Short Report

Frequency and causes for exclusion from randomization of healthy volunteers screened for a phase 1 study in India

N.J. GOGTAY, U.M. THATTE, P.S. KULKARNI

ABSTRACT

Background. Only a proportion of screened potential participants were actually randomized while conducting a phase 1 study of a humanized rabies monoclonal antibody. We aimed to assess the challenges in defining who is a normal volunteer and the issues that affect volunteer recruitment and thus accrual.

Methods. One hundred and fifty-six volunteers were screened and 74 (47.4%) were randomized in a phase 1 study. Data on all participants screened for the study were analysed and reasons for their non-randomization were classified.

Results. The reasons for volunteers not being randomized were: (i) deranged laboratory parameters ($n=62$); (ii) non-laboratory causes ($n=4$); and (iii) withdrawal of consent ($n=16$). A large proportion of screen failures were due to low haemoglobin levels, which led to the protocol being amended midway during the study. An informal interview of those who declined consent showed that they had only wanted to get themselves investigated thoroughly or were interested in getting their HIV status evaluated.

Conclusions. Our study shows that < 50% participants screened for a phase 1 study in a developing country actually get randomized. The main reason for non-randomization is abnormal laboratory tests. This may help investigators and sponsors to 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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INTRODUCTION

Recruiting participants for research studies is a daunting, time-consuming and laborious task. The primary objective of phase 1 studies is to assess safety and the quantity of maximum tolerated dose without causing side-effects. These studies are more demanding than other studies in terms of recruitment as this involves participants to accept 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 on the basis of 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 expanded considerably and it is known that the chance of finding abnormalities rises with the increase in number of tests.[5]

We present our experience of 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 address the issue of the nature of participants, their education level and why some may have declined consent.

METHODS

This was an open-label, dose-escalation study conducted 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 has been completed. These participants were recruited by word of mouth from within the institution as well as neighbouring 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 after randomization. Exclusion criteria included any acute febrile illness in the past 15 days, a history of dog bite, 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 I.

RESULTS

Over an 8-month period, a total of 165 potential participants were counselled and given basic information regarding the study in groups of two or three. Three were excluded due to a history of dog bite, while 6 declined upfront citing limited compensation. Thus, 156 (146 men, 10 women) were screened after written informed consent, which was administered to each individual separately. Their ages ranged from 18 to 40 years. Of these, 74 (47.4%) were eventually randomized of whom only 5 were women. Of the 82 (52.5%) who could not be randomized, the reasons were: (i) deranged laboratory parameters (n=61; Table II); (ii) non-laboratory

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causes (*n*=5); and (iii) withdrawal of consent (*n*=16). The non-laboratory causes included asymptomatic goitre, essential hypertension, hepatosplenomegaly, an acute febrile illness, and refusal to use contraception. When an informal interview was held for the 16 participants to elicit 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, midway during the study, the protocol was amended to lower the haemoglobin cut-off level to 13 g/dl and the necessary approvals were taken.

We also analysed the data for educational status and employment and found that all 156 participants were literate (defined as having completed at least grade 8 of primary schooling). Seventy-six participants (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 1 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 analysed screening data on 156 apparently normal participants for a phase 1 study has shown that <50% of them were eventually randomized. While the main reason was abnormal laboratory parameters, an interesting finding was that 10.2% of participants declined consent after initially agreeing to participate.

Joubert and Pannall studied 34 healthy volunteers with 1653 biochemical and haematological tests and 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 testing.[6]

Sibille and Vital Durand[3] in their paper on laboratory screening for normal volunteers listed approaches by several authors to define 'normality' to minimize loss of participants. These include: (i) accepting a 10% extension of the defined upper and normal ranges; (ii) rejection of the upper and lower 1% of the distribution of test results; and (iii) use of confidence limits mathematically adjusted for the number of variables.[7–9] They also postulated their own method for minimizing loss of participants based on the 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 of a particular study.

The large number of men in our study with low haemoglobin levels in particular is suggestive of nutritional deficiency, which in turn is likely to be reflective of their socioeconomic 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 amendment of haemoglobin cut-off values done midway during the study is also reflective of this discrepancy.

There are limited data on what motivates normal people to participate in phase 1 trials. In the USA and elsewhere, the financial reward appears to be an important motivating factor for participation in research particularly 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 who 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. There is abundant literature on issues of personality traits, motivations for volunteering, interaction between these factors and repeated volunteering rendering then 'not normal'.[11]

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

TABLE I. Laboratory inclusion criteria for the study

Parameter (units)	Normal range (male)	Normal range (female)
White blood cells (cmm)	4500–11 000	4500–11 000
Platelets (cmm)	150 000–400 000	150 000–400 000
Haemoglobin (g/dl)	13.5–18	12–16
Creatinine (mg/dl)	0.7–1.2	0.5–0.9
Blood urea nitrogen (mg/dl)	6–20	6–20
Aspartate aminotransferase (IU/L)	0–40	0–32
Alanine aminotransferase (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 (%)	1–6	1–6
Urine RBC (high power field)	0–2	0–2

RBC Red blood cells

TABLE II. Analysis of deranged laboratory parameters (*n*=61)*

Parameter	Number of participants
Low haemoglobin level	27 (23 men)
Raised aspartate aminotransferase (IU/L)	6
Raised alanine aminotransferase (IU/L)	9
Raised serum creatinine and/or blood urea nitrogen	4
Raised alkaline phosphatase	6
Raised total bilirubin	7
Haematuria	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

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Conflict of interest: None

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