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UK-ROX 90

The 90 trial

Intensive Care Unit Randomised Trial Comparing Two Approaches to OXygen Therapy

Site Initiation Visit

IRAS ID: 288506
REC Ref: 20/SC/0423
Funding: NIHR HTA (130508)

NIHR CPMS ID: 46926
ISRCTN Registry: ISRCTN13384956
Sponsor: ICNARC (01/10/20)

Chief Investigators: Prof Daniel Martin & Mr Paul Mouncey

FUNDED BY NIHR | National Institute for Health Research

Agenda

- **Background and trial design**
- Patient flow

Background

- **Oxygen is the commonest drug administered to patients on ICU**
- Approx. 55,000 patients per year receive mechanical ventilation with supplemental oxygen in NHS ICUs
- Whilst severe hypoxaemia can be harmful, the administration of excessive oxygen may also be harmful
- Traditionally we have given *more* (rather than less) oxygen to avoid hypoxaemia
- **We do not know what the optimal amount of oxygen to give to patients is, or what their optimal oxygenation level should be**

Background

- High concentration oxygen is thought to be harmful to the lungs and induce a inflammatory response
- Retrospective studies have linked hyperoxaemia to worse clinical outcomes
- ***Conservative oxygen therapy*** (or permissive hypoxaemia) is the purposeful administration of less oxygen than usual to patients, to achieve lower than normal arterial oxygenation levels (SpO_2 / PaO_2)

Aim

- To evaluate the clinical and cost-effectiveness of conservative oxygen therapy for mechanically ventilated adult patients in ICU

Research question

Population	In adults receiving mechanical ventilation and supplemental oxygen in ICU
Intervention	is conservative oxygen therapy superior to
Comparator	usual oxygen therapy
Outcome	in terms of 90-day all-cause mortality?

