Trial Protocol

Nasal high-flow compared to non-invasive ventilation in treatment of acute acidotic hypercapnic exacerbation of chronic obstructive pulmonary disease – a randomized controlled noninferiority trial

ELVIS

Coordinating investigators

Prof. Dr. Hubert Wirtz

Department of Respiratory Medicine
University Hospital Leipzig AöR
Liebigstr. 20
04103 Leipzig

PD Dr. Jens Bräunlich

Clinic Emden
Hans-Susemihl hospital
Medical clinic
Bolardusstraße 20
26721 Emden

Biometry

Dr. rer. nat. habil. David Petroff

Leipzig University
Clinical Trial Centre Leipzig
Härtelstraße 16-18
04107 Leipzig

Responsible Institution

Leipzig University

Ritterstr. 26, 04109 Leipzig

Date: 16.12.2020

Version: Final 1.0

Table of Contents

GENERAL INFORMATION

Responsible parties

Responsible institution	**Leipzig University** Ritterstr. 26, 04109 Leipzig
Coordinating investigators	**Prof. Dr. med. Hubert Wirtz** Department of Respiratory Medicine University Hospital Leipzig AöR Liebigstr. 20, 04103 Leipzig Phone: +49 341 97 12600 Fax: +49 341 97 12609 E-Mail: hubert.wirtz@medizin.uni-leipzig.de **PD Dr. med. Jens Bräunlich** Clinic Emden Hans-Susemihl hospital Medical clinic Bolardusstraße 20, 26721 Emden Phone: +49 21 98 15 98 Fax: +49 21 98 12 79 E-Mail: j.braeunlich@klinikum-emden.de
Project Management	Nicole Köppe-Bauernfeind, M.Sc. Leipzig University Clinical Trial Centre Leipzig Härtelstraße 16-18, 04107 Leipzig Phone: + 49 341 97 16266 Fax: +49 341 97 16259 E-Mail: nicole.koeppe-bauernfeind@zks.uni-leipzig.de
Safety Management	Madlen Doerschmann Leipzig University Clinical Trial Centre Leipzig Härtelstr. 16-18, 04107 Leipzig Phone: +49 341 97 16129 Fax: +49 341 97 16278 E-Mail: pharmacovigilance@zks.uni-leipzig.de
Data Management	Anke Stolle Leipzig University Clinical Trial Centre Leipzig Härtelstr. 16-18, 04107 Leipzig Phone: +49 341 97 16268 Fax: +49 341 97 16259 E-Mail: elvis@zks.uni-leipzig.de
Biometry	Dr. rer. nat. habil. David Petroff Leipzig University Clinical Trial Centre Leipzig Härtelstr. 16-18, 04107 Leipzig Phone: +49 341 97 16354 Fax: +49 341 97 16189 E-Mail: david.petroff@zks.uni-leipzig.de

Monitoring	Nicole Köppe-Bauernfeind, M.Sc. Leipzig University Clinical Trial Centre Leipzig Härtelstr. 16-18, 04107 Leipzig Phone: +49 341 97 266 Fax: +49 341 97 16259 E-Mail: nicole.koeppe-bauernfeind@zks.uni-leipzig.de
Funding	Dr. Laura de la Cruz Bundesministerium für Bildung und Forschung (BMBF) DLR Projektträger Bereich Gesundheit Heinrich-Konen-Str. 1, 53227 Bonn Phone: +49 30 670557985 Fax: +49 228 3821 1257 E-Mail: laura.delacruz@dlr.de
Data Safety Monitoring Board	PD Dr. med. Thomas Köhnlein (chairman) Internistisches Facharztzentrum Teuchern Markt 7, 06682 Teuchern Phone: +49 34443 614 0 Fax: +49 34443 614 16 E-Mail: thomas.koehnlein@facharztzentrum-teuchern.de Prof. Dr. med. Christian Witt Leiter Forschungsbereich Pneumologie an der Charité – Universitätsmedizin Berlin Charitéplatz 1, 10117 Berlin Phone: +49 30 450 565 021 E-Mail: christian.witt@charite.de Jörn Rau Medical statistics Coordinating Center for Clinical Trials Philipps-University of Marburg Karl-von-Frisch-Straße 4, 35043 Marburg Phone: +49 6421 286 6509 E-Mail: joern.rau@kks.uni-marburg.de

Summary of the revision history – Amendments

Number of Amendment	Contents	Date of approval
n.a.		

Synopsis

Title of the trial	Nasal high-flow compared to non-invasive ventilation in treatment of acute acidotic hypercapnic exacerbation of chronic obstructive pulmonary disease – a randomized controlled non-inferiority trial
Acronym	ELVIS
Indication	acute acidotic hypercapnic exacerbation of chronic obstructive pulmonary disease (**AECOPD**)
Primary efficacy end point	Proportion with treatment failure of allocated respiratory support within 72 h after start of respiratory support. Treatment failure defined as a) intubation or b) switch to another method of non-invasive ventilation or c) death
Secondary end points	1. proportions of single components of primary endpoint 2. proportion intubated within 7 calendar days after hospitalisation/randomization 3. overall survival at day 28 and 90 4. (invasive) ventilator-free days until day 28 5. (invasive) ventilator-free hours until assessment of the primary endpoint (within the first 72 hours after begin of therapy) 6. ICU/hospital length of stay 7. sedation required <u>Safety endpoints:</u> 1. (S)AE until discharge/day 28 (whichever comes first) 2. device related intolerance/complications 3. complications including severe diseases acquired under treatment
Trial design	Prospective, randomized, multi-centre open label trial following a non-inferiority design
Trial population	<u>Inclusion criteria:</u> 1. Acute hypercapnic exacerbation of chronic obstructive pulmonary disease with pH < 7.35 2. pCO2 > 45mmHg 3. age ≥ 18 years 4. written informed consent <u>Exclusion criteria:</u> 1. immediate need for intubation (acc. to intubation criteria in this protocol) 2. pH < 7.15 3. BMI ≥ 35 kg/m² 4. established home-NIV or home-CPAP 5. end-stage disease with DNI/DNR order 6. diseases that could influence the primary endpoint: e.g. acute heart infarction, cardiogenic lung edema, acute and massive lung embolism (hypertensive), chronic

	dialysis with metabolic acidosis, unstable rib fracture influencing ventilation, injury to the face prohibiting use of a face mask 7. acute disease that precludes participation in the trial 8. tracheotomized patients 9. psychological/mental or other inabilities to supply required informed consent 10. participation in other interventional trials 11. suspected lack of compliance
Sample size	To be assessed for eligibility: 1500 patients To be allocated to trial: 720 patients To be analysed: 720 patients (ITT analysis)
Therapy	Experimental intervention: Respiratory support with nasal high-flow (NHF) Control intervention: Respiratory support with non-invasive ventilation (NIV) Duration of intervention per patient: until randomized device no longer needed or discharge (whichever comes first) Follow-up per patient: clinical assessment up to discharge, for survival: days 28 and 90
Biometry	Efficacy: rates per arm and absolute risk reduction (NIV-NHF) with 95%-confidence intervals (CI) for primary and major secondary endpoints; multivariate logistic regression analysis to adjust for covariates and/or protocol deviations; no interim analysis Description of the primary efficacy analysis and population: Full Analysis Set based on an intent to treat philosophy Safety: all patients according to the treatment received Secondary endpoints: Proportions analysed analogously to primary endpoint; Cox regression models and Kaplan-Meier curves/ results of logrank tests for survival data within both full and per-protocol set of patients; ventilator-free days/hours by linear regression model including treatment as factor and stratification criteria as covariate exploratory analysis of patients with switch to another therapy to investigate the potential of rescue therapy
Trial Duration	Recruitment period (months): 30 Duration per patient (days): 90 First patient in to last patient out (months): 33 Time for data clearance and analysis (months): 8 Duration of the entire trial (months): 41

Synopse (German version)

Studientitel	Nasaler High-Flow im Vergleich zur nicht-invasiver Beatmung bei der Behandlung einer akuten azidotischen hyperkapnischen Exazerbation einer chronisch obstruktiven Lungenerkrankung
Akronym	**ELVIS**
Indikation	akute azidotische hyperkapnische Exazerbation einer chronisch obstruktiven Lungenerkrankung (AECOPD)
Primäres Ziel der Studie/ primärer Endpunkt	Anteil Patienten mit Therapieversagen der zugewiesenen Atemunterstützung innerhalb von 72 h nach Beginn der Atemunterstützung. Definition des Therapieversagens: a) Intubation oder b) Wechsel zu anderer nichtinvasiver Beatmungsmethode oder c) Tod
Sekundäre Ziele der Studie/ sekundäre Endpunkte	1. Anteile der einzelnen Komponenten des primären Endpunkts 2. Anteil der intubierten Patienten innerhalb von 7 Kalendertagen nach Hospitalisierung/Randomisation 3. Gesamtüberleben an Tag 28 und 90 4. Beatmungsfreie (invasiv) Tage bis Tag 28 5. Beatmungsfreie (invasiv) Stunden bis zur Bewertung des primären Endpunktes (innerhalb der ersten 72 Stunden nach Beginn der Therapie 6. Intensivstation/Dauer des Krankenhausaufenthaltes 7. Sedierung erforderlich <u>Sicherheits-Endpunkte:</u> 1. (schwerwiegende) unerwünschte Ereignisse bis zur Krankenhausentlassung/Tag 28 (was zuerst eintritt) 2. Gerätebedingte Intoleranz/Komplikationen 3. Komplikationen inklusive schwerwiegende Erkrankungen, die unter Therapie auftreten
Studiendesign	Prospektive, randomisierte, multizentrische, offene Studie nach einem Nicht-Unterlegenheits-Design
Studienpopulation	<u>Einschlusskriterien:</u> 1. akute hyperkapnische Exazerbation einer chronisch obstruktiven Lungenerkrankung mit pH < 7.35 2. pCO2 > 45mmHg 3. Alter ≥ 18 Jahre 4. unterschriebene Einwilligungserklärung <u>Ausschlusskriterien:</u> 1. unmittelbare Notwendigkeit einer Intubation (gemäß den definierten Intubationskriterien) 2. pH < 7.15 3. BMI ≥ 35 kg/m² 4. etablierte Nutzung der NIV oder CPAP zu Hause 5. Erkrankung im Endstadium mit Kontraindikation/Ablehnung einer Beatmung/Reanimation 6. Erkrankungen, die den primären Endpunkt beeinflussen könnten: z.B. akuter Herzinfarkt, kardiogenes Lungenödem,

