BMJ Open

High-flow weaning strategies for infants with bronchiolitis: protocol for a pilot randomised controlled trial in the UK

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To cite: Towriss C, Dafydd C, Edwards M. High-flow weaning strategies for infants with bronchiolitis: protocol for a pilot randomised controlled trial in the UK. *BMJ Open* 2024;**14**:e087672. doi:10.1136/bmjopen-2024-087672

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-087672).

Received 16 April 2024
Accepted 09 October 2024

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ABSTRACT

Introduction Ward-based high-flow nasal cannula (HFNC) is an effective therapy for children with bronchiolitis who have failed standard oxygen therapy. However, HFNC can increase hospital length of stay perhaps because there is a lack of evidence to guide weaning strategies.

We aim to conduct a pilot study to identify the most effective weaning strategy for infants, up to 12 months, supported on HFNC for bronchiolitis. This may lead to reduced time on respiratory support and shorter length of stay. If this pilot study is deemed feasible, it will inform a larger multicentre trial.

Methods and analysis This open label, non-blinded, randomised controlled trial will be conducted over 24 months at the Noah's Ark Children's Hospital for Wales, Cardiff, and will aim to recruit 20 patients. It will compare high-flow only weaning (high-flow discontinued at FiO_2 of 21%) to HFNC and low-flow weaning (HFNC discontinued at 30% and replaced by low-flow up to 2 L/min). HFNC therapy will be delivered at 2 L/kg/min (maximum 20 L/min). The primary outcome is to examine the feasibility of different weaning strategies for infants with bronchiolitis requiring HFNC. Secondary outcomes include the time from decision to wean HFNC to the patient no longer requiring respiratory support and a safety assessment of the weaning strategies.

Ethics and dissemination Health Research Authority and Health and Care Research Wales approval was granted on 8 September 2020 following review by the NHS research ethics committee.The sponsor is Cardiff and Vale University Health Board. We will publish the results in a peer-reviewed medical journal, via websites and newsletters.

Trial registration number NCT04287959.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Questionnaires for parents and staff will be used to examine the acceptability of the different weaning strategies.
⇒ This pilot study will be conducted at a single children's hospital and if deemed feasible, it will inform a larger multicentre trial.
⇒ This is a non-blinded trial because it is impractical to blind different oxygen delivery devices.

INTRODUCTION

Bronchiolitis is an acute viral lower respiratory tract infection among infants and children. It is most commonly caused by respiratory syncytial virus (RSV) and is the leading cause of infant hospital admissions.[1–3] To reduce variations and inconsistencies in the management of bronchiolitis, many countries have published national guidance to promote supportive rather than interventional therapies. Most guidelines recommend against routine diagnostic testing and the use of treatments such as corticosteroids and antibiotics, instead they advocate supporting hydration and oxygenation.[4–6]

High-flow nasal cannula in bronchiolitis

Traditionally oxygenation support has been delivered to patients using low-flow oxygen provided on the paediatric wards. If escalation of support was required, it would be given via continuous positive airway pressure (CPAP) or mechanical ventilation within a paediatric intensive care unit (PICU).[7 8] These strategies require highly skilled staff, are costly, and are associated with significant risks of adverse events.[9]

High-flow nasal cannula (HFNC) therapy has emerged as an alternative form of non-invasive ventilation for the treatment of bronchiolitis in paediatric wards.[10–12] It works by delivering a blended mixture of oxygen and air which is humidified and heated. Definitions of HFNC vary but most commonly it is defined as 2–3 L/min delivered via nasal prongs and is thought to work by providing a degree of positive pressure, which washes out the nasopharyngeal dead space and decreases upper airway resistance.[1 13] Over the last decade, HFNC therapy has migrated from the PICU to the inpatient paediatric ward, resulting in a growing body of evidence to support this transition.[12]

