Protocol Full Title:

Tear film SARS-nCoV-2 detection in symptomatic and pauci-symptomatic patients.

Protocol Acronym/short title:

Eye-COVID

Version and date of protocol:

V8.0 dd 16-09-2020

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Title of clinical trial	Tear film SARS-nCoV-2 detection in symptomatic and pauci-symptomatic patients.
Protocol Short Title/Acronym	Eye-COVID
Funding	R95328
Principal Investigator	Dr. H. Delbeke
Sponsor	University Hospitals Leuven Herestraat 49 3000 Leuven
Sponsor Reference Number	S 64002
Purpose of clinical trial	To investigate the presence of SARS-nCoV-2 in the tear film of symptomatic and pauci-symptomatic SARS-nCoV-2 positive patients.
Trial Design	Exploratory study using biological samples
Summary of eligibility criteria	• ≥ 18 years old. • Willing to undergo sampling of the conjunctiva. • Willing to fill in a questionnaire. • Fluent in written and verbal Dutch. • Capable of giving informed consent. • Part 1 only: positive test for SARS-nCoV-2 on a nasopharyngeal swab.

	• Part 2 only: mild symptoms of COVID-19 including symptoms of upper or lower respiratory tract infection and any body temperature elevation (criteria Sciensano for testing patients and healthcare workers (April 12 2020)) without the need for hospitalization.
Version and date of final protocol	V8.0 dd 16-09-2020

Table of contents

1. Background, rationale and novelty

A novel coronavirus, severe acute respiratory syndrome new coronavirus 2 (SARS-nCoV-2) was first described early December 2019 (Wuhan, China) (1). Since these first reports, the virus has been spreading and causing disease around the globe. Since the 11th of March 2020, the World Health Organization (WHO) declared the disease as a pandemic (2).

This corona virus disease (COVID-19) causes flu-like symptoms (fever, myalgia, fatigue and cough), which can evolve to a severe bilateral pneumonia with significant dyspnea and chest pains. A subset of patients further deteriorates to an acute respiratory distress syndrome with the need for intensive care unit (ICU) administration and oxygen therapy. COVID-19 is a contagious infection spread by droplets and aerosols (3). Besides the flu-like symptoms, certain publications report the presence of anosmia as well as ageusia as one of the first presenting symptoms of COVID-19 (4).

This is consistent with the Google Trends analysis. The most common coronavirus related search queries are loss of smell, fever, and chills. While nasal congestion and diarrhea were fifth and sixth on the search terms. It is the fourth most searched term - eye pain - that has now caught the eye (quite literally) of researchers as it could be a possible symptom of the COVID 19 (5).

Independent of the severity of respiratory symptoms, the presence of the virus in tears (positive for SARS-nCoV-2 via qPCR assessment) has been described in patients with conjunctivitis (6,7). This in line with earlier results during the SARS epidemic of 2003 (8). However, the presence of SARS-nCoV-2 in tears, implies that the disease might possibly be transmitted via this body fluid, especially during certain specific procedures such as pneumotonometry and excimer refractive laser surgery. Specific to these procedures is the use of a jet of air and a laser beam, transforming tears to **small droplets** (9–11).

To further investigate the potential spread of the virus through tears, we aim to set up a two-part study. The first part of our study is to confirm the detectability of the SARS-nCoV-2 in the tear film of **symptomatic** patients. Patients admitted at our University Hospital Leuven, Belgium with a positive nasopharyngeal swab for SARS-nCoV-2 will be informed about our project. They will be asked to sign an informed consent for serial swabbing of the conjunctiva every 3 days until the end of their hospitalization.

A conjunctival swab is chosen above other methods such as Schirmer's test since a swab is besides faster also easier to teach and requires less contact with the volunteer. The serial swabbing will not only be informative on the duration of viral shedding in the tears, but also on the timing that SARS-nCoV-2 becomes detectable with qPCR in the tear film. Furthermore, a questionnaire (*cf. Addendum A*) will be used to search for correlations between SARS-nCoV-2 positive conjunctival swabs and the patient's disease stage (including results of routine blood samples), presence of ocular symptoms and/or

perception of anosmia and/or ageusia. Especially this anosmia part might be interesting. A correlation between anosmia and a positive PCR in the tear film is suspected based on the connection between the nose and eyes via the nasolacrimal duct and the proximity of the olfactory nerve to the orbital cavity and eye.

