# Incidental Findings in UK Healthy Volunteers Screened for a COVID-19 Vaccine Trial

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**KEYWORDS**

Incidental; healthy; trial

**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 vaccines 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).

**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 unrecognised medical conditions. The frequency of incidental findings (IFs) in healthy volunteers who attend for clinical trial screening is unclear. To assess this we retrospectively analysed data for 1838 'healthy volunteers' screened for enrolment in a UK multi-centre, Phase 1/2 SARS-COV-2 vaccine trial. Participants were predominantly Caucasian (89.7% 1640/1828) with a median age of 34 years (IQR 27 - 44). 27.7% of participants (510/1838) had at least one IF detected. The likelihood of identifying a new blood-borne virus infection was low (1 in 238 participants) compared with identification of an elevated ALT (1 in 17 participants). A large proportion of participants described social habits that could impact negatively on their health; 18% consumed alcohol in excess, 10% were current smokers, 11% described recreational drug use and only 48% had body weight in the ideal range. Our data demonstrate that screening prior to enrolment 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.

## 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 enrolment[2]. This screening process may identify previously unrecognised 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 medicalisation 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, haematuria in a menstruating woman is unlikely to be significant whereas haematuria 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.

Whilst 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 healthcare. 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, whilst 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-enrolment[11], however there is no such guidance available for the definition of IFs identified during screening, or the management of such IFs. Whilst 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 tests[4] 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 UK, screened for participation in a Phase Ia/Ib SARS-COV-2 vaccine study[14].

## METHODS

COV001 is a phase 1/2, participant-blinded, multicentre, randomised 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 centres in the UK; 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 UK 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 emphasised that individuals needed to be in 'good health' in order to participate and that individuals with chronic diseases would be excluded[14].

184 At the screening appointment, written informed consent was obtained from all individuals
185 prior to any study procedures. The screening appointment consisted of a medical review,
186 which included a medical history (including alcohol intake and recreational drug use) and
187 full examination, including physical observations (blood pressure, pulse, temperature,
188 weight and height). Blood samples were taken (HIV antigen/antibody test, hepatitis B
189 surface antigen, hepatitis C antibody, full blood count, urea and electrolytes and liver
190 function tests). Urinalysis was performed for blood, protein, glucose and, in women of
191 childbearing potential, pregnancy, using point of care tests. All laboratory assays on sera
192 were performed at UKAS accredited clinical laboratories. If an individual was found to be
193 ineligible for the study at any point during screening assessment, screening was halted, and
194 no further procedures performed. When abnormalities of undetermined significance were
195 found on initial testing, participants were able to be invited back for repeat testing at the
196 discretion of the local study team. Primary care records were obtained to corroborate the
197 medical history, examination and laboratory findings.
198
199 The study was open to male and female volunteers aged 18 to 55 years. Exclusion criteria
200 for the study have been previously published (Supplementary Material),[14] however, briefly,
201 the study excluded: individuals with any serious chronic disease, history of severe allergies,
202 immunocompromise or alcohol or drug dependency. Subsequently the study was amended
203 to add body mass index (BMI)[3] above 40kg/$m^2$ or below 18kg/$m^2$ as an exclusion criteria.
204
205 Local site physicians assessed screening data to determine eligibility according to local
206 laboratory references ranges and criteria outlined in the clinical study plan documents,
207 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 Supplementary Table 1. Urinalysis and physical observations were graded according to criteria in Table 6 and Supplementary Table 3 respectively. With the exception of alanine transaminase (ALT) (Supplementary Table 4), 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 analyse 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 used GraphPad Prism (GraphPad Software, Version 9.0.2, San Diego, CA, USA). A two tailed alpha value of $<0.05$ was considered significant.

## RESULTS

### Demographics of population

1943 healthy volunteers underwent screening assessment for the trial across five clinical trial sites in the UK between March and April 2020. 105 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 COVID cases, history of symptoms consistent with COVID and disclosure of medical conditions meeting the study exclusion criteria. Screening data from 1838 participants were analysed. The majority of volunteers were screened at the Oxford site (52%, 954/1838, Supplementary Table 5). 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).