The largest randomised multicentre trial, PARIS, compared HFNC (2 L/kg/min) to low-flow oxygen therapy in children with bronchiolitis. Significantly fewer treatment failures occurred in the HFNC group (7%

vs 16%).[11 14] Another trial (single centre) found HFNC did not significantly reduce the length of time on oxygen compared with low-flow, but did have fewer treatment failures (14% vs 33%).[15] Of the combined 200 patients who failed low-flow from both trials, 61% were rescued by HFNC.[13] Importantly, a recent systematic review found no difference in adverse outcomes when comparing HFNC to low-flow.[11] Together, this evidence supports the use of HFNC as an escalation therapy once low-flow oxygen therapy fails, rather than as a primary treatment for hypoxaemia.

The use of HFNC is 'becoming widespread' with growing evidence associating it with an increased length of stay among patients with bronchiolitis.[5 16] Results from the PARIS-2 trial suggest early use of HFNC in hypoxic children increases both the time on respiratory support and length of hospital stay. The difference may be explained by a number of factors including a reluctance to wean or variations in weaning practice.[17 18] It is feasible that the introduction of weaning protocols may reduce the length of stay in infants with bronchiolitis on HFNC.

Study rationale

During the seasonal peak of RSV infections, there is greater demand for inpatient paediatric beds. Reducing the time patients spend on respiratory support can mitigate demand. Quality improvement initiatives have devised HFNC weaning protocols which were associated with a shorter admission among children with bronchiolitis.[19 20] However, there is a lack of quality evidence to determine the most effective and safest method of weaning.

The All Wales Bronchiolitis guideline advocates the discontinuation of HFNC once the FiO_2 is weaned to 30% and the patient is stable. HFNC is then replaced by low-flow oxygen at 2 L/min which is then weaned.[21] In contrast, the PARIS trial weaned the FiO_2 to 21%, then HFNC was continued for another 4 hours before being stopped (the flow rate was not altered).[14]

Among infants with bronchiolitis, it is unknown whether HFNC weaning alone, or a combination of HFNC and low-flow weaning influences either the time taken to wean patients off respiratory support or length of hospital stay.

Study objective and purpose

We aim to conduct a pilot study to identify the weaning strategy most effective for infants, up to 12 months, supported on HFNC for bronchiolitis. This may lead to shorter total length of stay in hospital, without compromising care. Infants with bronchiolitis who are on HFNC (the devices used will be Airvo 2, Fisher & Paykel Healthcare) will be on a flow of 2 L/kg/min (maximum 20 L/min) and variable oxygen concentration to maintain target oxygen saturations >90%.

Primary aim

- To examine the feasibility of different weaning strategies for infants with bronchiolitis requiring HFNC.

The progression from pilot study to RCT will be assessed using the 'traffic light system'. Preset criteria will be judged using threshold percentage scores as to whether they are 'red' (insolvable issues in this area which cannot be remedied and therefore no progression), 'amber' (issues in this area can be remedied and therefore a larger trial can proceed with caution) or 'green' (where there are no concerning issues, a larger trial can proceed).[22 23]

- The following endpoints will be used to determine feasibility of further study:
  - Identify the proportion of eligible patients approached who consent to the study.
  - Identify the proportion of recruited patients who supply primary outcome data (time spent in hospital).
  - Assess adherence to the weaning protocol assigned during randomisation, in particular if this can be complied with in a ward setting with a large number of healthcare staff.
  - Identify which secondary outcomes are important to include, and how best to assess them.
  - Identify barriers to patient recruitment and site set-up.
  - Assess the acceptability of HFNC by parents and healthcare staff (via questionnaire responses with staff and parents).
- To assess the acceptability of HFNC by parents and healthcare staff. This will be done by analysing questionnaire results from parents and healthcare staff.

