IQWiG Reports – Commission No. N20-02

Self-administered high-flow therapy in advanced chronic obstructive pulmonary disease or chronic type 1 respiratory failure[1]

Extract

1 Translation of Chapters 1 to 6 of the final report N20-02 High-Flow-Therapie zur Selbstanwendung bei fortgeschrittener chronisch obstruktiver Lungenerkrankung oder chronischer respiratorischer Insuffizienz Typ 1 (Version N20-02; Status: 6 July 2021 [German original], 23 August 2021 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Self-administered high-flow therapy in advanced chronic obstructive pulmonary disease or chronic type 1 respiratory failure

Commissioning agency
Federal Joint Committee

Commission awarded on
11 June 2020

Internal Commission No.
N20-02

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A10 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Wolfram Windisch, Lung Hospital, Hospitals of the City of Cologne

IQWiG thanks the external expert for his collaboration in the project.

IQWiG employees

- Lina Rodenhäuser
- Daniela Rüttgers
- Moritz Felsch
- Ulrike Lampert
- Martina Markes

Keywords

High Flow Therapy, Pulmonary Disease – Chronic Obstructive, Respiratory Insufficiency, Benefit Assessment, Systematic Review

Key statement

Research question

This study aims to assess the benefit of self-administered high-flow therapy (HFT) in comparison with standard treatment without HFT in patients with stable, advanced chronic obstructive pulmonary disease (COPD) or in patients with chronic respiratory failure (CRF) type 1 with regard to patient-relevant outcomes. Self-administration is suitable for the home environment, at nursing facilities, at rehabilitation clinics, or at facilities of statutory health insurance physicians.

Conclusion

On the basis of 1 study on HFT in COPD associated with CRF type 1, no hint of any greater benefit or harm of oxygen administration via HFT in comparison with oxygen administration via mask was found when administered repeatedly during physical exercise. It remains unclear whether a comparable benefit might be present. Data from 1 study on the long-term use of HFT were unusable because only a subgroup of patients suffered from CRF type 1 and therefore received an appropriate comparator therapy.

For the application of HFT in comparison with oxygen administration alone in patients with CRF type 1 and an underlying disease other than COPD, 1 study with repeated application during exercise was found. The data were unusable for a benefit assessment.

Regarding the use of HFT in patients with COPD and CRF type 2, usable data were available from 1 included study. This study revealed no benefit or harm of HFT in comparison with noninvasive ventilation. Since the data of the study are difficult to interpret, it remains unclear whether a comparable benefit exists.

For COPD without CRF symptoms, data were available from only 1 study and unsuitable for a benefit assessment.

Across indications, the data do not suggest any harm of HFT.

For all 4 indications, both completed and ongoing randomized controlled trials (RCTs) were found for assessing HFT. From the described results of all included studies – i.e., with additional consideration of the studies not usable for the benefit assessment – it follows that the HFT method to be assessed has the potential of a required treatment alternative. Testing in initially 2 studies is deemed feasible and meaningful.

Table of contents

Page

Key statement ... **iii**
List of tables ... **v**
List of abbreviations ... **vi**
1 Background ... **1**
2 Research question ... **3**
3 Methods ... **4**
4 Results ... **6**
4.1 Results of the information retrieval ... **6**
4.2 Characteristics of the studies included in the assessment ... **6**
4.2.1 HFT in CRF ... 7
4.2.2 HFT in COPD without CRF ... 9
4.3 Overview of patient-relevant outcomes ... **9**
4.4 Assessment of the risk of bias of results ... **10**
4.5 Results on patient-relevant outcomes ... **11**
4.5.1 Results on all-cause mortality ... 11
4.5.2 Results on acute exacerbations ... 11
4.5.3 Results on dyspnoea ... 11
4.5.4 Results on COPD symptoms ... 12
4.5.5 Results on exercise performance ... 12
4.5.6 Results on activities of daily living ... 12
4.5.7 Results on hospital admissions ... 12
4.5.8 Results on serious adverse events and discontinuation due to adverse events ... 13
4.5.9 Results on health-related quality of life ... 13
4.6 Overall evaluation of results ... **13**
4.7 Key points for government co-sponsored studies ... **19**
4.7.1 Key points of a government co-sponsored study in COPD with CRF type 1 ... 19
4.7.2 Key points of a government co-sponsored study in COPD with CRF type 2 ... 20
5 Classification of the assessment result ... **22**
6 Conclusion ... **23**
7 References for English extract ... **24**
Appendix A Search strategies ... **28**
A.1 Searches in bibliographic databases ... **28**
A.2 Searches in study registries ... **31**

List of tables

Page

Table 1: Study pool of the benefit assessment 6
Table 2: Matrix of patient-relevant outcomes 10
Table 3: Evidence map regarding patient-relevant outcomes 14
Table 4: Studies without reported results – characteristics according to registry entry and potential suitability for demonstrating a benefit 18

List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walk test
AE	adverse event
COPD	chronic obstructive pulmonary disease
CRF	chronic respiratory failure
FEV1	forced expiratory volume in 1 second
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFT	high-flow therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LTOT	long-term oxygen therapy
mMRC	modified Medical Research Council
NIV	noninvasive ventilation
$PaCO_2$	arterial partial pressure of carbon dioxide
PaO_2	arterial partial pressure of oxygen
pCO_2	partial pressure of carbon dioxide
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SRI	Severe Respiratory Insufficiency Questionnaire

1 Background

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease in Germany and a common cause of death, with around 30,000 people dying from it each year [1]. COPD is a progressive disorder for which various risk factors have been described, most importantly smoking and other inhaled toxins [2,3]. As a result, COPD typically occurs in older people [4].

Noxious particles or gases in the respiratory air can lead to pneumonia. Patients with COPD have an abnormal form of this inflammatory reaction. It is unclear what triggers this overreaction [5]. Patients exhibit pathological changes such as chronic inflammation in various parts of the lung as well as structural changes, including in the bronchi. These changes lead to constriction of the respiratory flow and the accumulation of secretions. As part of COPD, emphysema can develop. Common symptoms are dyspnoea, coughing, and excess phlegm – either chronically or under exertion, even while doing everyday activities. COPD is characterized by exacerbations, during which symptoms worsen, potentially becoming as severe as acute respiratory distress. In advanced stages of COPD, chronic respiratory failure (CRF) can develop [6].

The clinical picture is characterized by reduced quality of life and comorbidities [5,6]. To classify the severity of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline has defined COPD stages (1 to 4) and patient groups. The 4 stages are based on the severity of obstruction. For this purpose, 2 values are measured via a pulmonary function test: after full inspiration, the volume of air that can be forcibly blown out in the first second (forced expiratory volume in 1 second, FEV1) as well as the volume of air that can be exhaled (forced vital capacity, FVC). Patient groups are defined using the 2 criteria “frequency of exacerbations in the past 12 months” and “level of symptoms” [5].

For therapy, the risk of exacerbations is particularly relevant [5,6].

Since COPD is irreversible, patients primarily receive symptomatic therapy alongside the recommendation to avoid inhaling noxious particles. Therapy is chosen in part based on the severity of disease. Alongside physical therapy, mechanical devices such as positive expiratory pressure (PEP) mask systems can help improve the elimination of secretions [6].

Chronic respiratory failure as an advanced stage of COPD and other diseases

In advanced stages of COPD, CRF can develop. Alongside COPD, numerous other diseases such as cystic fibrosis, pulmonary arterial hypertension, and neuromuscular diseases can lead to CRF [7].

