sample size of 84. The study is registered with the clinical trials registry of India (CTRI/2009/091/000465) and is nearing completion at the time of writing this paper. These participants were recruited by word of mouth from within the institution as well as neighboring research institutions and colleges after approval from the Institutional Review Board and the Drugs Controller General of India. The inclusion criteria for the study were those of either gender, aged 18-50 years, non smokers for at least 6 months, willing to consent and comply with protocol requirements and willing to use contraception for at least a year post study. Exclusion criteria included any acute febrile illness in the past 15 days, major congenital defects, breastfeeding women, history of allergies, any chronic illness and thrombocytopenia or bleeding disorders. Laboratory inclusion criteria for the study are given in Table 1.

Results

Over an 8 month period, a total of 165 potential participants were counseled and given basic information regarding the study in groups of two or three. A total of 3 were excluded due to a history of dog bite, while 6 declined upfront citing limited compensation. Thus, 156 [146 males, 10 females] were screened after written informed consent, which was administered to each individual separately. The age ranged from 18-40 years. Of these, 74/156 (47.43%) were eventually randomized. Of these, only 5 were women. Of the 82/156 (52.5%) that could not be randomized, the reasons could be broadly classified into 3 categories i) deranged laboratory parameters (n = 61) ii) non laboratory causes (n = 5) and iii) withdrawal of consent (n = 16). The details of deranged laboratory parameters are given in Table 2. The non laboratory causes included asymptomatic goiter, essential hypertension, hepatosplenomegaly, an acute febrile illness, and refusal to use contraception. When an informal interview was held for the 16 participants as to the reasons why they withdrew consent, it ranged from "I only wanted to get myself thoroughly investigated" to "check my HIV status" to "limited incentive". In view of the large number of exclusions, mid way during the study, the protocol was amended to lower the hemoglobin cut off to 13g/dl and the necessary approvals taken.

We also analyzed the data for educational status and employment and found that all 156 participants were literate (defined as having completed at least the 8th grade of primary schooling). The vast majority 76 (48.7%) were students while the remaining were carpenters, plumbers, school teachers, security guards or holding similar jobs. A total of 101(64.7%) signed the consent form in Marathi, the local language, 16 (10.2%) signed it in Hindi, the national language and 39 (25%) signed it in English.

Discussion

The choice of the participant population in a Phase I trial depends partly on a trial's scientific objectives. In many cases, healthy people provide the "cleanest" data, for it can be difficult to separate the effects of a study intervention from those caused by a patient's disease or medications. The present study which analyzed screening data on 156 apparently normal participants screened for a Phase 1 study has shown that less than 50% of them eventually got randomized. While the main reason has been abnormal laboratory parameters one interesting finding has been that 10.2% of participants declined consent after initially agreeing to participate.

A study by Joubart and Pannall in 34 healthy volunteers with 1653 biochemical and hematological tests showed an incidence of 11% abnormal tests. Only 4 subjects had all tests within normal limits and when these were repeated only 1 subject still had all results within normal limits. The authors recommended a volunteer bank or pool with regular physical examinations and also commended on development of realistic protocols and minimization of human error in the testing. [6]

Sibille and Durand [3] in their paper on laboratory screening for normal volunteers have listed approaches by several authors to define "normality" to minimize participant loss. These include 1) accepting a 10% extension of the defined upper and normal ranges 2) rejection of the upper and lower 1% of the distribution of test results and the 3) use of confidence limits mathematically adjusted for the number of variables. [7, 8, 9] They also postulated their own method for minimizing participant losses based on Bayesian probability theory and emphasized the need for not fixing laboratory normal ranges once and for all, but redefining them as a function of the population being investigated and the objectives a particular study.

The large number of subjects in our study with low hemoglobin and males in particular is suggestive of nutritional deficiency in them which in turn is likely to be reflective of their socio-economic status. In India, a steady decline in the prevalence of severe nutritional deficiencies has been noted, but the pace has been slow and well short of the National and Millennium development goals. [10] In the present study, normal ranges were not defined by the in house laboratory of the department but by the Contract Research Organization that carried out the tests. It is possible that the population used by them to define normality was different from the one that participated in the present study and the hemoglobin amendment made midway during the study is also reflective of this.

There is limited data on what motivates NHVs to participate in phase 1 trials. In the United States and elsewhere, financial reward appears to be a significant motivating factor for research participation in particular by subjects with low education status and low monthly income. [8] While this is being investigated as part of another study, money may have been an important factor in this study, given the number of subjects that either declined to participate upfront or declined consent post screening. The question of whether individuals who volunteer for research are normal and healthy has been a subject of long-standing methodological and philosophical debate. Literature on issues of personality traits, motivations for volunteering, interaction between these factors and repeated volunteering rendering then "not normal" is abundant. [11]

The present study is limited by the fact the findings are from a single centre, and information of this nature already exists in literature from the developed world. However, given the fact that by the end of 2010 India will host nearly a fifth of all global clinical trials, [12] it is important that investigators in this country appreciate methodological challenges in the conduct of such studies. This will help them plan protocols better, define normal ranges with acceptable variations based on their own populations *a priori* and have more pragmatic accrual targets.

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Conflict of interest

None

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Table 1 – Laboratory inclusion criteria for the study

Parameter (units)	Normal range (Male)	Normal range (Female)
WBC(/mm3)	4500-11000	4500-11000
Platelets(/mm3)	150000-400000	150000-400000
Hemoglobin (g/dl)	13.5-18	12-16
Creatinine mg/dl	0.7-1.2	0.5-0.9
BUN mg/dl	6-20	6-20
AST IU/L	0-40	0-32
ALT IU/L	0-41	0-33
Alkaline phosphatase IU/L	40-129	35-104
Bilirubin mg/dl	0-0.99	0-0.99
Random glucose mg/dl	45-130	45-130
Eosinophils (percent)	1-6	1-6
Urine RBC (hpf)	0-2	0-2

Table 2- Analysis of deranged laboratory parameters (N = 61)*

Parameter	**Number of participants**
Low hemoglobin	27 (23 males)
Raised AST	6
Raised ALT	9
Raised serum creatinine and/or Blood urea nitrogen	4
Raised Alkaline phosphatase	6
Raised total bilirubin	7
Hematuria	6
Raised random blood sugar	2
Low platelet count	2
Low white cell count	6
Raised eosinophils	1
Australia antigen positivity	2

*A participant may have had more than one deranged parameter