Secondary aim

- The comparison of time taken to wean from HFNC support to air. This is defined as the time taken from when the decision was made to wean HFNC to when the patient no longer requires respiratory support.
- To assess the safety of the different weaning strategies used.
- The safety outcome measures comprise the following:
  - Rates of failure to wean strategy (defined as fulfilment of the 'failure to wean criteria' which results in a patient becoming temporarily ineligible for oxygen weaning).
  - Rates of respiratory support escalation requiring CPAP or invasive ventilation.
  - Rates of air leaks and other morbidities such as pneumothorax or mucosal injury.
  - Readmission rates within 14 days of discharge from hospital.
  - Mortality rates.

Methods and analysis

Study design and setting

This is an open label, non-blinded, randomised controlled trial comparing HFNC weaning strategies. As no randomised trial has yet been conducted to investigate the efficacy or safety of different HFNC weaning methods, we opt to conduct a pilot study. The delivery

of a pilot study will help determine the acceptability of our intervention and highlight problems with recruitment or outcome measures. Our recruitment data will inform sample size calculations for a larger randomised controlled trial. It will be conducted at a single site, the general paediatric wards of The Noah's Ark Children's Hospital for Wales in Cardiff.

Definitions

All infants aged from 4 weeks to 12 months with symptoms of bronchiolitis and the need for HFNC support are eligible for enrolment in the trial. Bronchiolitis is defined as signs and symptoms of respiratory distress associated with symptoms of a viral respiratory tract infection.[24 25] The need for HFNC will be determined using the paediatric observation chart and the attending clinician's judgement.

Although the threshold for providing oxygen supplementation in bronchiolitis varies, a transcutaneous haemoglobin oxygen saturation (SpO_2) of 90% or over will be used in line with UK national guidance.[5]

Randomisation

Randomisation will occur once informed consent has been obtained. The randomisation process will be completed prior to the study opening. It will be performed using a computer-generated, block randomisation programme using an allocation ratio of 1:1. The arm allocation details will be placed in sequentially numbered, sealed, opaque randomisation envelopes each labelled with a unique trial participant number. Once a participant has been consented and recruited, they will be assigned a trial participant number. The corresponding numbered envelope will be matched to the participant number. Once the participant is deemed ready to wean, the healthcare team will open the randomisation envelope to determine the allocation. The trial schedule is outlined in figure 1.

Choice of 2 L/min flow rate

The maximal inspiratory flow achieved by a healthy infant during regular breathing is 0.8 L/min/kg per breath. A child unwell with a respiratory condition such as bronchiolitis generates a flow of up to 1.0–1.6 L/min/kg per breath.[26–28] The aim of HFNC therapy is to equal the maximal inspiratory flow rate generated by the infant. A safety margin of 2 L/min/kg is given, and this is the most commonly used flow rate for these infants. There is no evidence that using a higher flow rate is beneficial.[11 29] Therefore, in our study, all infants supported with HFNC will receive a flow of 2 L/min/kg.

Ready to wean

Patients are defined as ready to wean once they fulfil all three of the following criteria:

- Have received HFNC (2 L/min/kg) for a minimum of 12 hours.
- Have a paediatric early warning score of less than 3 for at least 2 hours.
- Are requiring an FiO_2 of less than 40%.

The bedside nurse will be responsible for both the assessment of the 'ready to wean' criteria and for carrying out both arm A and B weaning strategies. If the bedside nurse has a clinical concern, a review by clinical team is indicated. Further, the weaning process can be halted at any time if indicated by a member of the clinical team.

Treatment arms

Arm A: high-flow only weaning (weaning HFNC oxygen to 21%)

Once the 'ready to wean' criteria are met, the process of weaning oxygen can start. The flow rate will be kept at 2 L/kg/min while the FiO_2 is decreased to maintain target SpO_2 of 90% and above. This process will repeat itself every 2 hours until the patient is at FiO_2 of 21%. If the patient fulfils the 'failure to wean' criteria at any point, the FiO_2 should be kept constant or be increased to achieve SpO_2 of 90% and above (the bedside nurse should also consider a clinical team review and an escalation of treatment). The patient should then be reassessed for weaning after 2 hours. After 4 hours at FiO_2 21%, and not meeting the failure criteria, HFNC is discontinued (it will be restarted if the failure to wean criteria are fulfilled) (see online supplemental figure A). Any decision regarding feeding and hydration will be made independently to decisions concerning weaning of respiratory support.