Respiratory failure is classified as type 1 (hypoxaemic) or type 2 (hypercapnic). Both involve a problem with the gas exchange in the lung. In type 1 respiratory failure, the primary issue is an inability to adequately oxygenate (O_2) the blood (hypoxaemia). Type 2 respiratory failure

additionally involves an accumulation of carbon dioxide (CO_2) (hypercapnia). Both can be acute or chronic [6].

Respiratory failure, whether associated with COPD or as the symptom of another disease, is treated using similar core treatment approaches: (long-term) oxygen therapy (LTOT) is recommended for the treatment of (chronic) hypoxaemia. Various applications are available for this purpose. Hypercapnic respiratory failure requires oxygen administration as well as support in the elimination of carbon dioxide; therefore, ventilation therapy is used. Ventilation can be invasive or noninvasive [6,7].

High-flow therapy

High-flow therapy (HFT) can modify the treatment of both type 1 respiratory failure (LTOT) and COPD (LTOT and ventilation). In HFT, patients regularly receive moistened and warmed room air at high flow rates, typically for several hours, via a nasal cannula. Supplemental oxygen can be added to HFT. The goal is to support breathing and to eliminate secretions by moistening the respiratory tract, increasing airway pressure (positive airway pressure), relieving the respiratory muscle pump, and high flow rates [8,9].

HFT can be administered either in an inpatient setting for acute cases or in the home environment as long-term therapy. For the present research question, its use in acute cases is irrelevant.

Experience reports from affected people for supplementary information

To enhance the introduction to the clinical picture, IQWiG makes available individual experience reports from patients and/or family members. The anonymized experience reports can provide insights into how the disease is experienced and how its consequences are handled. The reports can thus help understand the perspectives of affected people.

In the form of interview summaries, the experience reports are published on the IQWiG website www.gesundheitsinformation.de. They are not representative, and views expressed in the experience reports do not represent IQWiG recommendations.

More detailed information on the methods used for generating the experience reports is found in the General Methods 6.0 [10]. Experience reports are found at https://www.informedhealth.org/i-know-people-who-have-the-same-disease.html.

2 Research question

This study aims to assess the benefit of self-administered high-flow therapy (HFT) in comparison with standard treatment without HFT in patients with stable, advanced chronic obstructive pulmonary disease (COPD) or in patients with chronic respiratory failure (CRF) type 1 with regard to patient-relevant outcomes. Self-administration is suitable for the home environment, at nursing facilities, at rehabilitation clinics, or at facilities of statutory health insurance physicians.

3 Methods

The target population of the benefit assessment is adult patients with stable, advanced COPD as well as children and adults with CRF type 1. The experimental intervention is self-administered HFT over an extended time period. The comparator intervention is standard treatment without HFT.

The investigation examined the following patient-relevant outcomes:

- Mortality
- Morbidity (e.g., exacerbations, exercise performance, respiratory symptoms)
- Hospital admissions and/or outpatient medical treatment due to exacerbations
- Health-related quality of life
- Adverse events

It included randomized controlled trials (RCTs). If the available RCT-based evidence was insufficient for a benefit assessment, nonrandomized comparative interventional studies and prospective comparative cohort studies were to be included as well. There were no restrictions regarding the study duration.

In parallel to the preparation of the report plan, a search for systematic reviews was conducted in the MEDLINE database (which includes the Cochrane Database of Systematic Reviews) and the HTA database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least 1 high quality, current systematic review existed whose information retrieval was a suitable basis for the assessment.

When such a high-quality, current, systematic review was available, in a 2nd step, a supplementary search was conducted for studies for the time period not covered by the systematic review(s). Otherwise, the search for studies was carried out without restricting the time period.

The systematic search for studies was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials.

The following sources of information and search techniques were additionally used: study registries, manufacturer queries, publicly accessible documents from regulatory authorities, documents sent by the Federal Joint Committee (G-BA), reviews of reference lists, documents made available from hearing procedures, and requests to authors.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To

assess the qualitative certainty of results, outcome-specific and study-level criteria for the risk of bias were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were organized according to outcomes and described.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met. A final summary assessment of the information was performed in any case.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter is the case if no data are available or the available data do not permit classification into one of the 3 other categories. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

If there was no hint of any (greater) benefit or (greater) harm, a conclusion was to be drawn regarding any potential, and the key points of a possible government co-sponsored study were to be specified.

4 Results

4.1 Results of the information retrieval

No systematic reviews were rated as being current and of high quality and included for the identification of primary studies.

The information retrieval found 5 RCTs to be relevant for the research question of this benefit assessment. One planned and 3 ongoing studies were found. Furthermore, 2 studies of unclear status and 1 completed study without reported results were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 14 August 2020.

A total of 5 relevant studies were identified through the various search steps (see also Table 1).

Table 1: Study pool of the benefit assessment

Study	Available documents		
	Full publication (in professional journals)	**Registry entry / results report from the study registries**	**Clinical study report from manufacturer documents (not publicly accessible)**
HFT in CRF			
COPD with CRF type 1			
HFT as long-term treatment			
Storgaard 2018[a]	Yes [11-14]	Yes [15] / no	Yes [16]
HFT used repeatedly during exercise			
Vitacca 2020	Yes [17,18]	Yes [19] / no	No
CRF type 1 in the context of other diseases			
Chihara 2020[a]	Yes[b] [20]	Yes [21] / no	No
COPD with CRF type 2			
Bräunlich 2019	Yes [22,23]	Yes [24] / no	No
HFT in COPD without CRF			
Rea 2010[a]	Yes [25]	Yes [26] / no	No

a. No usable data were available.
b. This is a preliminary version of a manuscript (preprint) that had not completed peer review at a journal by the editorial deadline of the preliminary report.

COPD: chronic obstructive pulmonary disease; CRF: chronic respiratory failure; HFT: high-flow therapy

4.2 Characteristics of the studies included in the assessment

Hereinbelow, the identified studies are categorized on the basis of the clinical picture and clinical setting in which HFT was used:

In the studies, HFT was used to treat (1) CRF (chronic hypoxaemia and COPD with chronic hypercapnia) and (2) COPD without CRF. Typically, HFT was administered as long-term

treatment (for several months) for several hours daily. For chronic hypoxaemia, however, some studies investigated its use during repeated exercise (physical training).

4.2.1 HFT in CRF

COPD with CRF type 1

HFT as long-term treatment

One study (**Storgaard 2018** [11]) was found on the long-term use of HFT in patients with chronic hypoxaemia. This study investigated the use of HFT as an adjunct to LTOT in comparison with LTOT alone.

The **Storgaard 2018** study [11] was conducted in 4 Danish hospitals between 2013 and 2015. A total of 200 patients with stable COPD and chronic hypoxaemia were included. The study did not define any explicit inclusion or exclusion criteria regarding COPD severity. However, based on low FEV1 values at baseline and the fact that it included only patients who had received LTOT for at least 3 months, COPD can be assumed to have been severe or very severe. A post hoc analysis [14] shows that 117 of the 200 included patients were not only hypoxaemic but also hypercapnic and hence suffered from CRF type 2. The study excluded any patients who received noninvasive ventilation (NIV). Patients were randomized to either LTOT plus HFT or to LTOT alone – both for self-administration at home. In the intervention group, patients received HFT with oxygen-enriched room air at a recommended flow rate of 20 L/min. HFT was to be applied at night and for at least 8 out of 24 hours. Patients of the intervention group as well as those of the control group continued to receive their usual medical care. The outcomes of all-cause mortality, acute exacerbations, dyspnoea, quality of life, exercise performance, and hospital admissions were recorded over the study duration of 12 months. However, LTOT is the appropriate comparator therapy only for the 83 patients with CRF type 1. As per the guideline [6], the 117 patients with CRF type 2 should have received NIV. The study was included but is not further presented below because the study's authors were unable to send any usable data on the patient population relevant for the research question before the completion of this report.

