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UK-ROX Protocol Addendum

A study within a trial to determine the effect of skin tone on the diagnostic accuracy of pulse oximeters.

STUDY SHORT TITLE

Exploring Pulse O**X**imeter **A**ccuracy Across S**K**in **T**ones (**EXAKT**).

[This document is an addendum to the UK-ROX protocol to include the EXAKT sub-study. All procedures outlined in the UK-ROX main protocol will continue to be applicable to patients that are enrolled into UK-ROX and EXAKT.]

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Contents

Abbreviations

ABG	Arterial blood gas
Co-Hb	Carboxyhaemoglobin
CMP	Case Mix Programme
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring & Ethics Committee
F-Hb	Foetal Haemoglobin
Hb	Haemoglobin
HTA	Health Technology Assessment
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
LEDs	Light Emitting Diodes
Met-Hb	Methaemoglobin
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
RCT	Randomised Clinical Trial
RWPC	Research Without Prior Consent
REC	Research Ethics Committee
SaO_2	Arterial Oxygen Saturation
SOP	Standard Operating Procedure
SpO_2	Peripheral Arterial Oxygen Saturation
TMG	Trial Management Group
TSC	Trial Steering Committee

1. Background and rationale

UK-ROX sub-study: A study within a trial to determine the effect of skin tone on the diagnostic accuracy of pulse oximeters.

Pulse oximeters are a non-invasive device that determine peripheral arterial oxygen saturation (SpO_2), an estimation of true arterial oxygen saturation (SaO_2) measured by an arterial blood gas (ABG) machine. Finger probe pulse oximeters are placed on the fingertip and consist of light emitting diodes (LEDs) on one side of the finger and a photodetector on the other. Light of two specific wavelengths is emitted from the LEDs and transmitted through the underlying tissue to the photodetector. Oxygenated and deoxygenated haemoglobin possess different light absorptive capacities, therefore the ratio of light absorbance by each haemoglobin species can be used to determine their relative quantities. The light signal received by the photodetector is composed of a pulsatile and non-pulsatile component; the former represents the arterial signal, and the latter is derived from tissues and other parts of the circulation (venous blood, bone, skin, and fingernail). An algorithm within the device interprets the photodetected light signals to produce an overall estimate of arterial oxygenation. The quality of the light signal transmitted during pulse oximetry can be affected by several patient-related factors, resulting in inaccurate SpO_2 estimations. Skin pigmentation is known to be one of these factors.

Reports that pulse oximeters may be inaccurate have been published since the early 1990s. In one report summarising data from a number of small studies found that in Black patients, SpO_2 was consistently 3-5% higher than SaO_2.[1] Two studies that followed this report, tested several different models of pulse oximeters, again concluding that in people with pigmented skin, SpO_2 was over-estimated during hypoxaemia.[2, 3] These findings have serious clinical implications. For example, if a patient with pigmented skin has a true SaO_2 of 88%, a pulse oximeter may produce an SpO_2 of up to 93%. At 93%, clinicians may not be concerned about hypoxaemia and decide no treatment is indicated for that patient; yet if the clinician had known the patient had an SaO_2 of 88%, they may have chosen to intervene.

In 2020, investigators in the USA revisited the question of whether skin pigmentation affects the accuracy of SpO_2 readings. Using two separate datasets (one historical open-access Intensive Care Unit database and their own institution's current data from hospitalised patients) the authors compared concomitantly measured pulse oximeter-derived SpO_2 and co-oximeter-derived SaO_2 readings.[4] The authors defined 'occult hypoxaemia' as an SaO_2 of <88% when a paired SpO_2 reading was 92-96%. In the open-access Intensive Care Unit (ICU) cohort, occult hypoxaemia was detected in 160 of 939 measurements in Black patients (17.0%; 95% CI, 12.2 to 23.3) and in 546 of 8795 measurements in White patients (6.2%; 95% CI, 5.4 to 7.1). In their institution, occult hypoxaemia was detected in 88 of 749 measurements in Black patients (11.7%; 95% CI, 8.5 to 16.0) and in 99 of 2778 measurements in White patients (3.6%; 95% CI, 2.7 to 4.7). Their data also confirmed the previous observations that the disparity between SpO_2 and SaO_2 tended to be larger at lower SaO_2 readings, i.e., around 88 to 92%.

The safe and effective care of patients with low oxygen levels relies on accurate measurement of SpO_2 with a pulse oximeter and there exists a significant potential to under-treat people with pigmented skin if pulse oximeters over-estimate true SaO_2.

2. Aim and objectives

2.1 Aim

To determine the impact of skin tone on the diagnostic accuracy of fingertip pulse oximeters in adult patients.

2.2 Objectives

- To compare paired pulse oximeter-derived SpO_2 measurements to ABG machine-derived co-oximeter SaO_2 for a range of fingertip pulse oximeters used by the *NHS COVID Oximetry @home* scheme (https://www.england.nhs.uk/nhs-at-home/covid-oximetry-at-home/), in an ethnically diverse group of adult patients admitted to NHS ICUs.
- To evaluate the effect of SaO_2 on the relationship between SpO_2 and SaO_2 in these patients.
- To quantify disparities for each pulse oximeter across a wide range of skin tones for a clinically relevant range of SaO_2 values.