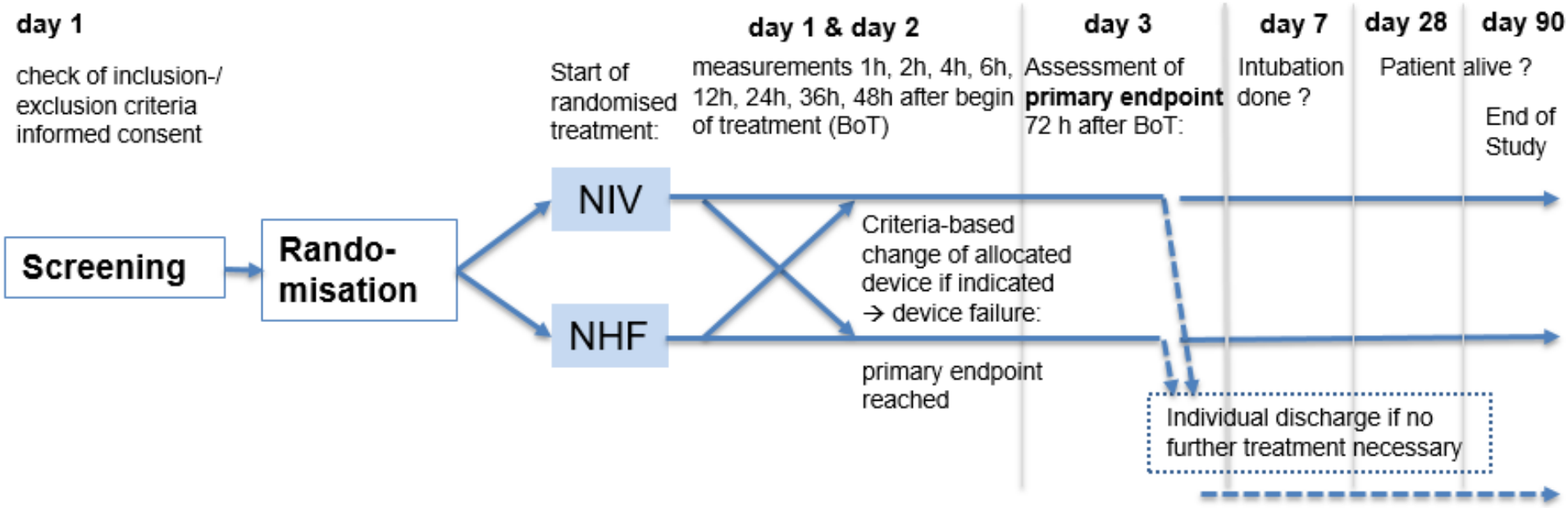
	akute und massive Lungenembolie (hypertonisch), chronische Dialyse mit metabolischer Azidose, instabile Rippenfraktur, die die Beatmung beeinflusst, Gesichtsverletzungen, die das Tragen einer Gesichtsmaske verhindern 7. akute Erkrankung, die eine Teilnahme an der klinischen Prüfung ausschließt 8. tracheotomierte Patienten 9. psychische/geistige oder sonstige Einschränkungen, um die erforderliche Einwilligung nach Aufklärung zu erteilen 10. Teilnahme an anderen interventionellen Studien 11. unzureichende Compliance
Patientenzahl	gescreent: 1500 Patienten randomisert: 720 Patienten analysiert: 720 Patienten
Therapie	Experimentelle Intervention: Atemunterstützung mit nasalem high-flow (NHF) Kontroll-Intervention: Atemunterstützung mit nicht-invasiver Beatmung (NIV) Dauer der Intervention pro Patient: bis das randomisierte Beatmungsgerät nicht mehr benötigt wird oder bis zur Entlassung (was zuerst eintritt) Follow-up pro Patient: Klinische Bewertung bis zur Krankenhausentlassung für das Überleben: Tag 28 und Tag 90
Biometrie	Konfirmatorische Analyse: Rate pro Arm und absolute Risikoreduktion (NIV-NHF) mit 95%-Konfidenzintervallen für primaren Endpunkt; ergänzt durch multivariate logistische Regression zur Adjustierung bzgl. Kovariaten (z.B. Stratifikationskriterien) und/oder Protokollabweichungen; keine geplante Interimanalyse Analysepopulation: Full Analysis Set gemäß Intent-to-treat Prinzip Sicherheitsanalysen: alle Patienten gemäß der tatsächlich applizierten Methode Analysen sekundäre Endpunkte: Raten analog zu primärem Endpunkt: Cox regression und Kaplan-Meier curves/ Logrank-Tests für Survivaldaten in Full analysis und Per-protokoll Population; beatmungsfreie days/hours mittels Linearer Regression mit Arm/Behandlung als factor und Stratifikationskriterien als Kovariaten Explorative Analysen zu Wechseln zu einer anderen Beatmungsmethode mit dem Ziel, das Potential aller eingesetzten Methoden als Rescue-Therapie zu untersuchen
Zeitplan	Rekrutierungszeitraum (Monate): 30 Studiendauer pro Patient (Tage): 90 Dauer von First patient in bis last patient out (Monate): 33 Zeit für Datenbereinigung und Analyse (Monate): 8 Dauer der gesamten Studie (Monate): 50

Schedule of assessments and procedures

Examination / Assessment		Treatment											Follow-up		
	Screen-ing	Visit 0	Visit 1						Visit 2		Visit 3		Visit 4	Visit 5[1]	Visit 6[1]
timepoint		**0 h**	**1h** ± 30 min	**2h** ± 30 min	**4h** ± 30 min	**6h** ± 30 min	**12h** ± 60 min	**24h** ± 60 min	**36h** ± 90 min	**48h** ± 120 min	**72h** ± 180 min	**discharge**	**day 7[2]** ± 1 day	**day 28**	**day 90**
Informed consent	X[3]											X[4]			
Inclusion criteria/exclusion criteria	X														
Randomization		X													
patients characteristics (anamnesis, comorbidity)	X														
medication	X							X[5]		X[5]	X[5]	X			
Clinical parameters (heart rate, respiratory rate, blood pressure, Borg's scale)	X		X	X	X	X	X	X	X	X	X	X	X		
Adverse Events/side-effects			X	X	X	X	X	X	X	X	X	X	X	X	X
Glasgow coma scale (GCS)	X		X	X	X	X	X	X	X	X	X	X			
Blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2	X		X	X	X	X	X	X	X	X	X	X	X		
Therapy according to allocated device: device parameters		X	X[6]	X	X	X	X	X	X	X	X	X	X[7]	X[6]	X[6]
Therapy: oxygen supplement		X	X	X	X	X	X	X	X	X	X	X	X[6]	X[6]	X[6]
infection parameters and biomarkers (optional)	X							X[5]			X[5]				

[1] Visit 5 and 6 are conducted by telephone
[2] Assessment of intubation; not applicable, if patient is already discharged since no intubation can be stated in this care
[3] Standard (long) version of informed consent OR concise (short) version of informed consent
[4] Standard (long) version of informed consent, if patient is still able to give informed consent
[5] All medications within the last 24h resp. laboratory paramenters any time within the last 24h
[6] A change of device is possible, if switch criteria are fulfiled OR need for intubation criteria are met before 72h → primary endpoint reached
[7] Ongoing treatment, if patient still hospitalized

Flow chart


day 1
check of inclusion-/ exclusion criteria informed consent
Screening
Rando-misation
day 1 & day 2
Start of randomised treatment:
measurements 1h, 2h, 4h, 6h, 12h, 24h, 36h, 48h after begin of treatment (BoT)
NIV
NHF
Criteria-based change of allocated device if indicated → device failure:
primary endpoint reached
day 3
Assessment of primary endpoint 72 h after BoT:
day 7
Intubation done ?
day 28
Patient alive ?
day 90
End of Study
Individual discharge if no further treatment necessary

1 RATIONALE, MEDICAL BACKGROUND

1.1 Medical background

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases. COPD is a leading cause of morbidity and mortality worldwide. Prevalence of COPD is much higher in smokers and ex-smokers, in subjects of ≥40 years of age, and in men. 384 million people suffered from COPD in 2010, with a global prevalence of 11.7%. Globally, around three million deaths occur annually. The occurrence of COPD is expected to rise over the next 30 years. Globally, the COPD burden is expected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population [1-3].

The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016 [1.32]. Globally, it is estimated that 3.17 million deaths were caused by the disease in 2015 (that is, 5% of all deaths globally in that year). Most patients with COPD develop relevant exacerbations of the disease during their lifetime. Some cases were admitted to hospital and present respiratory acidosis. Data from the European COPD audit in 13 countries recruited patients from 422 hospitals **Fehler! Verweisquelle konnte nicht gefunden werden.**. The study period ran from October 25 to December 19, 2010 or from January 3 until February 27, 2011 according to the seasonal peak of COPD exacerbations. 16016 patients were monitored. Of the patients who had blood gases at admission (13069) 5933 had hypercapnia (45.4%). 2452 of 13041 (18.8%) demonstrated respiratory acidosis.

Acute exacerbations of COPD are important events in the management of COPD because they negatively affect health status, rates of hospitalization/ readmission, and progression. AECOPD is characterized by symptoms such as dyspnea, increased sputum purulence and volume. Severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) can lead to acute hypercapnia acidotic respiratory failure, a life-threatening condition. 183 out of 1000 patients die during hypercapnic AECOPD and 341 out of 1000 will be intubated [4].

In December 2019, we searched the following databases for recent evidence: MEDLINE, Cochrane Central, the Cochrane library, clinical trials, DRKS, ICTRP (nasal high flow, COPD; no limits), see appendix 2. To date, non-invasive ventilation (NIV) is the standard therapy for hypercapnic acidotic respiratory failure in AECOPD according to established national/ international guidelines [5]. Solid evidence of its effectiveness has been generated for more than two decades. RCTs demonstrated a rapid improvement in blood gases and reduction of respiratory rate, in reduced rate of intubation, length of hospital stay, and mortality [4-7]. Despite its beneficial effects, NIV is often poorly tolerated (11-34 % failure rate) [4,8,9]. In most cases, the adaptation is difficult and time-consuming and may require patient sedation. Nasal high-flow (NHF) provides warmed and humidified gas administered through slightly enlarged nasal prongs. The almost saturated and warmed gas flow is the basis of very good tolerance even at high flow rates. NHF results in only a small increase in airway pressure (further reduced by opening the mouth). NHF reduces minute volume, lowers respiratory rate, and decreases the work of breathing. Exhaled gas in the upper airways is rapidly washed out, and thus physiological dead-space is reduced [10-14]. The high flow rates delivered by NHF are sufficient to cover even high peak inspiratory flows, thereby avoiding the admixture of ambient air. In a recent study, NHF was found to be superior to standard nasal prongs (SNP) and NIV in patients

with severe hypoxemic respiratory failure with regard to intubation rates and mortality [15]. The reintubation rate in the NHF arm was non-inferior or better compared to either venturi mask, SNP or NIV respectively [16,17] in a mixed hypoxemic population. In addition, there is growing evidence that NHF results in pCO_2 reduction in hypercapnic patients over short periods [18-20]. In a small pilot trial in patients with stable hypercapnic COPD over 6 weeks of duration NHF was found to be not inferior compared to NIV in reducing pCO2 [21]. Together with CO_2 wash-out studies these results led us to hypothesize that acute hypercapnic COPD patients might benefit from NHF as well. A couple of recent smaller trials in the acute setting appear to confirm this hypothesis in mixed populations with a subset of hypercapnic COPD patients [22,23]. They demonstrated significant improvements in blood gases during NHF therapy. In a very recent retrospective trial hypercapnic acidotic AECOPD patients were switched to NHF if they did not tolerate a prior NIV trial. The authors found comparable improvements to former NIV trials in terms of blood gases [24] - observational results arguing in the same direction.

1.2 Justification of investigation Design

There is no doubt growing interest in the use of NHF in ventilatory failure. So far most RCT´s exploring the use of NHF in acute respiratory failure have excluded hypercapnic patients [15,16,25]. It is not surprising that in these studies the investigators found only a small decrease of pCO_2. Most data about efficiency of NHF exists in postextubation respiratory failure. This entitiy includes also respiratory acidosis defined as pH<7.35 and $paCO_2$ more than 45 mmHg. Interestingly in the two studies by Hernandez et al. a non-significant trend of decreasing respiratory acidosis rate during NHF therapy was seen [17,25]. These trends were found in comparison to conventional oxygen and non-invasive ventilation (NIV). This finding would be important because of the prophylactic use of NIV in the postextubation phase have produced discordant results. The best domain for NIV in postextubation process was only documented in COPD patients [5].