HFT during repeated physical exercise

One study was found on the use of HFT during repeated physical exercise in COPD with CRF type 1. The multicentre study **Vitacca 2020** [17] was conducted in Italy between 2017 and 2018. It included 171 patients with COPD and chronic hypoxaemia. Another inclusion criterion was having been on LTOT treatment for at least the prior 3 months. Patients were randomized to 2 study arms, where they received either oxygen-enriched HFT or oxygen administered via Venturi mask during 30 minutes of physical exercise. In both study arms, each patient participated in 5 training units per week for 4 weeks. The primary study outcome was endurance in a stress test at a constant work rate, but results were reported for only 25.9% (46/171) of the included patients. This study also recorded exercise performance by means of the 6-minute walk test (6MWT) as well as activities of daily living.

CRF type 1 in the context of other diseases

Regarding CRF type 1 in the context of other diseases, 1 study was found in which HFT was used during repeated exercise.

The preprint of the **Chihara 2020** [20] RCT reports data on 32 patients. The study included patients with CRF who were willing to participate in an inpatient rehabilitation program and had been on LTOT for at least the prior 3 months. Since they required supplemental oxygen, the patients can be assumed to have had CRF type 1. Their respiratory failure was due to various underlying diseases: 13 patients had COPD, 15 patients had idiopathic pulmonary fibrosis, and 4 patients had bronchiectasis. During the study, the patients exercised on a cycle ergometer, completing 5 units per week for a duration of 4 weeks. The intervention group received oxygen-enriched HFT at a flow rate of 50 L/min during exercise. The control group was administered oxygen without HFT via nasal cannula. The primary study outcome was change in exercise performance, measured by 6MWT.

While COPD is an obstructive lung disease, idiopathic pulmonary fibrosis is a restrictive one. Hence, the patient populations differ not only in quality of life and the prognosis associated with acute exacerbation, but also in the pathophysiology of the underlying disease with regard to the potential mechanism of action of HFT. Assessing both clinical pictures together was therefore deemed inappropriate. However, the study fails to break down the results by underlying clinical picture. Therefore, the study is unsuitable for drawing conclusions on any of the individual clinical pictures associated with CRF type 1 (COPD, pulmonary fibrosis, or bronchiectasis). Its results are not presented below.

No studies were found on further clinical pictures associated with CRF type 1.

COPD with CRF type 2

One study was found on the use of HFT in patients with COPD and chronic hypercapnia. In this study, HFT was used to replace NIV.

The **Bräunlich 2019** [22] multicentric cross-over study was conducted in Germany between 2011 and 2016. A total of 102 patients with COPD and chronic hypercapnia (average partial pressure of carbon dioxide [pCO_2] reported as 56.5 ± 5.4 mmHg) were randomized. The majority of patients were at a high risk of exacerbations, and 90% of patients were categorized into group D of the GOLD classification [5]. This means that, in the past year, they had suffered from either 2 or more exacerbations or from 1 exacerbation leading to hospital admission and severe symptoms. In addition, most patients had low pulmonary function values (mean FEV1 of 28.5%). Over a period of 6 weeks each, patients received either first HFT followed by NIV (HFT-NIV sequence) or vice versa (first NIV followed by HFT [NIV-HFT sequence]). Both HFT and NIV were recommended for night-time use and a minimum duration of 6 hours per day. For HFT, a nasal cannula was used. The flow rate was 20 L/min, and oxygen was constantly supplied. For NIV, the pressure was adjusted according to the patient's tolerance to obtain the maximum possible reduction of partial pressure of carbon dioxide. The primary

outcome of the study was reduction in pCO_2. The study also recorded mortality, dyspnoea, exercise performance, quality of life, adverse events (AEs), and health status, all measured by a visual analogue scale. Only 67 of 94 patients who started treatment completed the study. Among them, 26 of 44 patients (59%) completed the HFT-NIV sequence, compared to 41 of 50 patients (82%) with the NIV-HFT sequence. The two study sequences differed by 23% in terms of persons with complete data. The study was prematurely discontinued by 29% of patients.

4.2.2 HFT in COPD without CRF

One study was found on the use of HFT in COPD patients without CRF.

The **Rea 2010** study [25] investigated HFT in 108 patients with COPD or bronchiectasis and a high risk of exacerbation. Inclusion criteria for this study were at least 2 exacerbations in the prior year as well as a daily sputum production of more than 5 mL. In the intervention group, patients received humidified, maximally saturated room air at a flow rate of 20 to 25 L/min. No oxygen was added, except in patients who received oxygen in pre-existing LTOT. Patients in the comparator group received standard care. No blood gas analysis results were reported. The study had a mixed patient population (COPD and bronchiectasis, different COPD severities, unclear percentage of patients with LTOT), which cannot be unequivocally said to suffer from advanced COPD. Further, no subgroup analyses are available for patients with advanced COPD. The patient population also cannot be allocated to any other clinical picture in the presence of CRF type 1. Consequently, the data available from the study are unsuitable for assessing the effect of HFT (1) in COPD without CRF or (2) in a clinical picture without COPD in the presence of CRF type 1. The study's results are not presented below.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 2 studies (Vitacca 2020 and Bräunlich 2019). Table 2 presents an overview of the data on patient-relevant outcomes from the included studies.

Three studies (Storgaard 2018, Chihara 2020 and Rea 2010), provided no usable results (see Sections 4.2.1 and 4.2.2).

An overview of the employed measuring instruments is found in Section A7 of the full report.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes									
	Mortality	Morbidity								QoL
	All-cause mortality	Exacerbations	Dyspnoea	COPD symptoms	Exercise performance	Activities of daily living	Hospital admissions	SAE	Discontinuation due to AEs	Health-related quality of life
HFT in CRF										
COPD with CRF type 1										
HFT as long-term treatment										
Storgaard 2018	*Data from the study are unusable*									
HFT used repeatedly during exercise										
Vitacca 2020	–	–	○	○	○[a, b] / ●[c]	●[d]	–	–	–	○
CRF type 1 in the context of other diseases										
Chihara 2020	*Data from the study are unusable*									
COPD with CRF type 2										
Bräunlich 2019	○	○	●	–	●[a, c]	–	–	●	–	●[c]
HFT in COPD without CRF										
Rea 2010	*Data from the study are unusable*									

●: Data were reported and were usable.
○: Data were reported but unusable for the benefit assessment.
–: No data were reported (no further information) / The outcome was not surveyed.
a. Surveyed by 6MWT (distance).
b. Surveyed by CWRET.
c. Surveyed by the modified Borg scale.
d. Surveyed by the Barthel index.
e. Surveyed by SGRQ, SRI, and VAS.

