NICE advice

FreeO2 automatic oxygen titration for chronic obstructive pulmonary disease and respiratory distress syndrome

Medtech innovation briefing
Published: 7 December 2021

www.nice.org.uk/guidance/mib281

Summary

- The **technology** described in this briefing is FreeO$_2$ automatic oxygen titration. It is designed to use blood oxygen saturation (SpO$_2$) levels to automatically adjust the flow of oxygen to a person, with the goal of achieving and maintaining target SpO$_2$.
- The **innovative aspects** are that it offers automatic oxygen titration.
- The intended **place in therapy** would be in a hospital setting instead of standard manual oxygen therapy.
- The **main points from the evidence** summarised in this briefing are from 6 studies including 4 randomised controlled trials and 2 prospective single-centre crossover trials with a total of 552 people. They show that FreeO$_2$ may increase time spent in

target SpO_2 range compared with standard manual oxygen therapy and may also reduce onward admissions to intensive care.

- **Key uncertainties** are that the evidence base is developing and currently limited to non-UK based settings. It would further benefit from evidence showing long-term patient outcomes, evidence across populations of people with acute respiratory distress from COVID-19, and evidence in babies and children. Further evaluation is also needed to understand differences in the precision of SpO_2 monitors across different skin colours.
- **Experts** advised that the technology was novel but lacked evidence on efficacy in some patient groups. They added that the device could reduce risk from oxygen toxicity. They also reported some gaps in the evidence base, including the cost benefits of the device and its implementation into the healthcare system.
- The **cost** of $FreeO_2$ is £9,600 per unit (excluding VAT). The **resource impact** would be in addition to standard care. The expected lifespan of $FreeO_2$ is 5 years, with a yearly preventative maintenance and calibration cost of £450.

The technology

$FreeO_2$ automatic oxygen titration (OxyNov) uses the measure of oxygen saturation of arterial blood (SpO_2) to automatically adjust the flow of oxygen to a person through a nasal cannula or non-occlusive mask. The technology operates on a closed loop and continuously adjusts the flow rate administered based on SpO_2, to achieve and maintain a target SpO_2. The device includes a safety feature that informs the user by an alarm if there is a breakdown or failure of oxygen supply.

The device is intended to be used in a hospital setting for treating chronic obstructive pulmonary disease (COPD) or acute respiratory distress syndrome (ARDS), which may be caused by COVID-19. The $FreeO_2$ aims to reduce the time a person spends in hypoxia or hyperoxia, improving clinical outcomes and reducing hospital stays.

The $FreeO_2$ system has an inbuilt pulse oximeter to measure SpO_2 levels. It automatically adjusts the oxygen flow rates (between 0 and 20 litres per minute, with or without humidification) based on this. This is measured using an oximeter worn continuously by the patient, which connects to the system by either Bluetooth or a standard 9-pin connector. The SpO_2 monitor continuously feeds the algorithm at a rate of 1 value per second. A proportional integral controller adjusts the oxygen flow delivered by a mass-

flow controller from 0 litres per minute to 20 litres per minute, to maintain SpO_2 at a predefined target. The $FreeO_2$ system also provides continuous monitoring of respiratory parameters in people who are spontaneously breathing. This can be displayed in graph format for up to 72 hours after collection to support management. The device uses mains supply with a battery back up in the case of power supply interruption.

The system was developed in collaboration with the Department of Electronic and Informatics Engineering, Laval University, Quebec and University Occidental Britany Brest, France and the 2 associated University Hospitals.

Innovations

The company claims the device is a new innovative technology offering automatic oxygen titration and weaning to regulate SpO_2 levels, that is not available with standard manual measurements.

Current care pathway

NICE's guideline on chronic obstructive pulmonary disease (COPD) recommends oxygen therapy as a treatment option for exacerbations of COPD. ARDs caused by COVID-19 may also need passive oxygen therapy before further treatment considerations such as continuous positive airway pressure (CPAP) intubation and mechanical ventilation. The British Thoracic Society's guideline for oxygen use in healthcare and emergency settings – summary of recommendations states that pulse oximetry must be available in all locations where emergency oxygen is used, and oxygen saturation should be checked by pulse oximetry in all patients who are breathless and acutely ill.