1.2.1 Evidence from physiological/ preliminary/ retrospective/ observational trials

An increasing number of studies and case reports with hypercapnic patients have been reported [10,13,19,24]. Most of the studies investigating the effects of NHF on (relevant) chronic hypercapnia were done in COPD patients. The first study was the investigation by Bräunlich et al. in 2013 [19]. This physiological study was the first to describe the complex changes of respiratory patterns in healthy volunteers, patients with COPD and lung fibrosis. Here patients with stable daytime values of capillary pCO2 using NHF for 8 hours with a flow of 24l/min showed a decrease in capillary pCO2 by 0.69 ± 0.2 kPa 14. These changes were found despite a decrease in respiratory rate and minute volume. Additionally, significant changes were also found in patients with interstitial lung disease (ILD). Another study by the same group published in 2016 confirmed these results and documented a decrease of capillary pCO_2 in 54 COPD patients [20]. The main finding was the higher grade of decarboxylation by using higher flow rates. The mean decrease in 20l/min was 91 ± 6.7% and in 30l/min 87.4 ± 6.2% after a two hours treatment period. Therefore in according to the study by Frizzola et al. decrease in hypercapnia was a flow-dependent effect [26]. Another interesting study came from a group from Milano. Pisani et al. investigated patients with COPD and showed a decrease in arterial pCO_2 at a flow rate of 20 and 30 l/min with closed mouth condition. In 30 l/min but not in 20 l/min there was also a decrease in pO_2 but with decreasing respiratory rate [27]. The retrospective clinical study by Jeong et al. revealed the potential decrease in hypercapnia during NHF

therapy also in a cohort of 46 patients with and without COPD in an emergency department [28]. Most of the patients in the hypercapnic group had a COPD and acute exacerbation. The hypercapnia decreased significantly while increasing paO_2. But this observation was only found in hypercapnic patients.

The only study comparing NIV and NHF in a long time setting was conducted in 2015. Ten patients without an exacerbation in the last 4 weeks were eligible for participation. These patients used NHF in the first 6 weeks with a flow rate of 20l/min. After a study visit a low intensity NIV for additional 6 weeks was conducted. In this preliminary study the authors found effectiveness in decreasing hypercapnia during NHF therapy.

Between NIV and NHF no significant differences were found [21]. Additionally there exists more small studies and case reports.

Two studies were published in acute AECOPD. The first observational study was conducted by Bräunlich et al. [24] Patients with NIV failure were treated with NHF. The authors found an increase in pH and a decreasing hypercapnia. These results were confirmed by an Italian group [29] .

In contrast to studies in hypoxemic respiratory failure, most studies investigating the effects in decreasing hypercapnia had low numbers of recruited patients. Stability of oxygenation or statements about spontaneous reversibility of hypercapnia or time to former hypercapnic exacerbations are often lacking. As mentioned all available studies are very different in design and patients selection. So a definitive conclusion is premature.

1.2.2 Evidence from randomized controlled trials

The TIBICO trial is a cross over study using either NHF or standard NIV in stable hypercapnic COPD patients for 6 weeks periods each. The authors found non-inferiority of NHF compared to NIV in terms of decreasing hypercapnia and improvement in quality of life. This is the first randomized controlled trial which confirmes with a high quality level the beneficial effect of NHF in hypercapnic patients [30].

1.2.3 The need for a trial and justification of design aspects

Novelty: Preliminary data shows nasal high-flow (NHF) to be comparably effective in improving blood gases although only few investigations have been performed. A confirmatory trial involving a sufficient number of patients is lacking. NHF is well tolerated and simple to use [20].

Clinical impact: First: NHF might be an option for those patients who do not tolerate NIV therapy. Second, the need of sedation and co-medication may be reduced. Third, NHF is easy to use, time-saving in application and well tolerated. Therefore, longer usage times are expected. All of these reasons may contribute to the effectiveness of NHF (pCO2 decrease, pH normalization, lower respiratory rate, lower intubation rate, possible increase in survival)

Patient benefits: Patients who do not tolerate NIV are usually treated with oxygen and a large fraction of these patients will have to be intubated due to worsening respiratory conditions - associated with poorer prognosis. For these patients NHF might be an important and potentially life-saving alternative. Improved tolerance of NHF may lead to longer usage periods [30]. In contrast to NIV, patients during NHF are able to eat, drink and speak, resulting in improved quality of life.

Humidification during NHF is superior compared to NIV and improves mucociliary clearance [31]. NHF is not associated with skin rash, bruises, ulceration, or the drying of mucosal surfaces as observed with NIV.

Socioeconomic impact: Intubated and mechanically ventilated patients with AECOPD require cost-intensive ICU specific care. If NHF proves to be similarly effective and better tolerated, a cost-lowering effect is expected. Due to the high prevalence of AECOPD, this might add up to considerable savings. NHF might reduce the use of resources (including staff) even outside the ICU-setting.

In summary, this trial may contribute to extend the treatment of patients with hypercapnic acidotic AECOPD. In case of non-inferiority, it might provide a new and resource-efficient therapeutic option especially in patients not who do not tolerante NIV.

1.3 Risks and benefits

The major risk exists in case of failure of respiratory support by using the NHF device. Therefore, we implemented the opportunity to switch the device. This switch can be used as a so called “rescue NIV”. This approach has the benefit to avoid intubation in case of device failure. The same procedure can be used in case of NIV failure (“rescue NHF”).

The pronounced benefit is the use of another non-invasive respiratory support device (NHF) in case of NIV intolerance. As stated above during optimal study situations 11% of AECOPD patients did not tolerate NIV. For these patients only oxygen administration is available (but dangerous/ insufficient in case of muscle pump failure). In real life up to 30% of acidotic AECOPD patients decline NIV for several reasons. Avoiding intubation could be the most relevant benefit in these patients.

NIV requires trained staff, needs special experience, is time intensive and probably often started at ICU. NHF if beneficial is easy to use and preserves ressources. Hence deficient respiratory support as documented in the study by Hartl et al. could be avoided [1.32].

Residual risks associated with the investigational device might be an intolerance of the high flow or temperature, nose bleeds, dehydration of the nasal mucous membrane, ingestion of air or loud noise resulting from the applicator behind the ear.

Risks with NIV might be a pressure points on the nose, felling of fullness, drying of the mouth and throat area, allergic reactions, sneezing fits, ingestion of air, runny nose, conjunctivitis, headache, chest pain and device leakage.

2 OBJECTIVES

The main objective of the project is to compare nasal high-flow (NHF) with non-invasive ventilation (NIV) in cases of acute acidotic hypercapnic exacerbation of chronic obstructive pulmonary disease (AECOPD).

2.1 Hypotheses of the clinical investigation

Non-inferiority of NHF compared to NIV in acidotic hypercapnic AECOPD.

2.2 Primary objective

The primary objective is to analyse treatment failure of allocated respiratory support within 72h after start of respiratory support. The precise definition of the corresponding endpoints are provided in the section on Biometry.

2.3 Secondary objectives

The secondary objectives are to determine and compare the reasons and types of failure, the need for ventilation and for sedation. Compliance and acceptance of devices will also be investigated. Safety issues of interest are device related intolerance/complications and severe diseases acquired under treatment. The corresponding endpoints are defined in the Biometry section.

3 TRIAL DESIGN AND DESCRIPTION

3.1 Trial design

ELVIS is a prospective, randomized, multi-centre open label trial following a non-inferiority design.

3.2 Requirements at the Trial Sites regarding Personnel and Equipment

The **co-ordinating Investigator** is licenced to practice medicine, is a medical specialist in pneumology and/or intensive care medicine and has at least two years of working experience in the study specific indication. He/She has theoretical and practical experience in conducting clinical trials.

Investigator and Sub-Investigators are licenced to practice medicine, are medical specialists in pneumology and/or intensive care medicine and have at least *one* year of work experience in study specific indication.

The Investigator is responsible for selecting and assembling the trial team members (especially the medical staff) according to the requirements of this trial protocol. The co-ordinating investigator/responsible institution will provide these to each trial site. Furthermore, the investigator is responsible for training and supervision of the trial team and providing all necessary information during the course of the trial. This has to be documented accordingly.

All study sites must have

1. In-depth experience in using NIV and NHF
2. access to intensive/intermediate care units
3. access to medical emergency units
4. the general opportunity to recruit patients in this trial.

Each trial site receives a study-specific NHF device, though other specified devices may also be used (see chapter 0). The handling of the devices is carried out according to the manufacturer's instructions.

3.3 Trial Sites and Number of Trial Subjects

Planned number of participating sites are 35.

The total number of patients are 720 (see sample size discussion in chapter 8.4)

3.4 Trial Duration

Individual trial duration:

Duration per patient: 90 days

All patients will remain in the study until the end of the follow-up, which is reached 90 days after randomization of the last patient. For an expected recruitment period of 30 months, the longest study duration is 33 months.

Total duration of the study:

Expected duration of recruitment:	30 months
Expected time from first patient in to last patient out:	33 months

Start of the study is defined as date of the first written informed consent (first patient in - FPI). End of study corresponds to last patient out (LPO).

3.5 Premature Termination of the Trial

Premature termination of the trial for a single patient is described in chapter 6.10.2.

3.5.1 Premature termination of the trial at a trial site

The trial can be aborted at a single site if:

- the protocol is not adhered to,
- the quality of data is deficient,
- there is inadequate recruitment

The co-ordinating investigator decides whether or not to exclude the site, together with the responsible institution and biometrician.

Investigators and sites no longer participating in the trial must inform the co-ordinating investigator immediately and should provide justification for the decision. Further treatment of patients still involved in the trial has to be arranged together with the co-ordinating investigator.

CAUTION: Trial site may be temporarily placed on hold or closed by the co-ordinating investigator if no or insufficiently qualified personnel is available.

3.5.2 Termination of the whole trial or individual arms of the trial

The trial can be terminated prematurely by the co-ordinating investigator in the event of

- serious adverse events
- changes in the risk-benefit considerations, e.g. as a result of unexpected adverse events
- new insights from other trials
- an insufficient recruitment rate.

The responsible ethics committee(s) might also revoke the favourable opinion due to e. g. information from other clinical investigations.

The final decision regarding the premature termination of the trial will be made by the co-ordinating investigator in consultation with the DSMB.

4 TRIAL SUBJECTS

Chronic obstructive pulmonary disease (COPD) is a progressive life-threatening lung disease that causes breathlessness (initially with exertion) and predisposes to exacerbations and serious illness.

Most COPD patients have exacerbations 1 or 2 times a year. As mentioned above, in case of severe illness a relevant number of these patients were hospitalized. If severe respiratory symptoms occur, patients will be hospitalized by entering the emergency room. Acute exacerbation of COPD is one of the most reasons for acute presentation. To calculate the expected number of patients we requested number of recruitable patients by the centers.

4.1 Inclusion criteria

Definition of the trial population

1. acute hypercapnic exacerbation of chronic obstructive pulmonary disease with respiratory acidosis (pH < 7.35)
2. pCO2 > 45mmHg

Regulatory requirements

3. age ≥ 18 years
4. written informed consent (see chapter 6.2)

4.2 Exclusion criteria[8]

Intervention impossible (due to anatomic/medical reasons)

1. immediate need for intubation (acc. to defining intubation criteria, see chapter 0)
2. pH < 7.15
3. BMI ≥ 35 kg/m²
4. established home-NIV or home-CPAP
5. end-stage disease with DNI/DNR order
6. diseases that could influence the primary endpoint: e.g. acute heart infarction, cardiogenic lung edema, acute and massive lung embolism (hypertensive), chronic dialysis with metabolic acidosis, unstable rib fracture influencing ventilation, injury to the face prohibiting use of a face mask
7. acute disease that precludes participation in the trial

Contraindications

8. tracheotomized patients

Regulatory requirements

9. psychological/mental or other inabilities to supply required informed consent
10. participation in other interventional trials

Others

11. suspected lack of compliance

[8] In an emergency situation, the examination of the exclusion criteria will be carried out to the best of one's knowledge at the time of inclusion.

4.3 Justification for the Inclusion of vulnerable Populations

This clinical trial will not include vulnerable individuals.

5 INVESTIGATIONAL INTERVENTION/PRODUCT

5.1 Non-invasive ventilation (NIV)

Use of NIV devices of any manufacturer are allowed that are used routinely.

