Ultrasound of the Diaphragm Excursion Ratio as physiological biomarker in acute exacerbations of Chronic Obstructive Pulmonary Disease

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(non-WMO study protocol)

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1. Study organization

Study title:	Ultrasound of the Diaphragm Excursion Ratio as physiological biomarker in acute exacerbations of Chronic Obstructive Pulmonary Disease	
Planned start date and estimated completion date *Please note that the study may only start <u>after</u> approval and that the start date should allow for time needed for the approval process.*		Immediately after approval, july/august/september 2025. Estimated completion date: july 2026
Members of the *UMCG* study team. *Please extend section if there are more than 9 members in the study team.* *Please note that this is not a delegation log.*	**Information** *Name/ function/ department / center*	**Role in study** *E.g: Principal investigator, coordinating investigator, researcher, research nurse.*
	1 *<text>*	*CI*
	2 *M.L. Duiverman, Pulmonologist, Pulmonology, UMCG*	PI UMCG
	3 *E.A.M.D. ter Haar, physician-researcher, Pulmonology, UMCG*	*Researcher*
	4 *J.E. Hartman*	*Researcher*
	5 *<text>*	*<text>*
	6 *<text>*	*<text>*
	7 *<text>*	*<text>*
	8 *<text>*	*<text>*
	9 *<text>*	*<text>*
If applicable: **Senior members of the *non-UMCG* study team(s).**	**Information** *Name/ function/ department / centre*	**Role in study** *Limit to: Principal investigator, coordinating investigator.*

Please limit to the principal and coordinating investigators for each centre. Extend section if there are more than 7 non-UMCG members in the study team(s). *Please note that this is not a delegation log.*	**1**	*W.S. de Boer, PhD candidate and AIOS, Pulmonology, UMCG and Isala.*	*PI Isala*
	2	*Q.S.D. Muller*	*Researcher*
	3	*M.A. Edens*	*Epidemiologist*
	4	*<text>*	*<text>*
	5	*<text>*	*<text>*
	6	*<text>*	*<text>*
	7	*<text>*	*<text>*

Principal investigator , *contact information* *(The Principal Investigator heads the research team. Is responsible for planning and conducting the scientific study. The role is akin to that of project leader. In Dutch also 'hoofdonderzoeker'.)*	Name	*W.S. de Boer*
	E-mail	*W.s.de.boer@isala.nl / W.s.de.boer@umcg.nl*
Corresponding researcher UMCG, *contact information*	Name	*Wytze de Boer*
	E-mail	*W.s.de.boer@isala.nl / W.s.de.boer@umcg.nl*
	Telephone	*0646312031*
Sponsor (Dutch: verrichter/opdrachtgever)	UMCG: ☒ Investigator initiated.	Other: ☐ If other please note name of sponsor: *<text>*
Financial support / subsidy provider	NA	☒
	Organisation name	*<text>*
Collaboration with non-profit Laboratory / **research sites** **(in- and outside UMCG)**	NA	☒
	Organisation name	*Isala*
	Contact person	*W.S. de Boer*
	Email	*w.s.de.boer@isala.nl*

	Telephone	*06-46312031*		
Collaboration with for-profit / commercial parties / companies **(in- and outside UMCG)**	NA	☐		
	Organisation name	*<text>*		
	Contact person	*<text>*		
	Email	*<text>*		
	Telephone	*<text>*		
Is this study connected to a previous nWMO or WMO application	Yes ☐	No ☒		
If yes, please provide the following information and/or documentation regarding the previous application	Please add the name of the previous study	*<text>*		
	Please add the panama number of the previous study	*<text>*		
	Has the ethical approval of the previous application been added to the current application	NA ☐	Yes ☐	No ☐
	Has the study protocol of the previous application been added to the current application	NA ☐	Yes ☐	No ☐
	Has the patient information (DIF) of the previous application been added to the current application	NA ☐	Yes ☐	No ☐
	Has the Informed Consent form (IC) of the previous	NA ☐	Yes ☐	No ☐

	application been added to the current application			

2. Protocol Signature Sheet

The undersigned principal investigator (NL: hoofdonderzoeker) UMCG and head of department UMCG confirm that the study protocol is compliant with the UMCG researchcode, the nWMO Kaderreglement UMCG and other legislation (such as the (U)AVG and WGBO).