Oxygen therapy as an appropriate intervention should be prescribed according to a target saturation range and be monitored to remain in this range. Standard care involves using a manual oxygen flow regulator and a SpO_2 monitor. This needs healthcare professionals to manually measure both inspired oxygen concentration and SpO_2, which may be used to inform and monitor according to the National Early Warning Score (more information available in NICE's medtech innovation briefing on National Early Warning Score systems that alert to deteriorating adult patients in hospital). If oxygen levels are below the target range for the patient or if the saturation falls by 3% or more then oxygen therapy should be prescribed to achieve a target saturation (94% to 98% for most people who are acutely ill). Oxygen is given through a nasal cannula or a face mask. The measurements should be

repeated regularly, and appropriate oxygen flow adjustments made to bring SpO_2 into the individual target range. NICE guidance highlights that inappropriate oxygen therapy in people with COPD may cause respiratory distress.

The following publications have been identified as relevant to this care pathway:

- NICE's COVID-19 rapid guideline: community-based care of patients with chronic obstructive pulmonary disease (COPD)
- NICE's guideline on chronic obstructive pulmonary disease in over 16s: diagnosis and management
- NICE's medtech innovation briefing on OxyMask for delivering oxygen therapy
- NICE's medtech innovation briefing on myAIRVO2 for the treatment of chronic obstructive pulmonary disease
- Cochrane Library (2020) oxygen therapy in the pre-hospital setting for acute exacerbations of chronic obstructive pulmonary disease.

Population, setting and intended user

$FreeO_2$ is suitable for people who need oxygen therapy, from babies over 1 month old to adults. It is intended to be used after admission to A&E and after triage until SpO_2 levels are considered to be managed, or for the length of stay in hospital.

Various healthcare professionals may give oxygen therapy once appropriate training has been done. Staff giving oxygen should be trained across a range of devices to ensure oxygen is given safely, using appropriate devices and flow rates to achieve the target saturation.

Costs

Technology costs

The $FreeO_2$ system is available for purchase at £9,600 per unit (excluding VAT). There are no additional consumable costs related specifically to the use of this system. The expected lifespan of $FreeO_2$ is 5 years, with a yearly preventative maintenance and

calibration cost of £450.

Costs of standard care

Various SpO_2 monitors are available ranging in price from £144 to £450, with separate sensors varying in price from £42 to £225.

Resource consequences

The $FreeO_2$ device is not currently used in the NHS.

Using $FreeO_2$ in the NHS would incur an additional cost compared with standard manual delivery of oxygen. Assuming reliable SpO_2 measurements and adjustments are produced, this may be offset if the claimed benefits of reduced morbidities and length of hospital stay are seen. There is limited published evidence to support these claimed benefits.

One economic evaluation was located relating to the cost of $FreeO_2$ technology (Poder et al. 2018). This examined the cost effectiveness of $FreeO_2$ in 47 people hospitalised with acute exacerbation of COPD in Quebec. The study reported generated savings of 20.7% of the per-patient costs at 180 days (£1,695.31). This decrease is not significant at the 95% threshold ($p=0.13$), but the time spent at target oxygen saturation, time spent in hyperoxia, and level of severe hypoxaemia all improved ($p<0.001$). The incremental cost-effectiveness ratios reported indicate that $FreeO_2$ is more cost effective than manual oxygen titration.

The company provides free onsite user training on instillation and implementation. Ongoing staff training can be delivered on request. No changes in facilities and infrastructure were identified for the adoption of $FreeO_2$.

Regulatory information

$FreeO_2$ is a CE-marked class IIb medical device.

One field safety notice was located on this technology, reported in November 2020. Short-term software parameter amendments were suggested by the company for users and long-term software amendments were made by the company to resolve the issue.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Chronic obstructive pulmonary disease (COPD) is a chronic condition, which may mean someone is disabled if this has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act.

The US Food and Drug Administration (FDA) has highlighted differences in precision of SpO_2 monitors across different skin colours which may result in risk of inaccuracy for individuals with darker skin pigmentations. It reports that further evaluation on this association is needed (FDA safety communication, 2021).

