

ARTICLE

Incidental findings in UK healthy volunteers screened for a COVID-19 vaccine trial

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Abstract

The safety of novel therapeutics and vaccines are typically assessed in early phase clinical trials involving “healthy volunteers.” Abnormalities in such individuals can be difficult to interpret and may indicate previously unrecognized medical conditions. The frequency of incidental findings (IFs) in healthy volunteers who attend for clinical trial screening is unclear. To assess this, we retrospectively analyzed data for 1838 “healthy volunteers” screened for enrolment in a UK multicenter, phase I/II severe acute respiratory syndrome-coronavirus 2 (SARS-COV-2) vaccine trial. Participants were predominantly White (89.7%, 1640/1828) with a median age of 34 years (interquartile range [IQR] = 27–44). There were 27.7% of participants (510/1838) who had at least one IF detected. The likelihood of identifying evidence of a potential, new blood-borne virus infection was low (1 in 238 participants) compared with identification of an elevated alanine transaminase (ALT; 1 in 17 participants). A large proportion of participants described social habits that could impact negatively on their health; 21% consumed alcohol in excess, 10% were current smokers, 11% described recreational drug

[Correction added on 25 November 2021 after first publication: The author name Katrina M. Pollock was mis-spelled and has been corrected in this version.]

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use, and only 48% had body weight in the ideal range. Our data demonstrate that screening prior to enrollment in early phase clinical trials identifies a range of IFs, which should inform discussion during the consent process. Greater clarity is needed to ensure an appropriate balance is struck between early identification of medical problems and avoidance of exclusion of volunteers due to spurious or physiological abnormalities. Debate should inform the role of the trial physician in highlighting and advising about unhealthy social habits.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The frequency of incidental findings (IFs) in “healthy volunteers” detected on routine physical observations, urinalysis, or simple blood tests is unclear despite how frequently these tests are performed. No clear guidelines or consensus exist regarding the definition of an IF or the appropriate management of such a finding.

WHAT QUESTION DID THIS STUDY ADDRESS?

To describe the incidence of IFs in 1838 “healthy volunteers” screened for enrollment in a UK multicenter, phase I/II severe acute respiratory syndrome-coronavirus 2 (SARS-COV-2) vaccine trial.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This work presents the largest and most detailed dataset of IFs in healthy volunteers to date, with data from multiple sites working according to a single protocol. A high proportion of participants (27.7%; 510/1838) who considered themselves “healthy” had at least one IF detected. A considerable proportion of participants described social habits that could impact negatively on their health.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

- ☑ Inform development of guidelines for the definition and management of IFs to ensure an appropriate balance is struck between early identification of medical problems and avoidance of exclusion of volunteers due to spurious or physiological abnormalities.
- ☑ Improve consent processes by allowing the relative likelihood of detection of an IFs to influence the weighting of discussion about these tests.
- ☑ Inform debate regarding the role of the trial physician in highlighting and advising about unhealthy social habits.
- ☑ Inform accurate resource and process planning for screening of “healthy volunteers” in early phase clinical trials.

INTRODUCTION

The safety of novel therapeutics and vaccines is typically assessed in early phase clinical trials involving “healthy volunteers” before assessment in studies targeting specific populations. Not all volunteers who consider themselves “healthy” are eligible to participate in clinical trials.¹

“Healthy volunteers” are usually screened using rigorous clinical assessment to assess eligibility prior to enrollment.² This screening process may identify previously unrecognized abnormalities that mean an individual is unable to participate in the study. The identification of such findings may in some circumstances be a motivating

factor for an individual to volunteer for a study,³ especially as such tests may not be easily accessible for those without symptoms or signs of disease.³

Interpreting abnormal findings in healthy individuals can be difficult and needs to balance avoiding the medicalization of well individuals with spurious or physiological abnormalities, against the need to act on findings that facilitate the early detection and treatment of disease. “Normal” ranges are typically statistically derived from healthy population data and defined as two standard deviations around the mean of the sample population. Normality therefore does not categorically infer health, nor does an abnormal value always indicate disease. Similarly, the greater the number of

tests one performs, the greater the statistical probability of having a test result fall out of the “normal” range. Abnormal results are therefore to be expected in healthy volunteers. The challenge is differentiating spurious abnormal results from clinically relevant findings of concern.

An incidental finding (IF) has been described as a finding “that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study.”⁴ However, no widely accepted criteria exist for what findings would meet this definition. In addition, abnormalities often require clinical context in order to be assessed. For example, hematuria in a menstruating woman is unlikely to be significant whereas hematuria in a man would require investigation. In addition, a finding may only be significant if persistently detected. For example, mild proteinuria or hypertension detected on a single occasion would rarely warrant investigation or treatment but could indicate underlying pathology.