Name	Signature	Date
Principal Investigator UMCG:	M.L. Duiverman, pulmonologist	<dd-mm-yyyy>
Head of the department UMCG:	Prof. Slebos, Head of Department for Pulmonary Medicine.	<dd-mm-yyyy>
Departmental Scientific review board (if applicable)	<name and function>	<dd-mm-yyyy>
If tissues are requested from a biobank or data from a databank, please add a signature from the biobank administrator (NL: beheerder) here.	<name and function>	<dd-mm-yyyy>
If tissues are requested from the UMCG biobank pathology, please add a signature from the tissue review board pathology here.	<name and function>	<dd-mm-yyyy>

3. Study summary

Max 1000 words

3.1 Introduction and rationale

In 2020 an estimate of 562.700 people had Chronic Obstructive Pulmonary Disease (COPD) in the Netherlands, resulting in 21.335 hospital admissions.[1] An acute exacerbation COPD (AECOPD) in combination with hospital admission is associated with high mortality and morbidity. [2]

Noninvasive ventilation (NIV) has been very effective in the context of AECOPD, since it efficiently offloads respiratory muscles and counteracts dynamic hyperinflation. This method often prevents intubation as a bridge to administering effective therapies (e.g., glucocorticoids, bronchodilators, and antibiotic agents)[3], and may reduce mortality.[4]
Current guidelines recommend NIV for the treatment of acute respiratory failure in patients with respiratory distress, pH < 7.35, and PaCO2 > 6 kPA (with exclusion of patients requiring invasive ventilation, see guideline).[5,6] National guidelines do not recommend NIV in AECOPD with increased work of breathing without respiratory acidosis due to lack of evidence. [5]

Ultrasound of the diaphragm can identify atrophy and impaired motion or contractility of the diaphragm[10], and has been shown to predict mortality and NIV failure during NIV treatment for respiratory acidosis due to AECOPD.[11-15] Whether ultrasound of the diaphragm may predict mortality or need for (non-)invasive ventilation in AECOPD without respiratory acidosis on initial presentation is unknown.

During exploratory analysis of a previous study (unpublished; NCT05671198) we might have found a marker that has the potential to predict progression to NIV or death during hospitalization for AECOPD without respiratory acidosis:

The difference between diaphragm motion during tidal breathing and maximal breathing, used as a surrogate for inspiratory reserve volume (IRV), was significantly lower in patients requiring NIV or who died in-hospital compared to those who did not (1.59 cm, SD 1.91 vs. 3.14 cm, SD 2.45; p = 0.033). We performed a ROC curve analysis to assess the predictive value of these variables, which yielded an area under the ROC curve (AUROC) of 0.752 (95% CI: 0.535 - 0.968, p = 0.033), indicating a statistically significant discriminatory ability. The best cut-off value, as determined with the Youden's J statistic, was 1.74 cm, with a sensitivity of 86% and specificity of 70% for predicting NIV requirement or inhospital death.

However, the number of events was low and the study was primarily powered for another outcome. Therefore, prospective validation is needed before we impose treatment based on this marker. In case the suggested ultrasound measurement (see introduction) proofs to be a discriminatory marker for deterioration during hospitalization or predictive of progression to Non-Invasive Ventilation, we hope to be able to perform a follow-up study in which patient will be randomized to either standard of care or 'elective' NIV (to avoid emergency NIV need) based on yet to determine cut-off values.

3.2 Design (including population, method, confounders and outcomes)

A multi-center, prospective observational cohort study conducted at Isala Hospital and UMCG aimed at determining the value of the sonographic motion ratio (tidal/maximum) of the diaphragm in AECOPD after hospital admission. After enrollment, the sonographic diaphragm motion will be assessed as additional measurement during standard-of-care lung ultrasound (POCUS), after which hospital outcomes will be registered. Primary outcome will be the sensitivity

of this ultrasound marker for in-hospital deterioration (progression to NIV of death). Secondary analysis will include predictive models. **3.3 Research question** What is the sensitivity of the diaphragm motion ratio (tidal/maximum) during ultrasound for in-hospital deterioration (progression to NIV or death) in AECOPD.