The other parts of our study aims to confirm the detectability of the SARS-nCoV-2 virus in the tear film of **pauci-symptomatic** volunteers, more specifically patients presenting at the emergency room of the University Hospitals Leuven, health care workers with mild symptoms and patients admitted for other reasons though SARS-nCoV-2 positive. Presumably, the rate of pauci-symptomatic carriers is higher within health care workers compared to the general population. Emergency patients and health care workers are preferred over pauci-symptomatic pre-operative patients, since prevalence of SARS-nCoV-2 is low in these pre-operative patients (data UZ Leuven Laboratory Medicine (1 June 2020): prevalence of around 0.2%). Similar to the symptomatic patients, all volunteers will be informed about our project and asked to sign an informed consent for simultaneous swabbing of the conjunctiva and the nasopharynx. The pauci-symptomatic group will include only volunteers already listed for nasopharyngeal swabbing based on their symptoms (to avoid unnecessary use of nasopharyngeal swabs). By testing pauci-symptomatic volunteers, we intend to better substantiate current guidelines in ophthalmology practice. Mostly “deemed-healthy” patients visit outpatient clinics, but when carrying the virus, they are the highest risk of contaminating health care workers. Proving presence of (viable) SARS-nCoV-2 virus in the tear film of pauci-symptomatic volunteers might change our ophthalmology practice in the long run. Furthermore, we want to compare results of both the ocular and nasopharyngeal swab (both positive for SARS-nCoV-2; both negative for SARS-nCoV-2; discordant results, with either eye or nasopharynx positive and the corresponding sample negative for SARS-nCoV-2). For patients with discordant results, we purpose to identify potential correlations between disease-severity and detection of SARS-nCoV-2 in different body fluids by using the same questionnaire mentioned above (*cf. Addendum A)*. The difference in RNA viral load (by means of quantitative result (Cycle threshold (Ct) of the SARS-CoV-2 PCR) in the tears of different patients at different moments in time (i.e. the assessment of the evolution of quantitative result) will be indicative for the transmissibility of the virus. However, to evaluate genuine transmissibility, swabs positive for SARS-CoV-2 via qPCR will be sent to the REGA institute (i.e. the Laboratory of Piet Maes) for **viral culture and detection of subgenomic (sg) RNA**. This is in contrast to most previously published studies focusing only on the detection of SARS-CoV-2 RNA by PCR. SARS-CoV-2 PCR is not able to differentiate between live or dead virus (6–8). It is important to make that difference in order to draw conclusions on potential transmission of the virus by tears. Detection by culture indicates if viable virus is present in the sample. Detection of sgRNA is an indicator for replication of the virus. The viability of the virus collected from tear samples will determine the risk of spreading the virus via tears.

This research project intends to provide a more thorough understanding of the presence of this new virus in the tear film of SARS-nCoV-2 positive patients. Furthermore, it could provide insight in the timing of the contagiousness of tears and highlights correlations with other signs and symptoms.