The Medicines and Healthcare products Regulatory Agency (MHRA) highlights a number of factors that can affect the accuracy of pulse oximeters, including skin pigmentation (MHRA use and regulation of pulse oximeters, 2021). It reports that darker skin pigmentation may cause an overestimation of SpO_2 saturations, so the relative changes in an individual person's reading should be considered as well as the numerical value.

Race is a protected characteristic under the Equality Act.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 6 studies summarised in this briefing, including 552 people, selected as the most relevant and best quality evidence relating to the technology. Four studies were randomised controlled trials and 2 were prospective single-centre crossover studies.

An economic study was also located (Poder et al. 2018) and is commented on in the resource consequences section.

The clinical evidence and its strengths and limitations are summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for the technology is of moderate methodological quality. All studies had standard care comparators. Two used multi-site recruitment and both had good size populations. One study reported upon its use in babies and children. All studies suggest that FreeO_2 may increase the time in the target SpO_2 range. None of the reported studies are based in the NHS. Although the company reports that the device can be used to treat acute respiratory distress syndrome (ARDs) from COVID-19, none of the summarised evidence includes this indication.

Further evidence would benefit from use of the device in UK-based settings across both chronic obstructive pulmonary disease (COPD) and ARD indications and in all ages.

Ouanes et al. 2021

Study size, design and location

Prospective single-centre crossover cohort study in people with acute respiratory failure admitted to intensive care in Tunisia (n=51).

Intervention and comparator

FreeO_2 and constant flow modes.

Key outcomes

Time spent within target SpO_2 range was significantly higher with FreeO_2 mode compared with constant O_2 flow mode (86.92% [77.11% to 92.39%] compared with 43.17% [5.08% to 75.37%]; p<0.001). Time with hyperoxia was lower with FreeO_2 mode: 8.68% (2.96% to 15.59%) compared with 38.28% (2.02% to 86.34%). Times with hypoxaemia and with severe desaturation were similar. At the end of FreeO_2 mode, O_2 flow was lower than 1 litre/

min in 28 people (54.9%), with a median of 0.99 litre/min.

Strengths and limitations

This was a pilot crossover design focused on physiological parameters without collecting patient-centred outcomes. People were not recruited consecutively because of availability of 1 $FreeO_2$ device. Some results were reported to not be interpretable because of loss of the SpO_2 signal.

Roué et al. 2021

Study size, design and location

Open-label randomised controlled pilot study in babies and children with acute hypoxemic respiratory distress admitted to University Hospital in France (n=60).

Intervention and comparator

$FreeO_2$ and standard manual O_2.

Key outcomes

Time spent within the SpO_2 predefined target range was significantly increased in the $FreeO_2$ group (94.6% plus or minus 6%, compared with 76.3% plus or minus 22%), showing a difference of 18.4 (confidence interval [CI] 10.1 to 26.7). Secondary measure of time spent with severe desaturation did not significantly differ between groups (0.04% plus or minus 0.17%, compared with 0.15% plus or minus 0.62% in the control group). The children in the $FreeO_2$ group spent significantly less time with hypoxemia, especially in the older children group (0.8% in the $FreeO_2$ group and 22% in the control group).

Strengths and limitations

The $FreeO_2$ device used in the pilot study was a prototype using an algorithm that was subsequently modified in the latest version of the device. Authors recognised the limitation of the low mean number of changes in oxygen flow seen in the control group, which may be affected by the patient-nurse ratio. The device was only used in the first 24 hours of hospitalisation and for a mean duration of 210 minutes. One author is a

cofounder and shareholder of the research and development company for $FreeO_2$.

L'Her et al. 2021

Study size, design and location

Multisite randomised controlled trial across 5 university hospitals in France and Canada (n=198).

Intervention and comparator

Automated closed-loop oxygen administration using $FreeO_2$ (n=103) and standard closed-loop oxygen administration (n=95).

Key outcomes

The primary outcome was the percentage of time within the oxygenated range during a 3-day time frame, which was shown to be 31.9% increased time in the range in the automated group (95% CI -42.8% to 59.2%). The secondary outcomes results included: periods of hypoxaemia reduced in the automated group by -10.2% (95% CI -13.9 to -6.6%), periods of hyperoxaemia reduced in the automated group by -22.0% (95% CI -27.6% to -16.4%).