4. Study design

4.1 Mono- or multicenter study.		Monocenter study ☐	Multicenter study ☒
4.2 Retrospective study (available data/ biomaterials only) **or prospective study** (data/ biomaterials from [some] participants will be collected), (click both if mixed-method).		Retrospective study ☐	Prospective study ☒
4.3 Cross-sectional or follow-up study (click both if mixed-method).		Cross-sectional study ☐	Follow-up study ☒
4.4 Quantitative or qualitative study (click both if mixed-method).		Quantitative study ☒	Qualitative study ☐
4.5 Pilot or explorative study?	Not applicable ☐	Pilot study ☒	Explorative study ☒
Explain why it is a pilot or explorative study. See next question/answer In case of a pilot study, what are the concrete follow-up plans. In case the suggested ultrasound measurement (see introduction) proofs to be a discriminatory marker for deterioration during hospitalization or predictive of progression to Non-Invasive Ventilation, we hope to perform a follow-up study in which patient will be randomized to either standard of care or 'elective' NIV (to avoid emergency NIV need) based on this marker.			

5. Population

5.1 Research participants (tick all that apply)	
Healthy volunteers Patients	☐ ☒
5.2 Participant classification (tick all that apply)	
Participants ≥ 16 years	☒
Children between 12 and 16 years *(if applicable, written informed consent will be obtained from child and both parents - if both have authority, or guardian [or parents/guardian only if incapacitated child])*	☐
Children < 12 years *(if applicable, written informed consent will be obtained from both parents - if both have authority, or guardian)*	☐
Explain purpose limitation ('doelbinding' in Dutch) if you plan to include minors below 16 of age. This means that this data may only be gathered if participation of that age group is utterly essential (Dutch: persoonsgegevens alleen verzamelen met een gerechtvaardigd doel waarvoor die leeftijdsgroep noodzakelijk is). *<text>*	

5.3 Incapacitated adults		
Participants can be incapacitated/decisionally impaired adults *(if applicable, written informed consent must be obtained from legal representative)*	Yes ☐	No ☒
If yes, explain purpose limitation ('doelbinding' in Dutch). This means that this data may only be gathered if participation of this group is utterly essential (persoonsgegevens alleen verzamelen met een gerechtvaardigd doel waarvoor deze groep noodzakelijk is). *<text>*		
5.4 Inclusion and exclusion criteria • Inclusion criteria: In order to be eligible to participate in this study, a subject must meet all of the following criteria: - Hospitalization primarily because of severe acute exacerbation of COPD - Spirometry record within last 5 years, with: post-bronchodilator FEV1/FVC < 0,70 and FEV1% < 80%predicted - Minimum of 10 packyears • Exclusion criteria: A potential subject who meets any of the following criteria will be excluded from participation in this study: - Established diagnosis of diaphragm diaphragm paralysis. - Inability for diaphragm imaging (e.g. mechanical ventilation, or unable to follow vocal instructions). - Those not able or unwilling to give written informed consent. - Pregnant women		

6. Study data, and analysis

This section needs to be completed for both quantitative as well as qualitative designs.
Outcomes should be realistic, sample size adequate, minimal but sufficient data should be collected, patient burden should be balanced with the usefulness of the outcomes and the analysis should be appropriate. To clarify that this has been given careful consideration, completion of section 6 is required.

6.1 Data collected

For primary outcomes:

- Tidal excursion of the diaphragm as measured with ultrasound (time expenditure: aprox. 1 minute)
- Maximal excursion of the diaphragm as measured with ultrasound (time expenditure: aprox. 1 minute)
- Progression to NIV or in-hospital death, data collected from the EPD.

For secondary outcomes and other outcomes:

- Baseline dyspnea score as determined with a numeric rating scale (NRS)
- From EPD: Age, sex, BMI, FEV1 (% predicted), pH, $PaCO_2$

If not applicable to your study please explain the reason and the alternative outcomes:
<text>

Have all the data for the primary and secondary outcomes been described or the alternatives?	Yes x	No ☐

6.2 Number of participants:
Target total number of participants: 186
Target number of UMCG participants: 62

6.3 Justification of sample size
Sample size justification is required according to the AVG/GDPR law. The number of subjects should always be large enough to reliably answer the research questions; but not more than necessary.

The sample size can be justified in several ways. Often the easiest is a power analysis, alternatively a comparison with the sample size of closely related studies may be applicable (specification is required), or a saturation design. Other options may apply.

Pilot studies and/or exploratory studies comply with different sample size rules, but for these please also indicate on what basis the sample sized has been decided.

The primary outcome of this study is the sensitivity of the diaphragm ultrasound marker for predicting in-hospital deterioration (defined as progression to non-invasive ventilation or in-hospital death). Based on preliminary findings (NCT05671198), we expect a sensitivity of approximately 86%. To estimate this sensitivity with a 95% confidence interval and a total width of 10% (±5%), a minimum of 186 patients is required.

