

Appendix 5: Detailed research recommendations and future priorities for HFNT

This appendix provides the detailed research recommendations and future priorities supporting Section 11 of the Clinical Statement.

Acute Hypoxaemic Respiratory Failure

Current Evidence Gaps

Evidence remains heterogeneous regarding:

- Optimal first-line role of HFNT versus COT or NIV
- Appropriate timing of initiation
- Identification of responders versus non-responders
- Escalation thresholds to invasive ventilation
- Utility across differing aetiologies of acute hypoxaemia

Most studies focus on pneumonia and de novo hypoxaemia, with limited evidence in mixed respiratory populations.

Research Recommendations

Comparative Effectiveness Trials

Large multicentre RCTs are required comparing:

- HFNT versus NIV
- HFNT versus CPAP
- HFNT versus COT
- Sequential HFNT/NIV strategies

Primary outcomes should include:

- Intubation rates
- Mortality
- ICU admission
- Patient comfort
- Duration of respiratory support

Disease-Specific Research

Future studies should evaluate HFNT across:

- Pneumonia
- ILD

- Cardiogenic pulmonary oedema
- Immunocompromised populations
- Post-operative respiratory failure

Physiological Mechanisms

Further mechanistic studies are required to define:

- Optimal flow rates
- Work of breathing reduction
- Effects on inspiratory demand
- Dead space washout physiology
- Impact on patient self-inflicted lung injury

Biomarkers and Monitoring

Research should identify:

- Predictors of HFNT success or failure
- Physiological monitoring thresholds
- Role of ROX index refinement
- Early warning systems for deterioration
- Remote monitoring technologies

Acute Hypercapnic Respiratory Failure

Current Evidence Gaps

Evidence for HFNT in AHRF remains limited and inconsistent.

Uncertainty persists regarding:

- Appropriate patient selection
- Comparative efficacy versus NIV
- Role following NIV intolerance
- Effects in severe hypercapnia
- Safety in overlap syndromes

Research Recommendations

HFNT versus NIV Trials

Future multicentre RCTs should evaluate:

- HFNT as first-line therapy
- HFNT as step-down therapy after NIV
- HFNT in NIV intolerance

- Combined HFNT/NIV strategies

Outcomes should include:

- PaCO₂ reduction
- Treatment failure
- Need for intubation
- Symptom burden
- Sleep quality
- Adherence

COPD Phenotyping

Future studies should stratify patients according to:

- Degree of hypercapnia
- Exacerbation frequency
- Prior NIV use
- Overlap syndrome (COPD/OSA)
- Frailty and comorbidity burden

Non-COPD Hypercapnic Respiratory Failure

There is an urgent need for research in:

- Neuromuscular disease
- Chest wall disease
- Obesity hypoventilation syndrome
- Bronchiectasis-associated hypercapnia
- ILD-associated hypercapnia

Chronic Hypoxaemic Respiratory Failure

Current Evidence Gaps

Evidence for domiciliary HFNT remains limited, particularly in ILD and bronchiectasis.

There remains uncertainty regarding:

- Optimal duration of use
- Minimum effective daily usage
- Long-term adherence
- Survival benefit
- Impact on hospitalisation
- Appropriate oxygen delivery protocols

Research Recommendations

Long-Term Domiciliary HFNT Trials

Future studies should evaluate:

- Long-term exacerbation prevention
- Exercise capacity
- Quality of life
- Healthcare utilisation
- Mortality
- Cost-effectiveness

Disease-Specific Research

Further RCTs are required in:

- Bronchiectasis
- Fibrotic ILD
- Pulmonary hypertension
- Cystic fibrosis
- Pulmonary rehabilitation populations

Community Service Delivery Models

Research should evaluate:

- Hospital-at-home pathways
- Community respiratory team delivery
- Telemonitoring models
- Remote adherence monitoring
- Shared-care frameworks