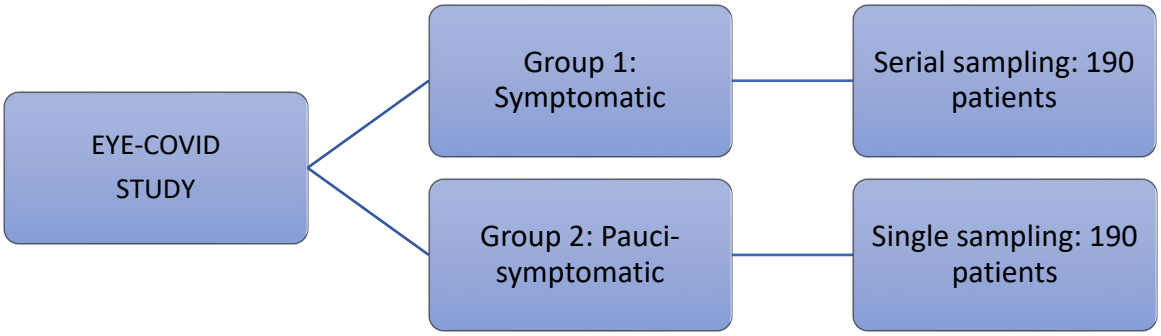

Figure 1: study design.

2. Trial objectives and design

Primary outcome measures

1) The presence of SARS-nCoV-2 in the tear film of symptomatic and pauci-symptomatic SARS-nCoV-2 positive patients.

2) Correlations between SARS-nCoV-2 in the tear film and mild (like anosmia, ageusia, upper and lower respiratory tract infection) or severe symptoms (as pneumonia, need for hospitalization) of COVID-19.

Secondary outcome measures

1) The stage of disease when SARS-nCoV-2 becomes detectable in the tears.

2) Duration of shedding of SARS-nCoV-2 RNA in the tears.

3) Difference in RNA viral load (by means of quantitative result (Cycle threshold (Ct) of the SARS-nCoV-2 PCR) in tears of different patients at different moments in time in order to estimate potential difference in transmissibility of the virus by tears.

4) Assessment of evolution of quantitative result (Cycle threshold (Ct)) of the SARS-nCoV-2 PCR over time within conjunctival SARS-nCoV-2 PCR positive patients

5) Searching for a correlation between both quantitative and qualitative results of SARS-nCoV-2 PCR on the nasopharyngeal and conjunctival swab (both positive for SARS-nCoV-2; both negative for SARS-nCoV-2; discordant results, with either eye or nasopharynx positive and the corresponding sample negative for SARS-nCoV-2).

6) Exploring the possibility of testing the tear film on SARS-nCoV-2 as a screening tool for early disease.

7) Exploring the replication of the SARS-nCoV-2 virus, by differentiating between death and alive SARS-nCoV-2 virus through sg RNA-testing and tissue culture.

2.1 Preparation, organization and management of this exploratory study

Part 1: Serial sampling of symptomatic and confirmed positive patients

Patients will be informed about the study by a health care worker at a non-ICU unit ("rampen unit") of the University Hospitals Leuven, Belgium.

In case a candidate is interested in participating and tested positive for SARS-nCoV-2 on his/her nasopharyngeal swab, he/she will be informed about the study goals by the same health care worker. The volunteer will receive an information letter and a copy of the informed consent to take home.

Study procedure

After signing the informed consent, each patient will be asked to fill in a questionnaire (*cfr. Addendum A*).

The simplicity of performing a conjunctival swab makes it possible **to implement in the daily routine** of health care workers**, avoiding additional waste of personal protective equipment**.

Conjunctival sampling will be performed on both eyes after the application of a drop of topical anesthesia (Minims® Oxybuprocaine Hydrochloride 0.4%, Bausch and Lomb, Aubenas, Frankrijk). A timed 5 minutes will be in between application of the drop and the sampling. The sampling will be performed by a trained nurse and/or medical student and/or resident after proper training of correct sampling (*cfr Addendum B*).

Each eye will be sampled with a single, sterile, nylon, flocked swab (FLOQSwabs®; Copan, Brescia, Italy). This FLOQSwabs® is a **different** swab than the one used for routine nasopharynx SARS-nCoV-2 testing.

The sampling will be done from the nasal to temporal inferior conjunctival sac, the swab will be swirled in the opposite direction of the sampling itself.

The swabs will be placed in a tube with universal transport medium (UTM) and transferred to a −80°C freezer until further processing.

The conjunctival swab will be tested for SARS-nCoV-2 presence by making use of in-house reverse transcription real-time polymerase chain reaction (RT-PCR) designed for routine diagnostics targeting specific SARS-nCoV-2 genes in the clinical laboratory of the University Hospitals Leuven or at the REGA institute (laboratory of Dirk Daelemans).