Has the sample size justification been described?	NA	Yes	No
	☐	☒	☐ *If no please indicate why: <text>*

6.4 Data minimisation

Only the essential baseline characteristics and data, that are required to answer the research question, will be collected:	Yes	No
	☒	☐

6.5 Statistical and/or qualitative analysis

Please specify Statistical Analysis Plan (SAP):

a. Description of study population:

   prospective observational cohort study evaluating the predictive value of the diaphragm motion ratio in AECOPD patients.

b. Description of preparation of the data for analyses:

   Primary Predictor:
   Diaphragm motion ratio = Tidal excursion / Maximal excursion.

   Primary Outcome:
   Composite of progression to NIV or in-hospital death; dichotomized.

   Other Variables (for adjustment or secondary analysis):
   Age, sex, BMI, FEV1 (% predicted), pH, $PaCO_2$, baseline dyspnea score.

c. Specify all applicable statistical and/ or qualitative methods. This usually requires an extensive description of the planned analyses and covariates:

The primary endpoint is the sensitivity of the diaphragm motion ratio (ultrasound marker) for predicting in-hospital deterioration (defined as progression to non-invasive ventilation or in-hospital death). Sensitivity will be calculated as: True Positives/(True Positives+False Negatives)

Additionally, univariate logistic regression to assess association between diaphragm motion ratio and in-hospital deterioration is performed. Results reported as odds ratios (ORs) with 95% CIs. Additionally we will supply, a Receiver Operating Characteristic (ROC) analysis, including Area Under the Curve (AUROC), the optimal cut-off point determined by Youden's J statistic, and sensitivity, specificity, positive/negative predictive values, and likelihood ratios at the optimal cut-off.

Continuous variables will be presented as mean ± standard deviation for normally distributed data or median and range for non-normally distributed data. Categorical variables will be summarized using frequencies and percentages. Statistical significance will be set at $p < 0.05$, and all analyses will be conducted using SPSS Statistics version 28.0.

d. Clarify how this analysis plan, study setup, sample size and design will answer the study questions:

This prospective, multi-center observational study is specifically designed to evaluate whether the diaphragm motion ratio is a sensitive and predictive tool in-hospital deterioration (progression to non-invasive ventilation or death) in patients with AECOPD. The analysis plan includes ROC analysis and logistic regression to assess the predictive performance and independent association of this ultrasound marker. The sample size is based on the expected event rate and the need for sufficient events per variable to ensure statistical validity. Together, the focused design, appropriate sample size, and targeted analysis approach will address the study question and provide clinically relevant insights into early risk stratification using bedside ultrasound for future intervention studies.

Has the statistical analysis section (6.5) been completed?	Yes ☒	No ☐

7. Recruitment and informed consent/objection

7.1 Data collection Please check the data source that is applicable to your study, more may apply:	
Data will be prospectively collected (data/ biomaterials from [some] participants will be collected)	☒
Data will be collected from (electronic) patient records (e.g. 'EPD UMCG')	☒
Data will be collected from an already existing bio- or databank *Please add documents that demonstrate (ethical) approval at the instalment of the bio- or databank*	☐
Data will be collected from a previous study (e.g. 'FAIR data' - internal/external). *Please note that the templates of the patient information and the (original) Informed Consent form need to be added to the application.*	☐

