Protocol Full Title prospective trial: **COVID-19: The study of aerosol generation with the droplet reduction mouthpiece during esophagogastroduodenoscopy**

Protocol Acronym/short title: aerosols generation with modified mouthpiece in EGD (S65197)

Version and date of final protocol: version 2 – 04MAR2021

Sponsor: UZLeuven

Address: Herestraat 49, 3000 Leuven

Principal Investigators:

Name: Prof. Jan Tack
Address: Herestraat 49, box 701, 3000 Leuven
Telephone: +32 (0)16 330816
Email: jan.tack@kuleuven.be

Name: Prof. Raf Bisschops
Address: Herestraat 49, box 701, 3000 Leuven
Email: raf.bisschops@uzleuven.be

Sub-investigator:

Name: Dr. I-Hsuan Huang
Address: Herestraat 49, box 701, 3000 Leuven
Email: ihsuan.huang@kuleuven.be

Name: Dr. Pieter Sinonquel
Address: Herestraat 49, box 701, 3000 Leuven
Email: pieter.sinonquel@kuleuven.be

Name: Kristof Buysschaert
Address: Herestraat 49, box 701, 3000 Leuven
Email: kristof.buysschaert@uzleuven.be

Name: Hilde Willekens
Address: Herestraat 49, box 701, 3000 Leuven
Email: Hilde.Willekens@uzleuven.be

Name: Herman Devriese
Address: Herestraat 49, box 701, 3000 Leuven
Email: herman.devriese@uzleuven.be

Signatures

- **Jan Tack**

_____	_____
Principal Investigator	Date

- **Raf Bisschops**

_____	_____
Principal Investigator	Date

- **I-Hsuan Huang**

_____	_____
Sub-investigator	Date

- **Pieter Sinonquel**

_____	_____
Sub-investigator	Date

- **Hilde Willekens**

_____	_____
Sub-investigator	Date

- **Kristof Buysschaert**

_____	_____
Sub-investigator	Date

- **Herman Devriese**

_____	_____
Sub-investigator	Date

Table of Contents

1. Study Synopsis

Title of clinical trial	The study of aerosol generation with the droplet reduction mouthpiece during esophagogastroduodenoscopy
Principal Investigator	Prof. Dr. Jan Tack
Medical condition or disease under investigation	Aerosol generation with the droplet reduction mouthpiece during endoscopy procedures
Purpose of clinical trial	To investigate the effect of droplet reduction mouthpiece on aerosol particle generation during esophagogastroduodenoscopy
Primary objective	Generation of aerosol particles by esophagogastroduodenoscopy with the droplet reduction mouthpiece
Secondary objective (s)	None
Trial Design	Prospective interventional study
Sample Size	80 patients undergoing elective upper GI endoscopy
Summary of eligibility criteria	Patients undergoing elective upper gastrointestinal endoscopy
Maximum duration of treatment of a subject	Not applicable
Version and date of final protocol	Version 2: 04 March 2021
Version and date of protocol amendments	Not Applicable

2. Background and rationale

Gastrointestinal (GI) endoscopy is one of the most commonly performed invasive procedures in clinical practice. Health care workers (HCW) at the endoscopy unit are at constant occupational risk for many infectious diseases as they perform daily procedures that are believed to generate aerosol and droplets, which may harvest respiratory pathogens. The size of particles determines the time of suspension in air and the distance of transmission. Currently, droplets are defined by a particle size larger than 5 µm in diameter while particles below 5 µm diameter are referred to as aerosols (1). Generally, all endoscopic procedures are considered potentially aerosol generating (2). Current guidelines recommend using high-level protection with N95 mask, FFP2 or FFP3, gloves, face shield and gown for high-risk patients during endoscopic procedures (3, 4). A growing number of scientific reports confirm that esophagogastroduodenoscopy is an aerosol-generating procedure (5, 6). A number of approaches to decrease the amount of aerosol generated have been reported including, for instance, the use of dental sucker in the oral cavity for continuous suction during the procedure or placing patients with their heads covered by a plastic enclosure, “endoscopic shield” (5, 6). Nevertheless, either use of the dental sucker or endoscopic shield may be less comfortable for patients and requires time and personnel and may therefore also be inconvenient for HCW.