6MWT: 6-minute walk test; AE: adverse event; COPD: chronic obstructive pulmonary disease; CRF: chronic respiratory failure; CWRET: Constant Work Rate Exercise Test; HFT: high-flow therapy; QoL: quality of life; SAE: serious adverse event; SGRQ: St George's Respiratory Questionnaire; SRI: Severe Respiratory Insufficiency Questionnaire; VAS: visual analogue scale

4.4 Assessment of the risk of bias of results

HFT in COPD with CRF type 1

For Vitacca 2020, the risk of bias at study level has been assessed as low. The study's outcome-specific risk of bias for the results on exercise performance and on activities of daily living was rated as high because the intention-to-treat principle was inadequately implemented.

HFT in COPD with CRF type 2

The Bräunlich 2019 study was rated as having a high risk of bias across outcomes. This was due to an insufficient description of the statistical model used for the analysis and a large number of missing values.

4.5 Results on patient-relevant outcomes

No usable data are available for the indication of CRF type 1 in the context of diseases other than COPD.

4.5.1 Results on all-cause mortality

HFT in COPD with CRF type 1

For the outcome of mortality, no usable data were reported.

HFT in COPD with CRF type 2

Bräunlich 2019 reported 2 deaths on HFT and 2 on NIV therapy. Due to the cross-over design, however, these results cannot be meaningfully interpreted.

4.5.2 Results on acute exacerbations

HFT in COPD with CRF type 1

No usable data were available on the outcome of acute exacerbations.

HFT in COPD with CRF type 2

In Bräunlich 2019, acute exacerbations were found both on HFT and on NIV. Due to the study design (cross-over design without wash-out phase) and the short study duration of only 6 weeks per intervention, the results cannot be meaningfully interpreted.

4.5.3 Results on dyspnoea

HFT in COPD with CRF type 1

No usable results on dyspnoea were reported.

HFT in COPD with CRF type 2

In the Bräunlich 2019 study, 4.3% of patients on NIV exhibited dyspnoea during the 6-week treatment period. None of the patients suffered from dyspnoea while on HFT. No information is available as to whether the events occurred in patients allocated to the HFT-NIV or the NIV-HFT sequence. This makes it impossible to correctly calculate the effect size by means of the odds ratio.

For the outcome of dyspnoea, there is consequently no hint of benefit of HFT versus NIV in COPD with CRF and chronic hypercapnia.

4.5.4 Results on COPD symptoms

HFT in COPD with CRF type 1

No usable data were available on COPD symptoms.

HFT in COPD with CRF type 2

No data were available on this outcome.

4.5.5 Results on exercise performance

HFT in COPD with CRF type 1

Usable results on exercise performance were surveyed in 1 study with repeated use of HFT during physical exercise (Vitacca 2020).

The modified Borg scale showed no significant difference in exercise performance between patients on HFT versus those on oxygen without HFT during the training units.

For the outcome of exercise performance, this results in no hint of benefit or harm of HFT versus the administration of oxygen alone during exercise in COPD with CRF type 1.

HFT in COPD with CRF type 2

Bräunlich 2019 showed no statistically significant difference for the outcome of exercise performance.

For this outcome, this results in no hint of benefit or harm of HFT versus NIV in COPD with CRF type 2.

4.5.6 Results on activities of daily living

HFT in COPD with CRF type 1

Results on activities of daily living, surveyed using the Barthel index, were reported by the Vitacca 2020 study. No statistically significant difference in the Barthel index was found between the intervention and control groups.

This results in no hint of benefit or harm of HFT versus the administration of oxygen alone during exercise in COPD with CRF type 1.

HFT in COPD with CRF type 2

Bräunlich 2019 did not collect any data on activities of daily living.

4.5.7 Results on hospital admissions

HFT in COPD with CRF type 1

For the outcome of hospital admissions, no usable data are available.

HFT in COPD with CRF type 2

Bräunlich 2019 collected no data on hospital admissions.

4.5.8 Results on serious adverse events and discontinuation due to adverse events

HFT in COPD with CRF type 1

Vitacca 2020 provided no data on serious adverse events or discontinuation due to adverse events.

HFT in COPD with CRF type 2

In Bräunlich 2019, at least 1 serious adverse event (SAE) occurred in 13.8% of patients on HFT compared to 12.8% of patients on NIV. Since no information is available as to whether the events occurred in patients allocated to the HFT-NIV or NIV-HFT sequence, the effect size cannot be correctly calculated using the odds ratio.

This results in no hint of harm of HFT versus NIV in COPD with CRF type 2.

4.5.9 Results on health-related quality of life

HFT in COPD with CRF type 1

For the outcome of health-related quality of life, no usable data were available.

HFT in COPD with CRF type 2

Bräunlich 2019 surveyed data on quality of life using St George's Respiratory Questionnaire (SGRQ, developed for COPD patients) and the Severe Respiratory Insufficiency Questionnaire (SRI, developed for CRF patients). In addition, quality of life was surveyed using a visual analogue scale. None of these scales (sum scores or relevant subscales) revealed any statistically significant difference in mean differences (all p-values ≥ 0.28).

For the outcome of health-related quality of life, this results in no hint of benefit of HFT versus NIV in COPD with CRF type 2.

4.6 Overall evaluation of results

Evidence map

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes

Indication	Mortality	Morbidity								QoL
	All-cause mortality	Exacerbations	Dyspnoea	COPD symptoms	Exercise performance	Activities of daily living	Hospital admissions	SAE	Discontinuation due to AEs	Health-related quality of life
HFT in CRF										
COPD in CRF type 1[a]	–	–	–	–	⇔	⇔	–	–	–	–
CRF type 1 in the context of further diseases	*N/A since data from the study are unusable*									
COPD with CRF type 2	–	⇔	⇔	–	⇔	–	–	⇔	–	⇔
HFT in COPD without CRF	*N/A since data from the study are unusable*									

⇔: no hint, indication, or proof; homogeneous result

a. HFT during repeated physical exercise.

–: Data were not reported or unusable.

AE: adverse event; COPD: chronic obstructive pulmonary disease; CRF: chronic respiratory failure; HFT: high-flow therapy; N/A: not applicable; QoL: quality of life; SAE: serious adverse event

Assessment of the volume of unpublished data

The information retrieval found 2 study registry entries whose identified study end date was more than 1.5 years in the past; therefore, study results could have been published. However, no results have been reported so far (see Table 12 of the full report). Since the study entries have not been updated at all after their original creation, it is unclear whether the studies ever started.

The existence of these study registry entries does not affect the overall conclusions for 2 reasons: (1) due to the uncertainty regarding the study start, and (2) due to the questionable relevance of the study population in both studies.

Weighing of benefits versus harm

HFT in COPD with CRF type 1

Data from 1 study using HFT during repeated physical exercise were used for the assessment. No hint of benefit was found on the basis of the outcomes of activities of daily living and exercise performance. No usable data were available on HFT's long-term use, which is more relevant in care. Therefore, it is unclear whether a comparable benefit exists.

Vitacca 2020 reported no harm of HFT; however, due to the short study duration and the short duration of use (5 training units per week at 30 minutes each), the study was subject to some limitations concerning its suitability for drawing conclusions on the potential harm of long-term use of HFT.

Insufficient data are available for a final benefit-harm assessment.

HFT in CRF type 1 in the context of another disease

For this indication, 1 study was included, but its data were unusable. Hence, no data are available for a final benefit-harm assessment.