Participants were predominantly Caucasian (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 (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. 8.1% (149/1838) were eligible but not enrolled. 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 (Supplementary Table 6).

**Social factors and obesity**

The majority of participants regularly consumed alcohol, with men drinking more than women (median 10 v 6 units[15] per week, p = *<0.0001, Fishers exact test,* Supplementary Table 7). 21% 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). 10% of participants were current smokers (182/1794). Men were more likely than women to report use of recreational drug use in the five years preceding screening (13.7% v 7.8%, *p=0.0001 Fishers exact test*).

Only 52% of participants had an ideal body weight (IBW) for their height according to recorded BMI at screening (Supplementary Table 8). Women were more likely to have an IBW than men (*p=<0.0001, Fishers exact test*). Of those participants with a BMI >25kg/$m^2$, men were more likely than women to be overweight (*p=<0.0001, Fishers exact test*) or obese (*p=<0.0001, Fishers exact test*). 9.7% of participants (179/1838) were found to have a BMI $\geq$ 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 commonest 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 commonest finding being a systolic heart murmur which was identified in 0.6% of participants (10/1778) (Table 4).

**Blood tests**

The frequency of laboratory IFs at screening varied according to site, potentially reflecting differences in laboratory assays at sites (Supplementary Table 9). Laboratory IFs were more likely to be detected in men than women (16% v 7%, *p=<0.0001, Fishers exact test)*.

The most common laboratory IF at screening was a raised alanine transaminase (ALT), which was identified in 5.9% of participants (Table 5) and accounted for 46% of laboratory IFs (Supplementary Table 10). Elevated ALT was more likely to be detected in men than women (*p=<0.0001, Fishers exact test*) (Supplementary Table 11). 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 hyperbilirubinaemia, affecting 1.8% of participants and accounting for 14% of all laboratory IFs detected.

Hypokalaemia (grade 2 or above) was detected in 0.9% of participants and accounted for 7.5% of laboratory abnormalities. Of note, all cases were detected at the Oxford site (Supplementary Table 12). Further analysis of the data from the Oxford site suggested that the observed pseudo-hypokalaemia was related to both ambient air temperature and a

delay in time to centrifugation (Supplementary Figure 1 and 2)[17-19] and may have been exacerbated by the use of plasma rather than serum samples at this site[20] (Supplementary Figure 3).

Eosinophilia was the commonest haematological 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 enrolment*

3% of participants (53/1700) had normal bloods at screening and then an IF detected on the day of enrolment, 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% v 3%, p=0.165, Fishers exact test*).

Elevated ALT was the most common, new, IF detected, accounting for 40% of new abnormalities at enrolment (Supplementary Table 13). All of these were grade 1 in severity (ALT 113-225 IU/L). Eosinophilia was the next most common new laboratory abnormality detected at enrolment, accounting for 19% of new abnormalities. All of these were grade 1 in severity (0.65-1.5 x $10^9$/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. 23 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 (Supplementary Table 14). 30% (7/23) of these laboratory IFs were grade 2 elevated ALT (ALT > 2.5 x upper limit of normal) and 35% (8/23) were grade 2 or 3 hypokalaemia (2.5-3.1 mmol/L) (Supplementary Table 16).

**Urinalysis**

Haematuria was the commonest IF detected on urine analysis, affecting 7% of participants (116/1768) (Table 6). Women were more likely to have haematuria detected (> trace on dipstick) compared to men (*12% v 2%, p=<0.0001, Fishers exact test*) (Supplementary Table 15). 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 haematuria 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, Fishers exact test*) and there was no difference in the likelihood of resolution of the haematuria between the two sexes (*p=0.642, Fisher's exact test*) (Supplementary Table 15). 57% (30/53) of participants for whom a sample was re-tested then had no haematuria.