Although screened individuals may not be representative of the general population, IFs can provide insight into the prevalence of morbidity in “healthy” individuals, who might not otherwise access health care. These data can also provide insight into the prevalence of findings that are common in a trial population, but are of limited clinical significance, such as isolated raised bilirubin, which may be indicative of Gilbert’s syndrome.⁵ Understanding the frequency and nature of IFs in healthy volunteers can inform resource planning for clinical trials, allowing more accurate estimation of the proportion of healthy volunteers likely to be excluded.

To date, IFs in healthy volunteers participating in imaging studies have been the most studied.^{4,6–10} However, few data exist to inform the incidence of IFs in healthy volunteers, detected on routine physical observations, urinalysis, or simple blood tests, despite how frequently these tests are performed.² In addition, whereas protocols for clinical trials explicitly state exclusion criteria, no clear consensus exists regarding the definition of a potentially clinically significant IF or the appropriate management of such a finding. Published guidance by the US Food and Drug Administration (FDA) for the definition and grading of adverse events in healthy volunteers participating in vaccine trials do provide parameters for abnormal findings post-enrollment,¹¹ however, there is no such guidance available for the definition of IFs identified during screening, or the management of such IFs. Although the ethical responsibilities of researchers to identify and act on IFs have been discussed,^{12,13} without clear definitions of IFs it is difficult to ensure appropriate and consistent management. Estimates of the likelihood of identifying IFs are also important when explaining to volunteers the possible consequences of screening tests⁴ and for allowing researchers to estimate what proportion of screened volunteers may be excluded.

Here, we present detailed analysis of the IFs prospectively identified in a large, healthy volunteer cohort from multiple sites in the United Kingdom, screened for participation in a phase Ia/Ib severe acute respiratory syndrome-coronavirus 2 (SARS-COV-2) vaccine study.¹⁴

METHODS

COV001 is a phase I/II, participant-blinded, multicenter, randomized controlled trial of the SARS-COV-2 vaccine; ChAdOx-nCOV19 in healthy adult participants aged 18–55 years (NCT04324606).¹⁴ It is being conducted at five centers in the United Kingdom; The Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford (Oxford); NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton (Southampton); Clinical Research Facility, Imperial College London (Imperial); Vaccine Institute, St. Georges University of London and University Hospital NHS Foundation Trust (St. Georges); and University Hospitals Bristol and Weston NHS Foundation Trust (Bristol).

This study was approved in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (reference 21584/0424/001-0001) and the South Central Berkshire Research Ethics Committee (reference 20/SC/0145). The trial is being performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Potential participants were recruited through local advertisement, the majority of which were via posts on social media. Healthcare staff in local hospitals were also recruited via email. Individuals were asked to review the study participant information sheet (PIS; Supplementary Material) prior to attending a screening clinic appointment to assess eligibility. The PIS emphasized that individuals needed to be in “good health” in order to participate and that individuals with chronic diseases would be excluded.¹⁴

At the screening appointment, written informed consent was obtained from all individuals prior to any study procedures. The screening appointment consisted of a medical review, which included a medical history (including alcohol intake and recreational drug use) and full examination, including physical observations (blood pressure, pulse, temperature, weight, and height). Blood samples were taken (HIV antigen/antibody test, hepatitis B surface antigen, hepatitis C antibody, full blood count, urea and electrolytes, and liver function tests [LFTs]). Urinalysis was performed for blood, protein, glucose, and, in women of childbearing potential, pregnancy, using point of care tests. All laboratory assays on sera were

TABLE 1 Definitions used in analysis

Definitions				
	Laboratory assays	Urinalysis	Physical Observations	Clinical Examination
Abnormality	Any finding outside specified laboratory ranges	Any finding of protein, blood, or glucose in urine	Any finding outside normal range ^b	Any finding not typically present
Incidental finding	Finding of potential clinical significance ^a	Any glycosuria, > trace proteinuria or > trace hematuria	Findings \geq grade 1 in severity ^c	Any finding of potential clinical significance

^aAs defined in Table S1.

^bAs defined by Sapra et al.²⁸

^cAs defined in Table S3.

performed at UKAS accredited clinical laboratories. If an individual was found to be ineligible for the study at any point during screening assessment, screening was halted, and no further procedures were performed. When abnormalities of undetermined significance were found on initial testing, participants were able to be invited back for repeat testing at the discretion of the local study team. Primary care records were obtained to corroborate the medical history, examination, and laboratory findings.

The study was open to male and female volunteers aged between 18 and 55 years. Exclusion criteria for the study have been previously published (Supplementary Material),¹⁴ however, briefly, the study excluded: individuals with any serious chronic disease, history of severe allergies, immunocompromise, or alcohol or drug dependency. Subsequently, the study was amended to add body mass index (BMI)³ above 40 kg/m² or below 18 kg/m² as an exclusion criteria.