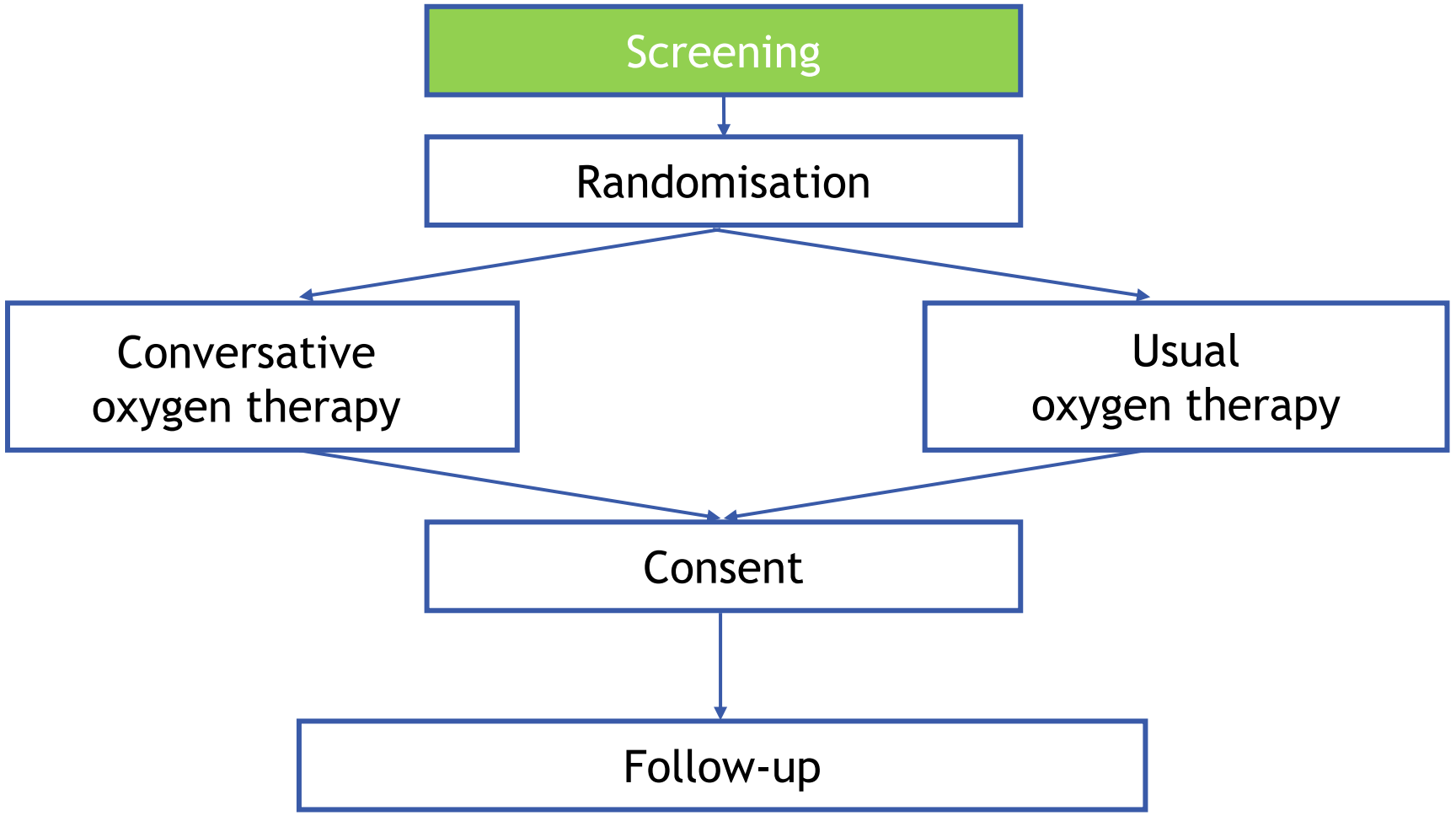
Trial design

- Large-scale, multi-centre, data-enabled, registry-embedded, RCT with an internal pilot and integrated economic evaluation
- 16,500 patients (randomised 1:1)
  - Provides 90% power to detect a 2.5% absolute risk reduction in 90-day mortality (from 37% to 34.5%), with allowances for missing data
  - Recruited from approx. 100 ICUs
  - 24-month recruitment period

Agenda

- Background and trial design
- **Patient flow**

Patient flow



Eligibility

See SOP 003

- Inclusion criteria
  - Aged ≥18 years
  - Receiving invasive mechanical ventilation following an unplanned ICU admission OR invasive mechanical ventilation started in the ICU
  - F_IO_2 >0.21 at time of randomisation

- Exclusion criteria
  - Previously randomised to UK-ROX in last 90 days
  - Currently receiving ECMO
  - The treating clinician considers that one study treatment arm is either indicated or contraindicated

- Patients must be randomised within 12 hours of starting invasive mechanical ventilation in ICU

Screening & randomising

See SOP 003

- Screen all patients receiving invasive mechanical ventilation in ICU
  - Eligible if intubated at ICU admission OR later during the ICU stay

- Aiming to embed screening within routine clinical practice
- Timely randomisation essential (12-hour window)
- Simple trial procedures
- Coverage for out-of-hours randomisations
  - clinical staff training and engagement

Screening Tool (optional)

See SOP 003

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Screening Tool

Date:

Hospital number	Aged ≥ 18 years? (Y/N)	Date/time started invasive mechanical ventilation	Screened within 12 hours of starting invasive mechanical ventilation? (Y/N)	FiO_2> 0.21? (Y/N)	If all Yes, then review exclusion criteria and complete Randomisation Form if all eligibility criteria are met	Eligibility confirmed by Name of staff	If randomised Trial Number	If not randomised Provide reason

Exclusion criteria

- Previously randomised into UK-ROX in the last 90 days
- Currently receiving ECMO
- The treating clinician considers that one study treatment arm is either indicated or contraindicated

Unsure if a patient is eligible? Contact:

- Your Principal Investigator or research team for assistance
- ICNARC CTU: **020 7269 9277** or uk-rox@icnarc.org