During esophagogastroduodenoscopy (EGD), a hard-plastic mouthpiece is used to protect the endoscope from being bitten and to enable its smooth insertion. In September 2020, the droplet reduction Mouthpiece “B1” (Mouthpiece MPC-ST GMDN:62534 Generic name: Endoscopic bite block, basic, reusable) was launched by Fujifilm Corporation, Tokyo, Japan and imported to Europe by Fujifilm Europe. The droplet reduction mouthpiece is used in the same way as the conventional mouthpiece but differs from current mouthpieces by the inclusion of a sponge rubber incorporated into the mouthpiece orifice, and a drape shield specifically created to catch and reduce the droplets emitted by the patient during upper gastrointestinal endoscopy. This newly developed mouthpiece is considered for application during routine endoscopy at our facility during the COVID-19 pandemic, helping to minimize the risk to HCW and patients from becoming infected with COVID-19 and various other pathogens. However, there is a lack of scientific evidence on the amount of aerosol reduction with the modified mouthpiece when upper GI endoscopy is being performed.

The aim of the present study is to quantify the generation of aerosols when performing upper GI endoscopy with the modified mouthpiece. We intend to quantify the number of particles in the air near the patient. The duration of therapeutic upper gastrointestinal endoscopies can vary extremely. To avoid risk of imbalance in procedure durations, we are limiting the protocol to standard diagnostic EGDs. We assume that aerosol generations during short procedures can be extrapolated to longer procedures and hence this should not invalidate the findings.

3. Trial objectives and Design

3.1 Trial objectives

To perform a study to quantify the number of aerosol generation during EGD, using the droplet reduction mouthpiece, in the phases of COVID-19 pandemic.

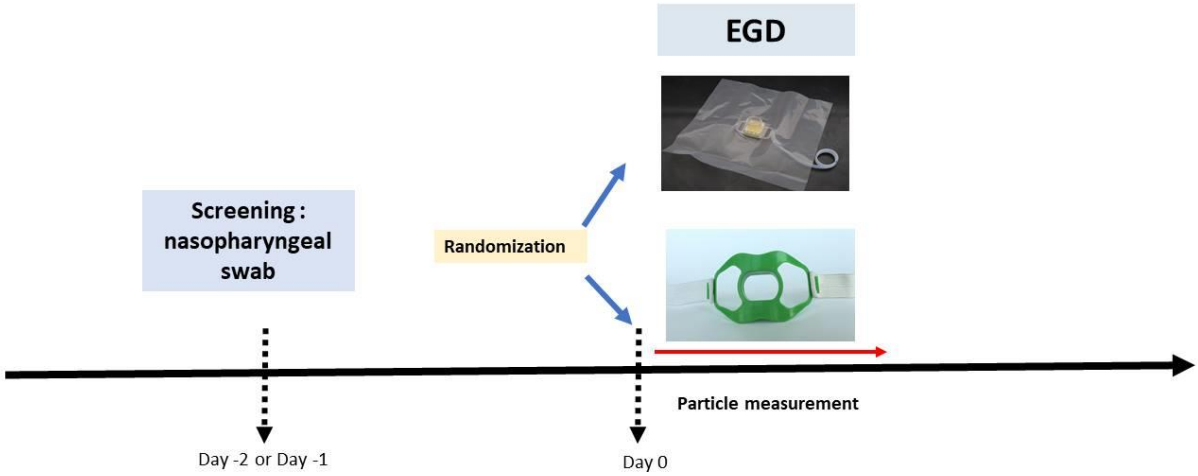
3.2 Primary endpoints

Generation of aerosol particles by esophagogastroduodenoscopy with the droplet reduction mouthpiece.

3.3 Secondary endpoints

None

3.4 Trial Design



3.5 Trial Flowchart

Study Procedures	Timing
PCR testing on nasopharyngeal swab 24 hours prior to the test performed and negative	Day -2 or day -1
Informed consent	Day -2, -1 or Day 0
EGD	Day 0
Measurement of aerosol generation	Day 0

4 Selection and withdrawal of subjects

4.1 Inclusion criteria

- Aged >18 years old;
- Male or female patients;
- Patients undergoing elective standard diagnostic EGD;
- Negative PCR on nasopharyngeal swab 24 or 48 hours prior to the test;
- No anatomical deformity of nose and throat, no known diseases of nose and throat;
- Signed informed consent.

4.2 Exclusion criteria

- Females who are pregnant or lactating.

4.3 Expected duration of trial

The duration of this protocol is estimated at 3 months.

4.4 Recruitment of subjects

Patients are recruited from the gastroenterology clinic at the University Hospitals Leuven. Patients undergoing elective EGD will be invited to participate in the study.