7.2 Informed consent procedure			
7.2.1 Participants will be asked informed consent		Yes ☒ *If yes: please complete 7.2.2 and 7.3.*	No ☐ *If no: please complete 7.2.3 and 7.3.*
7.2.2 *If consent is asked* complete this section			
7.2.2.1 *<u>if the potential participant is a patient</u>:*			
	First contact with potential participant is made by the treatment provider, either by accompanying letter or in person.	Yes x	No
	Informed consent procedure, including signing the IC, will be carried out by the researcher/ research nurse (*not the treatment provider).*	Yes ☒	No ☐
7.2.2.2 *<u>For participants that are either patients or non-patients</u>:*			
• <u>Recruitment:</u> Please describe how eligible participants will be approached and recruited The physician in the emergency ward will present the patient the trial information. On arrival on the pulmonology ward, the researcher will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The patient will be given the opportunity to ask questions and enough time for consideration. The patient will receive the Patient Information / Informed Consent Form in duplicate. If signed, one of the two original Patient Information / Informed Consent Forms must be stored by the principal investigator. The second signed Patient Information / Informed Consent Form will be given to the patient.			
• <u>Information provision:</u> The participant will *only* be contacted via telephone if they have given prior permission for this:	NA ☒	Yes ☐	No ☐
Contact via telephone only serves to provide additional information, it cannot be used to ask informed consent:	NA ☒	Yes ☐	No ☐
If either of the above 2 items are answered with 'no' please elaborate on the reason for this: *<text>*			
• <u>Time to consider:</u> The participant will have at least 14 days to consider participation:		Yes ☐	No x
If this is not the case please describe the reason for this and what time is allotted for the participant to consider participation. *The intended measurements are time-sensitive and must take please immediately after hospitalization to be of any potential predictive value. Since we don't know when patient might need hospitalization in advance, we cannot comply with the suggested 14 days to consider.* *The additional measurements during standard of care POCUS are non-invasive, cause no harm, are quick (aprox. 2 minutes total), and are very well tolerated; we therefore suggest a minimal amout of time for consideration of 1 hour.*			

• Informed consent recording: Informed consent will be recorded either on paper via signature or electronically:	Yes ☒	No ☐
If no, please elaborate on how will the informed consent be recorded? See above, on paper via signature.		
• Use of templates Have the UMCG templates been used for both DIF and IC-form: *Attach participant information letter and informed consent form to the present study protocol. Please note that all sections of the templates need to be present in the file DIF and IC.*	Yes ☒	No ☐
7.2.3 *If consent cannot be asked* please complete this section:		
Total number of participants who will not be asked informed consent: <*number*> Total number of *UMCG participants* who will not be asked informed consent: <*number*>		
Which WGBO argumentation applies to your study (see SOP Obtaining Informed Consent nWMO):		
• Asking permission **is reasonably impossible**, because it would burden the patient to such an extent that it might cause psychological distress.		☐
• Asking permission **is reasonably impossible**, because a large part of the participant group is likely deceased or cannot be located.		☐
• Consent **cannot be required** because obtaining it would entail a disproportionate amount of time and effort, such as in the case of large numbers of patients or patients who were treated a long time ago		☐
• Consent **cannot be required** because requesting consent would lead to selective response, thereby potentially biasing the research results		☐
• Consent **cannot be required**, because: *<text>*		☐
Required: In addition to the broad categories above, please clarify *why* these arguments apply to your specific study: *<text>*		
The objection registry will be checked in case one or more UMCG patients will not be asked informed consent, the data from those who objected will be excluded from the analyses.	NA x	Yes ☐

7.3 Linking with (other) bio-/databank			
In case the data will be linked with a /another bio-/databank, informed consent will be/has been obtained for this linkage(s)	Yes, consent ☐	No consent ☐	Data will not be linked ☒

8. Only complete in case of collaboration with parties outside of the UMCG (also called: third parties)

8.1 Which party is in the lead?	UMCG ☒	Not the UMCG ☐
8.2 Is the leading party a commercial party?	Yes ☐	No ☒

8.3 *Only complete if UMCG is not in the lead:* **Is the role of the UMCG limited to supplying data?**	Yes ☐	No x

8.4 Description of the cooperation

Please describe the role and tasks that will be performed by the UMCG and by the partner(s). Please note that only the role and tasks described here can be mentioned in the contract.

The study will be conducted collaboratively between the University Medical Center Groningen (UMCG) and Isala Hospital. Both centers will serve as recruitment sites and will contribute to data collection.

- *UMCG*
  - *Acts as the coordinating center for the study.*
  - *Responsible for study design, protocol development, and obtaining ethical approval.*
  - *Will oversee central data management, statistical analysis, and reporting of study results.*
  - *Provides training and supervision for diaphragm ultrasound measurements to ensure protocol standardization.*
  - *Responsible for monitoring study progress, ensuring data quality, and safeguarding compliance with GDPR*
- *Isala Hospital*
  - *Acts as a recruitment and data collection site.*
  - *Responsible for identifying eligible patients, obtaining informed consent, performing ultrasound measurements, and recording clinical data as per protocol.*
  - *Ensures timely and secure transfer of pseudonymized data to UMCG for analysis.*
  - *Participates in regular coordination meetings and contributes to interpretation of findings and dissemination of results.*

8.5 Data and/or biomaterial management in combination with the partners

Please elaborate on the following aspects:

- Which data (and/or biomaterials) will be shared with the partners

In this study, only pseudonymized clinical data will be shared between the participating centers (UMCG and Isala Hospital). No biomaterials (e.g., blood, tissue, or other biological specimens) will be collected or exchanged.