Local site physicians assessed screening data to determine eligibility according to local laboratory references ranges and criteria outlined in the clinical study plan documents, which have been previously published.¹⁴

For the purposes of this paper, all raw screening data was pooled centrally. Blood results were graded according to a modified version of the US FDA “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, Guidance for Industry”¹¹ that is commonly applied in studies conducted at the Oxford Vaccine Centre, University of Oxford, and is outlined in Table S1. Urinalysis and physical observations were graded according to criteria in Table 1 and Table S3 respectively. With the exception of alanine transaminase (ALT; Table S4), analysis did not account for variations in local UKAS accredited laboratory reference ranges or variability in the performance of locally used point of care tests.

Definitions outlined in Table 1, for abnormal findings as defined in the protocol, were used for the purposes of this analysis. In addition, all IFs had to be previously unknown to the individual or their general practitioner. Not

all participants with IFs were excluded from trial participation. Patients, and, where appropriate, their primary care givers, were informed of IFs.

Statistical analysis

Due to the broad range and low frequency of individual abnormalities, descriptive methods were used to analyze clinical data and statistical analysis restricted to investigating associations with demographic factors (sex) using Mann–Whitney test for continuous variables and Fisher’s exact test for categorical variables. Statistical analysis was performed using GraphPad Prism (GraphPad Software, version 9.0.2). A two tailed alpha value of less than 0.05 was considered significant.

RESULTS

Demographics of population

1943 healthy volunteers underwent screening assessment for the trial across five clinical trial sites in the United Kingdom between March and April 2020. One hundred five volunteers were excluded from the study prior to physical examination, blood or urine sampling, and were excluded from further analysis (Figure 1). The reasons for exclusion of these participants included: difficulty committing to study visit schedule, recent travel to countries with known coronavirus disease (COVID) cases, history of symptoms consistent with COVID, and disclosure of medical conditions meeting the study exclusion criteria. Screening data from 1838 participants were analyzed. The majority of volunteers was screened at the Oxford site (52%, 954/1838; Table S5). Physical observations data were available for 98% (1799/1838), clinical examination data were available for 97% (1778/1838), urinalysis data were available for 97% (1777/1838), and blood test results were available for 90% (1647/1838; Figure 1).

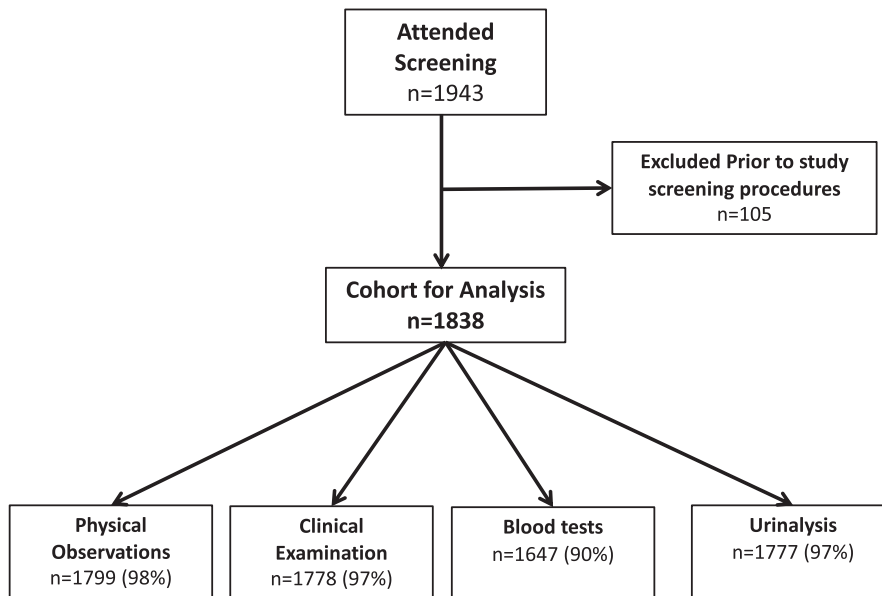


FIGURE 1 Consort diagram of individuals screened for COV001

TABLE 2 Demographics of individuals screened for COV001

		All	Female	Male
<i>N</i>		1838	49% (895/1838)	51% (943/1838)
Age (years)	Median (IQR)	34 (27–44)	34 (27–44)	34 (28–44)
	18–30	37% (679/1838)	39% (347/895)	35% (332/943)
	31–40	29% (542/1838)	26% (232/895)	33% (310/943)
	41–55	34% (617/1838)	35% (316/895)	32% (301/943)
Ethnicity	White	89.7% (1640/1828)	91.7% (818/892)	87.8% (822/936)
	Asian	5.3% (96/1828)	3.7% (33/892)	6.7% (63/936)
	Black	0.7% (12/1828)	0.3% (3/892)	1.0% (9/936)
	Arab	0.5% (10/1828)	0.4% (4/892)	0.6% (6/936)
	Mixed	2.2% (42/1828)	2.4% (21/892)	2.1% (20/936)
	Other	1.3% (24/1828)	1.0% (9/892)	1.6% (15/936)
	Not specified	0.3% (5/1828)	0.4% (4/892)	0.1% (1/936)

Abbreviation: IQR, interquartile range.