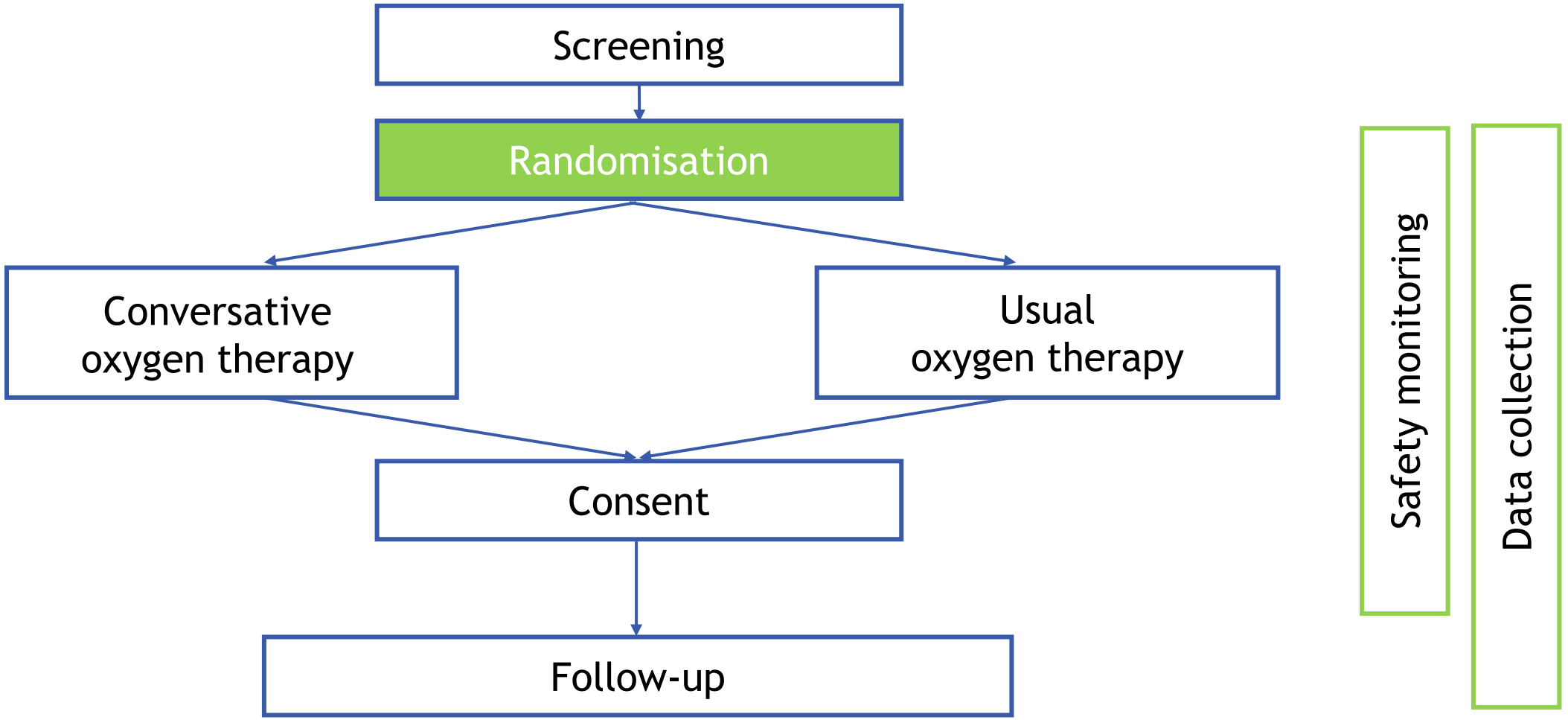
Co-enrolment

See SOP 004

- Observational studies (including those collecting samples)
  - Permitted without prior agreement

- Interventional studies
  - Decided case-by-case
  - Agreement in place with:
    - A2B
    - EFFORT
    - REMAP-CAP
    - VITDALIZE UK
    - VACIRiSS
    - STRESS-L
    - ADAPT-SEPSIS
    - RECOVERY
    - BLING III

