# Incidental Diagnosis in Healthy Clinical Trial Subjects

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**Abstract**

Previously unrecognized medical conditions identified in volunteers for early phase clinical studies have significant clinical and ethical implications for the participant. It is therefore crucial that the potential for unexpected diagnosis is addressed during the informed consent process. But the frequency of incidental diagnosis in healthy volunteers who attend for clinical trial screening remains unclear. To assess this we retrospectively analyzed 1,131 independent screening visits for 990 volunteers at a single academic center over a 10-year period to describe the frequency and nature of new clinical findings. Overall 23 of 990 volunteers (2.3%) were excluded at screening for a newly diagnosed medical abnormality. Some clinically important conditions, such as nephrotic syndrome and familial hypercholesterolemia were identified. The frequency of abnormalities was associated with increasing age in males ($p = 0.02$ $\chi^2$ for trend) but not females ($p = 0.82$). These data will assist those planning and conducting phase I/II vaccine trials in healthy volunteers, and importantly should strengthen the informed consent of future trial participants. Clin Trans Sci 2012; Volume 5: 348–350

**Keywords:** screening, incidental diagnosis, healthy volunteers, phase I clinical trials, early phase clinical investigation, prevalence, abnormalities, abnormal findings, ethics

## Introduction

Healthy individuals participate in clinical trials[1] and before trial enrolment they undergo rigorous screening procedures for medical abnormalities that may render them ineligible.[1,2] Screening can identify previously unrecognized medical conditions with clear ethical implications.[3] Conversely, obtaining information about personal health status can actually be a motivation for volunteer participation in such studies.[1]

Therefore estimates of the probability of incidental findings in healthy subjects are highly relevant to the informed consent of potential participants.[1–3] In addition, although these apparently healthy volunteers may not be entirely representative of the general population, data on incidental findings identified at screening provide a useful snapshot of morbidity in healthy individuals in the community setting who may infrequently access health services.

Despite the importance of incidental diagnosis at clinical trial screening, the frequency and nature of these findings have been largely unexplored in healthy subjects, and few data are available to guide those conducting healthy volunteer clinical trials. Here we describe the frequency and characteristics of incidental medical diagnoses in a large cohort of healthy clinical trial volunteers.

## Methods

### Participants and study design

Case report files (CRFs) of all healthy volunteers aged between 18 and 65 who were screened for participation in phase I/IIa candidate vaccine trials at the Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford, between July 1999 and June 2010 were reviewed.

Details of screening procedures undertaken have been described in detail,[4] and remained consistent throughout the study period. In brief, all participants underwent comprehensive clinical evaluation by a study investigator. Hematological, biochemical, and blood-borne virus testing was performed by the local diagnostic laboratory according to validated protocols. Family practitioners were contacted (with participant consent) to corroborate medical history and previous testing. The lead investigator in each trial was responsible for determining the clinical significance of any laboratory abnormalities with reference to the relevant clinical trial protocol and standardized laboratory reference ranges, which remained consistent throughout the study period. The lead investigator identified clinical diagnoses in consultation with the principal trial investigator ± the local safety monitor. All volunteers excluded on medical grounds were referred to their family practitioner or an appropriate specialist.

Demographic and clinical data were extracted from CRFs and entered into an electronic database (Microsoft Excel, Microsoft, Redmond, WA, USA), and 10% of entries were crosschecked with source documents to ensure accurate transcription. We excluded from the analysis volunteers with out of range laboratory findings for which the clinical significance could not be determined, and volunteers with preexisting medical diagnoses that had been established before screening procedures were undertaken (i.e., reported by the volunteer or identified in a report from the family practitioner).

### Ethics

All trials were conducted according to the principles of Good Medical Practice and the Declaration of Helsinki. The Oxfordshire Research Ethics Committee (OxREC) and/or the UK Department of Health Gene Therapy Advisory Committee (GTAC) provided ethical committee approval for all studies. All participants provided written informed consent before any study procedure being carried out.

### Statistical analysis

Due to the broad range and low frequency of individual abnormalities, descriptive methods were used to analyze clinical data on newly identified medical abnormalities, and statistical