Participants were predominantly White (89.7%, 1640/1828), with those of Asian or mixed ethnicity the next most common groups (5.3%, 96/1828 and 0.7%, 12/1828, respectively). The median age of participants was 34 years (interquartile range [IQR] 27–44; Table 2). The population was equally balanced between men (51%, 943/1838) and women (49%, 895/1838).

Screening outcomes

60.2% (1016/1838) of participants were enrolled in the study. Of them, 8.1% (149/1838) were eligible but not enrolled, and 19% (355/1838) of participants were excluded due to detection of IFs at screening. Other reasons for exclusion included weight, COVID exposure, logistical

factors, such as lack of telephone or personal transport, and pre-existing medical conditions (Table S6).

Social factors and obesity

The majority of participants regularly consumed alcohol, with men drinking more than women (median 10 vs. 6 units¹⁵ per week, $p < 0.0001$, Fisher's exact test; Table S7). Twenty-one percent of participants reported drinking in excess of the 14 units per week limit recommended by the UK National Health Service (median 20 units per week, IQR 16–24), and 10% of participants were current smokers (182/1794). Men were more likely than women to report recreational drug use in the 5 years preceding screening (13.7% vs. 7.8%, $p = 0.0001$, Fisher's exact test).

Only 52% of participants had an ideal body weight (IBW) for their height according to BMI recorded at screening (Table S8). Women were more likely to have an IBW than men ($p = <0.0001$, Fisher's exact test). Of those participants with a BMI greater than 25 kg/m², men were more likely than women to be overweight ($p = <0.0001$, Fisher's exact test) or obese ($p < 0.0001$, Fisher's exact test). 9.7% of participants (179/1838) were found to have a BMI greater than or equal to 30, classifying them as obese and this was considered an IF in further analyses.

Physical observations and findings on clinical examination

16.9% of patients (304/1799) had an IF detected on assessment of physical observations, the most common of which was bradycardia (8%, 136/1796; Table 3). Systolic and diastolic hypertension present on repeat testing in the same clinic appointment was also observed frequently in 7% (127/1794) and 5% (89/1795) of participants, respectively.¹⁶ IFs were detected on clinical examination in a small proportion of participants (0.96%, 17/1778), with the most common finding being a systolic heart murmur, which was identified in 0.6% of participants (10/1778; Table 4).

TABLE 3 Abnormal physical observations for individuals screened for COV001

	Criteria	%
Systolic hypertension		
Grade 1	141–150 mmHg	4.6 (82/1794)
Grade 2	151–155 mmHg	0.8 (15/1794)
Grade 3	>155 mmHg	1.7 (30/1794)
Diastolic hypertension		
Grade 1	91–95 mmHg	3.3 (59/1795)
Grade 2	96–100 mmHg	0.8 (15/1795)
Grade 3	>100 mmHg	0.8 (15/1795)
Heart rate: tachycardia		
Grade 1	101–115 bpm	0.7 (13/1796)
Grade 2	116–130 bpm	0.1 (2/1796)
Grade 3	>130 bpm	0.0 (0/1796)
Heart rate: bradycardia		
Grade 1	50–54 bpm	5.6 (101/1796)
Grade 2	45–49 bpm	1.4 (25/1796)
Grade 3	<45 bpm	0.6 (10/1796)

Note: A diastolic but not systolic blood pressure reading was recorded for one participant. One participant had a fever of 37.9°C.

Blood tests

The frequency of laboratory IFs at screening varied according to site, potentially reflecting differences in laboratory assays at sites (Table S9). Laboratory IFs were more likely to be detected in men than women (16% vs. 7%, $p < 0.0001$, Fisher's exact test).

The most common laboratory IF at screening was a raised ALT, which was identified in 5.9% of participants (Table 5) and accounted for 46% of laboratory IFs (Table S10). Elevated ALT was more likely to be detected in men than women ($p < 0.0001$, Fisher's exact test; Table S11). There was a weak correlation between BMI and ALT ($n = 1634$, $r = 0.299$, $p < 0.0001$, Spearman Rank) and ALT and reported weekly alcohol intake ($n = 1636$, $r = 0.118$, $p < 0.0001$, Spearman Rank).

The second most common laboratory IF was isolated hyperbilirubinemia, affecting 1.8% of participants and accounting for 14% of all laboratory IFs detected.

Hypokalemia (grade 2 or above) was detected in 0.9% of participants and accounted for 8% of laboratory abnormalities. Of note, all cases were detected at the Oxford site (Table S12). Further analysis of the data from the Oxford site suggested that the observed pseudo-hypokalemia was related to both ambient air temperature and a delay in time to centrifugation (Figures S1 and S2)^{17–19} and may have been exacerbated by the use of plasma rather than serum samples at this site²⁰ (Figure S3).