Patient flow

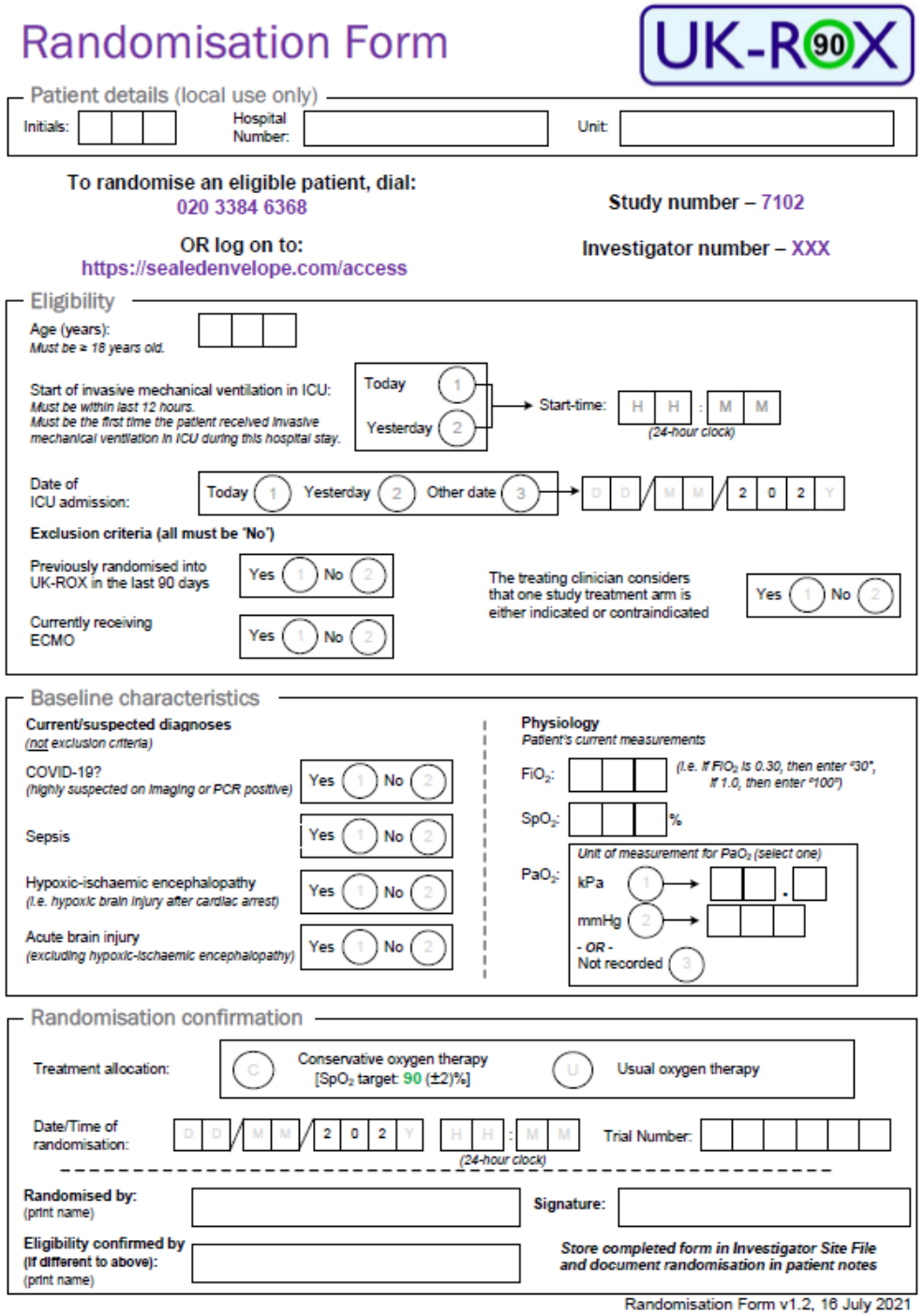


Randomisation

See SOP 004

- Dedicated 24/7 randomisation service
- Telephone randomisation
  - Dial: 020 3384 6368
  - Study number: 7102
  - Your investigator number will be assigned
- Web randomisation
  - Email uk-rox@icnarc.org to request an account
  - Can use generic/group or individual email addresses

- Trial training required to randomise (Training Log)
  - GCP training not required



Randomisation Form

UK-ROX 90

Patient details (local use only)

Initials: | Hospital Number: | Unit:

To randomise an eligible patient, dial:
020 3384 6368

OR log on to:
https://sealedenvelope.com/access

Study number – 7102

Investigator number – XXX

Eligibility

Age (years):
Must be ≥ 18 years old.

Start of invasive mechanical ventilation in ICU:
Must be within last 12 hours.
Must be the first time the patient received invasive mechanical ventilation in ICU during this hospital stay.
Today (1) / Yesterday (2) → Start-time: H H : M M (24-hour clock)

Date of ICU admission:
Today (1) Yesterday (2) Other date (3) → D D / M M / 2 0 2 Y

Exclusion criteria (all must be 'No')

Previously randomised into UK-ROX in the last 90 days: Yes (1) No (2)

Currently receiving ECMO: Yes (1) No (2)

The treating clinician considers that one study treatment arm is either indicated or contraindicated: Yes (1) No (2)

Baseline characteristics

Current/suspected diagnoses
(not exclusion criteria)

COVID-19?
(highly suspected on imaging or PCR positive): Yes (1) No (2)

Sepsis: Yes (1) No (2)

Hypoxic-ischaemic encephalopathy
(i.e. hypoxic brain injury after cardiac arrest): Yes (1) No (2)

Acute brain injury
(excluding hypoxic-ischaemic encephalopathy): Yes (1) No (2)

Physiology
Patient's current measurements

FiO_2: *(i.e. If FiO_2 is 0.30, then enter "30", If 1.0, then enter "100")*

SpO_2: %

PaO_2: *Unit of measurement for PaO_2 (select one)*
kPa (1) → .
mmHg (2) →
- OR -
Not recorded (3)

Randomisation confirmation

Treatment allocation: (C) Conservative oxygen therapy [SpO_2 target: 90 (±2)%] (U) Usual oxygen therapy

Date/Time of randomisation: D D / M M / 2 0 2 Y H H : M M (24-hour clock) Trial Number:

Randomised by: (print name) | **Signature:**

Eligibility confirmed by (if different to above): (print name)

Store completed form in Investigator Site File and document randomisation in patient notes