The following types of data will be shared:

- *Demographic data: age, sex, height, weight, BMI*
- *Clinical data: COPD history (e.g., GOLD stage, FEV1), current medications, comorbidities, blood gas values (pH, $PaCO_2$), vital signs, and relevant admission parameters*

- *Ultrasound data: diaphragm excursion measurements during tidal and maximal breathing, diaphragm motion ratio (tidal/max)*

- *Outcome data: requirement of non-invasive ventilation (NIV), in-hospital mortality, length of hospital stay, ICU admission if applicable*

All shared data will be pseudonymized at the site of collection before being transferred to the coordinating center (UMCG) for analysis. No direct identifiers (e.g., name, date of birth, patient ID) will be shared. Data transfer will follow institutional data protection protocols and applicable GDPR guidelines.

- How is the data (and/or biomaterials) saved and/or destroyed after study end.

No biomaterials will be collected or stored in this study. All pseudonymized data collected during the study will be stored securely on encrypted, access-controlled servers at the coordinating center (UMCG) and at the partner site (Isala Hospital), in accordance with institutional and GDPR data protection standards.

After the end of the study:

- *Study data will be retained for a period of 15 years in accordance with Dutch regulations.*
- *During this retention period, access will be limited to authorized study personnel for purposes such as audits, publication, or regulatory review.*
- *After the retention period, all digital data will be permanently deleted and any physical records will be shredded or incinerated in accordance with institutional procedures.*

8.6 With Informed consent *Please complete only if patients are asked for Informed Consent:* In case of collaboration with *commercial/for-profit* organizations. Has the research participant been informed in the DIF, or will they be informed, about the collaboration with commercial third parties.	Yes x	No ☐
Has or will informed consent be(en) obtained for data sharing with the third party?	Yes x	No ☐
8.7 Contracts For both with informed consent and without informed consent: will you contact the loket Contract Research to arrange the proper contracts?	Yes x	No ☐
8.8 Data Protection Impact Assessment (DPIA) Will a DPIA be drawn up?	Yes ☐	No x

If a DPIA will *not* be drawn up please elaborate on the reason for this:
A Data Protection Impact Assessment (DPIA) will not be drawn up for this study because the processing of personal data poses a low risk to the rights and freedoms of the participants. The study involves minimal data collection limited to routinely available clinical information and ultrasound measurements, without processing of special categories of data beyond standard health information. No large-scale or systematic monitoring will take place, and data will be pseudonymized prior to analysis. Additionally, the study is conducted in accordance with the General Data Protection Regulation (GDPR) and the participating hospitals' existing data protection policies. Given the limited scope and low privacy risk, a formal DPIA is not required.

9. Data Management Plan (DMP)

In this study the data will be collected, processed, and archived in accordance with the General Data Protection Regulation (GDPR) and the FAIR (Findable, Accessible, Interoperable, Reusable) principles under the responsibility of the Principal Investigator, as is required by the GDPR law.
Please note that completion of this section is *required.* A separate DMP will not be reviewed.

9.1 Handling and storage of data

The following are requirements with regards to handling and storage of data, please mark all that apply:

● Digital data will be archived following a strict security and back-up policy (akin to UMCG security level).	x
● Paper source data and study files will be archived according the UMCG policy	x
● Source data, study files and digital data will be archived 15 years after the study is completed.	x
● Tooling (eg. software and procedures) used for collecting, processing, analysing, and storing data will be compliant with the UMCG policy and Standard Operating Procedures in the UMCG Research Toolbox.	x

9.1.1 *If applicable:* Not all items in the above section 10.1 apply to my study. Please elaborate on the reason for this and the solutions.
<text>

9.2 Anonymization and pseudonymization

Data will be <u>anonymized</u> during data collection. *Please note that this means that the data can never be linked back to the participant and that in practice this usually means that very large numbers of participants in the dataset are required.*	Yes ☐	No x

If data is <u>anonymized:</u>

- Please explain what procedure is used:

  <text>
- Please reflect on the applicability of K1-anonimity on your dataset:

  <text>

If anonymized data please skip the rest of section 9.