Eosinophilia was the most common hematological IF detected affecting 1% of participants and accounting for 8% of laboratory IFs. Evidence of infection with a blood-borne virus was detected in 0.4% of participants.

New laboratory IFs detected between screening and enrollment

Three percent of participants (53/1700) had normal bloods at screening and then an IF detected on the day of

TABLE 4 incidental findings detected on clinical examination for individuals screened for COV001

Examination	Finding	$n = 1778$
Cardiovascular	Systolic murmur	0.6% (10/1778)
Respiratory	Crepitations	0.1% (2/1778)
Abdominal	Abdo mass	0.1% (2/1778)
Skin	Malar rash	0.06% (1/1778)
Lymphatic	Significant lymphadenopathy	0.06% (1/1778)
Other	Goiter	0.06% (1/1778)

enrollment, prior to vaccination. There was a maximum of 42 days (IQR 8–15) between screening and vaccination. No significant difference in the incidence of new IFs between men and women was seen (4% vs. 3%, $p = 0.165$, Fisher's exact test).

Elevated ALT was the most common, new, IF detected, accounting for 40% of new abnormalities at enrollment (Table S13). All of these were grade 1 in severity (ALT 1.1 - 2.5 x upper limit of normal (ULN). Eosinophilia was the next most common new laboratory abnormality detected at enrollment, accounting for 19% of new abnormalities. All of these were grade 1 in severity ($0.65\text{--}1.5 \times 10^9/\text{L}$).

Resolution of laboratory IFs detected at screening

Participants with laboratory IFs at screening were not routinely re-tested to assess for resolution, however, this did take place for some participants according to clinician discretion. Twenty-three participants with laboratory IFs at screening were subsequently enrolled with normal bloods on the day of vaccination, after repeat testing showed resolution of screening IFs (Table S14). Thirty percent (7/23) of these laboratory IFs were grade 2 elevated ALT (ALT $>2.5 \times$ ULN) and 35% (8/23) were grade 2 or 3 hypokalemia ($2.5\text{--}3.1$ mmol/L; Table S16).

Urinalysis

Hematuria was the most common IF detected on urine analysis, affecting 7% of participants (116/1768; Table 6). Women were more likely to have hematuria detected ($>$ trace on dipstick) compared with men (12% vs. 2%, $p < 0.0001$, Fisher's exact test; Table S15). However, data on timing of sampling in relation to menstruation was not routinely available and so a significant proportion of these cases may have been physiological. Repeat testing for hematuria was undertaken according to clinician discretion. Female and male participants were equally likely to have their urine retested at a later date ($p = 0.408$, Fisher's exact test) and there was no difference in the likelihood of resolution of the hematuria between the two sexes ($p = 0.642$, Fisher's exact test; Table S15). Fifty-seven percent (30/53) of participants for whom a sample was re-tested then had no hematuria.

Proteinuria was detected in 2% of participants (32/1765). There was no difference in the prevalence of proteinuria between the two sexes ($p = 0.476$, Fisher's exact test) or the likelihood of a sample being

retested at a subsequent date ($p = 0.633$, Fisher's exact test; Table S15). Eighty-eight percent (7/8) of the patients for whom a sample was retested then had no proteinuria.

Glycosuria was detected in 0.3% of participants (6/1766), and 0.1% (1/854) of female participants had a positive urine pregnancy test.

Proportion of population with incidental findings

27.7% of participants (510/1838) had at least one IF detected at screening. Overall, around one in four healthy volunteers had an IF. 3.3% of participants (61/1838) had

TABLE 5 Proportions of participants with significant abnormal laboratory findings at screening for COV001

	GRADE 1 % (n)	GRADE 2 % (n)	GRADE 3 % (n)
Biochemistry			
Hyponatraemia	*	0.06% (1)	0%
Hypernatraemia	*	0%	0%
Hypokalaemia	*	0.61% (10)	0.30% (5)
Hyperkalaemia	*	0.18% (3)	0.06% (1)
Urea	*	0.43% (7)	B
Creatinine	*	0%	0%
Bilirubin (normal LFTs)	*	1.64% (27)	0.18% (3)
ALT	5.34% (88)	0.24% (4)	0%
Alk phos	0.18% (3)	0%	0%
Albumin	*	0%	0%
Haematology			
Anaemia ^a	*	0.24% (4)	0%
Leucocytosis	*	0%	0%
Leucopenia	*	0%	0%
Thrombocytopenia	*	0.24% (4)	0.06% (1)
Neutropenia	*	0.61% (10)	0%
Lymphopenia	*	0%	0%
Eosinophilia	0.91% (15)	0.12% (2)	0%
Viral infection			
Hep C Ab +	0.36% (6)		
HIV Ab/Ag +	0.06% (1)		
Hep B SAg +	0%		

Note: % = % of participants affected. N = number of participants affected.
* = abnormality not deemed significant. Graded according to Table S1.
Individuals could have had more than one significant laboratory finding.
Abbreviations: ALT, Alanine transaminase; LFTs, liver function tests.