5.2 Nasal high-flow (NHF)

For the nasal high-flow, the device “TNI soft flow” is recommended and will be provided by the coordinating investigator before the start of the study. However, other dedicated nasal high-flow devices can also be used. Such devices must be capable of at least 50 litres per minute and sufficient humidification must be ensured. The applicators should also be heated sufficiently. Hybrid devices are not allowed. If questions should arise, decisions will be made regarding permitted devices after consultation with the coordinating investigator. Before the start of the study, the use of the available NHF devices will be checked and documented in the qualification documents for the trial centre.

For more details about the therapy see chapter 6.6.

6 DESCRIPTION OF THE TRIAL/TREATMENT PROCEDURES

6.1 Screening

The participating trial centres will screen all patients with acute acidotic hypercapnic exacerbation of chronic obstructive pulmonary disease, as far as the physician can be assessed, if the patient coming to the clinic via the emergency room, intensive care unit or normal ward. Patients that appear suitable for the trial (see inclusion and exclusion criteria) should be informed about the possibility of participation. All screened patients, who refuse to participate will be listed in an anonymous screening failure log. This document will include information on gender and age. Those willing to participate and giving written informed consent will be included into the trial and continue with the trial procedure.

6.2 Patient Information and Informed Consent

All patients in this trial are able to give informed consent. Patients who are not able to give informed consent will not be included into the study. An authorised trial physician will seek the patient's consent before performing any trial specific medical procedures with the patient.

Before obtaining informed consent, the potential trial participant will receive information regarding the clinical trial. It will be performed by a qualified medical member of the trial group authorised by the investigator for this task.

In accordance with international guidelines, the informed consent of trial participants will be in writing (written, dated and signed by the person performing the interview referred to below, and by the subject, if possible).

There are different departments where the patients with acute acidotic hypercapnic exacerbation of chronic obstructive pulmonary disease (AECOPD) can be informed about the ELVIS trial. A number of patients come to the clinics via emergency room and require rapid treatment with a ventilator. If the clinical situation does not permit the **standard version** (long version) of the consent form to be applied right away, a **concise version** (short version) may be used. The standard form will be completed by the patient at the latest before discharge.

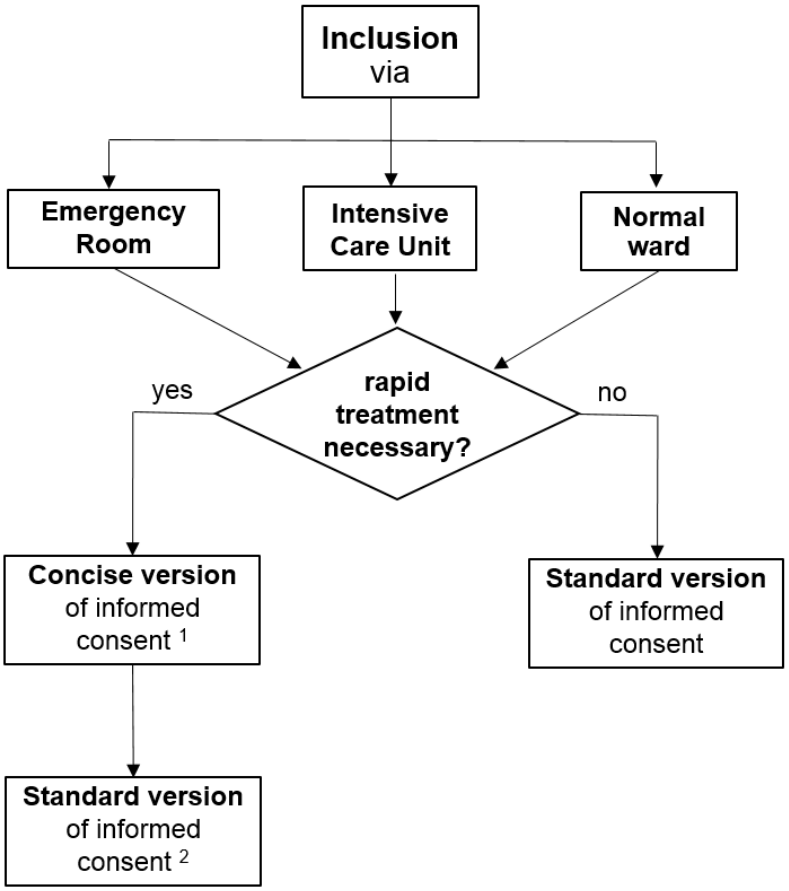
The standard and concise version includes the following items:

- the nature, objectives, benefits, implications, risks and potential inconveniences of the clinical trial
- the expected duration of the subject's participation in the clinical trial
- the information that the patient may withdraw his consent to participate at any time without giving reasons.
- potential treatment alternatives
- follow-up measures in case of early termination of the trial for the patient or overall
- the applicable damage compensation system in case of damage to a patient
- the right on data access, rectification and withdrawal of personal data (short information)

The patient gives his/her consent to the study and to data processing in both versions of the consent forms (concise and standard version).

If the patient is not able to sign the short version of informed consent himself, but the patient is responsive, it is possible to consent to the study in the presence of witnesses. Witnesses must be study-independent persons.

If the patient's state of health deteriorates and the patient is no longer able to give informed consent, the concise version of the informed consent is sufficient.



[1] if patient is not able to sign, but responsive → consent in the presence of witnesses possible
[2] if patient is still able to give consent at the latest before discharge

6.2.1 Withdrawal of informed consent

Patients may withdraw their informed consent in writing or orally at any time without giving reasons and without suffering any disadvantage. If patients withdraw their consent, no further data will be collected. However, the data processing carried out up to the date of withdrawal remains lawful.

Due to the research character of the study, the rights of the patients regarding data protection may be restricted in terms of time and/or content, because otherwise the scientifically correct execution of the research project would probably be rendered impossible or seriously impaired (Art. 17 (3d) EU-DSGVO) [1.35] and because the processing is carried out for scientific research purposes and the interests of the responsible institution in the processing considerably outweigh the interests of the person concerned in excluding the processing (Art. 89 EU-DSGVO in connection with § 27 BDSG). See also chapter 10.1 for further information.

6.3 Screening Visit

All patients, who meet the inclusion criteria and none of the exclusion critera are met, will continue with the qualifying screening visit, which will be structured as follows:

- confirm the patient fulfils inclusion and exclusion criteria
- obtaining standard (long) version of informed consent OR concise (short) version of informed consent
- patients characteristics (anamnesis, comorbidity, concomitant medication)
- clinical parameters: heart rate, respiratory rate, blood pressure measurements
- Borg's scale
- Glasgow coma scale (GCS)
- blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2
- therapy according to allocated device: NHF or NIV
- optional: infection parameters and biomarker: leucocytes, IL6, CRP, PCT

6.3.1 Discovery of the Violation of Eligibility Criteria after Inclusion

In general, the violation of eligibility criteria is not a reason for premature withdrawal of the patient from the trial therapy or from the whole trial.

If a violation of a selection criterion is discovered after randomization of a patient, this has to be documented in the eCRF, which will result in an automatic report to the responsible trial team members at the ZKS Leipzig.

After consultation with the co-ordinating investigator, project management of the ZKS Leipzig informs the investigator or authorised medical staff immediately regarding the further treatment of the patient. The patient's data will continue to be recorded unless the patient revokes his/her informed consent. For procedures after premature trial termination of a single patient see chapter 6.9.1 and 6.9.2.

6.4 Visit 0/Randomization

Visit 0 is the timepoint after checking the eligibility criteria and patients will be randomized. The responsible study personnel have to log on to the secure data base and enter the relevant data into the data base to initiate the randomization process. Randomisation will be performed centrally, via a secure web-based tool. The allocation to the intervention arm (randomisation ratio 1:1) uses computer generated allocation sequences. Randomization will be stratified by centre, pH-value ≤/>7.3 and BMI ≤/> 30 kg/m². The randomization result forwarded back automatically via email confirmation to the investigator and the Clinical Trial Centre Leipzig (email). After the result of the randomization is established, the treatment is started immediately (0 hour). The randomization is equal to start of ventilation.

The device parameters and oxygen supplement have to be documented to this timepoint.

6.5 Trial procedure(s) during treatment

Visit 1 (V1) includes the first day of treatment. The start of invervention (NIV or NHF) is usually the same day like the screening visit. The following examination must be performed **one, two, four, six** (± 30 minutes)**, twelve and twenty-four hours** (± 60 minutes) **after the start of ventilation**:

- clinical parameters: heart rate, respiratory rate, blood pressure measurements
- Borg's scale
- Glasgow coma scale (GCS)
- blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2
- documentation of adverse events/side effects
- documentation of device parameters and oxygen supplement
- therapy according to allocated device: NHF or NIV according to randomization
- optional to timepoint 24 hours: infection parameters and biomarker: leucocytes, IL6, CRP, PCT

A change of device during the treatment is possible, if switch criteria are fulfilled OR need for intubation criteria are met before 72 hours. For more details see chapter 0.

Visit 2 (V2) includes the second day after start of ventilation and the following examinations must be performed **thirty-six** (± 90 minutes) **and fourty-eight hours** (± 120 minutes) **after the start of ventilation:**

- clinical parameters: heart rate, respiratory rate, blood pressure measurements
- Borg's scale
- Glasgow coma scale (GCS)
- blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2
- documentation of adverse events/side effects
- documentation of device parameters and oxygen supplement
- therapy according to allocated device: NHF or NIV according to randomization
- optional to timepoint 48 hours: infection parameters and biomarker: Leucocytes, IL6, CRP, PCT

Visit 3 (V3) have to be performed **72 hours** (± 180 minutes) **after start of ventilation** with the following assessments:

- clinical parameters: heart rate, respiratory rate, blood pressure measurements
- Borg's scale
- Glasgow coma scale (GCS)
- blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2
- documentation of adverse events/side effects
- documentation of device parameters and oxygen supplement
- therapy according to allocated device: NHF or NIV according to randomization

The **discharge** of the patient is individual. Before the patient is discharged from hospital, the following examinations/processes must be carried out:

- obtaining the standard version of informed consent, if only give informed concent by concise version
- physical examination: heart rate, respiratory rate, blood pressure measurements
- Borg's scale

- Glasgow coma scale (GCS)
- blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2
- documentation of adverse events/side effects
- documentation of device parameters and oxygen supplement

After discharge treating physician should monitor reversibility of hypercapnia. In case of ongoing hypercapnia long-term NIV or NHF should be prescribed.

6.6 Dose, mode and scheme of intervention

Patients may be ventilated with NIV/NHF for a short time during transport or prior to randomization.

Following randomization, patients will be treated with the respiratory support device (NIV/NHF) according to allocation as medically required or until discharge (whichever comes first).

In the **NIV** arm, the physician will begin to apply NIV via facial mask. Pressure support will be **initiated with 18/4 mbar** for adaptation and then increased to achieve effective respiratory support with maintained tolerance.

NHF will **start with a flow of 30 l/min at 37 degrees**, generally with standard or large sized prongs. Later adjustments at a patient level are foreseen.

With both devices, oxygen should be supplemented to reach O_2 saturation of 88-92%.

The success of the intervention will be monitored by blood gases and outcome parameters. Patients should use respiratory support as long as possible, both day and night. The study intervention can be initiated on a regular ward or in intermediate or intensive care facilities, as well as emergency rooms.

6.7 Guidance for switching devices and the need for intubation

6.7.1 Switch from NIV to NHF or vice versa / rescue method in case of worsening of respiratory insufficency and in absence of intubation criteria

It is strongly recommended continuing with the allocated device unless there is clear evidence of device failure, defined as any one of the following:

1. **at 1h**:
   - an unacceptable decrease in pH (pH change of 0.06),
   - an unacceptable increase in pCO_2 (pCO_2 change of 10mmHg),
   - an unacceptable decrease in GCS,
   - an unacceptable increase in respiratory rate (RR>20% compare to last measurement),
   - insufficient compliance
2. **at 2h 4h, 6h, 12h and every 12h till 72h:**
   - unacceptable worsening in pH or pCO_2,
   - clinically unstable (beginning at 4h) compared to last status,
   - very poor compliance

All criteria which lead to the investigator's decision to switch treatment - including patient's incompliance - will be documented in the patient file and in the CRF so that post-hoc ratings are possible (based on the study's database).