HFT in COPD with CRF type 2

After 6 weeks of use of HFT in COPD with CRF type 2, no hint of benefit was found for the outcomes of exacerbations, dyspnoea, exercise performance, SAEs, or health-related quality of life. The data also did not result in any hint of benefit or harm on the study level. Due to key deficiencies in the conduct and analysis of the study, it is impossible to determine whether there might be a comparable benefit:

1) In the Bräunlich 2019 study, the results of HFT or NIV were surveyed after short treatment durations of only 6 weeks each. Further, a carry-over effect cannot be ruled out due to the lack of a wash-out phase.
2) The Bräunlich 2019 study exhibits problems with the application of the experimental and comparator interventions. Ventilation is intended to achieve normocapnia. Whether this is successful depends, among other things, on the pressure setting as well as the duration of ventilation [7]. It is unclear whether the low average inspiratory pressure setting of 20.5 (standard deviation [SD] 3.6) centimetres of water (cmH_2O) is the optimal treatment setting for both the intervention group and the comparator group. In addition, the study group prespecified, for both HFT and NIV, a minimum duration of use of at least 6 hours daily. The actual mean daily duration of use of was 5.2 (SD: 3.3) hours for HFT and 3.9 (SD: 2.5) hours for NIV. The mean duration of use significantly differed between groups in favour of HFT ($p < 0.001$).
3) Large amounts of missing data were replaced.

HFT in COPD without CRF

The included studies provided no usable data on the use of HFT in COPD without CRF. Hence, no data were available for weighing benefit and harm.

Assessment of the potential of a required treatment alternative

In all 4 indications, data are lacking or insufficient for weighing benefit versus harm.

To derive a conclusion on the potential of a required treatment alternative, the 5 studies included via the systematic search were used. The studies were listed in the study pool and described

(see Section 4.2 as well as Sections A3.1.3 and A3.2.1 of the full report); 3 of these 5 studies were not usable for the benefit assessment, the reasons are described in Section 4.2 (Chihara 2020, Rea 2010 and Storgaard 2018), but are used to assess the potential.

HFT in COPD with CRF type 1

For the use of HFT in COPD and CRF type 1, when used repeatedly under exercise, 1 study showed no hint of benefit or harm over oxygen by mask (Vitacca 2020). Data from 1 study (Storgaard 2018) on the long-term use of HFT were not usable for the benefit assessment because only a subgroup (83 of 200) of patients had CRF type 1 and thus received an adequate comparator therapy. This study showed a lower rate of acute exacerbations with HFT plus LTOT compared with LTOT alone for both the overall population (N = 200, Storgaard 2018) and the subgroup of COPD patients with CRF type 2 (N = 117, Storgaard 2020). Since similar results were observed both in the mixed overall population and in the subgroup of patients with COPD with CRF type 2, on the basis of these results, a possible advantage in terms of the rate of exacerbations in the sense of a potential can also be assumed for the subgroup of patients with COPD with CRF type 1. This results in a potential of HFT as a required treatment alternative in patients with COPD and CRF type 1.

HFT in an underlying condition other than COPD and CRF type 1

For the use of HFT versus oxygen-only administration in patients with an underlying condition other than COPD and CRF type 1, 1 study (Chihara 2020) with repeated use under exercise was identified. The study population was mixed. Idiopathic pulmonary fibrosis accounted for the largest proportion, approximately 50%. The results are not presented differentiated by underlying medical conditions. Therefore, the data were not usable for a conclusion on benefit. Based on results from the overall study population on the 6-minute walk test showing a numerical difference of HFT versus oxygen administration alone to the advantage of HFT, there is potential for HFT as a required treatment alternative for patients with idiopathic pulmonary fibrosis as an underlying condition and CRF type 1.

HFT in COPD with CRF type 2

For the use of HFT in patients with COPD and CRF type 2, usable data were available in 1 included study (Bräunlich 2019). This showed no benefit or harm of HFT compared with noninvasive ventilation. An equivalence of HFT and noninvasive ventilation cannot be assessed due to only limited interpretability of the data (see Section 4.6). In the study, the blood of those treated with HFT showed a reduction in carbon dioxide partial pressure – a plausible surrogate endpoint for improved expiration and thus reduced morbidity (dyspnoea, sleep disorder, etc.). This suggests a potential for the method as a required treatment alternative in patients with COPD and CRF type 2.

HFT in COPD

For COPD without CRF, data were available from 1 study (Rea 2010), which could not be used for a conclusion on benefit. Results are not presented differentiated by the underlying 2 conditions (COPD without CRF and bronchiectasis without CRF type 1). Study participation was not limited to advanced-stage COPD. 63 of the 108 patients had COPD. The proportion of those with advanced COPD is unclear. There is also no relevant subgroup analysis of patients with advanced COPD without CRF. In the mixed overall study population, there was a statistically significant effect in favour of HFT versus standard treatment for the number of days with exacerbation, time to first exacerbation, and quality of life. Because the mechanism of action is comparable in both conditions (COPD and bronchiectasis), there is potential for HFT as a required treatment alternative for patients with COPD without CRF.

In summary, for all 4 indications, the described results of the included studies indicate that HFT has the potential to be a required treatment alternative.

A look at ongoing studies does not suggest that sufficient data will be available in the future to weigh benefits and harms: Information retrieval identified an additional 3 entries on ongoing studies and 1 on a planned study. Table 4 outlines the study characteristics according to the registry entries and presents the extent to which the studies are in principle suitable to demonstrate a benefit of the method. This shows that there are no ongoing studies on the basis of which a demonstration of benefit can be expected, which is why key points for corresponding testing studies for 2 indications are formulated in the following section.

Table 4: Studies without reported results – characteristics according to registry entry and potential suitability for demonstrating a benefit

Study	Document type Citation	Study type	N	Status (planned end of study)	Patients Intervention Comparison Duration	Suitability for demonstrating a benefit
NCT03959982	Study registry entry [27]	RCT	30	Ongoing (01/2022)	Population: COPD, chronic bronchitis, no data on stability, on CRF Intervention: nocturnal HFT for min. 4 hrs Comparison: no data Primary outcomes: Breathlessness, quality of life, sleep quality, spirometry, exercise capacity 6 weeks	No clear suitability due to unclear patient population (stage of COPD) and unclear comparison
NCT04281316	Study registry entry [28]	RCT	36	Ongoing (01/2022)	Population: stable COPD, hypercapnia, lack of NIV adherence. Intervention: HFT of unclear duration Comparison: NIV as before (1-5 hrs per day). 3 months	Not suitable because reliable conclusions for the overall population cannot be derived from results of patients with known lack of NIV adherence
NTR7513	Study registry entry [29]	RCT	80	Planned (12/2020)	Population: stable COPD with hypoxaemia Intervention: HFT under repeated exercise Comparison: oxygen administration 40 applications	No clear suitability due to unclear study population (stage of COPD) and no long-term use
NCT03882372	Study registry entry [30]	RCT	46	Ongoing (04/2022)	Population: COPD III-IV Intervention: HFT for 8 hrs (additional LTOT if needed) Comparison: standard treatment (LTOT if needed) 6 months	No clear suitability as no clear comparison

COPD: chronic obstructive pulmonary disease; CRF: chronic respiratory failure; HFT: high-flow therapy; LTOT: long-term oxygen therapy; N: number of patients; NIV: noninvasive ventilation; RCT: randomized controlled trial; hrs: hours

4.7 Key points for government co-sponsored studies

In the following sections, government co-sponsored studies are suggested, initially for 2 indications, namely the epidemiologically more relevant clinical pictures of COPD with CRF type 1 and CRF type 2. On the basis of the experience gained from these government co-sponsored studies, at a later time, government co-sponsored studies on the two other indications (CRF with an underlying disease other than COPD as well as COPD without CRF) might be planned and conducted as well, making it possible to establish a benefit for all 4 indications.