^aLow haemoglobin was noted in 3 females and 1 male.

TABLE 6 Frequency of hematuria, proteinuria and glycosuria in participants screened for COV001 using urinalysis strips

	n = 1766		n = 1765		n = 1768	
Glycosuria	Negative	99.7% (1760/1766)	Proteinuria	Negative	Haematuria	Negative
	Any Glycosuria ^a	0.3% (6/1766)		Trace		Trace
	Trace/100 mg/dL	0.2% (3/1766)		>Trace ^a		>Trace ^a
	+ /250 mg/dL	0.06% (1/1766)		+ /30 mg/dL ^a		+ /small ^a
	+ + /500 mg/dL	0.1% (2/1766)		+ + /100 mg/dL ^a		+ + /moderate ^a
	+ + + /1000 mg/dL	0% (0/1766)		+ + + /300 mg/dL ^a		+ + + /large ^a

^aDeemed incidental finding.

two or more IFs detected at screening. When “softer” IFs were excluded (grade 1 eosinophilia, hematuria in women), the proportion of participants with at least one IF fell to 21.3% (393/1838) or one in five participants.

DISCUSSION

Our data demonstrate that approximately one in four participants who consider themselves healthy have an IF detected at screening and support the accepted importance of volunteer screening prior to enrollment in early phase clinical trials.² This figure is likely an underestimate of the true frequency to be expected in a normal distribution of individuals aged 18–55 years because younger adults were over-represented in our population (age range 27–44 years). Of note, our dataset has a high proportion of White individuals (90%), meaning it may not be representative of the general population.

Only two previous studies have examined IFs in healthy volunteers screened prior to participation in medical research.^{1,21} The first was a retrospective study of 1293 volunteers screened to join a UK Clinical Pharmacology Unit healthy volunteer panel over a 4 year period from 1990.²¹ The authors identified previously undiagnosed medical conditions in 9.7% of volunteers once alcohol excess, extremes of weight, or the presence of tattoos (considered a potential surrogate for hepatitis C infection) were excluded. Whereas definitions of blood test abnormalities were described, definitions of abnormalities in urinalysis and physical observations were not provided. Of interest, this study, in contrast to our work, assessed for and identified individuals with hyperlipidemia (1.1%, 8/1293), thalassemia trait (0.01%, 1/1293), and thyroid dysfunction (0.5%, 7/1293). The second study of 990 individuals screened for participation in early phase vaccine trials at The Jenner Institute, University of Oxford between 1999 and 2010, reported identification of a new medical condition in 2.3% of volunteers,² however, this study did not provide details on the incidence of IFs of unclear significance. Our work reports a notably higher incidence of IFs than both these studies, and is likely to be explained by the inclusion in our dataset of IFs that were spurious, physiological, or subsequently found to not be of clinical significance on repeat testing or follow-up, which was not routinely performed in our study.

Our work is novel in reporting a large dataset from multiple sites in the United Kingdom working according to a single protocol and the detail in which we report our findings. Although our data are from participants screened for a phase I/II first-in-human vaccine trial, the findings are of relevance to all early phase studies, although are specific to our population. By presenting IFs according to investigation, we allow assessment of the “yield” of various tests

for abnormalities. Given that all investigations identified findings, it is arguable that a thorough screening process should include all these assessments. Our data also inform upon the calculation of the number of healthy individuals required to be screened for a trial in our setting and the associated costs involved, especially those relating to repeat tests and correspondence with primary care. However, it should be noted that our data are not generalizable to all healthy volunteer studies; our population includes a large proportion of obese individuals and those with a high alcohol intake and represent data from a single clinical trial, where the majority of data was collected at a single site.

A key finding of our study is the high prevalence of elevated ALT in our population affecting 5.9% of screened individuals, with men more affected than women. The considerable proportion of our population who were overweight and consumed excessive alcohol may have contributed to this, however, our data mirror an increasing burden of liver disease in the United Kingdom, where a 400% increase in liver related mortality was seen between 1970 and 2010.²² ALT abnormalities detected in our study fluctuated, with some individuals showing normalization on retesting and others newly developing elevated ALT on the day of vaccination. Although it has been reported that less than 5% of asymptomatic individuals with abnormal LFTs are found to have significant liver disease,²³ the likelihood of significant pathology cannot always be predicted by the extent or duration of abnormality or by resolution on retesting, and further investigation is recommended unless the suspicion is high that it is a transient event.²² Indeed, a number of groups have advocated reducing current normal upper limits of ALT.^{24,25} In retrospect, our study would have benefited from a standardized approach to retesting of abnormal LFTs and criteria for exclusion²² such as that proposed by Rowland et al.²⁶

PIS and consent forms for early phase studies commonly highlight the risk of identifying blood-borne viruses on screening. However, in our cohort, the chance of identifying evidence of a potential, new HIV, hepatitis B, or hepatitis C infection was low (1 in 238 screened participants) compared to identification of an elevated ALT (1 in 17 screened participants). We suggest that the relative likelihood of abnormal findings as well as the significance of potential abnormal findings should influence the weighting of discussion about these tests during the consent process.