6.7.2 Need for intubation criteria

Individual decision of the physician in consideration of the clinical evaluation
Respiratory acidosis pH < 7.15 (strongly recommended, exceptions must be justified) **AND** at least one of the following (recommended)

1. GCS (Glasgow coma scale) <10 unless medically induced OR
2. Increasing hypoxemia despite adequate oxygenation (O_2 saturation <85% or $pcaO_2$<45 mmHg/ FiO_2 set>50%) OR
3. A respiratory rate above 40 cycles/min

Independent from the outcomes regarding device failure and/or intubation, all patients will be followed-up until 90d post randomization.

6.8 Additional treatments

Standard care follows the local COPD exacerbation protocol:

- oral prednisolone 40 mg/day for 5 days;
- antibiotics prescribed according to the following criteria:
  - fever (body temperature >38.5°C),
  - elevated C-reactive protein (CRP) >50 mg/L,
  - change in sputum colour, and/or
  - according to the physician's decision of severe illness, and/or
  - FEV1 <30% below of the predicted value
- inhaled corticosteroids, beta-agonists and/ or anticholinergics.

Oxygen will be prescribed in all patients through a standard low flow system in order to maintain adequate arterial oxygen saturation (SaO_2). Patients will be discharged with regular low flow oxygen once they fulfil the criteria for long-term oxygen therapy.

6.9 Follow-up procedures

The **first follow-up visit (visit 4)** will be performed **7days** (± 1 day) **after the start of ventilation.**

The following assessements have to be performed at this follow-up timepoint:

- clinical parameters: heart rate, respiratory rate, blood pressure measurements
- Borg's scale
- blood gas analysis (BGA): pO_2, pCO_2, pH, SpO_2, FIO_2
- documentation of adverse events/side-effects
- documentation of device parameters and oxygen supplement, if necessary
- Therapy according to allocated device, if patient still hospitalized on day 7

The **second and third follow-up (visit 5 and 6)** will be performed **28 and 90 days after the start of ventilation** by telephone only:

- Health status: question of adverse events/side-effects
- use of ventilation

For documentation purposes, a worksheet is made available to the trial center in order to document the desired parameters and to be able to place them as a source document in the patient file.

6.10 Premature termination of the therapy or follow-up for individual patients

The primary statistical analysis follows the intention to treat principle as closely as possible. For a valid analysis, it is of great importance to minimise the rate of drop-outs. Therefore, in patients who do not withdraw their consent, all trial visits shall be performed as scheduled.

In case of premature termination of therapy, it is necessary to document the date (as exactly as possible), the reason of termination and the current condition of the patient. Therefore, the eCRF "End of study (ES)" has to be completed for each patient. Data entry to this eCRF page will trigger an automatic report to the responsible trial team members at the ZKS Leipzig.

The "End of study"- eCRF routinely contains the following data*:*

- Date of individual end of trial
- Reason for trial termination
- Latest patient contact

6.10.1 Premature termination of therapy for individual patients

Trial therapy must be terminated prematurely, if the investigator decides/judges that

- an adverse event/incidence occurred to a patient and continuation of trial treatment would thus be an unaccepptable risk for this particular patient
- the worsening of a patient (who is not responding to treatment) contraindicates the treatment with trial therapy transiently or permanently
- a patient is significantly non-compliant with the requirements of the protocol, thereby endangering patient's safety
- any other reason of medical prudence applies

Trial therapy must also be terminated prematurely

- on request of the patient

With exception of the rules described above, premature termination of therapy should be avoided. In case the patient misses the scheduled visits, the investigator may contact the patient directly, in order to motivate him/her to continue.

All further trial visits until day 90 will take place as planned and described in section 6.9.

Termination of trial therapy does not necessarily mean that the patient is off-trial.

6.10.2 Premature trial termination for individual patients

All randomised patients will be followed up until day 90. Premature termination of trial therapy does not necessarily lead to individual trial termination.

The only circumstances in which a premature trial termination (i.e. no further trial visits) in a randomised patient is unavoidable are:

- a patient is worsening (and not responding to treatment) that contraindicates participation in any further trial visits
- withdrawal of informed consent,
- complete loss of contact to the patient or
- death of the patient.

6.10.3 Premature Termination of the Follow-up for Individual Patients

Follow-up can be prematurely terminated, if:

- Informed consent was withdrawn
- Complete loss of contact to the patient
- Death of the patient

6.11 Counterindicated/Forbidden Concomitant Medication or procedures

The following medication should not be given:

- Bicarbonate modifying newly started medication, e.g. bicarbonate modifying newly started medication Natriumhydrogenkarbonat (NaHCO)/Bicarnorm

6.12 Plan for Further Treatment

After the study patients should be treated to physician's discretion. The scenario include the continued usage or prescription of long-time NIV/NHF.

7 ADVERSE EVENTS (AE/SAE)

Both, the declaration of Helsinki [1.33], as well as the ISO 14155 [1.34], chapter 4c and 7.4, prioritize subject protection in clinical trials.

7.1 Adverse Events and Serious Adverse Events (SAE)

7.1.1 Definitions

Adverse Events (AE)

According to ISO 14155, 3.2: **Adverse event** (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.

Serious Adverse Event (SAE)

According to the ISO 14155: 2020; 3.45: **Serious adverse events** are adverse events that led to any of the following

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function including chronic diseases, or
   - in-patient or prolonged hospitalization, or
   - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

NOTE Planned hospitalization for a pre-existing condition without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE)

According to ISO 14155: 2020; 3.1: an **Adverse Device Effect** is defined as adverse event related to the use of an investigational medical device.

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

NOTE 3 This includes comparator if the comparator is a medical device.

Acoordingly, a **Serious Adverse Device Effect (SADE)** is an ADE fulfilling the criteria for seriousness given above.

7.1.2 Documentation of (Serious) Adverse Events

All Adverse Events will be documented on special AE-forms from start of ventilation until discharge or day 28 (whichever comes first) for each patient.

Information relevant to AEs will be solicited by the investigator at every patient's study visit. In addition, the patient will be trained to inform the clinical trial site of any health problems arising between visits by phone or personal visit.

Adverse Events are classified by their seriousness, intensity and relationship to the therapeutic intervention (see also chapter 15.1).

There will be no separate SAE-forms in the ELVIS trial. If an AE fulfils any of the criteria for a SAE (see chapter 7.1.1 for SAE-definition), the AE has to be marked as "serious" on the CRF. This applies to all SAEs, whether or not they are considered to be related to the study treatment.

For both serious and non-serious AEs, documentation should be supported by an entry in the patient's health record.

Required information includes: the type of AE, seriousness of the event, an estimate of its severity, start date, date of resolution, actions required, outcome and an assessment of its relationship to trial intervention.

All abnormal physical and/or laboratory results which are considered to be clinically relevant by the investigator should be recorded as (S)AEs.

The investigator will follow-up the event until the AE has been resolved, resolved with sequelae, or was fatal. The investigator should report each AE on according eCRF in a timely manner and continuously during the trial.

Responsibilities of the investigator/recruiting site

The ELVIS trial follows §23b MPG. Thus, there are **no SAE-reporting obligations to the competent authority**.

Should SAEs arise, they will be documented on the AE-form of the eCRF and marked as "serious" (see above). The criteria for seriousness will also be documented.

The investigators will be trained to enter data relevant for the safety evaluation of the trial into the eCRF without unduly delay. Within the database, a selection of the radio button "serious" will trigger an automatic E-mail-announcement of the SAE at ZKS Leipzig.

If any of the involved ethics committees should require SAE-reports, these will be derived from the trial database at the required intervals.

7.2 Device deficiencies and Incidents

7.2.1 Device deficiencies

‘Device deficiency’ means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer including labelling. (ISO 14155: 2020; 3.19)

If a device deficiency fulfils the criteria of a SAE, the investigator has to follow the procedures described in chapter 7.1.2.

7.2.2 Incidents

According to Directeive 93/42/EEC, Article 10: ‘Incident’ means:

a) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for usae which might lead to or might have led to the death of apatient or user or to a serious deterioration in his state of health.

b) This also includes any technical or medical reason in relation to the characteristics or performance of a device for the reasons reffered to in subparagraph a) leading to systematic recall of devices of the same type by the manufacturer.

7.2.3 Documentation and Reporting obligations: Investigator

Documentation and reporting of device deficiencies including serious device deficiencies and incidents follows **clinical routine according to MPSV §3**. Thus, the manufacturer is responsible for device deficiencies and reporting of these. Investigator and manufacturer colaborate for potential reporting to the competent authority.

Incidents have to be reported **according to clinical routine (MPSV §3)** using the „Formblatt für die Meldung von Vorkommnissen durch sonstige Inverkehrbringer sowie Betreiber und Anwender nach §3 Abs. 2 bis 4 der Medizinprodukte-Sicherheitsplanverordnung“, which is available from the website of the BfArM.

7.3 Concomitant diseases

If a disease or a condition existed at enrolment and continued unchanged thereafter, this is no AE. However, if the disease worsened considerably and/or required additional medical or pharmacologic treatment, it has to be reported as AE and SAE, if it fulfils at least one SAE criterion as described in section 7.1.1 .

7.3.1 Therapeutic measures

If the patient needs treatment due to an adverse event, it must be carried out according to the current state of medical research for diagnosis and treatment in order to restore the patient's health.

8 STATISTICAL CONSIDERATIONS

8.1 Biometrical Aspects of the Investigation Design

8.1.1 Measures to Prevent Bias

Randomisation of patients between NHF and NIV is performed centrally via a secure web-based tool using a modified minimisation procedure with stochastic component according to Pocock[4] in a 1:1 ratio. The algorithm takes into account the current distribution of patients already recruited for the trial in a complex manner which helps ensure allocation concealment.

Randomisation will be stratified according to the following criteria:

- trial site
- pH-value ≤/>7.3 and
- BMI ≤/> 30 kg/m²

Patient blinding is not possible due to the nature of interventions.

The choice to intubate in this open-label trial constitutes a potential bias. Hence we have provided specific recommendations regarding the need for intubation see chapter 0.

8.2 End Points

8.2.1 Primary Endpoint

The primary endpoint is the proportion of treatment failure of allocated respiratory support within 72h after start of respiratory support. Treatment failure is defined by

a) intubation or

b) switch to another method of non-invasive ventilation or

c) death

Guidance regarding points (a) and (b) are provided in section 6.7.

8.2.2 Secondary Endpoints

1. Proportion of single components identified for the primary endpoint assessment
2. Proportion of intubation within 7 days after hospitalisation/randomization
3. Overall survival at 28d and 90d
4. (Invasive) ventilator-free days until 28d
5. (Invasive) ventilator-free hours until assessment of the primary endpoint (within the first 72 hours after begin of therapy)
6. ICU and hospital lengths of stay
7. Proportion requiring sedation

8.2.3 Safety Endpoints

No specific safety endpoints have been defined, since the efficacy endpoints are closely related to the major saftey issues.

SAE(s) and AE(s) will be listed by treatment received and, as appropriate, those on and off device will be distinguished. Device related intolerance will be listed as will complications and major diseases acquired under treatment.

8.3 Statistical Description of the investigation hypothesis

8.3.1 Statistical Hypotheses/Statistical Estimation Method

We hypothesized that treatment failure in AECOPD is at most 8 percentage points more prevalent for patients with planned NHF compared to planned NIV.