Serial sampling

Sampling will be repeated every 3 days to evaluate if PCR becomes positive during the course of disease and to monitor the duration of detectability of the virus in tears.

Part 2: Single sampling of pauci – symptomatic patients

Emergency patients, health care workers and patients hospitalized for a different condition/reason with a limited amount of symptoms (cfr. Inclusion criteria) that apply for a nasopharyngeal swab to confirm COVID-19 will be informed about the study by a pre-indicated health care worker.

When the patient is interested in participating he/she will be informed about the study goals by the same health care worker. The volunteer will receive an information letter and a copy of the informed consent to take home.

After signing the informed consent, each patient will be asked to fill in a questionnaire (*cfr. Addendum A*).

Study procedure

The conjunctival swabbing has been explained in detail in part 1.

3. Selection and withdrawal of subjects

3.1 Inclusion criteria

- Subject needs to be above 18 years old.
- The subject is willing to undergo sampling of the conjunctiva.
- The subject is willing to fill in a questionnaire.
- The subject is fluent in written and verbal Dutch.
- The subject is capable of giving informed consent.
- Applicable for part 1 only: the subject test positive for SARS-nCoV-2 on a nasopharyngeal swab. The time window between a positive nasopharyngeal swab and the first conjunctival swab may be no more than 3 days.
- Applicable for part 2 only: mild symptoms of COVID-19 including symptoms of upper or lower respiratory tract infection and/or any body temperature elevation (criteria Sciensano for testing healthcare workers (April 12 2020)) without the need for hospitalization.

3.2 Exclusion criteria

- Allergy to Oxybuprocainehydrochloride
- Pregnancy or lactation

3.3 Expected duration of trial

Inclusion is planned between the end of April till the end of April 2021.

4. Trial procedures

4.1 Summary of visits

Part 1: Serial sampling of symptomatic patients

Sampling will take place at the "rampen unit" of the University Hospitals Leuven, Belgium. Once the patient is admitted and tested positive for SARS-nCoV-2 on nasopharyngeal swab, conjunctival sampling will take place every three days until the day of discharge. The time window between a positive nasopharyngeal swab and the first conjunctival swab may be no more than 3 days.

Part 2: Single sampling of pauci-symptomatic patients

Sampling will take place at the emergency department of the University Hospitals Leuven, Belgium by the swab team. The sampling will not be repeated.

4.2 Supervision and responsibilities

The study will be performed under the supervision of dr. H. Delbeke. The subjects will be recruited at the equivalent of the former "rampen unit", the emergency department and via a flyer *(cfr. Addendum C)* at several outpatient clinics of the University Hospitals Leuven, Belgium and by making an announcement on the intranet webpage of the University Hospitals Leuven, Belgium. The sampling of the conjunctiva will be performed by a trained nurse and/ or medical student and/or resident (*cfr. Addendum B*). Volunteers will receive information about the study. Sampling will only occur upon written informed consent of the participants. The participating investigators will perform their part of the study fully in accordance with the terms of the Protocol, the applicable national and international laws (amongst others: the European General Data Protection Regulation of May 25, 2018) and apply and adhere to regulations and rules as, amongst others, the Declaration of Helsinki (2008) and ICH GCP Guidelines. Prof. M. Joossens is assigned as a free of charge consulting sub-investigator without the power to recruit patients.

Insurance

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, UZ/KU Leuven shall assume, even without fault, the responsibility of any damages incurred by a Study Patient from the UZ/KU Leuven site and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through their insurance (Amlin Corporate Insurance, polisnr. 299.053.700, Vanbreda Risk & Benefits, Plantin en Moretuslei 297, 2140 Antwerp).

Informed consent

The Participating Site acknowledges that the Study can and will be conducted only on the basis of prior informed consent by the Subjects 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 local Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

5. Assessment of efficacy

Not applicable.