Data will be <u>pseudonymized</u> during data collection (i.e. data cannot directly be linked back to the participant).	Yes x	No ☐

If data is <u>pseudonymized</u>, please explain what procedure is used.
All participant data collected in this study will be pseudonymized at the point of collection at each study site (UMCG and Isala Hospital) before being stored or shared. The pseudonymization procedure includes the following steps:

1. *Assignment of a unique study code to each participant at inclusion. This code will replace all directly identifying personal data in the study database.*
2. *A secure, site-specific key file (linking study codes to patient identities) will be stored separately in a restricted-access, encrypted location within each participating hospital. This file will only be accessible to designated local study personnel and will not be shared with the coordinating center or other partners.*
3. *The pseudonymized dataset, containing only study codes and research-relevant variables, will be securely transferred to the coordinating center (UMCG) for analysis.*
4. *All data transfers will occur through encrypted and authorized channels (e.g., secure hospital servers, institutional file transfer systems) to prevent unauthorized access.*

9.3 Pseudonymization requirements

9.3.1 The following are requirements when pseudonymized data is used, please mark all that apply:

● Indirect and direct identifiable information collected will be minimized and only collected for the purpose of this study	x
● Direct identifiable information (e.g. contact details, code list, encryption key, participant identification log) will be stored separately from pseudonymized data	x
● Direct identifiable information can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator.	x
● Pseudonymized data can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator.	x
● Data roles, responsibilities, access and authorization, during the study and after study completion, will be managed and documented (e.g. in the DMP or study delegation log).	x

9.3.2 *If applicable:* not all items in the above list of pseudonymization requirements apply to my study. Please elaborate on the reason for this and the alternative solutions.

NA

10. FAIR Data and Data Sharing

10.1 FAIR data

The following statements concern FAIR data, which is the UMCG policy. *Please note that FAIR is not the same as Open Access.*

Data will be made findable by including the description of the study (and type of data (i.e. metadata) in the UMCG FAIR data catalogue and other discipline specific catalogue(s).	Yes x	No ☐

If 'no' is answered on the above question, please elaborate on the reason for this.
<*text*>

10.2 Data Sharing

In case data (and biomaterials) will leave or enter the UMCG, will you contact the loket Contract Research to arrange the proper contracts? (Loket_Contract_Research@umcg.nl)	Yes x	No ☐	No data will leave or enter UMCG ☐

11. Management of Biomaterials (either newly collected or from an existing biobank)

11.1 Will biomaterials be collected, processed, analyzed and/or stored for the purpose of this study?	Yes ☐	No x *skip and delete rest of section 11*

12. Burden, Risks & Benefits

12.1 Burden Is there a (potential) burden for the participant as a result of participating in this study? *For example: feeling tired after performing tests, reliving bad memories.*	Yes, minimal burden ☐	Yes, more than minimal burden ☐	No x
If yes, please explain what the burden is/might be *NA* Clarify what is done to alleviate the burden *NA*			
12.2 Risk Does the participant run a risk of injuries and/or other discomfort as a result of participating in this study? *For example: risk of falling while doing exercises*	Yes, minimal risk ☐	Yes, more than minimal risk ☐	No x
If yes, please explain what the risk entails. *NA* Clarify what is done to alleviate the risk. *NA*			
12.3 Benefits Does the participant receive benefits/reward/incentives for participating in this study:		Yes ☐	No x
If yes, please explain what the benefits/reward/incentives entail. *NA*			

13. Incidental findings

Is there a risk of incidental findings?	yes, minimal risk x	yes, ≥ substantial risk ☐	No ☐
If yes, please explain the nature of the incidental findings.			

Incidental findings in this study are expected to be minimal, as the ultrasound examination is focused solely on assessing diaphragm motion (tidal and maximal excursion) for research purposes. However, there is a small risk that during the ultrasound procedure, other unexpected abnormalities—such as diaphragmatic paralysis, severely impaired motion, or atypical thoracic or upper abdominal structures—may be visualized.

Procedure to assess if a finding should be returned to the participant, or not

These findings are outside the scope of the study but may have clinical relevance. In such cases, the findings will be communicated to the treating physician for further evaluation if deemed clinically significant.

Procedure to inform the participant

The treating physician will assess the significance of the finding in the context of the patient's overall clinical condition. If the finding is considered relevant, the participant will be informed in a timely and appropriate manner by their treating physician, who can provide medical context, follow-up steps, and answer any related questions.