Strengths and limitations

Investigators were not blinded. Monitoring in the standard group was done using the $FreeO_2$ device, which may have resulted in more frequent monitoring than standard care and have reduced the benefits seen in automated administration. One author of L'Her is a cofounder and shareholder of the research and development company for $FreeO_2$.

L'Her et al. 2017

Study size, design and location

Multi centre randomised controlled trial in people presenting with acute respiratory distress in the emergency department in France and Canada (n=187).

Intervention and comparator

$FreeO_2$ (n=93) and manual oxygen titration (n=94).

Key outcomes

Time within the SpO_2 target was higher under automated titration (81% plus or minus 21% compared with 51% plus or minus 30%, p<0.001). Automated titration significantly reduced time with hypoxaemia (3% plus or minus 9% compared with 5% plus or minus 12%, p=0.04) and hyperoxia under O2 (4% plus or minus 9% compared with 22% plus or minus 30%, p<0.001). Oxygen could be weaned at the end of the study in 14.1% compared with 4.3% of people in the automated and manual titration group, respectively (p<0.001). O_2 duration during the hospital stay was significantly reduced (5.6 days plus or minus 5.4 compared with 7.1 days plus or minus 6.3, p=0.002).

Strengths and limitations

Randomisation was sealed to the intervention and intention-to-treat analysis was used. However, the length of follow-up period (3 hours) may not have captured outcome improvement. One author (L'Her) is a cofounder and shareholder of the research and development company for $FreeO_2$.

Lellouche et al. 2016

Study size, design and location

Single centre pilot randomised trial in Canada in people with COPD (n=50).

Intervention and comparator

$FreeO_2$ and manual oxygen titration.

Key outcomes

Significantly higher percentage of time spent in target SpO_2 and reduced time in severe desaturation and hyperoxia. Time from study inclusion to hospital discharge was reduced but not significantly (5.8 days plus or minus 4.4 with $FreeO_2$ and 8.4 days plus or minus 6.0 with usual oxygen administration; p=0.051).

Strengths and limitations

Blinding of all investigators was not possible because of the practical set up of the system, but steps were taken to blind those that could be. The study has a small sample size and may not be generalisable to a wider range of disease severity. Two authors are coinventors of FreeO$_2$. Two authors participate in Onnovair, a company that owns shares in OxyNov.

Schneeberger et al. 2021

Study size, design and location

A prospective randomised controlled, double-blind crossover trial in people with COPD in Germany (n=50).

Intervention and comparator

FreeO$_2$ and constant flow modes.

Key outcomes

This study found significantly and clinically relevant improvements in walking endurance time, with 68% of people walking for longer in the automated titration group. Reasons for stopping the endurance shuttle walk tests was significantly different between constant titration and automated titration support (p=0.001). Dyspnoea was the main reason (in 70% of people) for stopping the test with constant flow modes, compared with 48% stopping because of breathlessness with automatic oxygen titration. People in the study also reported to prefer the automatic O$_2$ system.

Strengths and limitations

The authors highlighted that 14 people reached the maximum exercise duration and the effect size may have been different with extended time periods. The study represents the immediate effects of O$_2$ therapy and might not reflect longer usage scenarios. The authors recommend that future studies should consider medium and long-term effects of using automatically titrating oxygen system. No conflicts were declared.

Sustainability

The device is reported to optimise oxygen use and may reduce overall oxygen use as shown in Poder et al. 2018 and L'Her et al. 2021.

Recent and ongoing studies

- Automated administration of oxygen using the $FreeO_2$ device in ambulances for COPD and trauma patients: a feasibility study. Trial identifier: NCT03696563. Status: not yet recruiting. Indication: COPD exacerbation, trauma. Devices: automated oxygen administration ($FreeO_2$) compared with standard administration. Estimated completion date: December 2021. Countries not listed.

- Reduction of length of stay by automated adjustment of oxygen on patient with acute COPD exacerbation - $FreeO_2$ HypHop. Trial identifier: NCT03835741. Status: recruiting. Indication: oxygen toxicity, COPD exacerbation, hyperoxia, hypoxemia, hypoxic respiratory failure. Devices: $FreeO_2$ compared with manual titration. Estimated completion date: June 2022. Country: Canada.