8.4 Sample Size Discussion

Two RCT´s have compared NHF and NIV regarding non-inferiority (Doshi et al. 2018; Hernández et al. 2016) up to now. Although these studies considered different patients they provide rough estimates for the expected difference between the arms and choices of non-inferioroty margins (15 and 10 percentage points). The reduction of intubation rates from NIV studies reported in a recent systematic Cochrane Review (Osadnik et al. 2017) wee 12% vs 34% (N=1105 of all 17 RCTs) and an absolute risk reduction ARR_{total}=-22.1 [-17.3;-26.9] % (RR=0.36 [0.28; 0.46]). This review (Osadnik et al. 2017, see also Plant et al. 2001 and Carrera et al. 2009) presented ARR point estimates of -12.7/ -20.7/ -11.9% and corresponding lower confidence limits of ARR of -3.4/ -2.0/ -1.6%. Based on these numbers, we defined a statistically and medically reasonable non-inferiority margin of Δ=8%. This choice is more conservative than in other trials and isfar below the lower confidence limit of ARR_{total} as requested within statistical guidelines (CHMP/ICH; CHMP/EWP).

Although our endpoint definition varies to some extent from that in other studies, we based our sample size calculations primariily on the reported “need for intubation” rates since intubation represents the next step of the therapeutic escalation after NIV therapy and intubation can usually be avoided only in a minor proportion of patients by NIV application following NHF. We assume that 15% of patients will have treatment failure and that it is equal in both randomization arms.

PASS sample size software (Hintze 2011) was used choosing a non-inferiority test for the difference between two groups (by continuity corrected Z-test with pooled variance). To ensure an alpha level of 0.025 (1-sided) and a power of ≥0.8, data from a total of N≈680 patients should be analysed. The result is expected to be somewhat conservative since the primary analysis uses regression methods an thus takes covariates into account. Moreover, continuity correction leads to slightly greater sample sizes than without.

Dropouts and losses to follow up

Non-compliance and dropout rates are expected to be rather low with regard to the in-hospital assessment of the primary endpoint after 72h when its assessment is performed. Therefore, the dropout rate is assumed to be <10 %.

Per arm 360 patients - therefore about 720 patients in total - should be enrolled in the trial to ensure sufficiently precise estimations of endpoints after 90d.

Accordingly, we expect that about 1500 patients will have to be screened for the trial.

8.5 Statistical Methods

8.5.1 Analysis Population

Full analysis set

The full analysis set (FAS, based on the intention-to-treat (ITT) strategy) is defined to be all randomized patients with AECOPD and started on ventilatory support. If, for example, pneumonia is detected within 48h (nosocomial), such patients will not be included in the final analysis. Patients who test positive for SARS-CoV-2 within 48h will not be included in the full analysis set.

Per protocol set

The per-protocol (PPS) set is defined by all patients belonging to the FAS without major violations of the study protocol.
The following protocol violations are classified as major:

- Violation of an eligibility criterion
- Did not begin use of the allocated device
- Discontinued use as a result of poor compliance within 72h

This is not an exclusive list. In the light of protocol violations which actually may occur during study conduct, all major protocol violations will be defined, e.g. as part of the statistical analysis plan. The completed list will be finalised before database closure and start of the final analysis.

Safety analysis set

The safety population is defined to be all randomized patients belonging to the FAS. In safety analyses, patients will be classified acoording to the ventilator support applied, irrespective of the randomized group allocation.

8.5.2 Planned Methods for Analysis

For the confirmatory analysis, linear regression with the stratification variables and the arm as covariates will be used and where the dependent variable will be coded as 0, 1. A 95% two-sided Wald confidence interval for the arm term can then be interpreted in terms of absolute risk and the null hypothesis is rejected if it lies entirely to the right of the non-inferiority margin of −8 percentage points. As a sensitivity analysis, a two-sided 95%-Wilson confidence interval for the difference in proportions will be calculated. Only few missing data regarding all relevant endpoints are expected given the rather short period of observation. Nevertheless, conservative imputations will be performed independent of treatment arm. Further sensitivity analyses are planned to adjust for covariates, possibly imbalanced baseline characteristics between groups and/or protocol deviations in multivariable regression models, e.g. for (components of) the primary endpoint and/ or in subgroups, which arose from stratification criteria. Furthermore, the odds ratios from logistic regression will be computed to have a relative risk measure in addition to the absolute one, as recommended by statistical guidelines.

Absolute risk differences of major secondary endpoints will be analysed in the same way as the primary endpoint.

Kaplan-Meier curves/ results of logrank tests will be presented for 28d- and 90d-mortality. We expect the time to death to be (nearly) always available.

Ventilator-free hours (until 72h assessment) will be analyzed by a linear regression model including randomization arm as factor and stratification criteria as covariates.

Neither imputation of missing values nor adjustments for multiple testing is planned for secondary/safety endpoints. No interim analysis is planned.

The proportion of patients (with 95% confidence limits) who were randomly allocated to NIV therapy, but changed to NHF due to insufficient efficacy and avoid an immediate intubation and vice versa will be analysed. Both the proportion with and without later intubation will be provided. Although these NIV-to-NHF proportions are a form of data exploration, useful estimates on the value of NHF as rescue treatment in cases who do not tolerate NIV may be derived, especially if compared to usually reported proportions of intubation immediately initiated after NIV.

The proportion of switches to another device before intubation will also be compared to investigate potentially existing preferences in favour of NIV, which are assumed by the applicants.

8.6 Statistical Monitoring

Regular monitoring visits and timely supervision of study documentation including statistical monitoring and an established query management will be performed to ensure data quality and completeness.

The trial conduct will be closely supervised by means of central and statistical monitoring according to ISO 14155: 2020 chapter 6.7. The objectives are

- to detect safety relevant signals as soon as possible
- to detect non-compliance and relevant protocol violations and to prevent their future occurrence by prompt reaction
- to assess potential sources of bias
- to prevent missing visits or measurements by prompt reminders

Therefore, the following issues will be monitored and discussed:

- With regard to safety
  - Patients with treatment discontinuation due to adverse events
  - Serious adverse events
- With regard to protocol compliance
  - Proportion of patients per site with a switch of device and correct application of the criteria for doing so
  - Correct settings for each of the devices
- With regard to potential bias
  - Whether or not the patients were ventilated before inclusion in the trial
  - The time lapse between randomization and therapy begin
  - The point in time for switching devices will be compared by device around the 72 h mark to ensure that patients are not switched with deliberate delay
  - All cases in which intubation is performed without documented fulfillment of the guidance criteria
  - All cases in which data suggest that intubation should have been performed, but was not

  - Violation of inclusion or exclusion criteria that were discovered after randomization – particularly use of NIV or CPAP at home which may not be known when patients arrive in an emergency setting.
- With regard to missing information
  - Missing visits or visits outside the pre-defined time windows
  - Missing blood gas analysis
  - Missing documentation of the reason for switching devices
  - Missing dates and information on discharge
  - Problems with data when transferring between wards

Statistical monitoring will be continuously adapted in response to new problems/risks which might arise during trial implementation.

8.7 Final Analysis

The final analysis will be performed when the data of all enrolled patients have been collected, all data management procedures have been finalised and the database has been cleaned for analysis.

In case of a premature termination of the whole trial (due to organisational, financial or other reasons) a limited analysis of the data available up to then may be suitable if available sample size is sufficient. A power analysis may add information regarding the study results and for future trials.
The decision on the appropriate extent of an analysis will be made jointly between the ZKS Leipzig und the coordinating investigator.

No interim analysis is planned.

9 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

All persons participating in the conduct of the trial (responsible institution, co-ordinating investigator, investigators, etc.) commit themselves to observe the Declaration of Helsinki of the WMA (in its current version), as well as all pertinent national laws and the ISO 14155) (where appropriate and applicable).

9.1 Submission

According to the professional code of conduct for doctors (§ 15) the clinical trial will be submitted to the ethics committee responsible for the co-ordinating investigator, as well as the ethics committees responsible for further participating trial sites. The latter also receive the primary statement issued by the ethics committee of the co-ordinating investigator.

9.2 Protocol Amendments

Changes made to the protocol that was appraised positively by the ethics committee must be positively reappraised and approved if the changes

- are such that they may affect the subjects' safety, e.g. fundamental changes to the therapeutic procedures
- result in further data collection that necessitates changes to the patient information and/or informed consent form,
- affect the interpretation of the scientific documents upon which the trial is based or the significance of the results of the trial,
- significantly affect the leadership or conduct of the trial,
- concern the quality or the innocuousness of the investigational device.

These changes have to be approved by co-ordinating investigators, if applicable in agreement with the biometrician and/or DSMB.

After the approval/favourable opinion of the changes was obtained, all trial sites will be informed of the changes and supplied with changed documents (if applicable).

10 DATA MANAGEMENT AND DATA PROTECTION

10.1 Data protection and professional confidentiality

Leipzig University responsible institution, together with ZKS Leipzig and the trial sites, is responsible for the implementation and data processing in accordance with Article 4(7) of the General Data Protection Regulation 2016/679 in this trial. The ZKS Leipzig is responsible for implementation of procedures for data collection, storage, protection, retention and destruction. The data stored in the trial database is secured against unauthorized access. The database are located at the ZKS Leipzig at Härtelstr. 16-18, 04107 Leipzig in access-protected server rooms. The ZKS Leipzig is responsible for the security of the stored data and has a corresponding IT security and data protection concept according to the requirements of the German Federal Office for Information Security (www.bsi.bund.de).

All data will be initially collected by investigators in the recruiting trial sites. Together with information on the trial, eligible patients will be informed about data capture, transmission, analysis processes and their rights according to the General Data Protection Regulation (GDPR). Once a patient is eligible and has given his/her informed consent (concise version) to trial participation and data collection, the investigator will assign the patient a unique patient identification code. Patient identification code lists will be generated in advance by ZKS Leipzig and forwarded to the recruiting sites. These lists are part of the investigator site file and remain at the recruiting site. These lists are the only documents that allow for re-identification of the patients.

All clinical data entered by the investigators (or their designated staff) into eCRFs will be recorded in a pseudonymized form (i.e. without reference to the patient's name and date of birth) exclusively using the patient's identification code.

Clinical monitors appointed by ZKS Leipzig will regularly visit the recruiting sites and verify the informed consent forms. This serves to verify that the patient has unambiguously given his or her consent for trial participation as well as for data capture, transmission and analysis. The patients are informed of this fact and agree to the procedure with the patient information/informed consent.

Patients may withdraw their informed consent in writing or orally at any time without giving reasons and without suffering any disadvantage. If patients withdraw their consent, no further data will be collected. However, the data processing carried out up to the date of withdrawal remains lawful.

If the informed consent is withdrawn, the patient has the right of data deletion according to the GDPR. Information as to when and why a patient was randomised and when he withdrew consent must be retained in the documentation.

According to GDPR, the responsible institution conducting the study is generally obliged to delete its data from the study database after withdrawal of consent. Within the framework of this study, the coordinating investigator would like to limit this right to deletion, as is permitted in Article 17 paragraph 3 point of the GDPR, and continue to process and not delete the security-relevant data that has been collected until the withdrawal of consent. In this study, safety-relevant data is all information about possible side effects of the NIV or NHF devices.

10.2 Declaration regarding Data Protection

We hereby confirm that all clinical trial information will be recorded, processed, handled and stored by ZKS Leipzig, Härtelstr. 16-18, 04107 Leipzig, Germany on behalf of the responsible institution.

Data captured by the investigators will be processed in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected. Data capture and processing will be in accordance with the applicable law on personal data protection and with the GDPR (EC) 2016/679 of the European parliament and of the council.

Access to the data is strictly limited to authorised persons. Data are protected against unauthorised access.

10.3 Data protection rights

According to the basic data protection regulation, the study participants have the following rights regarding their personal data:

The right to be informed about their personal data that are collected, processed or, if applicable, transferred to third parties in the course of the clinical trial. (if necessary, handing out a copy free of charge).

Right to have incorrect personal data corrected.

Right to have their personal data deleted, with the exception of the security data described above.

Right to limit processing (in exceptional cases). The right to limit processing must be requested from the investigator or the data protection officer of the trial site.