6. Assessment of safety

Sampling with topical anesthesia can cause a transient stinging and blurring of the vision after instillation. When used in larger amounts, epitheliopathy of the cornea can be noticed. This is rare in the case of only one drop. Systemic absorption will be reduced by asking the patient to gently close the lids and to press on the medial canthus for a minute following the instillation of the drops. There are no known interactions with other medical products. It will not be used during pregnancy or lactation, nor will it be used in patients with a known hypersensitivity to the product.

After sampling the conjunctiva, there is a small possibility of a minor bleeding in the conjunctival sac which can induce a feeling of bruising of the tissue. Scarring due to the intervention is extremely rare (<0.01%).

6.1 Recording of adverse events

The risks associated with the study-specific intervention, i.e. the conjunctival sampling and the use of topical anesthesia are listed above *(6. Assessment of safety).*

The participant will be asked to report any adverse event related to the study-specific intervention to the study team. These reported events will be documented by the Investigator in the source documents.

The following minimum information should be recorded for each adverse reaction:

- Adverse event description

- Start and stop date of the adverse reaction

- Severity

- Seriousness
- Causality assessment to the study interventions
- Outcome

6.2 Reporting to the Ethics Committee

The sponsor will assess whether any relevant safety information that becomes available during the study should be reported ad hoc to the Ethics Committee of the University Hospitals Leuven, Belgium.

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the Ethics Committee of the University Hospitals Leuven, Belgium containing an overview of all serious adverse events that occurred during the reporting period and taking in to account all new available safety information received during the reporting period.

7. Statistics

7.1 Sample size

Although this is a pilot study, we have calculated our sample size based on the data on SARS-CoV-2 positive Belgian citizens (58 517 011, data from Sciensano, bulletin of the 1st of May 2020) with a confidence interval of 5 and a confidence level of 95%. This will be the largest investigated cohort so far.

7.2 Analysis

The statistical analyses will be performed using statistical software such as R-studio or SPSS. The Shapiro-Wilk test will be used for normality testing. Depending their distribution, continuous variables will be summarized as mean ± standard deviation or median with interquartile range. Categorical variables will be summarized in absolute numbers and percentages. All statistical test will be significant if the P-value ≤ 0.05.

Primary outcome measures

The presence or absence of the virus in the tears is the primary objective. A multivariate analysis will be used to interpret the questionnaire.

Secondary outcome measures

For secondary outcome measures, we first have to indicate the different disease stages. We define them as early, intermediate and late stadium, respectively indicated by onset disease symptoms (cough, fever, fatigue, myalgia and lesser reported symptoms such ass headache, diarrhea and abdominal pain, ageusia and anosmia, conjunctivitis), development of chest pains and dyspnea with need for hospitalization and eventually development of SARS and need for ICU administration (12). We also define a remission stage in which symptoms start to decline.

For investigation of the disease stage in which the SARS-nCoV-2 becomes detectable in the tears we aim to use an ANOVA analysis.

8. Quality assurance

To assure maximal quality and reproducibility, the trial protocol will be followed rigorously.

9. Direct access to source data and documents

Only data gathered in the context of the trial will be used.

10. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of Good Clinical Practice 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.

The Study will be conducted only on the basis of prior informed consent by the Subjects to participate in the Study. We 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 (local) Ethics Committee, if required. We shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

11. Data Handling

We shall treat all information and data 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, will comply with applicable personal data protection and the processing of personal data (the European General Data Protection Regulation of May 25, 2018). We will 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 will be stored separately from their research data and replaced with a unique code to create a new identity for the subject.

12. Data Management

The questionnaires will be collected by Websurveyserver KU Leuven and all data will be stored in on a secured database named Redcap, which is protected within the firewall of the University Hospitals Leuven, Belgium with a unique pseudonymised identifier for every subject. In the future, these data could also be used for related projects.

13. Publication Policy

Any publication will be submitted to all co-authors at least thirty (30) days prior to submission or disclosure.

14. Financial Aspects

No commercial conflict of interest is related to this study. There will be no financial compensation for the volunteers.