A large proportion of our screened cohort described social habits that could impact negatively on their health; 21% reported consuming alcohol in excess, 10% were current smokers, and 11% described recreational drug use. Only 48% of screened participants were calculated to have an BMI within a healthy range. These findings may have influenced the incidence of IF in our cohort and limit the

generalizability of our findings to other settings. Such findings would not normally prompt advice or referral to primary care by trial physicians at our centers and of interest these participants still considered themselves healthy. However, such risk factors could have greater significance for a participant's health than a single laboratory abnormality. Future debate should inform the role of the trial physician in highlighting and advising about unhealthy social habits (for example, advice about smoking cessation or recommended alcohol intake) and consideration made of participants' perception of such advice.

One of the main limitations of this study is that the ultimate significance of these IFs is unknown. Ethical approval for this work permitted analysis of data prior to enrollment only, so we are unable to assess if IFs persisted or were associated with adverse outcomes in the study for enrolled participants. Conversely, for those participants who were excluded from the study because of an IF, we are unable to establish whether the IFs were found to be clinically significant after further investigation.

Early phase clinical trialists are rightly cautious and exclude individuals with "softer" abnormalities, which could complicate the interpretation of adverse events post-enrollment. However, such abnormalities may resolve on

BOX 1 Recommendations

- Abnormalities can be divided into those of:
 - a. *No clinical significance*
 - b. *Possible clinical significance*
 - c. *Unequivocal clinical significance*
- Sponsors should consider eligibility criteria that allow for clinician discretion when interpreting laboratory results.
- There is a need for evidence-based guidelines for the definition and management of IFs in early phase clinical trials in particular with regard to elevated bilirubin, ALT, and hypertension.
- Volunteers should be counselled prior to consent about the high likelihood of identifying an incidental finding on screening and the steps that would be undertaken in this event.
- Clinical investigators have a duty of care to ensure potentially clinically significant findings are appropriately communicated with the participant and where appropriate followed up and communicated with the volunteer's primary healthcare provider.
- Clarification is needed as to whether duty of care of a trial physician should extend to advice about the impact of lifestyle choices.

repeat testing, as our data demonstrate. Given that volunteer recruitment commonly limits study progress,²⁷ repeat testing of abnormalities of questionable clinical significance can help prevent unnecessary exclusion of healthy volunteers. In addition, if clinical investigators identify abnormalities of potential clinical significance, arguably they also have the responsibility to repeat such tests rather than burdening healthcare providers with the need to perform these tests and in the process medicalize otherwise healthy individuals.

CONCLUSION

This work presents the largest and most detailed datasets of IFs in healthy volunteers to date and supports the need for detailed screening of healthy participants volunteering for early phase clinical trials.² Guidelines for the definition and management of abnormalities identified in healthy participants are needed to ensure an appropriate balance is struck between early identification of medical problems and avoidance of unnecessary investigations (Box 1).

CONFLICT OF INTEREST

All authors have worked or are currently working on the UK clinical trials of the SARS-CoV-2 candidate vaccine; ChAdOx-1 nCoV-19. AJP is Chair of UK Dept. Health and Social Care's (DHSC) Joint Committee on Vaccination & Immunisation (JCVI), and is a member of the WHO's SAGE. The views expressed in this article do not necessarily represent the views of DHSC, JCVI, NIHR or WHO. AJP is the Chief Investigator of UK studies of ChAdOx nCoV-2 vaccine. The University of Oxford has entered into a partnership with AstraZeneca on coronavirus vaccine development. SNF acts as UK Chief Investigator for other commercial and non-commercial COVID-19 vaccine studies (Janssen adult and paediatric COVID-19 vaccine trials, Valneva COVID-19 vaccine trials, Oxford/AZ paediatric vaccine trial and the Imperial College COVID-19 vaccine trial). PTH acts as UK Chief Investigator for the Novavax COVID 19 vaccine trial and as an investigator for other commercial and non-commercial COVID-19 vaccine trials (Valneva COVID-19 vaccine trials, Oxford/AZ paediatric vaccine trial, Pfizer pregnancy COVID-19 trial and the Imperial College COVID-19 vaccine trial). KMP acts as Chief Investigator and investigator for other commercial and non-commercial COVID-19 vaccine studies (Imperial College London COVID-19 vaccine trial and Janssen adult COVID-19 vaccine trial). RL acts as Principal and Chief Investigator for other commercial and non-commercial COVID 19 vaccine studies (Valneva

COVID-19 vaccine trials, University of Oxford COMCOV study, Janssen adult COVID-19 vaccine trial).