Right to data transfer of personal data collected about the study participant. This data shall be transmitted either to the trial participant himself or, if technically possible, to another body designated by the trial participant.

Right to refuse (conditionally) the use of the data (see also right to cancellation)

The data protection officer of the responsible institution is:

Datenschutzbeauftragter Medizinischen Fakultät der Universität Leipzig
Philipp-Rosenthal-Straße 27
04103 Leipzig
Telefon: +49 (0)341 / 97-16105
E-Mail: dsbmf@medizin.uni-leipzig.de

10.4 Data management/Case Report Forms (CRF)

In the context of a database for electronic data capture only, the Case Report Form (CRF) will be designed by the ZKS Leipzig in cooperation with the Co-ordinating investigator and provided as electronic form (eCRF). In order to facilitate the documentation as per protocol in case of malfunction of the electronic system or any of its components, a paper version of the

CRF (interim CRF) will be provided in the ISF (investigator site file). The data on this paper version will be transferred to the eCRF as soon as the electronic system is available again.

Special CRF forms will be provided as paper CRF:

- **Patient dairy** since these will be filled in by the patient directly
- **Randomization** for randomization by fax, if the online tool does not work

An eCRF will be provided for each patient. The patient will be identified as per patient-ID only. The eCRF must be completed shortly after each trial visit according to ISO 14155:2020 chapter 7.8.1 and to enable central monitoring of the trial data.

Access to the data base will be limited to authorised staff only. Authorisation is granted by the site's investigator using the trial specific staff signature and delegation log. Based on the staff signature and delegation log access to the eCRF will be granted by the responsible staff at the ZKS Leipzig.

Authorised staff members on site will be able to enter and update data as well as finalise data by electronic signature during the conduct of the trial according to a trial specific concept for documentation. This concept is based on the internal Standard Operating Procedures implemented by the ZKS Leipzig and follows the ISO 14155: 2020. All entries and data changes will be tracked automatically including date, time and person who entered/changed information (audit trail). Major correction(s) or major missing data have to be explained.

10.5 Patient File and Source Data

All information required by the protocol and therefore collected during the clinical trial must be recorded by the Investigator or an authorised member of the trial team as source data in the source documentation for the trial (e.g. patient file).

Source data according to ISO 14155: 2020 chapter 3.47 are defined as any information in original records and/or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

The Source Data Agreement is defining source data and their location for respective CRF entries. It will be filled in at the initiation visit, signed by the investigator and filed in the trial master file.

In order to confirm the completeness, accuracy and consistency of the data with the data in the source documents the principal investigator has to electronically sign each patient's CRF after the individual end of trial participation.

10.6 Data Management

For creation of the trial database a clinical data management system will be used. The trial database will be validated according to the Standard Operating Procedures (SOPs) of the ZKS Leipzig prior to data capture.

Data management will be done according to the SOPs of the ZKS Leipzig.

During the whole course of the trial, a backup of the data is made on a daily basis according to the backup policies of the IT-Network IMISE/ZKS Leipzig. Unauthorised access to pseudonomyzed patient data is prevented by the access concept of the trial database, which

is based on a strict hierarchy and role concept. Any change of data (e.g. when data is changed in the database during query management) is recorded automatically via audit trail within the database.

At the end of the trial, once the data entry has been declared complete, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between responsible institution/co-ordinating investigator, biometrician and data manager.

10.7 Archiving

All relevant trial documentation (Trial Master File), the electronically stored data, the original CRFs and the final report will be stored for at least 10 years at the university archive Leipzig after the regular or premature end of the trial.

At the investigating sites, the investigators' files, patient identification lists, signed written consent forms, copies of all CRFs and the patients' files will be stored for at least 10 years after the regular or premature end of the trial.

10.7.1 Anonymization of Data after the end of Archiving

After the end of the archiving period, all clinical data present at the ZKS Leipzig will be stored in an anonymous form.

All data will be subject to an anonymization process removing personalised data as far as possible, i.e. without endangering the possibility to answer scientific questions related to the trial. Anonymised data will be relocated to a separate, access restricted, file location and secondary data sources will be deleted. The data protection officer of the co-ordinating investigator will be contacted before anonymization to ensure a correct and actual implementation of this process.

11 SUPERVISION OF THE CLINICAL TRIAL

11.1 Access to Source Data

According to ISO 14155: 2020 chapter 6.7, the principal investigator must permit all authorized third parties access to the trial site and the medical records of the trial subjects (source data). These include the clinical trial monitors, auditors and other authorized employees of the sponsor, as well as members of the local or federal authorities. All these persons are sworn to secrecy.

11.2 Monitoring

The ZKS Leipzig will be responsible for trial monitoring. Initiation, regular and close-out visits will be performed in all trial sites. A risk-based monitoring strategy will be implemented, as required by ISO 14155: 2020 chapter 6.7.

During trial conduct, central and statistical monitoring procedures will be combined with on-site monitoring visits in order to achieve high protocol compliance and data quality, as well as to ensure patients' safety and rights. The choosen monitoring strategy depends on the results of the risk analysis done during the protocol development and will described in the trial specific monitoring plan.

In general, a first monitoring visit at a trial site will be scheduled after the inclusion of the site's first three patients, checking protocol compliance and preventing further systematic errors due to misunderstandings. All trial sites will then be visited regularly. The frequency of further on-site monitoring visits will depend on the trial site's recruitment rate and on whether problems have been detected with the site, either by prior on-site visits or by central monitoring.

Prior to every scheduled on-site visit, the monitor will be provided patient synopses summarising the data already available in the database, and indicating possible protocol deviations or inconsistencies. If deemed necessary (e. g. in case of a high number of data inconsistencies/queries), queries rised by vigilance and/or from the statistical monitoring will be communicated to the site in due time before the on site visit, to enable a timely processing.

During the visits the monitor will:

- check informed consent forms of all patients enrolled
- perform source data verification of the key data (selected baseline parameters, therapy delivery, serious adverse events, follow-up) in a random sample of the site's patients
- perform targeted source data verification for patients with possible deviations
- discuss open queries raised by data management or drug safety personnel
- check essential parts of the investigator site file (see monitoring plan)
- check source data for AEs or SAEs, which have not been properly reported in the eCRF
- check for major violation of the respective guidelines and laws and/or protocol violations according to the trial specific monitoring plan.

11.3 Audits

The responsible institution might conduct site audits in order to guarantee that the conduct of the trial is in accordance with the DoH, DIN ISO 14155 and the trial protocol.

The investigator agrees to provide access to the auditor for all relevant documents.

11.4 Independent Supervision of the Trial

An Independent Data Safety Monitoring Board (DSMB) will meet periodically to perform a review and an evaluation of the accumulated study data regarding:

- safety of the trial intervention
- integrity and validity of the data
- appropriate study conduct
- study progress

to guarantee the subject's safety.

The DSMB will consist of three individual experts who are not involved in the ELVIS clinical trial activities and who have no conflict of interest (financial, proprietary, professional or other) with any of the participating organisations.

These core members have sufficient combined expertise in the medical disciplines at hand:

- the clinical aspects of the underlying disease (AECOPD)
- complications associated with the treatment of AECOPD
- biostatistics
- clinical trial conduct and methodology

Other ad hoc specialists may be invited as a non-voting member of the DSMB whenever additional expertise is required.

In addition, the DSMB will advise the co-ordinating investigator concerning further trial implementation (unchanged continuation, continuation with changes, interruption, termination).

A DSMB-charter will further specify the tasks of the DSMB.

In order to allow the DSMB to fulfil its responsibilities, the DSMB will receive safety reports on a regular basis by the ZKS Leipzig. While reviewing, the DSMB will consider the study-specific data as well as any relevant background knowledge of AECOPD treatment, the therapeutic procedures and the information provided about the patient population in the study.

The DSMB will specifically review:

- the quality, completeness, accuracy and timeliness of the collected data
- the collected data that may provide evidence of study-related adverse effects so far
- the performance of the individual clinical centres that are involved in the study
- the overall compliance with the study protocol and the goals for recruitment and retention
- all factors internal or external to the study that may affect the study outcome, compromise the confidentiality or the ethics of the study or impact patient safety (protocol violations, newly available scientific or therapeutic developments…)

The DSMB will meet at regular intervals (twice a year, preferably by telephone, but in person if needed) in open sessions. The DSMB will maintain the data confidentiality during all phases of the reviews and deliberations.

Following DSMB meetings, the DSMB will provide written recommendations to the co-ordinating investigators on the continuation, modification or termination of the clinical trial. Such recommendations can be based on the detection of emerging negative data trends or prospects of ethical or safety guidelines not being met. The DSMB may also request contacts between itself and the co-ordinating investigator by telephone or in person.

The ZKS Leipzig will support the DSMB by providing updated data in appropriate format for analyses.

12 ADMINISTRATIVE AGREEMENTS

12.1 Adherence to the protocol

The study will be conducted in accordance with the protocol and DIN ISO 14155 as well as applicable regulatory requirements.

Protocol violations are all deviations from the procedures outlined in this document, e.g.

- examinations that are missed or that take place at the wrong time
- non-compliance
- intake of prohibited medication

After a patient has been enrolled, it is the investigator's responsibility to avoid protocol violations in order to obtain unbiased data for the trial.

Those protocol violations deemed to be major are defined by the risk analysis performed before and during trial implementation and will be further detailed in separate documents belonging to the risk assessment/monitoring plan. This list can be augmented in the course of the trial. Major protocol violations will be reported to the ZKS Leipzig, which will inform the co-ordinating investigator.

All protocol violations will be documented and discussed with the responsible biometrician before closing the data base and carrying out the statistical analysis.

The investigator must ensure that the recorded data are documented as per protocol. Minor variations are inevitable in clinical routine, but must be documented together with a justification.

12.2 Funding and Insurance

The trial is funded by the Bundesministerium für Bildung und Forschung (Förderkennzeichen: 01KG2002).

All trial participants will be insured during trial participation by a volunteers' trial insurance to the medical faculty of the Leipzig University:

Policy number:	28 138971 03764
Policy holder:	HDI Global SE, Eisenbahnstr. 1-3, 04315 Leipzig
Maximum sum insured:	500.000 €

A copy of the insurance policy and the insurance conditions will be filed in the investigator site file and the second will be handed to the subject on their request.

12.3 Publication Policy and Registration

The results of this trial will be submitted for publication in a peer-reviewed, international English-language journal of appropriate aim and scope. Accordingly, the clinical trial will be registered at clinicaltrials.gov before recruitment starts. According to the results of main and concomitant studies, the results may be submitted in separate or combined manuscripts; decisions about the form and scope of individual manuscripts will be discussed among all persons participating in the design, conduct and analysis of the trial who qualify for authorship. The co-ordinating investigator together with the biometrician(s) is responsible for drafting and

circulating manuscripts and for discussing and handling requests by co-authors and co-ordinating investigator to edit the text.

The authorship will follow the criteria for authorship developed by the International Committee of Medical Journal Editors (ICMJE), including those that distinguish authors from other contributors.

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria will be acknowledged in the manuscript.

The scientific use of data resulting from this trial by local trial sites is ruled by the site contracts between the co-ordinating investigator/responsible institution and the local trial sites. Generally, sites might use data for own scientific questions (independent from the questions discussed in this trial protocol) and publication after consultation with the co-ordinating investigator.

12.4 Data Sharing Statement

According to the recommendations on data sharing by the International Committee of Medical Journal Editors (ICMJE) data resulting from the ELVIS trial will be made available to the scientific community as follows:

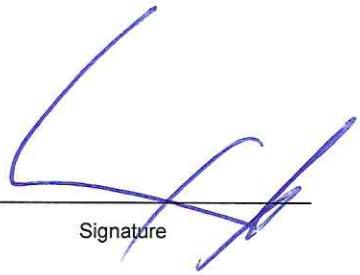
After publication of the major results and upon reasonable request from researchers performing an individual patient data meta-analysis, individual patient data that underlie published results will be shared after de-identification. This requires approval by the local ethics committee of the researcher requesting the data along with public registration of the meta-analysis. The coordinating investigator will contact the data protection officer before de-identification to ensure a correct and actual implementation of this process.