Arm B: high-flow and low-flow weaning (weaning HFNC oxygen to 30%)

Once the 'ready to wean' are met, the process of weaning oxygen can start. The flow rate will be kept at 2 L/kg/min while the FiO_2 is decreased to maintain target oxygen saturations of 90% and above. This process will repeat itself every 2 hours until the patient is at FiO_2 of 30%. Provided the patient has been stable for 4 hours on 2 L/kg/min with an FiO_2 of 30%, the HFNC will be discontinued. Low-flow oxygen (up to 2 L/min) may be commenced to maintain saturations of 90% and above. The low-flow oxygen will be weaned by 0.5 L/min every 2 hours until the patient maintains oxygen saturations of 90% and above without supplementary low-flow oxygen. If the patient fulfils the 'failure to wean' criteria at any point, the FiO_2 or oxygen flow rate (if on low-flow) should kept constant or be increased to achieve SpO_2 of 90% and above (HFNC may need to be restarted if the patient is on low-flow oxygen). The bedside nurse should consider a clinical review and an escalation of care should be considered if the patient fulfils the 'failure to wean criteria'. The patient should then be reassessed for weaning after 2 hours (see online supplemental figure B). Any decision regarding feeding and hydration will be made independently to decisions concerning weaning of respiratory support.

Fit for discharge

For the purpose of the trial, patients are considered fit for discharge after 4 hours of maintaining their oxygen saturations of 90% and above without respiratory support,