Randomisation Form v1.2, 16 July 2021

See SOP 004

How to randomise

Details required by randomisation service

- Confirmation of eligibility
- Key baseline data

Confirmation of randomisation

Sign off by trained staff member

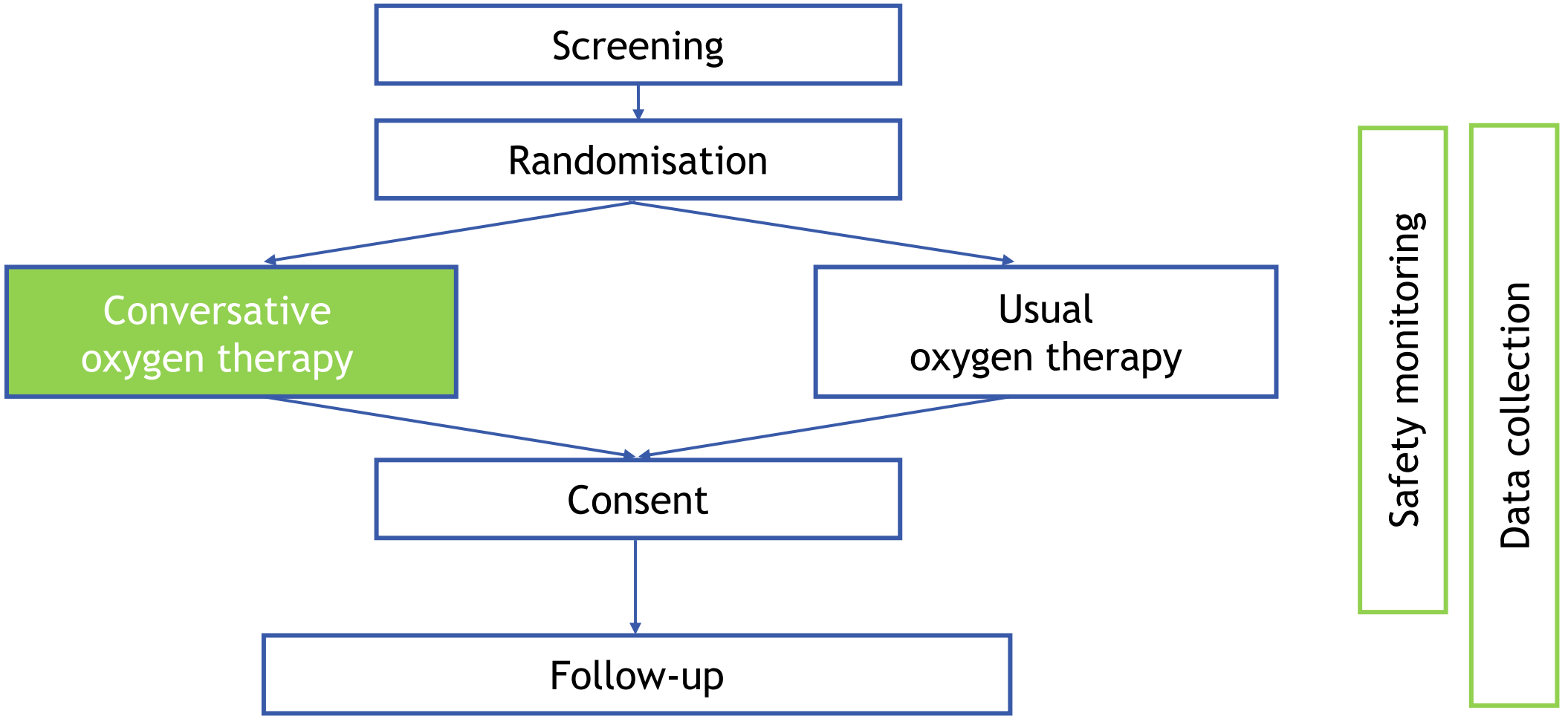
Randomisation

See SOP 004

- Auto-generated randomisation notification emails
  - Email uk-rox@icnarc.org to add recipients

- Errors
  - Once randomised, patient is in trial and included in analysis – consent and data collection must be carried out per protocol
  - If patient accidentally randomised twice, use **first** randomisation
    - Check email notification if unsure of the status of a randomisation (or contact local team/ICNARC CTU)
    - Do not re-use the second randomisation details

Patient flow



Intervention period

See SOP 006

- Begins immediately following randomisation
- The interventions remain the same once a patient is extubated, regardless of the modality by which they receive oxygen therapy
- The interventions should be continued until ICU discharge or 90 days after randomisation, whichever is sooner
  - If readmitted to ICU within the 90 days, the intervention should be recommenced

Conservative oxygen therapy

See SOP 005

- **The lowest concentration of oxygen possible should be administered to maintain the patient's SpO_2 at 90(±2)%**
- For patients receiving oxygen, SpO_2 should not rise above **92%** (monitor alarm set to 93%)
- SpO_2 should not fall lower than **88%**

Conservative oxygen therapy

See SOP 005

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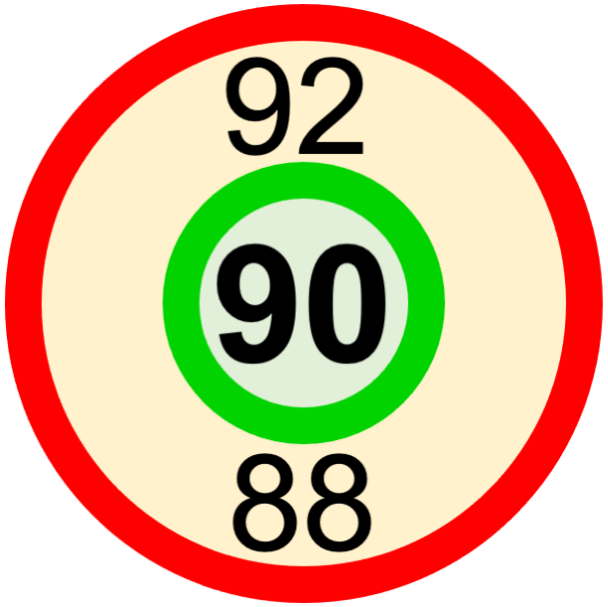
CONSERVATIVE OXYGEN THERAPY