3. Methods

3.1 Design

Multi-centre, diagnostic accuracy study embedded within the UK-ROX trial. The data collected from this sub-study will be collected, analysed, and reported separate to the data from the main UK-ROX trial.

3.2 Setting

A total of 24 sites participating in the UK-ROX trial will be selected to enrol patients for this sub-study. Sites will be selected to ensure ethnic diversity within the sample and based on current recruitment rate to the UK-ROX main trial.

3.3 Population

Mechanically ventilated adult participants (aged ≥18 years) from two distinct groups, outlined below:

i) Patients enrolled into the UK-ROX trial,
ii) Patients screened for but not included in the UK-ROX trial (e.g., patients falling outside of the 12-hour recruitment window, the UK-ROX intervention is deemed indicated or contraindicated or there is a clinical reason not to randomise the patient).

3.3.1 Co-enrolment

Co-enrolment will be permitted with all studies without prior agreement needed.

3.4 Recruitment and consent

3.4.1 Patients already enrolled into the UK-ROX trial

At the point of randomisation into the UK-ROX trial, sites will be notified whether the patient should also be enrolled into the EXAKT sub-study following the research without prior consent (RWPC) model already employed in the UK-ROX trial. The consent process will be incorporated into the existing consent procedures for the UK-ROX trial.

Following randomisation, consent will be sought for the EXAKT sub-study from a Personal Consultee (i.e., relative or close friend), Nominated Consultee (e.g., Independent Mental Capacity Advocate appointed by the NHS Hospital Trust or an independent doctor, i.e., not involved in the trial), and/or the patient themselves. As part of the deferred consent conversation for the main UK-ROX trial, consultees and/or patients will be asked for consent for the data collected as part of the EXAKT sub-study.

In the rare situation where a patient has been deemed by the treating clinical team to have full capacity and is able to give informed consent at the point of meeting the eligibility criteria, they will be approached directly prior to randomisation into the main UK-ROX trial and for inclusion into the sub-study. No data for the EXAKT sub-study will be entered into the study database prior to agreement from the Consultee or patient.

3.4.2 Patients screened and not randomised into the UK-ROX trial

For patients screened and not randomised into the UK-ROX trial but deemed eligible for the EXAKT sub-study, agreement will be obtained from the patient if they have full mental capacity or from a Personal or Nominated Consultee *prior* to the patient being enrolled into the EXAKT sub-study.

3.5 Interventions

The sub-study involves the following measurements for the participant:

1. Additional SpO_2 measurements from two brands of finger-tip pulse oximeters under evaluation.
2. SpO_2 measurements from the ICU pulse oximeter that is used as part of routine care.
3. Arterial blood gas derived SaO_2 measurements taken as part of routine care.
4. Skin tone measurements using the Konica Minolta CM-600d spectrophotometer.

The clinical management of patients in the sub-study will be as per the main UK-ROX trial or their usual clinical care.

3.5.1 Index test – Pulse oximetry-derived SpO_2 measurement from models used within the NHS COVID Oximetry @home scheme

The *NHS COVID Oximetry @home scheme* will provide pulse oximeters that require evaluation. Currently there are four available, but this could alter over the course of the study. Each site participating in the sub-study will be randomly allocated two brands of pulse oximeters from the COVID Oximetry @home list to evaluate. This will aim to ensure balance in geography, anticipated recruitment numbers, and ethnicity. Sites will continue to use the ICU pulse oximeter that is used as part of routine care.

The pulse oximeters to be evaluated will be placed onto the patient's fingers on the same hand (ensuring nail varnish has been removed from the patient's finger prior to this), with the screen displaying the SpO_2 on the dorsal surface of the finger, according to NHS England advice to patients using pulse oximeters at home (https://www.england.nhs.uk/nhs-at-home/covid-oximetry-at-home/). Once the SpO_2 values have stabilised they will be recorded along with the ICU pulse oximeter SpO_2 (i.e., a total of three SpO_2 values).

3.5.2 Reference standard – Arterial oxygen saturation (SaO_2) measured through blood gas analysis

ABGs will only be taken when clinically indicated for participants in the sub-study. It is usual practice for mechanically ventilated patients to have indwelling arterial catheters, from which these measurements will be taken. Fingertip pulse oximeter SpO_2 values will be recorded along with a corresponding SaO_2 measurement derived from an ABG sample. This process will occur only when routine ABG samples are due, so no additional ABG samples will be required for this study. Evaluation of the pulse oximeters will continue in this way for 24 hours. As ABG samples tend to be taken every 4-6 hours, this will provide approximately 4-6 readings per patient per pulse oximeter.