- Influence of automatic oxygen titration device ($FreeO_2$) on percentage of time within oxygen saturation target and induced hypercapnia during noninvasive ventilation for patients hospitalised for an acute exacerbation of COPD or a bariatric surgery. Trial identifier: NCT04136717. Status: recruiting. Indication: oxygen toxicity, COPD exacerbation, abdominal obesity, surgery. Devices: $FreeO_2$. Estimated completion date: January 2021. Country: Canada.

- Clinical evaluation of the automatic oxygen adjustment by $FreeO_2$ in a medical population in hospital. Trial identifier: NCT03119727. Status: unknown. Indication: respiratory disease or failure, COPD exacerbation, asthma, pneumonia. Devices: $FreeO_2$. Estimated completion date: December 2019. Country: Canada.

- Using a closed-loop system for oxygen delivery ($FreeO_2$) to optimise oxygen therapy in patients with exacerbations of chronic obstructive pulmonary disease. Trial identifier: NCT01393015. Status: unknown. Indication: COPD exacerbation. Devices: $FreeO_2$ compared with automated settings. Estimated completion date: December 2011. Country: Canada.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

None of the 3 experts were familiar with the device and reported that they did not believe it was currently in use in the NHS.

Level of innovation

All 3 experts described the technology to be novel with uncertain safety and efficacy. Two experts said that the technology cannot replace standard care, but that it could be used alongside standard care and may be a useful addition in some settings and individuals. All experts said that they were not aware of any alternative technologies for this function.

Potential patient impact

Two experts reported that the device could reduce patient risk and morbidity from oxygen toxicity. Both agreed that it could assist in weaning O_2 for patients with complex needs, potentially resulting in reduced length of hospital stay. One expert highlighted the potential to reduce medical error with the use of this device.

All experts described people with chronic obstructive pulmonary disease (COPD) as a subgroup who may particularly benefit from this technology, alongside people needing supplemental oxygen with viral pneumonias such as COVID-19.

Potential system impact

Experts said the device could reduce length of stays and improve hyperoxia outcomes and oxygen use. More specifically 1 expert stated that it could reduce the length of stay in people with acute exacerbations of COPD because of improved weaning of oxygen supplementation.

All experts agreed that the technology would cost more than standard care and the cost benefits were not clear. One expert did raise the potential for reduced nursing time needed from using the technology. Experts raised several aspects around the costs that would

need to be better understood, including the costs associated with consumables, maintenance, servicing, software updates and training. All experts said that additional training would be needed with the device to ensure its safe use.

Experts highlighted implementation considerations for the technology. One expert raised the connectivity of the device to monitors needing either Bluetooth or 9-pin connectors and the significant capital investment that would be needed for Bluetooth monitors.

General comments

Experts listed a number of potential risks for harm with the device. One expert discussed the theoretical risk of machine failure, and theoretical risk of death from hypoxia if the machine failed, as well as risk of signal loss and software failure. Another expert stated that the lack of applicability of the procedure in people who are haemodynamically compromised and people with poor peripheral circulation that would need facilities for manual oxygen titration to be available in parallel. One expert highlighted that the evidence base includes predominantly single-centre studies, or short durations which may not capture adverse events.

Experts highlighted several evidence gaps that would be beneficial to address. One expert queried if the increased time spent in target saturation showed significant changes to hard clinical outcomes (such as mortality, length of stay and readmission rates). Two experts voiced a need for in depth economic analysis to show the cost benefits. Another expert highlighted the gap in evidence for its use in people with respiratory distress syndrome.

Expert commentators

The following clinicians contributed to this briefing:

- Rahul Mukherjee, consultant physician and honorary senior clinical lecturer, University Hospitals Birmingham NHS Foundation Trust. Did not declare any interests.
- Pearlene Antoine-Pitterson, respiratory physiotherapist, University Hospitals Birmingham NHS Foundation Trust. Did not declare any interests.
- Dr Ben Messer, consultant in intensive care medicine and home ventilation. Newcastle-upon-Tyne NHS Hospitals Foundation Trust. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-4354-8