4.7.1 Key points of a government co-sponsored study in COPD with CRF type 1

Any benefit of HFT in patients with COPD with hypoxaemia in the context of CRF type 1 should be investigated in the form of an RCT.

This RCT should include patients with stable COPD and CRF type 1 who require LTOT (blood gas analysis results in patients with severe chronic hypoxaemia without severe hypercapnia: arterial partial pressure of oxygen (PaO_2) ≤ 55 mmHg, arterial partial pressure of carbon dioxide ($PaCO_2$) ≤ 50 mmHg or in chronic hypoxaemia and pulmonary heart disease with(out) cor pulmonale and/or secondary polycythaemia PaO_2 55–60 mmHg; see [31]). The study should exclude patients with contraindications for the investigational or comparator intervention according to guidelines as well as any patients in whom stable COPD can be ruled out or who are thought to suffer from acute rather than chronic respiratory failure.

The intervention should be self-administered HFT with oxygen-enriched air as an adjunct to LTOT for a duration of 6 months. The comparator therapy should be LTOT as recommended by the guidelines [31].

Study hypothesis, outcomes, estimated number of cases

The study objective should be to prove that, in patients with COPD and CRF type 1, HFT as an adjunct to LTOT is superior to LTOT alone with regard to the primary outcome. The primary outcome should be health-related quality of life, measured by a validated instrument (e.g., SRI [32,33]).

Particularly relevant secondary outcomes would be all-cause mortality, acute exacerbations, severity of dyspnoea (measured by a validated instrument, such as the modified Medical Research Council [mMRC]), length of hospital stay, and AEs.

The below discussion of estimated case numbers is not intended as a binding calculation but as an approximate estimate of the case numbers required. Case numbers with binding effect must be planned during the specific planning of the study.

Assuming a mean effect size of Hedges' g = 0.5 (based on the Storgaard 2018 results), a 2-sided significance level of 5%, a power of 90% and the use of a t-test, 172 cases would be needed, i.e., 86 patients per treatment arm. At an assumed drop-out rate of about 30%, this results in a total of 246 patients to be included (123 per treatment arm).

The study should be multicentric. Ideally, patients should be recruited via outpatient centres, inpatient centres, or local cooperating hospitals that offer both treatment methods. The time required for patient recruitment determines the estimated study duration. If a recruitment period of 2 years can be achieved, the study duration including study preparation, recruitment, follow-up, and analysis would equal about 4 years.

The study must be conducted in compliance with the Guideline for Good Clinical Practice (GCP).

Prospects of success for government co-sponsored studies

In principle, it is possible to conduct a government co-sponsored study suitable for obtaining the necessary information for assessing the method's benefit.

In Germany, enough patients meeting the inclusion criteria for the government co-sponsored study are thought to be available for reaching the estimated number of cases.

Study costs

For studies with small case numbers and normal or high resource requirements, the study-specific cost would be about €10,000 or €12,000, respectively, per participant. On the basis of these assumptions, the estimated study costs equal €2.5 million to €3 million.

These cost estimates are intended to provide an orientation and are not to be used as the basis for contractual cost agreements.

4.7.2 Key points of a government co-sponsored study in COPD with CRF type 2

The benefit of HFT in patients with COPD and hypercapnia in the context of CRF type 2 should be investigated in the form of an RCT.

The study should include patients with stable COPD and CRF type 2 requiring NIV (blood gas analysis: $PaO_2 \leq 55$ mmHg, $PaCO_2 > 50$ mmHg; see [7]). It should exclude patients with contraindications for the investigational or comparator intervention according to guidelines as well as any patients in whom stable COPD can be ruled out or who are thought to suffer from acute rather than chronic respiratory failure.

The intervention should be HFT self-administered for 6 months in comparison with NIV as per guideline recommendation [7].

Study hypothesis, outcomes, estimated number of cases

The study objective should be to prove that, in patients with COPD and CRF type 2, HFT is superior to NIV with regard to the primary outcome. The primary outcome should be quality of life, measured by a validated instrument (e.g., SRI).

Particularly relevant secondary outcomes would be all-cause mortality, acute exacerbations, severity of dyspnoea (measured by a validated instrument, such as the mMRC), length of hospital stay, and AEs.

The below discussion of estimated case numbers is not intended as a binding calculation but as an approximate estimate of the case numbers required. Case numbers with binding effect must be planned during the specific study planning.

Assuming a mean effect size of Hedges' g = 0.5 (based on the Storgaard 2018 results), a 2-sided significance level of 5%, a power of 90% and the use of a t-test, 172 cases would be needed, i.e., 86 patients per treatment arm. At an assumed drop-out rate of about 30%, this results in a total of 246 patients to be included (123 per treatment arm).

The study should be multicentric. Ideally, patients should be recruited for the study through centres or local cooperating hospitals that offer both treatment methods. Effective NIV as specified by guidelines (duration of use, ventilation pressure) must be ensured. If a recruitment period of 2 years can be achieved, the study duration including study preparation, recruitment, follow-up, and analysis would equal about 4 years.

The study must be conducted in compliance with the Guideline of Good Clinical Practice (GCP).

Prospects of success for government co-sponsored studies

In principle, it is possible to conduct a government co-sponsored study suitable for obtaining the necessary information for assessing the method's benefit.

In Germany, enough patients meeting the inclusion criteria for the government co-sponsored study are thought to be available for reaching the estimated number of cases.

Study costs

For studies with small case numbers and normal or high resource requirements, the study-specific cost would be about €10,000 or €12,000, respectively, per participant. On the basis of these assumptions, the estimated study costs equal €2.5 million to €3 million.

These cost estimates are intended to provide an orientation and are not to be used as the basis for contractual cost agreements.

5 Classification of the assessment result

CRF type 1 and type 2 differ in pathophysiology (lung impairment and associated pulmonary failure and hypoxaemia versus respiratory pump failure and associated ventilatory failure and [additional] hypercapnia) as do the therapies' mechanisms of action. Due to differences in the treatment mechanism, it is deemed inappropriate to jointly analyse studies on HFT as a comparator for LTOT and NIV. For this reason, key parameters have been defined for 2 separate government co-sponsored studies with 2 different comparator treatments. In COPD and CRF type 1, HFT should be investigated as an adjunct to LTOT versus LTOT alone. In COPD and CRF type 2, HFT can be used as an alternative to NIV.

One study provided usable data on the use of HFT in patients with CRF type 1. Due to its objective and duration, this study did not survey outcomes such as mortality or acute exacerbations. Doing so would require a study duration of 1 year (or more). Although a study on the long-term use of HFT which included patients with COPD and hypoxaemia was found, namely Storgaard 2018, this study also included patients with COPD and hypercapnia, who therefore received a comparator intervention that is not in compliance with the guideline. By the time the final report was completed, no data which would be adequate for a benefit assessment were made available for the subgroup of patients with CRF type 1.