3.5.3 Direct skin colour assessment using the Konica Minolta CM-600d spectrophotometer

The Konica Minolta CM-600d spectrophotometers is a battery-operated, hand-held device designed to accurately measure colour. Each site will be provided with a device and following appropriate training, it will be used to make a one-off measurement of participant skin tone. The non-invasive process of measuring skin tone will be provided to each site in a detailed SOP. The device works by shining light at the skin and measuring the light reflected back to the device. Skin tone will be measured in four separate areas on the back of the non-dominant hand and the average of these readings recorded as the patient's numerical skin tone. Data from these four readings will be recorded in the Case Report Form (CRF). The values that make up this measurement can then be translated into descriptive colours. [5] Data will be recorded in the CRF to allow comparison of oxygenation values and to skin tone.

3.6 Data collection

No data for the EXAKT sub-study will be entered into the study database prior to agreement from the Consultee or patient. A separate trial number will be generated for patients enrolled into the sub-study.

3.6.1 Primary data collection

The data collection for all patients in the sub-study will include:

- Patient consent/consultee opinion
- SpO_2 measurements
- SaO_2 measurements
- Skin tone measurements
- Haemoglobin (Hb) – *where available*
- Carboxyhaemoglobin (CO-Hb) – *where available*
- Methaemoglobin (Met-Hb) – *where available*
- Foetal haemoglobin (F-Hb) – *where available*

Hb, CO-Hb, Met-Hb and F-Hb from the ABG analysis will be used to see whether anaemia or other haemoglobin species influence the accuracy of the pulse oximeters.

The option of entry first onto a paper CRF will be available to sites.

3.7 Outcomes

3.7.1 Primary outcome

- Accuracy of SpO_2 measurement, validated against co-oximeter derived SaO_2 ABG analysis (calculated as SpO_2 minus paired SaO_2).

3.7.2 Secondary outcomes

- Diagnostic accuracy (area under the receiver operating characteristic curve and sensitivity and specificity at relevant cut-points) for SpO_2 as a predictor of $SaO_2 \leq 92\%$.
- 'Occult hypoxaemia' ($SaO_2 < 88\%$ among participants with a paired SpO_2 reading of 92- 96%).

4. Statistics and data analysis

4.1 Sample size

Based on observed recruitment rates and screening log data from the UK-ROX trial, combined with information from the Case Mix Programme, the plan is to recruit a total of 900 patients.

The proposed sampling strategy is based on ethnicity rather than skin tone, as measurements of skin tone will only be taken once a patient has been recruited into the sub-study. The sampling frame has been designed to recruit approximately one third of patients of White ethnicity and two-thirds from all other ethnic groups combined. To achieve this, one additional question will be added to the randomisation system to record whether the patient's ethnicity is White or non-White. 100% of non-White patients randomised in participating sites will be included in the sub-study. White patients will be included at random based on sampling a proportion *p* of the White patients randomised. Whether or not the patient is to be included in the sub-study will be returned to the member of the site team performing the randomisation along with the patient's group allocation. The initial value for *p* will be determined from the observed UK-ROX data from sites participating in the sub-study. This will be kept under review and adjusted as required to deliver the required proportion of White patients.

Widening enrolment into the EXAKT sub-study to include all screened patients, will further enhance recruitment and ensure the enrolment of a diverse patient population.

5. Trial management and oversight

5.1 Study governance

As EXAKT is a sub-study, the governance of the study will be incorporated into the governance of the main UK-ROX trial i.e., the same sponsor, Research Ethics Committee (REC), Clinical Trials Unit (CTU), Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC). There will also be a study specific TMG to provide governance for the EXAKT sub-study.

6. Dissemination

The outputs from this study will be disseminated widely to encourage engagement and communication with the wider public and community groups. Outputs will be produced to cover both progress at the start, during the study and the results at the end. Given the sensitivities around the study, communication experts (such as the NIHR Centre for Dissemination and

Engagement and Science Media Centre) will be consulted to ensure the outputs are targeted to the public and policymakers, through the media and other outlets.

As part of the engagement and communications work package, community engagement partners will work on the following areas:

- *Insight work* – To engage with specific communities to gauge understanding of structural racism in acute health care, use of medical technology and what would be helpful to mitigate issues.
- *Community promotion of programme* – To work with specific community leaders to highlight that this critical work is being undertaken with the members of minoritised communities.
- *Coproduction of patient material* – A leaflet will be developed with representatives of specific communities for families and patients to explain why this work is being undertaken.
- *Programme oversight* – A lay and a scientific representative from targeted communities will be appointed to the study steering Group.
- *Communication of findings* – The community partner and members of the study steering group will be involved in synthesising and communicating the findings to the local and scientific communities.

7. Funding

National Institute for Health Research (NIHR) Health Technology Assessment grant (Project: NIHR152078).

8. Additional references

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4. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial Bias in Pulse Oximetry Measurement.[letter]. N Engl J Med 2020;383(25):2477-2478.
5. Ly BCK, Dyer EB, Feig JL, Chien AL, Del Bino S. Research Techniques Made Simple: Cutaneous Colorimetry: A Reliable Technique for Objective Skin Color Measurement. J Invest Dermatol. 2020;140:3-12.e1.

Appendix 1 – Protocol addendum version history.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	12 April 2022	-	Initial approved version