When receiving oxygen



Set upper alarm to prevent an SpO_2 >92%

Reduce FIO_2 until SpO_2 is 90%

Set lower alarm to prevent an SpO_2 <88%

* If SpO_2 is > 92% despite an FIO_2 of 0.21, the upper alarm will need to be removed

Conservative oxygen therapy

- **When a patient is not receiving additional oxygen**, a higher SpO_2 alarm should not be set
- Continue to monitor SpO_2
- If additional oxygen is required again, revert to the algorithm for patients receiving oxygen

Conservative oxygen therapy

- **Intervention 90±2% (88-92%)**
- This is the intervention we trialled in our UK feasibility study
- Every RCT to date has selected a different intervention target
- We originally selected 90—94% for UK-ROX but have reduced it to 88-92% in line with feedback from centres and following experiences during the COVID-19 pandemic

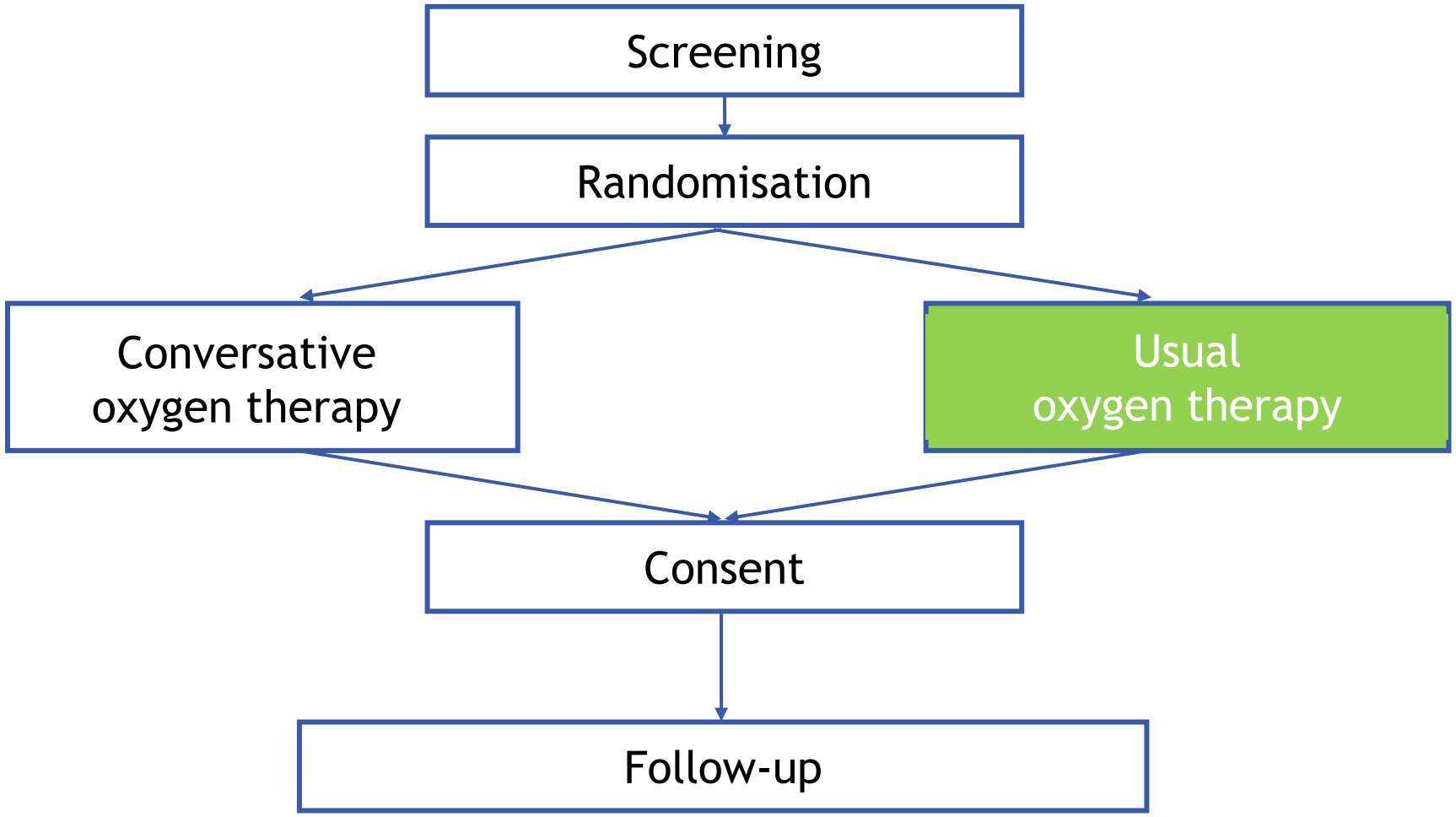
Protocol deviation

- Trigger to identify potential deviations:
  - where SpO_2 remains above 92% for three consecutive hours and FiO_2 is not reduced or at the lower limit of 0.21
- Sites contacted to find out reasons why oxygen was not reduced
  - Important that reasons are documented locally