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, Fishers exact test*) or the likelihood of a sample being retested at a subsequent date (*p=0.633, Fishers exact test*) (Supplementary Table 15). 88% (7/8) patients for whom a sample was retested then had no proteinuria.

Glycosuria was detected in 0.3% of participants (6/1766). 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 two or more IFs detected at screening. When 'softer' IFs of were excluded (Grade 1 hypokalaemia, Grade 1 eosinophilia, haematuria in women), the proportion of participants with at least one IF fell to 21.3% (255/1838) or 1 in five participants.

## DISCUSSION

Our data demonstrate that approximately 1 in 4 participants who consider themselves healthy have an IF detected at screening and support the accepted importance of volunteer screening prior to enrolment 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 Caucasian 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. Whilst 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 hyperlipidaemia (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 detail on the incidence of IFs of unclear significance. Our work reports a notably higher incidence of IFs than both

386 these studies, and is likely to be explained by the inclusion in our dataset of IFs that were
387 spurious, physiological or subsequently found to not be of clinical significance on repeat
388 testing or follow-up, which was not routinely performed in our study.
389
390 Our work is novel in reporting a large dataset from multiple sites in the UK working
391 according to a single protocol and the detail in which we report our findings. Whilst our data
392 are from participants screened for a Phase 1/2 first-in-human vaccine trial, the findings are
393 of relevance to all early phase studies, though are specific to our population. By presenting
394 IFs according to investigation, we allow assessment of the 'yield' of various tests for
395 abnormalities. Given that all investigations identified findings, it is arguable that a thorough
396 screening process should include all these assessments. Our data also inform upon the
397 calculation of the number of healthy individuals required to be screened for a trial in our
398 setting and the associated costs involved, especially those relating to repeat tests and
399 correspondence with primary care. However, it should be noted that our data are not
400 generalisable to all healthy volunteer studies; our population includes a large proportion of
401 obese individuals and those with a high alcohol intake and represent data from a single
402 clinical trial, where the majority of data was collected at a single site.
403
404 A key finding of our study is the high prevalence of elevated ALT in our population affecting
405 5.9% of screened individuals, with men more affected than women. The considerable
406 proportion of our population who were overweight and consumed excessive alcohol may
407 have contributed to this, however our data mirror an increasing burden of liver disease in
408 the UK, where a 400% increase in liver related mortality was seen between 1970 and
409 2010[22]. ALT abnormalities detected in our study fluctuated, with some individuals showing

normalisation on re-testing and others newly developing elevated ALT on the day of vaccination. Whilst it has been reported that <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 re-testing, 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 standardised approach to re-testing of abnormal LFTs and criteria for exclusion[22] such as that proposed by *Rowland et al*[26].

Participant information sheets 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 a 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 proposition of our screened cohort described social habits that could impact negatively on their health; 18% 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 generalisability of our findings to other settings. Such findings would not normally prompt advice or referral to primary care by trial

physicians at our centres 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 enrolment 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-enrolment. However, such abnormalities may resolve on 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 medicalise 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).

**Box 1: Recommendations**

- Abnormalities can be divided into those of:
    - *No clinical significance*
    - *Possible clinical significance*
    - *Unequivocal clinical significance*
- Sponsors should consider eligibility criteria that allow for clinician discretion when interpreting laboratory results.
- 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.

## 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 enrolment in a UK multi-centre, Phase 1/2 SARS-COV-2 vaccine trial.

### What does this study add to our knowledge?

This work presents the largest and most detailed datasets 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.