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| | Male | Female | Total (% of all screened) |
|---|---|---|---|
| All volunteers screened | 504 | 483 | 987 (99.7) |
| New diagnoses | 14 | 9 | 23 (2.4) |
| Median age at new diagnosis (IQR)* | 32.2 (22.1–32.2) | 25.4 (20.7–34.4) | 30.0 (21.2–37.5) |
| Age group† | | | |
| 18–29 | 5/341 | 6/338 | – |
| 30–40 | 6/111 | 2/100 | – |
| 41–65 | 3/52 | 1/45 | – |
| Alcohol excess with abnormal LFTs | 2 | 0 | 2 (0.2) |
| Nephrotic syndrome | 1 | 0 | 1 (0.1) |
| Hypercholesterolemia | 2 | 0 | 2 (0.2) |
| Hemoglobinopathy | 0 | 4 | 4 (0.4) |
| Iron deficiency anemia‡ | 0 | 2 | 2 (0.2) |
| Chronic hepatitis B | 1 | 0 | 1 (0.1) |
| Chronic hepatitis C | 2 | 0 | 2 (0.2) |
| Hypertension | 4 | 1 | 5 (0.5) |
| Cardiac murmur requiring investigation | 1 | 1 | 2 (0.2) |
| Supraclavicular mass | 0 | 1 | 1 (0.1) |
| Allergic skin rash with eosinophilia | 1 | 0 | 1 (0.1) |
| Tungiasis | 1 | 0 | 1 (0.1) |

More than one abnormality may coexist in a single participant. LFTs = liver function tests.
*IQR = interquartile range, Mann-Whitney $p = 0.27$.
†Chi-square for trend with age $p = 0.02$ males, $p = 0.82$ females.
‡Considered clinically significant in males or postmenopausal females, or in any volunteer if Hb < 10 g/dL.

**Table 1.** Frequency of new medical problems in healthy male and female volunteers.

analysis was restricted to investigating associations between abnormalities as a whole and demographic factors (age and gender) and screening period, using the chi-square and chi-square test for trend for categorical variables, and the Mann-Whitney test for continuous variables. Statistical analysis was performed using GraphPad Prism (GraphPad Software, Version 5.0, San Diego, CA, USA), and a two-tailed alpha value of <0.05 was considered significant.

## Results and Discussion

We analyzed 1,131 screening attendances for 990 healthy volunteers aged 18–65 (504 males, 483 females, 3 gender not specified), identifying previously unrecognized findings in 23 (2.3%) individuals (14 males, 9 females, $p = 0.12$, $\chi^2$). These are described in *Table 1*. We excluded from the analysis 25 of 990 (2.5%) individuals with out of range laboratory abnormalities for which clinical significance could not be determined from the database or from CRFs, and excluded 13 of 990 (1.3%) volunteers with previously diagnosed medical conditions.

We identified several clinically important diagnoses, such as nephrotic syndrome, familial hypercholesterolemia, and chronic viral hepatitis (*Table 1*), reinforcing the accepted importance of volunteer screening before enrolment.[1,2] Overall around one in 45 apparently healthy volunteers had an unexpected finding. This value is likely an underestimate of the true frequency that would be expected in a normal distribution of individuals aged 18–65, because younger volunteers were over represented in this cohort: Even within the oldest age group (range 41–65), the median ages of male and female volunteers were 46.6 years (interquartile range, IQR: 42.9–49.2) and 46.3 years (IQR: 43.3–50.2), respectively. Frequency of diagnosis in males increased with age ($p = 0.02$ $\chi^2$ for trend), although this trend was not observed in females ($p = 0.82$). However, the trend in male volunteers was not confounded by an increase in the ages of the male volunteers excluded within the oldest age group (median 42.2 [IQR: 40.2–46.4], $p = 0.08$ Mann–Whitney test). Intriguingly, a greater proportion of conditions were identified from 2009 compared to 1999–2008 ($p = 0.01$, $\chi^2$). Although clinical protocols were unchanged during this period, the increase in unexpected findings was temporally associated with an increase in volunteer recruitment,[5] possibly suggesting a change in the source of volunteers recruited, or alternatively an increase in the baseline morbidity of volunteers screened during this period.

As we have noted, the characteristics of this cohort might not reflect those of the general adult population, and may not be generalizable to healthy volunteer populations in other settings. Information on potential confounding factors such as ethnicity or socioeconomic status, and on the long-term outcome of the conditions identified was unavailable for this analysis. However, these data represent a large cohort of individuals screened at a single academic center using uniform procedures, and are consistent with a pharmaceutical industry healthy volunteer study,[6] and with similar data from over 20 years ago.[2] More recent studies have focused on African settings with greater baseline morbidity,[7] or on incidental findings during neuroimaging studies of healthy subjects,[8] but incidental clinical diagnosis in healthy subjects remains a largely unexplored area.

The informed consent process for healthy subjects recruited to clinical trials should always involve an indication of the probability of incidental diagnosis, together with a clear statement of the actions to be taken in response to any problems identified,[9,10] not least because information on incidental diagnosis may provide a valuable opportunity for clinical intervention.

## Conflicts of Interests

SCG, GAO, HM and AVSH are named inventors on patent applications for vectored vaccines and immunization regimens.

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