15. References

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16. Addenda

Addendum A: Questionnaire to be filled in by all subjects

BIJKOMSTIGE VRAGENLIJST EYE-COVID STUDIE

Deelnemerscode:	
Geboortedatum: DD/MM/JJJJ	
Geslacht: Man/Vrouw	
1ste dag ontstaan symptomen: DD/MM/JJJJ	

Geef aan of u volgende symptomen al dan niet ervaren heeft. Indien u 'Ja' antwoordde op het ervaren van symptomen, gelieve dan in de uiterst rechtse kolom de datum aan te geven waarop u deze symptomen voor het eerst heeft opgemerkt.

Vraag	**Aanwezigheid symptomen?**		**Datum ontstaan symptomen (DD/MM/JJJJ)**
Hebt u een verandering in de waarneming van **geuren** opgemerkt de afgelopen dagen?	Ja	Nee	...../...../.....
Hebt u een verandering in **smaak** waargenomen de afgelopen dagen?	Ja	Nee	...../...../.....
Hebt u de afgelopen dagen **roodheid** aan één of beide ogen opgemerkt?	Ja	Nee	...../...../.....
Hebt u **irritatie/pijn** aan een of beide ogen ervaren in de voorgaande dagen?	Ja	Nee	...../...../.....
Hebt u de laatste dagen **meer** last gehad van **tranende ogen**?	Ja	Nee	...../...../.....
Hebt u **etterige secreties thv de ogen** gehad de voorgaande dagen?	Ja	Nee	...../...../.....
Hebt u de afgelopen dagen **neusloop** ervaren?	Ja	Nee	...../...../.....
Hebt u de afgelopen dagen een **verstopte neus** ervaren?	Ja	Nee	...../...../.....
Moest u sinds kort meer en/ of heviger **hoesten**?	Ja	Nee	...../...../.....
Bent u de afgelopen dagen **kort van adem** geweest?	Ja	Nee	...../...../.....
Hebt u **pijn op de borst** ervaren de voorgaande dagen?	Ja	Nee	...../...../.....

Hebt u de afgelopen dagen **koorts** gemeten (een temperatuur boven de 38,5°)?	Ja	Nee	….../…../……
Hebt u de afgelopen dagen **spierpijnen** ervaren?	Ja	Nee	….../…../……
Hebt u de afgelopen dagen **hoofdpijn** ervaren?	Ja	Nee	….../…../……
Hebt u de afgelopen dagen last gehad van **diarree**?	Ja	Nee	….../…../……
Hebt u de afgelopen dagen last gehad van **buikpijnklachten**?	Ja	Nee	….../…../……

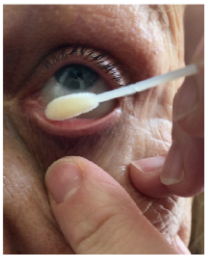
Addendum B: Explanation of the sampling

1. Bij het afnemen van het staal draai je de borstel in de tegengestelde richting van de beweging. Voor het linker oog is dat tegenwijzerzin, voor het rechter oog is dat wijzerzin (<u>geheugensteuntje:</u> wrijven weg van de neus, draaien naar de neus)
2. Plaats de borstel in het universeel transport medium (UTM)
3. Plaats het UTM met staal in de koelkast op -18°C
4. Binnen de 24 u moet het UTM met staal verplaatst worden naar -80°C

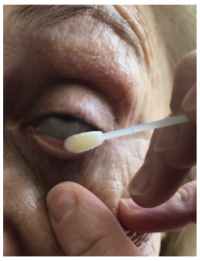
De steriele wisser openen aan de kant van de steel, dus weg van de borstel (vermijd direct contact met de borstel!).

De steriele wisser vasthouden aan de steel, zo ver mogelijk van de borstel om bijbesmetting van de handen te vermijden.

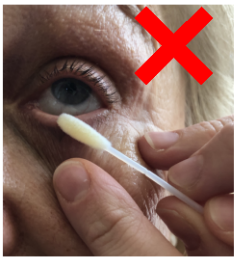
De steriele wisser vasthouden aan de steel, zo ver mogelijk van de borstel om bijbesmetting van de handen te vermijden.