5. Trial Procedures

5.1 Preparation room and patient

5.1.1 Room

The room is also equipped with an air particle counter (Lasair particle measure counter). A plastic tube, connected to the inlet of the counter, is placed within 10 cm from the mouth of the patient once the patient is set up in the room. The counter takes 1-minute air samples to quantify particles of 0.3, 0.5, 0.7, 1, 5 and 10 µm (6). Measurements of particle counts occur right before the endoscope insertion and 1, 3, 5, 10 and 15 minutes after the start of endoscopy, as well as after the completion of endoscopy. If the endoscopy is terminated before all measurements are done, the remaining measurements at time point 10 minutes and/or 15 minutes will be dropped.

5.1.2 Patient

Before the investigations, all patients need to have a negative SARS-CoV-2 test. Eligible patients will be randomly assigned to one of the following groups: the group using the droplet reduction mouthpiece, or the group using the conventional mouthpiece for EGD. Randomization will be generated via an online randomization program (www.randomization.com).

5.2 Esophagogastroduodenoscopy

A conventional gastrointestinal videoscope will be orally inserted into the stomach to observe the upper gastrointestinal tract. During the examination, patients will be placed on their left side. EGD for all patients will be performed by one endoscopist and one assistant nurse.

Premedication with anticholinergic agents or glucagon will not be used. Lidocaine (8%) will be sprayed into the posterior pharynx of all patients before insertion of the endoscope to reduce the gag reflex. Then, midazolam (0-5 mg) and pethidine (0-50 mg) can be administered intravenously for sedation, depending on the expected difficulty of the procedure and the anxiety level of the patient. Adequate monitoring of vital signs and oxygen saturation is performed throughout the examination.

6 Assessment of aerosol generation

Particle counts per cubic feet for each particle size will be measured prior to start of the procedure, and 1, 3, 5, 10 and 15 minutes after the start of endoscopy, as well as after the completion of endoscopy. If the endoscopy is terminated before all measurements are done, the remaining measurements at time point 10 minutes and/or 15 minutes will be dropped. The primary outcome will be to assess the changes of aerosols before, during, and after endoscopy and compare their trends in using droplet reduction mouthpiece and conventional mouthpiece groups. The changes in particle counts over time will be described and a random effect of repeated measures will be used in models to examine the effect of new mouthpiece.

7 Safety reporting

At the study visit, the investigator will determine whether any adverse events have occurred. The patient will be questioned in a general way and no specific symptoms will be suggested. If any adverse events have occurred, they will be recorded and we will act accordingly.

Since this is an Investigator driven study, the Sponsor is the Investigator and it should be interpreted as such.

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

7.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.

7.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Death
- A life-threatening[a] experience
- In-patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

[a] The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

7.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

Only events related to the study-specific intervention will be reported in the (e)CRF.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

7.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. If related to the study-specific intervention, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE page, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the study interventions
- outcome

7.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:**

- Severity must be evaluated by an Investigator according to the following definitions:
  - *Mild* – no or transient symptoms, no interference with the subject's daily activities
  - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
  - *Severe* – considerable interference with the subject's daily activities, unacceptable

- **Causality:**
  - *None* – An AE which is not related to the study-related interventions
  - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
  - *Possible* – An AE which might be due to the study-related interventions. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
  - *Probable* - An AE which might be due to the study-related intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
  - *Definitely* – An AE which is known as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

7.3.2 Timelines for reporting

After informed consent has been obtained and after initiation of study-related interventions:

- If related to the study-specific intervention AEs and SAEs causally related to a study-related intervention will be reported until 30 days after the last study-related intervention or until last follow-up visit (whichever occurs first).

If related to the study-specific intervention SAEs as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate

report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by Trial identification.

SAE details will be reported by the Investigator to the Sponsor:

- By completing the SAE form in the (e)CRF

If an authorised Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

7.3.3 Follow-up

The Investigator must record follow-up information by updating the medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

SAEs after the end of the trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the study-related interventions after the subject has ended the trial, the Investigator should report this SAE within the same timelines as for SAEs during the trial.

7.3.4 Pregnancy

NA

7.3.5 Death

All deaths will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event). The sponsor will notify all deaths, as soon as possible after becoming aware, to the Central EC and the EC of the concerned site and provide additional information if requested.

Reporting requirements to Ethics Committee's (EC's) The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and based on applicable legislation.

7.4 Reporting requirements to Ethics Committee's (EC's) and Competent Authorities (CA's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF.

The Investigator will promptly evaluate all SAEs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, EC's and applicable CA's based on applicable legislation.