Chronic Hypercapnic Respiratory Failure

Current Evidence Gaps

Current evidence suggests possible physiological and exacerbation-related benefits in COPD; however:

- NIV remains standard of care
- Comparative effectiveness remains unclear
- Existing studies are underpowered
- Long-term outcomes are uncertain

Research Recommendations

HFNT versus Home NIV

Future adequately powered RCTs should compare:

- HFNT versus domiciliary NIV
- Combination HFNT/NIV strategies
- Sequential overnight NIV and daytime HFNT approaches

Adherence and Acceptability

Future studies should evaluate:

- Treatment adherence
- Patient preference
- Sleep quality
- Device comfort
- Psychological burden
- Caregiver impact

Severe Hypercapnia

Further research is required in:

- Severe hypercapnia ($\text{PaCO}_2 > 8 \text{ kPa}$)
- NIV failure populations
- Frequent exacerbator phenotypes
- End-stage COPD populations

Secretion Management and Airway Clearance

Current Evidence Gaps

Evidence supporting HFNT for secretion management remains limited and predominantly observational.

Significant uncertainties include:

- Optimal flow settings
- Duration of therapy
- Mechanisms of mucociliary benefit
- Comparative efficacy versus standard airway clearance techniques
- Appropriate patient selection
- Whether HFNT provides benefit as an adjunct to physiotherapy-led airway clearance, rather than as a stand-alone secretion management intervention

Research Recommendations

Airway Clearance Trials

Future studies should evaluate HFNT as an adjunct to:

- Physiotherapy airway clearance
- Oscillatory PEP devices
- Mucolytic therapy
- Pulmonary rehabilitation

Disease-Specific Secretion Studies

Future trials are needed in:

- Non-CF bronchiectasis
- Cystic fibrosis
- COPD chronic bronchitis phenotypes
- Neuromuscular disease

Mechanistic Studies

Further research should investigate:

- Effects on ciliary beat frequency
- Mucous rheology
- Airway hydration
- Expiratory flow dynamics
- Patient-perceived secretion clearance

Outcome Measures

Future secretion management studies should standardise:

- Exacerbation frequency
- Sputum burden scores
- Ease of expectoration
- Quality of life metrics
- Hospital admissions

HFNT in Palliative and End-of-Life Care

Current Evidence Gaps

Evidence for HFNT in palliation remains extremely limited.

Major unanswered questions include:

- Whether HFNT improves refractory breathlessness

- Appropriate patient selection
- Optimal symptom management approaches
- Place of care implications
- Impact on quality of dying
- Family and caregiver experiences
- Best approaches to palliative use and withdrawal of HFNT

Research Recommendations

Symptom-Focused Trials

Future studies should evaluate:

- Breathlessness relief
- Anxiety reduction
- Communication ability
- Oral intake
- Sleep quality
- Patient comfort
- Comparison with conventional oxygen therapy

Palliative Withdrawal of HFNT Research

Prospective observational and qualitative studies are urgently required examining:

- Symptom trajectories during withdrawal
- Breathlessness management strategies
- Sedation approaches
- Family experience
- Clinician moral distress
- Home versus inpatient withdrawal pathways
- Impact of withdrawal protocols and flowcharts on symptom control, family experience and clinician confidence

Community and Hospice Delivery

Research should evaluate:

- Feasibility of home HFNT palliation
- Hospice implementation
- Resource implications
- Equipment logistics
- Community nursing support
- Integration with specialist palliative care

Future Trial Design Recommendations

Future HFNT studies should:

- Be multicentre and adequately powered
- Include clearly defined respiratory phenotypes
- Incorporate standardised HFNT protocols
- Include patient-reported outcomes
- Include health economic analysis
- Include long-term follow-up
- Evaluate implementation feasibility
- Include palliative and community care perspectives

Adaptive trial designs and pragmatic effectiveness studies may be particularly valuable given the heterogeneity of respiratory failure populations.