14. References

1. Gommer A.M., Hendriks C. (2022, sep 01). COPD Zorg. VZinfo. https://www.vzinfo.nl/copd/zorg

2. Roche N, Zureik M, Soussan D, Neukirch F, Perrotin D; Urgence BPCO (COPD Emergency) Scientific Committee. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. Eur Respir J. 2008 Oct;32(4):953-61. doi: 10.1183/09031936.00129507. Epub 2008 May 28. PMID: 18508819.

3. Munshi L, Mancebo J, Brochard LJ. Noninvasive Respiratory Support for Adults with Acute Respiratory Failure. N Engl J Med. 2022 Nov 3;387(18):1688-1698. doi: 10.1056/NEJMra2204556. PMID: 36322846.

4. Ram FS, Picot J, Lightowler J, Wedzicha JA, Ram FSF, Picot J, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstruc¬tive pulmonary disease. Update of Cochrane Database Syst Rev. 2004;(1). CD004104.

5. Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose. Non-invasieve beademing bij COPD. 2013.

6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD: 2022 report.

7. Gibson GJ. Diaphragmatic paresis: pathophysiology, clinical features, and investigation. Thorax. 1989 Nov;44(11):960-70. doi: 10.1136/thx.44.11.960. PMID: 2688182; PMCID: PMC462156.

8. Ricoy J, Rodríguez-Núñez N, Álvarez-Dobaño JM, Toubes ME, Riveiro V, Valdés L. Diaphragmatic dysfunction. Pulmonology. 2019 Jul-Aug;25(4):223-235. doi: 10.1016/j.pulmoe.2018.10.008. Epub 2018 Dec 1. PMID: 30509855.

9. Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med. 2003 Jul 1;168(1):10-48. doi: 10.1164/rccm.2206020. PMID: 12826594.

10. Boon AJ, Sekiguchi H, Harper CJ, Strommen JA, Ghahfarokhi LS, Watson JC, Sorenson EJ. Sensitivity and specificity of diagnostic ultrasound in the diagnosis of phrenic neuropathy.

Neurology. 2014 Sep 30;83(14):1264-70. doi: 10.1212/WNL.0000000000000841. Epub 2014 Aug 27. PMID: 25165390; PMCID: PMC4180486.
11. Shaikh H, Laghi F. Role of Diaphragm Ultrasound When NIV Fails in COPD Exacerbations. Respir Care. 2019 Dec;64(12):1600-1602. doi: 10.4187/respcare.07523. PMID: 31767688.
Cammarota G, Sguazzotti I, Zanoni M, Messina A, Colombo D, Vignazia GL, Vetrugno L, Garofalo E,
12. Bruni A, Navalesi P, Avanzi GC, Della Corte F, Volpicelli G, Vaschetto R. Diaphragmatic Ultrasound Assessment in Subjects With Acute Hypercapnic Respiratory Failure Admitted to the Emergency Department. Respir Care. 2019 Dec;64(12):1469-1477. doi: 10.4187/respcare.06803. Epub 2019 Aug 27. PMID: 31455684.
13. Kocyigit H, Gunalp M, Genc S, Oguz AB, Koca A, Polat O. Diaphragm dysfunction detected with ultrasound to predict noninvasive mechanical ventilation failure: A prospective cohort study. Am J Emerg Med. 2021 Jul;45:202-207. doi: 10.1016/j.ajem.2020.08.014. Epub 2020 Aug 17. PMID: 33046306.
14. archioni A, Castaniere I, Tonelli R, Fantini R, Fontana M, Tabbì L, Viani A, Giaroni F, Ruggieri V, Cerri S, Clini E. Ultrasound-assessed diaphragmatic impairment is a predictor of outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease undergoing noninvasive ventilation. Crit Care. 2018 Apr 27;22(1):109. doi: 10.1186/s13054-018-2033-x. PMID: 29703214; PMCID: PMC5921560.
15. Antenora F, Fantini R, Iattoni A, Castaniere I, Sdanganelli A, Livrieri F, Tonelli R, Zona S, Monelli M, Clini EM, Marchioni A. Prevalence and outcomes of diaphragmatic dysfunction assessed by ultrasound technology during acute exacerbation of COPD: A pilot study. Respirology. 2017 Feb;22(2):338-344. doi: 10.1111/resp.12916. Epub 2016 Oct 14. PMID: 27743430.

15. Appendices

<If applicable: text>