Naar boven kijken en met de wijsvinger het onderooglid naar beneden trekken.
De borstel mag enkel de binnenkant van het ooglid aanraken, niet de buitenkant.



De borstel zacht glijden aan binnenkant ooglid van de neuskant naar de oorkant. Draai de borstel in de tegengestelde richting, cf punt 4.



De borstel mag enkel de binnenkant van het ooglid aanraken, niet de buitenkant. Houd bovendien ook afstand van de borstel.

Heleen Delbeke©

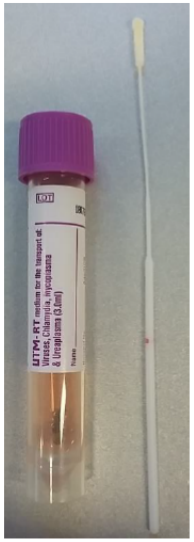
Na staalname de borstel onmiddellijk overbrengen naar de houder. Probeer aanraking met de borstel te allen tijde te vermijden!

Enkele cm's boven het borsteltje is er een rode verkleuring. Door deze op de rand van de houder te leggen, kan de borstel losgekraakt worden van de steel. de

Sluit onmiddellijk de houder en bewaar deze in de diepvries bij -20°C gedurende maximaal 2 dagen, nadien te bewaren op -80°C.

AFN-006E BLG-2
Versie 200227

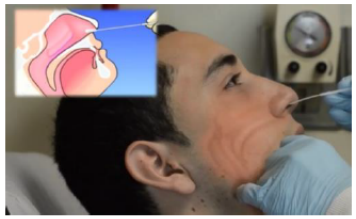
Nasofaryngeale afname procedure



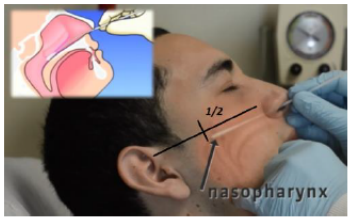
(Relatieve) contra-indicaties:
- Ziekte van Rendu-Osler-Weber
- Ernstige thrombopenie (< 15. 10^9/L)
- Recente neus cauterisatie en/of chirurgie

Consulteer de behandelende arts bij twijfel

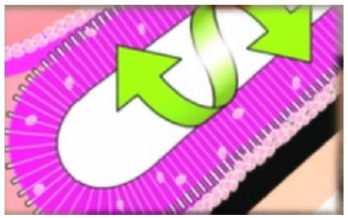
STOP tijdens de procedure en probeer via ander neusgat indien: weerstand bij het inbrengen van de Swab of pijn bij de patiënt



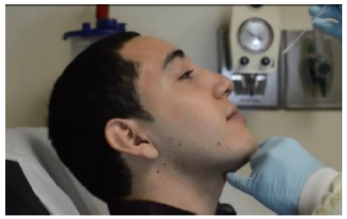
1 Buig het **hoofd lichtjes naar achteren** en breng de Swab in. Druk de Swab lichtjes tegen het onderste gedeelte van de neus aan.



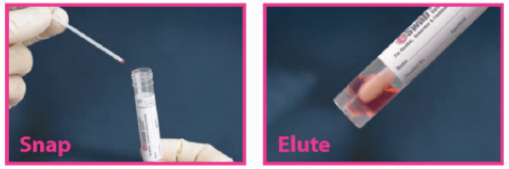
2 Breng de Swab tot in de nasofarynx. Dit is **ongeveer de helft van de lengte van de neus tot het oor.**



3 **Draai de Swab minimaal 3 maal rond** om voldoende materiaal op te nemen



4 **Verwijder** de Swab uit de neusholte.



5 **Breek de Swab** af in de bijhorende tube ter hoogte van de rode lijn. Sluit de tube en breng de **patiëntgegevens** aan op de tube.

Addendum C: Poster/flyer for the recruitment