Training

- Ensure staff are aware of trial and that they may be managing intervention group patients
  - Including temporary/bank/agency staff
- Ensure bedside staff are confident in titrating F_iO_2 to an SpO_2 target of 90 (±2)%
- Ensure alarms are set appropriately and SpO_2 targets handed over to subsequent shifts
- Discussion point at ward rounds
- Use of electronic patient record to monitor SpO_2 values and prompt titration of FiO_2?
- Use stickers/labels for intervention group patients

Patient flow

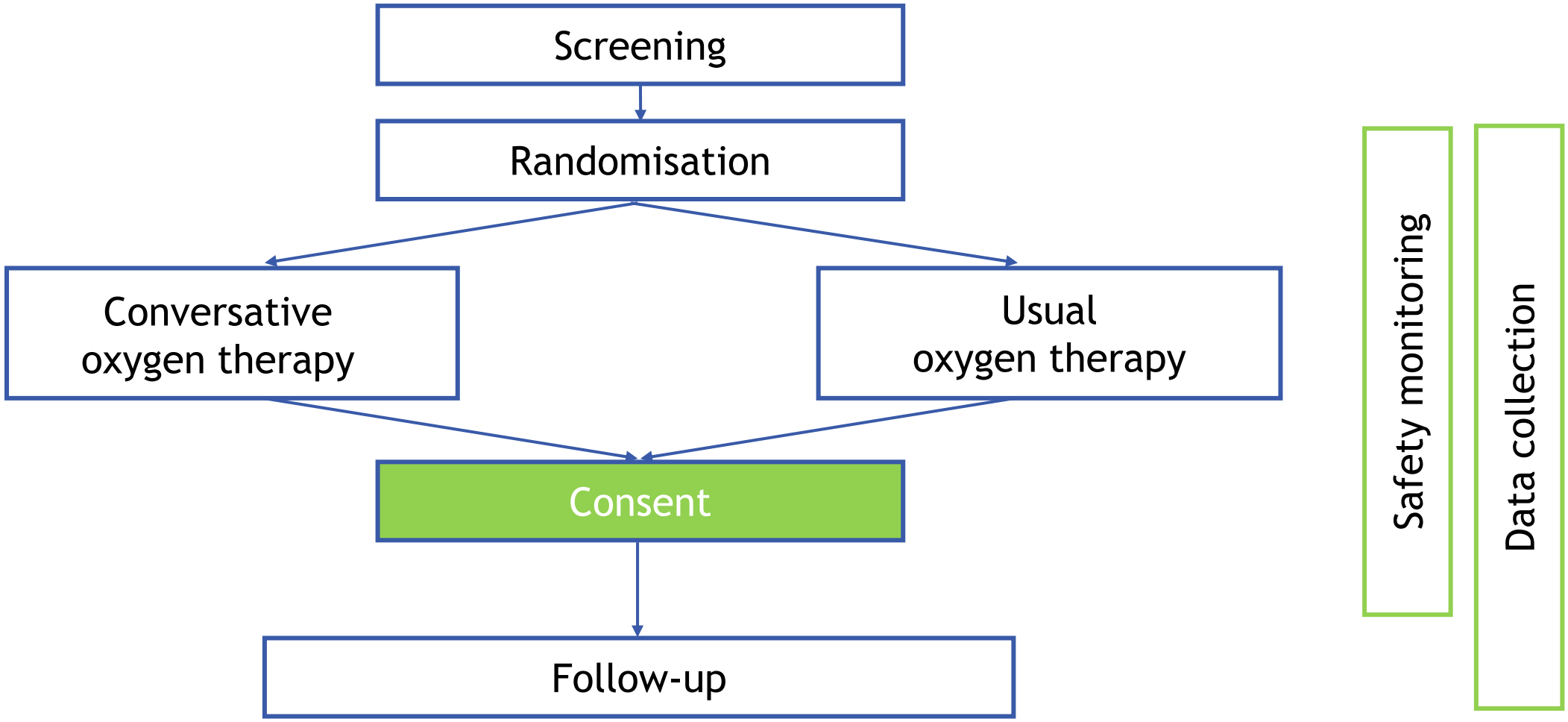


Usual oxygen therapy

See SOP 006

- Defined by local practice, determined by treating clinician
- Chosen SpO_2 targets should be documented daily
- A lower limit alarm can be set at the discretion of the treating clinician
- An upper SpO_2 alarm must not be used
- Research staff should avoid interactions that may influence usual care