7.4.2 Annual reporting

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's containing an overview of all SARs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

7.4.3 Overview reporting requirements

	WHAT		HOW	TO	TIMELINES
Investigator	AE		AE form	sponsor	as defined in protocol
	SAE		SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event) Exceptions: as defined in protocol
	death		SAE form	sponsor	asap
Sponsor	death		SAE form + narrative	Ethics Committees	asap
	Annual Progress Report		APR template	Ethics Committees	annually

AE = adverse event; SAE = serious adverse event; asap = as soon as possible; SUSAR = suspected unexpected serious adverse reaction; CIOMS = council for international organization of medical sciences; EC = ethics committee; CA = competent authority; DSUR = development safety update report; APR = annual progress report; ASR = annual safety report

8 Statistics

8.1 Sample size

The aim is to create a descriptive review on the aerosol contamination with the droplet reduction mouthpiece during endoscopy. As this is a descriptive analysis, no formal power calculation was performed. In total we will include 40 patients for endoscopy with the droplet reduction mouthpiece and 40 patients for endoscopy with the conventional mouthpiece. However, based on previous publications on aerosol generation with nasogastric intubation (7)

and on reduction of aerosol spread during upper endoscopy with a dental sucker (8), we consider this number adequate.

9 Quality assurance

Patient recruitment follows international consensus diagnostic standards. The aerosol counting device will be calibrated prior to and at 4-week intervals throughout the study.

10 Direct access to source data and documents

The investigator(s) and the institution will permit trial-related monitoring, audits, EC review and regulatory inspections (where appropriate) by providing direct access to source data and other documents (I.e. patients' case sheets, blood test reports, histology reports etc).

11 Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee of the University Hospitals Leuven and any subsequent protocol amendments will be submitted to this EC for approval.

The study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data

(Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data)

When data are **coded**, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers should be stored separately from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.

12 Data Handling

Data will be collected and analyzed by the study investigators (I-Hsuan Huang) of the Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Clinical and Experimental Medicine and University Hospitals Leuven.

Principal Investigator:
Jan Tack, MD, PhD
Sub-Investigators:
I-Hsuan Huang, MD
Pieter Sinonquel, MD
Kristof Buysschaert, RN
Hilde Willekens, RN
Herman Devriese, Ir

13 Data Management

All collected data will be coded and entered into an eCRF (REDCap). The access to REDCap and exported files are password protected and will only be granted to selected members of the study team.

14 Translational research

NA

15 Publication Policy

Publications will be coordinated by the study team. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

16 Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

17 Financial Aspects

No additional investigations are needed in this protocol. Patients that participate have already planned EGD. Therefore, no additional financial compensation is included in this protocol.

18 References

1. Fennelly KP. Particle sizes of infectious aerosols: implications for infection control. The Lancet Respiratory Medicine. 2020.
2. Soetikno R, Teoh AY, Kaltenbach T, Lau JY, Asokkumar R, Cabral-Prodigalidad P, et al. Considerations in performing endoscopy during the COVID-19 pandemic. Gastrointestinal endoscopy. 2020.
3. Sultan S, Lim JK, Altayar O, Davitkov P, Feuerstein JD, Siddique SM, et al. AGA rapid recommendations for gastrointestinal procedures during the COVID-19 pandemic. Gastroenterology. 2020;159(2):739-58. e4.
4. Gralnek IM, Hassan C, Beilenhoff U, Antonelli G, Ebigbo A, Pellisè M, et al. ESGE and ESGENA Position Statement on gastrointestinal endoscopy and the COVID-19 pandemic. Endoscopy. 2020;52(6):483.
5. Sagami R, Nishikiori H, Sato T, Tsuji H, Ono M, Togo K, et al. Aerosols Produced by Upper Gastrointestinal Endoscopy: A Quantitative Evaluation. Official journal of the American College of Gastroenterology| ACG. 2020;116(1):202-5.
6. Chan SM, Ma TW, Chong MK-C, Chan DL, Ng EKW, Chiu PWY. A proof of concept study: Esophagogastroduodenoscopy is an aerosol-generating procedure and continuous oral suction during the procedure reduces the amount of aerosol generated. Gastroenterology. 2020.
7. Verbeure W, Geeraerts A, Huang I-H, Timmermans L, Toth J, Geysen H, et al. Aerosol generation and droplet spread during nasogastric intubation in the COVID-19 era. Gut. 2020.
8. Chan SM, Ma TW, Chong MK-C, Chan DL, Ng EKW, Chiu PWY. A proof of concept study: esophagogastroduodenoscopy is an aerosol-generating procedure and continuous oral suction during the procedure reduces the amount of aerosol generated. Gastroenterology. 2020;159(5):1949-51. e4.