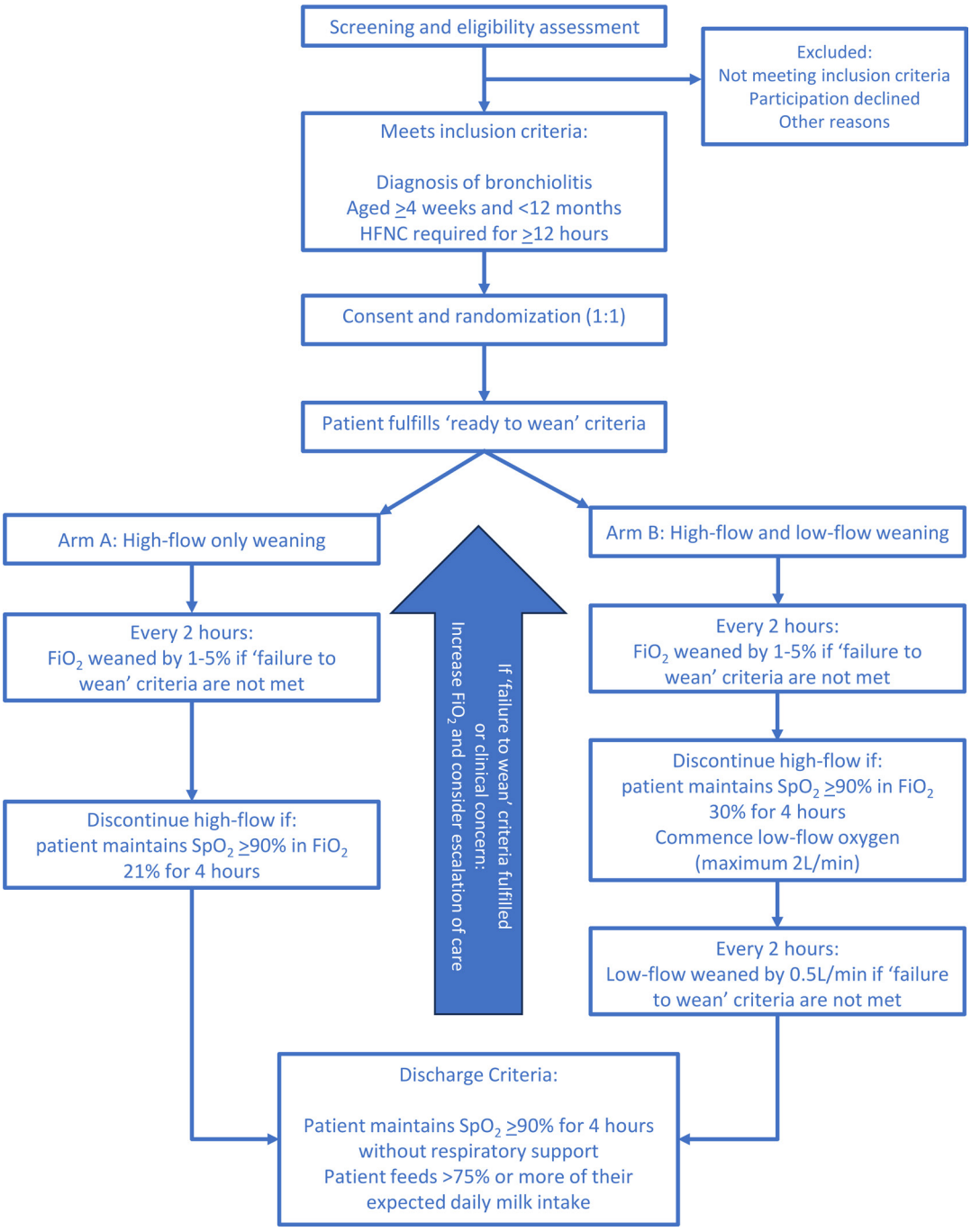

Figure 1 Trial flow diagram. HFNC, high-flow nasal cannula.

and orally feeding over 75% of their expected daily milk intake.[21]

Failure to wean

The failure of a weaning strategy will be defined by meeting one of the following criteria:

- Oxygen saturations <90%.
- Paediatric early warning score >3.
- Nursing or medical concerns over the clinical condition of the patient.

Should the participant fulfil the failure to wean criteria, the patient would be temporarily ineligible for weaning. After another 2 hours, the participant will be reassessed for weaning.

Paediatric early warning score

The Noah's Ark Children's Hospital for Wales uses a paediatric observation chart for all patients as an early warning tool. For the purpose of the study, the chart will be modified to assign a numerical score from 0 to 3 for each clinical parameter. A score of 0 will be assigned to observations within the normal range, increasing up to 3 for those observations furthest from the normal range. A total score will be obtained by totalling all the scores

for each clinical parameter. A total score of >3 will fulfil the criteria for failure to wean (see online supplemental figure C).

Acceptability of HFNC

A service evaluation will be conducted to obtain feedback, using questionnaires, to understand parents and healthcare professionals' experience on the use of HFNC for infants with bronchiolitis. Questionnaires will be given to parents as well as healthcare professionals to understand their experience of the use of high-flow for patients with bronchiolitis (see online supplemental material document D).

Subject selection

Patients will be screened on the general paediatric wards, the paediatric emergency department and the Same Day Emergency Care unit of Noah's Ark Children's Hospital.

All infants aged from 4 weeks to 12 months, with symptoms of bronchiolitis, and who require HFNC therapy for 12 hours or more, are eligible for enrolment into the trial.

We aim to recruit 2–4 patients per month during the seasonal peak of bronchiolitis. A 24-month study period will allow for two bronchiolitis seasons which will therefore increase participant recruitment.

Inclusion and exclusion criteria

Inclusion criteria

- Clinical diagnosis of bronchiolitis.
- Age >4 weeks and <12 months.
- HFNC respiratory support required in a ward setting for over 12 hours.