Summary statistics that go beyond the scope of published material will be made available to researchers for meta-analysis upon reasonable request and if the necessary data analysis is not unduly time-consuming. Together with publication of the main results, the trial protocol in full will be made publically available as well as the statistical analysis plan.

13 PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Coordinating investigator: Prof. Dr. Hubert Wirtz	18.12.2020 Date	 Signature
Coordinating investigator: PD Dr. Jens Bräunlich	_____ Date	_____ Signature
Biometrician: Dr. David Petroff	_____ Date	_____ Signature

13 PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Coordinating investigator: Prof. Dr. Hubert Wirtz	Date	Signature
Coordinating investigator: PD Dr. Jens Bräunlich	18.12.20 Date	PD Dr. med. habil. Jens Bräunlich Chefarzt Medizinische Klinik Signature
Biometrician: Dr. David Petroff	Date	Signature

13 PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Coordinating investigator: Prof. Dr. Hubert Wirtz	Date	Signature
Coordinating investigator: PD Dr. Jens Bräunlich	Date	Signature
Biometrician: Dr. David Petroff	17.12.2020 Date	 Signature

14 PROTOCOL AGREEMENT

Herewith I declare that I have read and understood the present protocol and agree to honour each part of it. I will ensure that all the patients enrolled in the trial by my site will be treated, observed and documented in accordance with this protocol. I will ensure that all persons assisting with the trial under my supervision are adequately informed about the protocol, the investigational product and their duties.

I further declare that I do not have any financial and other competing interests in this trial.

Centre-ID	ELVIS - ⎵⎵
Address trial site (stamp)	

Date

Signature Investigator

15 APPENDIX

15.1 Classification of Adverse Events

15.1.1 Degree of severity

The degree of severity of an Adverse Event will be determined in accordance with the definitions in 7.1.1.

15.1.2 Assessment of intensity

The assessment of the intensity accords with CTCAE V5.0

Mild Adverse Event	• asymptomatic or mild symptoms; • clinical or diagnostic observations only; • intervention not indicated.
Moderate Adverse Event	• minimal, local or noninvasive intervention indicated; • limiting age-appropriate instrumental ADL*[9].
Severe Adverse Event	• medically significant but not immediately life-threatening; • hospitalization or prolongation of hospitalization indicated; • disabling; • limiting self care ADL**
Life-threatening Adverse Event	• Life-threatening consequences; • urgent intervention indicated
Death related to Adverse Event	

15.1.3 Determining the causal relationship

The investigator must assess whether or not the Adverse Event is causally related to the investigational device. The following classification is to be used.

- Reasonable possibility
- No reasonable possibility

A reasonable possibility exists, if one of the following WHO-UMC criteria is met:

- occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be

[9] **Activities of Daily Living (ADL):**
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

- with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- more data is essential for a proper assessment or the additional data are under examination
- cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

No reasonable possibility exists, if the following WHO-UMC criterion is met:

- with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

15.1.4 Expected/Unexpected

Adverse Events are unexpected if they do not occur in the manner or with the intensity described in the reference document for the medical device (see investigator's files).

15.1.5 Outcome of an Adverse Event

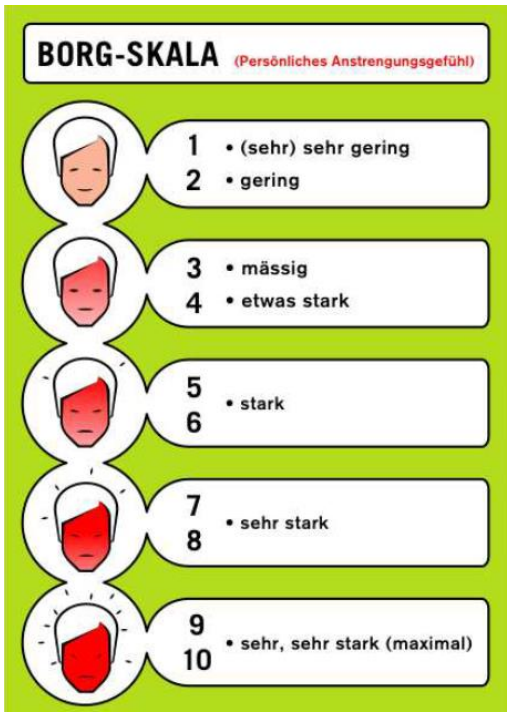
The outcome of an Adverse Event is classified as follows:

- recovered/resolved
- recovering/resolving
- not recovered/not resolved
- recovered/resolved with sequelae
- fatal*
- unknown

*Note: A patient's death is not in itself an event, but the consequence of one. The event that led to the patient's death must be documented completely and reported even if death occurs four weeks after stopping medication and independent of whether or not there is a relation to the therapy or not.

15.2 Definitions

15.2.1 Borg Scale



Borg CR10 Scale (1982)[12]

0	Nothing at all
0.5	Extremely weak (just noticeable)
1	Very weak
2	Weak (light)
3	Moderate
4	Somewhat strong
5	Strong (heavy)
6	
7	Very strong
8	
9	
10	Extremely strong (almost max)
•	Maximal

15.3 Acronyms

ADL	activities of daily living
ADE	adverse device effect
AE	adverse event
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
BGA	Blood gas analysis
BMI	Body-Mass-Index
COPD	Chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRP	C-reactive protein
DNI	Do Not Intubate
DNR	Do Not Resuscitate
DoH	Declaration of Helsinki
DSGVO	Datenschutzgrundverordnung
DSMB	data safety monitoring board
EC	ethics committee
eCRF	electronic case report form
FAS	full analysis set

FPI	First patient in
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IL6	Interleukin-6
IMISE	Institute for Medical Informatics, Statistics and Epidemiology
ISF	Investigator Site File
ITT	intention-to-treat
LPO	Last patient out
MPG	Medizinproduktegesetz
MPSV	Medizinprodukte-Sicherheitsplanverordnung
NHF	nasal high-flow
NIV	non-invasive ventilation
PCT	Procalcitonine
PPS	per protocol set
RCT	randomized controlled trial
SADE	serious adverse device effect
SAE	serious adverse event
TMF	Trial Master File
VFD	ventilator-free days
ZKS Leipzig	Zentrum für Klinische Studien Leipzig

15.4 Template trial protocol

This trial protocol was written based on a template by the ZKS Leipzig based on the SOPs of the ZKS Leipzig.

The used template version is: Draft 1.1 from 26.06.2020

16 REFERENCES

1. Decker R. 2020 REPORT. 2019:1–141.

2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11): e442.

3. Soriano JB, Abajobir AA, Abate KH, et al. Articles Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Respiratory 2017;5(9):691–706.

4. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;7:CD004104.

5. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2):1602426.

6. Plant PK, Owen JL, Elliott MW. Dr. Silke Hauer, Martina Vissiennon, Dr. Peggy Houben Thorax 2001;56(9):708–12.

7. Carrera M, Marin JM, Antón A, et al. A controlled trial of noninvasive ventilation for chronic obstructive pulmonary disease exacerbations. J Crit Care 2009;24(3):473.e7–14.

8. Confalonieri M, Garuti G, Cattaruzza MS, et al. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. European Respiratory Journal 2005;25(2):348–55.

9. Tissot A, Jaffre S, Gagnadoux F, et al. Home Non-Invasive Ventilation Fails to Improve Quality of Life in the Elderly: Results from a Multicenter Cohort Study. PLoS ONE 2015;10(10):e0141156.

10. Bräunlich J, Mauersberger F, Wirtz H. Effectiveness of nasal highflow in hypercapnic COPD patients is flow and leakage dependent. BMC Pulm Med 2018;18(1):14.

11. Bräunlich J, Beyer D, Mai D, Hammerschmidt S, Seyfarth H-J, Wirtz H. Effects of Nasal High Flow on Ventilation in Volunteers, COPD and Idiopathic Pulmonary Fibrosis Patients. Respiration 2013;85(4):319–25.

12. Bräunlich J, Goldner F, Wirtz H. Nasal Highflow eliminates CO2 from lower airways. 2017;242:86–8.

13. Bräunlich J, Dellweg D, Bastian A, et al. Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD . COPD 2019;Volume 14:1411–21.

14. Biselli P, Fricke K, Grote L, et al. Reductions in dead space ventilation with nasal high flow depend on physiological dead space volume: metabolic hood measurements during sleep in patients with COPD and controls. Eur Respir J 2018;51(5).

15. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185–96.

16. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal High-Flow versus Venturi Mask Oxygen Therapy after Extubation. Effects on Oxygenation, Comfort, and Clinical Outcome. American Journal of Respiratory and Critical Care Medicine 2014;190(3):282–8.

17. Hernández G, Vaquero C, Colinas L, et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA 2016;316(15):1565–74.

18. Bräunlich J, Mauersberger F, Wirtz H. Effectiveness of nasal highflow in hypercapnic COPD patients is flow and leakage dependent. BMC Pulm Med 2018;18(1):1–6.

19. Bräunlich J, Beyer D, Mai D, Hammerschmidt S, Seyfarth H-J, Wirtz H. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. Respiration 2013;85(4):319–25.

20. Bräunlich J, Köhler M, Wirtz H. Nasal highflow improves ventilation in patients with COPD. COPD 2016;11:1077–85.

21. Bräunlich J, Seyfarth H-J, Wirtz H. Nasal High-flow versus non-invasive ventilation in stable hypercapnic COPD: a preliminary report. Multidiscip Respir Med 2015;10(1):27.

22. Doshi P, Whittle JS, Bublewicz M, et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. Ann Emerg Med 2018;

23. Lee CC, Mankodi D, Shaharyar S, et al. High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: A systematic review. Respir Med 2016;121:100–8.

24. Bräunlich J, Wirtz H. Nasal high-flow in acute hypercapnic exacerbation of COPD. COPD 2018;13:3895–7.

25. Hernández G, Vaquero C, González P, et al. Supplementary Online content 2: Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. JAMA 2016;315(13):1354–61.

26. Frizzola M, Miller TL, Rodriguez ME, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. 2011;46(1):67–74.

27. Pisani L, Fasano L, Corcione N, et al. Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. Thorax 2017;72(4):373–5.

28. Jeong JH, Kim DH, Kim SC, et al. Changes in arterial blood gases after use of high-flow nasal cannula therapy in the ED. 2015;33(10):1344–9.

29. Pisani L, Betti S, Biglia C, et al. Effects of high-flow nasal cannula in patients with persistent hypercapnia after an acute COPD exacerbation: a prospective pilot study. 2020;:1–9.

30. Bräunlich J, Dellweg D, Bastian A, et al. Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD. COPD 2019;14:1411–21.

31. 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):525–33.

32. Hartl, S., Lopez-Campos, J. L., Pozo-Rodriguez, F., Castro-Acosta, A., Studnicka, M., Kaiser, B., & Roberts, C. M. (2016). Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. The European Respiratory Journal, 47(1), 113–121. http://doi.org/10.1183/13993003.01391-2014ZITAT Projections of Global Mortality and Burden of Disease from 2002 to 2030. Mathers CD, Loncar D. PLoS Medicine. 2006 Nov 28; 209–224

33. Declaration of Helsinki: Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki (Finland), June 1964. Last amendment by the 48th General Assembly, Somerset West (Rep. of South Africa) 1996

34. International Standard ISO 14155 vom 1. Juli 2020 für „Clinical investigation of medical devices for human subjects — Good clinical practice

35. Verordnung (EU) 2016/679 des Europäischen Parlaments und des Rates vom 27. April 2016 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten, zum freien Datenverkehr und zur Aufhebung der Richtlinie 95/46/EG (Datenschutz-Grundverordnung)