In addition to Bräunlich 2019, the systematic literature search found 1 further study on HFT in COPD and hypercapnia in the context of CRF type 2. Said study (Nagata 2018 [34]) was excluded and was therefore not usable for the benefit assessment. Nagata 2018 was excluded because the patients in the study received LTOT as the comparator therapy, which is not an appropriate comparator. As per the guideline, NIV is indicated at $PaCO_2$ values of ≥ 50 mmHg [31]. For the Nagata 2018 study population, values above 85 mmHg have been reported. Hence, treatment with NIV would be indicated, rather than LTOT as provided in the Nagata 2018 study. In Nagata 2018, patients exhibited a mean $PaCO_2$ of 51.5 mmHg (HFT + LTOT group) or 52.3 mmHg (LTOT group) and a PaO_2 of 89.2 mmHg (HFT + LTOT group) or 87.8 mmHg (LTOT group) at comparatively low oxygen flow rates of 1.2–1.4 L/min. The current guidelines on NIV and LTOT [7,31,35] recommend long-term NIV at a daytime $PaCO_2 \geq 50$ mmHg. LTOT is recommended if the PaO_2 value is repeatedly measured to be ≤ 55 mmHg or, in the presence of secondary polycythaemia or signs of cor pulmonale, already at a $PaO_2 \leq 60$ mmHg. For patients with severe (GOLD stage IV), stable hypercapnic COPD, a study conducted in the German healthcare system [36] shows considerably lower mortality for positive-pressure NIV compared to the control group without NIV (1-year mortality of 12% versus 33%, $p < 0.001$).

6 Conclusion

On the basis of 1 study on HFT in COPD associated with CRF type 1, no hint of any greater benefit or harm of oxygen administration via HFT in comparison with oxygen administration via mask was found when administered repeatedly during physical exercise. It remains unclear whether a comparable benefit might be present. Data from 1 study on the long-term use of HFT were unusable because only a subgroup of patients suffered from CRF type 1 and therefore received an appropriate comparator therapy.

For the application of HFT in comparison with oxygen administration alone in patients with CRF type 1 and an underlying disease other than COPD, 1 study with repeated application during exercise was found. The data were unusable for a benefit assessment.

Regarding the use of HFT in patients with COPD and CRF type 2, usable data were available from 1 included study. This study revealed no benefit or harm of HFT in comparison with noninvasive ventilation. Since the data of the study are difficult to interpret, it remains unclear whether a comparable benefit exists.

For COPD without CRF symptoms, data were available from only 1 study and unsuitable for a benefit assessment.

Across indications, the data do not suggest any harm of HFT.

For all 4 indications, both completed and ongoing RCTs were found for assessing HFT. From the described results of all included studies – i.e., with additional consideration of the studies not usable for the benefit assessment – it follows that the HFT method to be assessed has the potential of a required treatment alternative. Testing in initially 2 studies is deemed feasible and meaningful.

7 References for English extract

Please see full final report for full reference list.

1. Stepphuhn H, Buda S, Wienecke A et al. Zeitliche Trends in der Inzidenz und Sterblichkeit respiratorischer Krankheiten von hoher Public-Health-Relevanz in Deutschland. Journal of Health Monitoring 2017; 2(3): 3-35.

2. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet 2004; 364(9434): 613-620. https://dx.doi.org/10.1016/s0140-6736(04)16855-4.

3. Savran O, Ulrik CS. Early life insults as determinants of chronic obstructive pulmonary disease in adult life. Int J Chron Obstruct Pulmon Dis 2018; 13: 683-693. https://dx.doi.org/10.2147/copd.S153555.

4. Raherison C, Girodet PO. Epidemiology of COPD. Eur Respir Rev 2009; 18(114): 213-221. https://dx.doi.org/10.1183/09059180.00003609.

5. Global Initiative For Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2020 report [online]. 2020 [Accessed: 15.06.2020]. URL: https://goldcopd.org/gold-reports/.

6. Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, Deutsche Atemwegsliga, Österreichische Gesellschaft für Pneumologie. S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD) [online]. 2018 [Accessed: 15.06.2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-006l_S2k_COPD_chronisch-obstruktive-Lungenerkrankung_2018-01.pdf.

7. Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin. Nichtinvasive und invasive Beatmung als Therapie der chronischen respiratorischen Insuffizienz: S2k-Leitlinie [online]. 2017 [Accessed: 15.06.2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-008l_S2k_NIV_Nichtinvasive_invasive_Beatumung_Insuffizienz_2017-10.pdf.

8. Hyzy R. Heated and humidified high-flow nasal oxygen in adults: practical considerations and potential applications [online]. 2020 [Accessed: 15.06.2020]. URL: https://www.uptodate.com/contents/heated-and-humidified-high-flow-nasal-oxygen-in-adults-practical-considerations-and-potential-applications.

9. Bräunlich J, Nilius G. Nasaler Highflow (NHF): eine neue Therapiealternative zur Behandlung der respiratorischen Insuffizienz. Pneumologie 2016; 70(1): 49-54. https://dx.doi.org/10.1055/s-0041-110286.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf.

11. Storgaard LH, Hockey HU, Laursen BS et al. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. Int J Chron Obstruct Pulmon Dis 2018; 13: 1195-1205. https://dx.doi.org/10.2147/COPD.S159666.

12. Storgaard LH, Weinreich UM, Laursen BS. COPD patients' experience of long-term domestic oxygen-enriched nasal high flow treatment: a qualitative study. COPD 2020; 17(2): 175-183. https://dx.doi.org/10.1080/15412555.2020.1736998.

13. Weinreich UM. Domiciliary high-flow treatment in patients with COPD and chronic hypoxic failure: In whom can we reduce exacerbations and hospitalizations? PLoS One 2019; 14(12): e0227221. https://dx.doi.org/10.1371/journal.pone.0227221.

14. Storgaard LH, Hockey HU, Weinreich UM. Development in PaCO2 over 12 months in patients with COPD with persistent hypercapnic respiratory failure treated with high-flow nasal cannula-post-hoc analysis from a randomised controlled trial. BMJ Open Respir Res 2020; 7(1). https://dx.doi.org/10.1136/bmjresp-2020-000712.

15. Aalborg University Hospital. The effect of oxygen therapy with airvo high-flow heated humidification (HHCOPD) [online]. 2018 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT02731872.

16. Aalborg University Hospital. The effect of oxygen therapy with Airvo high-flow heated humidification for respiratory insufficiency in patients with chronic obstructive pulmonary disease [unpublished]. 2011.

17. Vitacca M, Paneroni M, Zampogna E et al. High-flow oxygen therapy during exercise training in patients with chronic obstructive pulmonary disease and chronic hypoxemia: a multicenter randomized controlled trial. Phys Ther 2020; 24: 24. https://dx.doi.org/10.1093/ptj/pzaa076.

18. Vitacca M, Pietta I, Lazzeri M et al. Effect of high-flow nasal therapy during exercise training in COPD patients with chronic respiratory failure: study protocol for a randomised controlled trial. Trials 2019; 20(1): 336. https://dx.doi.org/10.1186/s13063-019-3440-2.

19. Istituti Clinici Scientifici Maugeri SpA. Effect of exercise training under HFO device on endurance tolerance in patients with COPD and CRF: a randomized controlled study (HFO) [online]. 2019 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT03322787.

20. Chihara Y. Effectiveness of High-Flow Nasal Cannula on Pulmonary Rehabilitation in Subjects With Chronic Respiratory Failure [online]. 2020 [Accessed: 30.08.2020]. URL: https://www.researchsquare.com/article/rs-55544/v1.

21. National Hospital Organization Minami Kyoto Hospital. The efficacy of nasal high flow oxygen therapy with rehabilitation in the patients with chronic respiratory failure [online]. 2018 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT02804243.