AUTHOR CONTRIBUTIONS

S.H.H., K.P. and R.L. wrote the manuscript; S.H.H., K.R.W.E., K.P. and R.L. designed the research; S.H.H., P.I., J.L., S.R., H.M., C.C., E.G., S.I., N.L., A.M., S.M., D.O., M.P., M.S., S.F., P.H., A.P. and K.R.W.E. performed the research; S.H.H., P.I., J.L., S.R., H.M. and R.S. analysed the data.

REFERENCES

1. Sibille M. Selection of healthy volunteers for phase I studies. *Fundam Clin Pharmacol.* 1990;4(Suppl 2):167s-176s.
2. Duncan CJ, Rowland R, Lillie PJ, et al. Incidental diagnosis in healthy clinical trial subjects. *Clin Transl Sci.* 2012;5(4):348-350.
3. Pasqualetti G, Gori G, Blandizzi C, Del Tacca M. Healthy volunteers and early phases of clinical experimentation. *Eur J Clin Pharmacol.* 2010;66(7):647-653.
4. Wolf SM, Lawrenz FP, Nelson CA, et al. Managing incidental findings in human subjects research: analysis and recommendations. *J Law Med Ethics.* 2008;36(2):219-248, 211.
5. Thoguluva Chandrasekar V, John S. *Gilbert Syndrome.* StatPearls; 2021.
6. Hartwigsen G, Siebner HR, Deuschl G, Jansen O, Ulmer S. Incidental findings are frequent in young healthy individuals undergoing magnetic resonance imaging in brain research imaging studies: a prospective single-center study. *J Comput Assist Tomogr.* 2010;34(4):596-600.
7. Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. *JAMA.* 1999;282(1):36-39.
8. Pinato DJ, Stavrou C, Tanner M, et al. Clinical, ethical and financial implications of incidental imaging findings: experience from a phase I trial in healthy elderly volunteers. *PLoS One.* 2012;7(11):e49814.
9. Stip E, Miron JP, Nolin M, et al. Incidentaloma discoveries in the course of neuroimaging research. *Can J Neurol Sci.* 2019;46(3):275-279.
10. Oren O, Blankstein R, Bhatt DL. Incidental imaging findings in clinical trials. *JAMA.* 2020;323(7):603-604.
11. FDA. *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.* Guidance for Industry; 2007.
12. Wolf SM, Paradise J, Caga-Anan C. The law of incidental findings in human subjects research: establishing researchers' duties. *J Law Med Ethics.* 2008;36(2):361-383, 214.
13. Booth TC, Jackson A, Wardlaw JM, Taylor SA, Waldman AD. Incidental findings found in "healthy" volunteers during imaging performed for research: current legal and ethical implications. *Br J Radiol.* 2010;83(990):456-465.
14. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet.* 2020;396(10249):467-478.
15. National Health System (NHS). Alcohol Units. 2018. <https://www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/>.

16. Kario K, Thijs L, Staessen JA. Blood pressure measurement and treatment decisions. *Circ Res*. 2019;124(7):990-1008.
17. Masters PW, Lawson N, Marenah CB, Maile LJ. High ambient temperature: a spurious cause of hypokalaemia. *BMJ*. 1996;312(7047):1652-1653.
18. Ulahannan TJ, McVittie J, Keenan J. Ambient temperatures and potassium concentrations. *Lancet*. 1998;352(9141):1680-1681.
19. Turner HE, Peake RW, Allison JJ. Seasonal pseudohyperkalaemia: no longer an issue? *Ann Clin Biochem*. 2012;49(Pt 1):94-96.
20. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. *N Am J Med Sci*. 2013;5(4):255-259.
21. Singh SD, Williams AJ. The prevalence and incidence of medical conditions in healthy pharmaceutical company employees who volunteer to participate in medical research. *Br J Clin Pharmacol*. 1999;48(1):25-31.
22. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut*. 2018;67(1):6-19.
23. Lilford RJ, Bentham L, Girling A, et al. Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS): a prospective cohort study. *Health Technol Assess*. 2013;17(28):1-307.
24. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med*. 2002;137(1):1-10.
25. Kariv R, Leshno M, Beth-Or A, et al. Re-evaluation of serum alanine aminotransferase upper normal limit and its modulating factors in a large-scale population study. *Liver Int*. 2006;26(4):445-450.
26. Rowland R, O'Hara GA, Hamill M, et al. Determining the validity of hospital laboratory reference intervals for healthy young adults participating in early clinical trials of candidate vaccines. *Hum Vaccin Immunother*. 2013;9(8):1741-1751.
27. Harrington L, Van Damme P, Vandermeulen C, Mali S. Recruitment barriers for prophylactic vaccine trials: a study in Belgium. *Vaccine*. 2017;35(48 Pt B):6598-6603.
28. Sapra A, Malik A, Bhandari P. *Vital Sign Assessment*. StatPearls; 2021.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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