Exclusion criteria

- Requirement for imminent intubation and ventilation, or having received mechanical ventilation during the hospital admission.
- Requirement for imminent CPAP support.
- Weight >10 kg.
- Ready to wean HFNC after <12 hours of its initiation.
- Pre-existing or concomitant, non-viral respiratory infections.
- Pre-existing respiratory disease.
- Ex-premature infants (born at <32 weeks gestation).
- Low level of consciousness.
- Apnoeas (pause in breathing for 20 s or longer, or a shorter pause in breathing associated with bradycardia, cyanosis, pallor and/or hypotonia).
- Cyanotic heart disease.
- Basilar skull fracture.
- Upper airway obstruction.
- Craniofacial malformations.
- Infants on home oxygen.

Recruitment and consent

Recruitment will be conducted over 24 months. It will start in October 2023 and end in October 2025. Potential recruits identified by the clinical team will be checked by the research team for eligibility and appropriateness for recruitment. For any eligible infant, the parents/legal guardians will be given a parent information sheet and shown an animated trial explainer video. Informed consent will be sought from the parents/legal guardians of the infant once they have had adequate time to review the trial information.

For those infants who meet the eligibility criteria, consent will be obtained for enrolment in the trial by one of the research team. For those infants who do not meet eligibility criteria, or decline consent, the following information will be obtained: age; gender; reason not eligible for trial participation, or if they are eligible but decline.

All researchers with appropriate delegated responsibility will be allowed to obtain consent once they have been trained. They must hold a valid certificate of Good Clinical Practice.

Extensive discussion of the risks and possible benefits of the participation in the study will be provided to parents/guardians. Consent forms describing in detail the study procedures and risks are given to the parents/guardians and written documentation of informed consent is required prior to enrolling in the study (see online supplemental material document E). The parents/guardians can withdraw consent at any time during the study.

The service evaluation questionnaire does not directly impact on the research study so consent will not be obtained from the nursing staff.

Withdrawal of subjects

Parents/guardians have the option to opt out of recruitment at any stage. Parents/guardians have the right to withdraw their child at any point in the study. Any data collected up to the point of withdrawal will be kept and analysed. Parents/guardians who request will have all research data destroyed for their child.

Outcomes to be measured

Baseline characteristics of study participants will be collected which will include age, weight, sex, ethnicity, premature birth, neonatal respiratory support, previous admission for respiratory disease, diagnosis of congenital heart disease, history of wheeze, family history of wheeze or allergy. Although additional health-related data is not mandatory, chest radiograph reports, virology results and any blood results including blood gas analysis will be recorded if available.

The paediatric early warning charts will record the patient's clinical observations, including: respiratory rate, oxygen saturations, respiratory effort, heart rate, temperature and the total score. Clinical observations will be recorded at intervals as determined by the hospital protocol.

The time and date of admission, duration of clinical symptoms, total time on HFNC, time of decision to wean, feeding regimen, time to no longer needing respiratory support and time of discharge will also be recorded.

Data will also be recorded on whether the participant required an escalation of care (admission to high

dependency unit, PICU, restarting HFNC), had documented desaturation episodes, apnoeas, required readmission to hospital within 14 days of discharge, rates of pneumothorax.

Discontinuation/withdrawal of participants from study

Participants may be withdrawn from the trial for a valid medical reason by the decision-making clinician, the reason for withdrawal will be recorded. The parents/guardians can withdraw consent at any point without giving any reason. They will be asked to consent for the use of data already collected to be available for trial evaluation.

Products, devices, technique and tools

- **Devices:** Airvo 2 high-flow system from Fisher and Paykel healthcare. The devices are approved for the use in infants with bronchiolitis, and are currently in use at the Noah's Ark Children's Hospital for Wales.
- **Staff training:** the nursing staff on the wards are trained to use the Airvo 2 high-flow device.
- **Tools:** adapted validated questionnaires will be used to assess parent and nursing opinions on the use of high-flow on the quality of lives for the infants.

Definition of end of study

The end date of the study is October 2025. The project steering group will meet monthly to discuss any reasons for early closure of the study.