22. Bräunlich J, Dellweg D, Bastian A et al. Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD. Int J Chron Obstruct Pulmon Dis 2019; 14: 1411-1421. https://dx.doi.org/10.2147/COPD.S206111.

23. Bräunlich J, Seyfarth HJ, Wirtz H. Nasal high-flow versus non-invasive ventilation in stable hypercapnic COPD: a preliminary report. Multidiscip Respir Med 2015; 10(1): 27. https://dx.doi.org/10.1186/s40248-015-0019-y.

24. University of Leipzig. Effectiveness of TNI vs. BiPAP in chronic global insufficiency in COPD patients [online]. 2018 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT02007772.

25. Rea H, McAuley S, Jayaram L et al. The clinical utility of long-term humidification therapy in chronic airway disease. Respir Med 2010; 104(4): 525-533. https://dx.doi.org/10.1016/j.rmed.2009.12.016.

26. Fisher and Paykel Healthcare. Does home based humidification treatment reduce exacerbation frequency for people with COPD and bronchiectasis? [online]. 2015 [Accessed: 01.03.2021]. URL: https://anzctr.org.au/ACTRN12605000623695.aspx.

27. Spyridon Fortis. HHHFA in COPD patients, with chronic bronchitis: study details [online]. 2019 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT03959982.

28. University Hospital Grenoble. High-flow in hypercapnic stable COPD patients (high-flow) [online]. 2020 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT04281316.

29. Ciro Horn. Pulmonary rehabilitation with nasal-high-flow-support in COPD and effectiveness: the PRINCE study [online]. 2018 [Accessed: 01.03.2021]. URL: https://trialregister.nl/trial/7280.

30. ADIR Association. Nasal high flow to maintain the benefits of pulmonary rehabilitation in chronic obstructive pulmonary disease patients (PPR-NHF) [online]. 2020 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT03882372.

31. Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin. Leitlinie zur Langzeit-Sauerstofftherapie; AWMF-Registernummer 020-002 [online]. 2020 [Accessed: 04.01.2021]. URL: https://www.awmf.org/uploads/tx_szleitlinien/020-002l_S2k_Langzeit_Sauerstofftherapie_2020-08.pdf.

32. Windisch W, Freidel K, Schucher B et al. The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. J Clin Epidemiol 2003; 56(8): 752-759. https://dx.doi.org/10.1016/s0895-4356(03)00088-x.

33. Windisch W, Budweiser S, Heinemann F et al. The Severe Respiratory Insufficiency Questionnaire was valid for COPD patients with severe chronic respiratory failure. J Clin Epidemiol 2008; 61(8): 848-853. https://dx.doi.org/10.1016/j.jclinepi.2007.09.009.

34. Nagata K, Kikuchi T, Horie T et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease: a multicenter randomized crossover trial. Ann Am Thorac Soc 2018; 15(4): 432-439. https://dx.doi.org/10.1513/AnnalsATS.201706-425OC.

35. Ergan B, Oczkowski S, Rochwerg B et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. Eur Respir J 2019; 54(3): 1901003. https://dx.doi.org/10.1183/13993003.01003-2019.

36. Kohnlein T, Windisch W, Kohler D et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2014; 2(9): 698-705. https://dx.doi.org/10.1016/S2213-2600(14)70153-5.

37. Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

38. Lefebvre C, Glanville J, Briscoe S et al. Cochrane handbook for systematic reviews of interventions; version 6; technical supplement to chapter 4: searching for and selecting studies [online]. 2019 [Accessed: 15.01.2020]. URL: https://training.cochrane.org/handbook/version-6/chapter-4-tech-suppl.

39. Waffenschmidt S, Navarro-Ruan T, Hobson N et al. Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. Res Synth Methods 29.05.2020 [Epub ahead of print]. https://dx.doi.org/10.1002/jrsm.1425.

The full report (German version) is published under

https://www.iqwig.de/en/projects/n20-02.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to June 09, 2020

The following filters were adopted:

- Systematic review: Wong [37] – High specificity strategy

#	Searches
1	(high flow* adj2 (nasal* or oxygen* or humidified*)).ti,ab.
2	humidification*.ti,ab.
3	high flow.kf.
4	or/1-3
5	cochrane database of systematic reviews.jn.
6	(search or MEDLINE or systematic review).tw.
7	meta analysis.pt.
8	or/5-7
9	8 not (exp animals/ not humans.sh.)
10	and/4,9
11	10 and (english or german).lg.

2. HTA Database

Search interface: INAHTA

#	Searches
1	high flow*
2	nasal* OR oxygen* OR humidified*
3	#2 AND #1
4	humidification*
5	#4 OR #3

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to June Week 3, 2020
- Ovid MEDLINE(R) Daily Update June 29, 2020

The following filters were adopted:

- RCT: Lefebvre [38] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	(high flow* adj3 (nasal* or oxygen* or humidified*)).ti,ab.
2	humidification*.ti,ab.
3	high flow.kf.
4	or/1-3
5	randomized controlled trial.pt.
6	controlled clinical trial.pt.
7	(randomized or placebo or randomly or trial or groups).ab.
8	drug therapy.fs.
9	or/5-8
10	exp animals/ not humans.sh.
11	9 not 10
12	4 and 11
13	12 not (comment or editorial).pt.
14	13 and (english or german).lg.
15	remove duplicates from 14

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to June 29, 2020
- Ovid MEDLINE(R) Epub Ahead of Print June 29, 2020

#	**Searches**
1	(high flow* adj3 (nasal* or oxygen* or humidified*)).ti,ab.
2	humidification*.ti,ab.
3	high flow.kf.
4	or/1-3
5	(clinical trial* or random* or placebo).ti,ab.
6	trial.ti.
7	or/5-6
8	4 and 7
9	8 not (comment or editorial).pt.
10	9 and (english or german).lg.

2. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL < 1946 to August 13, 2020>

The following filters were adopted:

- Non-RCT: Search filter with best sensitivity for controlled NRS (Ovid MEDLINE, adapted from PubMed) [39]

#	**Searches**
1	(high flow* adj3 (nasal* or oxygen* or humidified*)).ti,ab.
2	humidification*.ti,ab.
3	high flow.kf.
4	or/1-3
5	exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
6	((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
7	or/5-6
8	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
9	hi.fs. or case report.mp.
10	or/8-9
11	7 not 10
12	4 and 11
13	12 and (english or german).lg.

3. Embase

Search interface: Ovid

- Embase 1974 to 2020 June 29

The following filters were adopted:

- RCT: Wong [37] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	(high flow* adj3 (nasal* or oxygen* or humidified*)).ti,ab.
2	humidification*.ti,ab.
3	high flow.kw.
4	or/1-3
5	(random* or double-blind*).tw.
6	placebo*.mp.

#	Searches
7	or/5-6 [Wong – Strategy minimizing difference between sensitivity and specificity]
8	4 and 7
9	8 not medline.cr.
10	9 not (exp animal/ not exp human/)
11	10 not (Conference Abstract or Conference Review or Editorial).pt.

4. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2020

#	Searches
#1	(high flow* near/3 (nasal* or oxygen* or humidified*)):ti,ab
#2	humidification*:ti,ab
#3	("high flow"):kw
#4	#1 OR #2 OR #3 in Trials

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
AREA[InterventionSearch] (high flow AND (nasal OR oxygen OR humidified) OR humidification OR humidifier)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
high flow AND nasal OR high flow AND oxygen OR humidified OR humidification OR humidifier