## FIGURE LEGENDS

**Figure 1: Consort diagram of individuals screened for COV001**

## TABLES

| 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^ | Any finding not typically present |
| **Incidental finding** | Finding of potential clinical significance* | Any glycosuria, > trace proteinuria or > trace haematuria | Findings ≥ Grade 1 in severity^^ | Any finding of potential clinical significance |

**Table 1: Definitions used in analysis.** *As defined in Supplementary Table 1. ^As defined by *Sapra et al*[28]. ^^As defined in Supplementary Table 3.

| | | All | Female | Male |
|---|---|---|---|---|
| n | | 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 | Caucasian | 89.70% (1640/1828) | 91.7% (818/892) | 87.8% (822/936) |
| | Asian | 5.30% (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) |

***Table 2: Demographics of individuals screened for eligibility for COV001***

| Systolic Hypertension | | |
|---|---|---|
| | **Criteria** | **%** |
| **Grade 1** | 141-150mmHg | 4.6 (82/1794) |
| **Grade 2** | 151-155mmHg | 0.8 (15/1794) |
| **Grade 3** | >155mmHg | 1.7 (30/1794) |

| Diastolic Hypertension | | |
|---|---|---|
| | **Criteria** | **%** |
| **Grade 1** | 91-95mmHg | 3.3 (59/1795) |
| **Grade 2** | 96-100mmHg | 0.8 (15/1795) |
| **Grade 3** | >100mmHg | 0.8 (15/1795) |

| Heart Rate: Tachycardia | | |
|---|---|---|
| | **Criteria** | **%** |
| **Grade 1** | 101-115bpm | 0.7 (13/1796) |
| **Grade 2** | 116-130bpm | 0.1 (2/1796) |
| **Grade 3** | >130bpm | 0.0 (0/1796) |

| Heart Rate: Bradycardia | | |
|---|---|---|
| | **Criteria** | **%** |
| **Grade 1** | 50-54bpm | 5.6 (101/1796) |
| **Grade 2** | 45-49bpm | 1.4 (25/1796) |
| **Grade 3** | <45bpm | 0.6 (10/1796) |

***Table 3: Abnormal physical observations for individuals screened for COV001.*** *For one participant a diastolic but not systolic BP reading was recorded. One participant had a fever of 37.9°C.*

| 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 | Goitre | 0.06% (1/1778) |

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551 ***Table 4: incidental findings detected on clinical examination for individuals screened for***
552 ***COV001***
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| | 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** | 5.65% (93) | 0.24% (4) | 0% |
| **Alk phos** | 0.18% (3) | 0% | 0% |
| **Albumin** | * | 0% | 0% |
| **HAEMATOLOGY** | | | |
| **Anaemia^** | * | 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% | | |

***Table 5: Proportions of participants with abnormal laboratory findings at screening.*** *% = % of participants affected. N= number of participants affected. *=abnormality not deemed incidental finding. Graded according to Supplementary Table 1. Individuals could have had more than one laboratory finding. ^Low haemoglobin was noted in 3 females and 1 male. LFTs= liver function tests. ALT = Alanine transaminase.*

| | | n=1766 | | | n=1765 | | | n=1768 |
|---|---|---|---|---|---|---|---|---|
| GLYCOSURIA | Negative | 99.7% (1760/1766) | PROTEINURIA | Negative | 92% (1626/1765) | HAEMATURIA | Negative | 83% (1470/1768) |
| | Any Glycosuria* | 0.3% (6/1766) | | Trace | 6% (107/1765) | | Trace | 10% (182/1768) |
| | Trace/100mg/dL | 0.2% (3/1766) | | > Trace* | 2% (32/1765) | | > Trace* | 7% (116/1768) |
| | +/250mg/dL | 0.06% (1/1766) | | +/30mg/dL* | 1.4% (24/1765) | | +/small* | 2% (44/1768) |
| | ++/500mg/dL | 0.1% (2/1766) | | ++/100mg/dL* | 0.4% (7/1765) | | ++/moderate* | 3% (51/1768) |
| | +++/1000mg/dL | 0% (0/1766) | | +++/300mg/dL* | 0.06% (1/1765) | | +++/large* | 1% (21/1768) |

***Table 6: Frequency of haematuria, proteinuria and glycosuria in participants screened for COV001 using urinalysis strips.*** **deemed incidental finding.*

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588 **AUTHOR CONTRIBUTIONS**

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590 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

591 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.,

592 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

593 the data.

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