Patient flow



Research Without Prior Consent

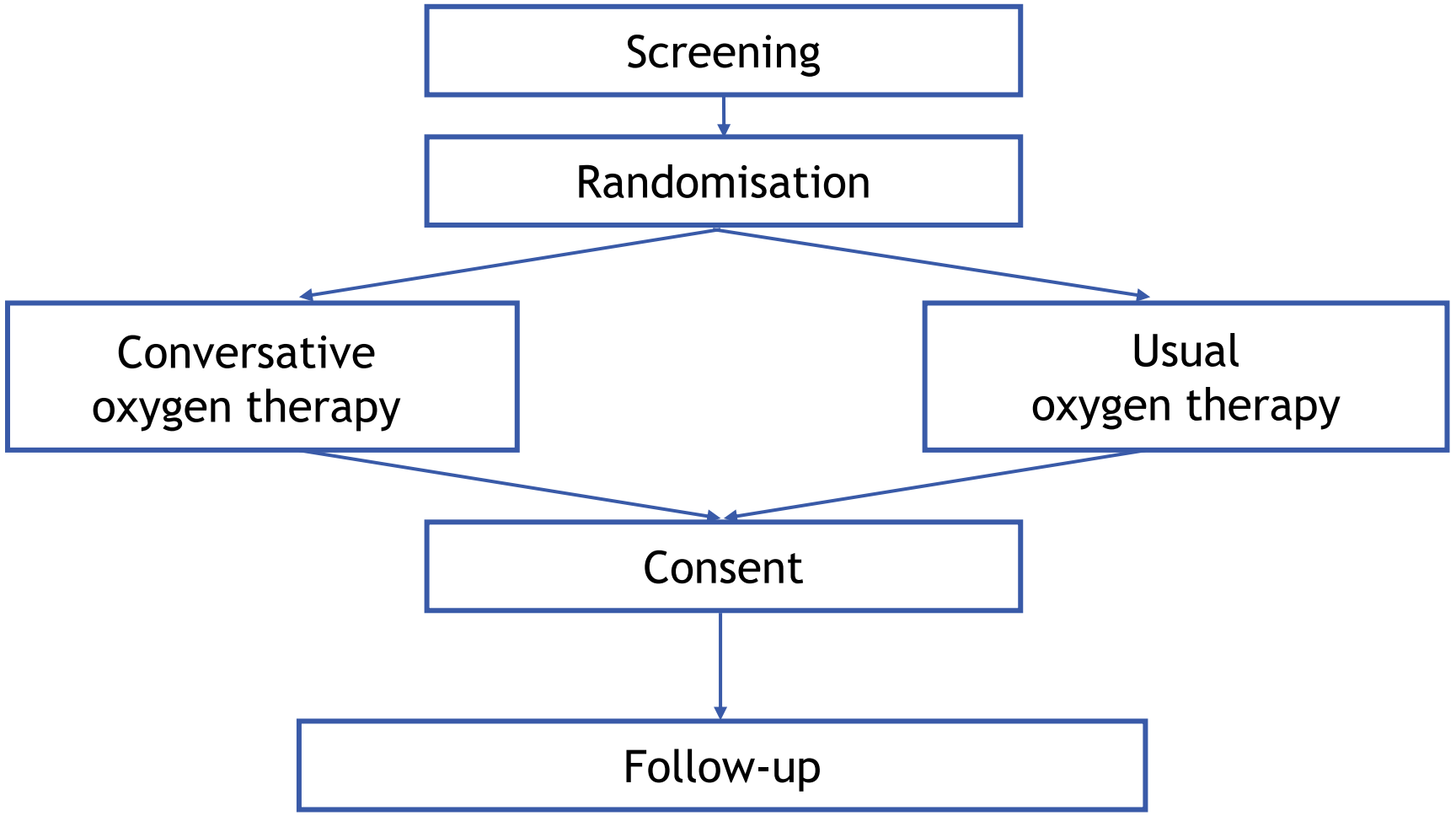
See SOP 007

- Patients will lack capacity at time of randomisation
- Emergency waiver of consent granted by REC (Mental Capacity Act)

- Once patient's medical situation is considered no longer an emergency, the consent procedures should begin
  - Consent sought after randomisation by GCP-trained team member
  - Expected to be within 24-48 hours of randomisation

- Posters and leaflets publicly available

Patient flow



Safety monitoring

Data collection

Safety monitoring

See SOP 009

- Monitor safety between randomisation and ICU discharge or 90 days (whichever comes first)*
- Serious Adverse Events (SAEs) reported to ICNARC CTU:

Expected Events	Unexpected Events
• Report all occurrences assessed as 'severe' or 'life-threatening' (SAEs): • Sinus tachycardia • Supraventricular tachycardia • Atrial fibrillation • Myocardial ischaemia/infarction • Mesenteric ischaemia	• Report only if considered to have reasonably occurred as a consequence of oxygen therapy (usual or conservative) • Not events that are part of the natural primary disease process or expected complications of critical illness (e.g. multi-organ failure)

**if readmitted to ICU within 90 days, safety monitoring recommences*

Thank you

- Any questions?

uk-rox@icnarc.org

020 7269 9277

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