Statistics and data

Sample size

Local data at the Noah's Ark Children's Hospital for Wales had an average of 75 patients needing HFNC support on the ward over the last 2 years. We aim to 20 patients into the trial. This number should be sufficient in order to assess the primary feasibility criteria.

Description of statistical and feasibility analysis

The primary feasibility metrics (recruitment, retention/follow-up, adherence rate) will be reported as point estimates alongside 95% CIs, and assessed against the prespecified traffic light progression criteria[22]:

- Recruitment rate (number screened and approached/number consented): >60% green, 30%–60% amber, <30% red.
- Retention/follow-up rate (number consented/number providing primary clinical outcome data): >80% green, 70%–80% amber, <70% red.
- Adherence rate (number consented/number fully adhered to the allocated weaning method): >80% green, 60%–80% amber, <60% red.

Descriptive statistics will be used to report on the baseline characteristics of the total study cohort. We will use an intention-to-treat analysis for all data. The 'time taken to wean' secondary endpoint is a measurement of time with the difference analysed using a paired t-test if the data is normally distributed, p value and 95% CIs. More detailed modelling will include survival analysis which includes regression models with other variables. Statistical significance is set at 0.05. If the data is not normally distributed it will be analysed using a Mann-Whitney U test. Analysis of secondary outcomes includes both comparisons of measurements and proportions, using CIs of differences as the major method of presentation where possible. A logistic regression analysis will be used to identify risk factors. Prespecified subgroups include age-based groups (<3 months, <6 months, <12 months), and viral status (RSV, other virus, mixed viruses, no virus identified).

Adverse events and monitoring/reporting

All adverse events and experiences will be recorded on the case report form. If the adverse event involves the use of the Airvo 2 high-flow system, the research team will notify the Medicine and Healthcare Products Regulatory Agency via the Yellow Card Scheme. All serious adverse events (SAE) will be reported directly to the chief investigator and reported using the SAE form within 24 hours. Protocol deviation logs will be completed to ensure any problems recurrent problems with the protocol is highlighted for review.

Data recording and record keeping

Study documents will be collected and retained in accordance with the data protection act 1998. Data will be stored for 5 years poststudy completion. Essential documents will be kept for a minimum of 21 years after completion of study. During and after the study, documents will be retained in a secure location within the Children and Young Adults Research Unit (CYARU), Noah's Ark Children's Hospital for Wales. Digital data will be stored on NHS computers within CYARU under password protection controlled by the principle investigator. Each participant will be assigned an individual study number which will be used in the study database. Original proformas, which could identify patients, will be held securely within CYARU. No patient identifiable information will be kept on the study database. Data will be analysed by the study team.

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Patient and public involvement

Protocol design was influenced by questionnaire responses obtained from parents whose children required HFNC for bronchiolitis. Parental feedback also led to simplification of the patient information sheets and informed the wording of the consent form.

Ethics and dissemination

Health Research Authority (HRA) and Health and Care Research Wales (HCRW) approval was granted on 8 September 2020 following review by the NHS research ethics committee—20/WA/0205. Protocol amendments will be submitted to HRA and HCRW for assessment and

approval (last amendment: protocol version 1.2, 6 March 2024).

The sponsor is Cardiff and Vale University Health Board. We will publish the results in a peer-reviewed medical journal and via websites and newsletters of Noah's Ark Children's Hospital and CYARU.

Acknowledgements The authors would like to thank Professor Paul McNamara for undertaking scientific review of the study design and methodology. Thank you to the team at CYARU for facilitating this work.

Contributors CT is responsible for the day to day running of the trial as detailed in this protocol. ME is the chief investigator and will oversee the trial and have overall responsibility. CD and ME devised the trial design and wrote the protocol. CT drafted this manuscript, and all authors reviewed the intellectual content critically. ME is responsible for the overall content as the guarantor.

Funding This research project is funded by the Noah's Ark Children's Hospital Charity (grant number N/A). There are no plans to pay participants any money or provide any other benefits (Declaration of Helsinki requirement).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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