Interventional study with investigational medical device (IMD)

Clinical Investigation Plan

Comparison of 3D Endoscopy with 2D Endoscopy during functional endoscopic sinus surgery

Design: International multicenter prospective randomized interventional study, "Endoscopic 3D study"

Study Type:	Prospective randomized interventional study comparing the 2D endoscopic camera technique with the novel 3D endoscopic camera technique
Study Categorization:	Clinical Trial with IMD Category A
Study Registration:	Comparison of 3D Endoscopy with 2D Endoscopy during functional endoscopic sinus surgery (ID 2018-00005)
Study Identifier:	
Sponsor, Sponsor-Investigator and Principal Investigator:	KD Dr. med. Hans Rudolf Briner ORL-Zentrum Klinik Hirslanden Witellikerstrasse 40 CH-8032 Zürich Tel: +41 44 387 28 00 E-mail: briner@orl-Zentrum.com
Investigational Product:	TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH
Investigation plan Version and Date:	Plan Version 2, 21.1.2018

SIGNATURE PAGE

Study number	**(ID 2018-00005)**
Study Title	**Comparison of 3D Endoscopy with 2D Endoscopy during Functional Endoscopic Sinus Surgery**

Sponsor-Investigator (Principal Investigator):

The Sponsor-Investigator and trial statistician have approved the investigation plan version 2 (21.1.2018) and confirm hereby to conduct the study according to the investigation plan, current version of the World Medical Association Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

Hans Rudolf Briner

Zurich, ~~24.1~~4.3.2018

Place/Date | Signature

Trial Statistican:

Not yet designed. Statistical analysis is planned to be conducted by the coordinating project investigator in Ulm, PD Dr. F. Sommer

\- | \-

Place/Date | Signature

Local Principal Investigator at study site:

I have read and understood this investigation plan and agree to conduct the trial as set out in this investigation plan, the current version of the World Medical Association Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

Project leader (lead center/site)

ORL-Zentrum Klinik Hirslanden

Name: KD Dr. med. Hans Rudolf Briner

Date: 4.3~~24.1~~.2018 _____ Signature: _____

Local Project Leader at local center/site (coordinating investigator):

HNO-Klinik der Universität Ulm

Name of Local Project Leader: Priv.-Doz. Dr. med. Fabian Sommer

Date: _____ Signature: _____

Local Project Leader at local center/site:

Rhinologie Zentrum Gärtnerklinik München

Name of Local Project Leader: Professor Andreas Leunig

Date: _____ Signature: _____

Local Project Leader at local center/site:

HNO-Klinik der Universität Graz

Name of Local Project Leader: Prof. Dr. med. Valentin Tomazic

Date: _____ Signature: _____

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Hans Rudolf Briner, MD, Klinischer Dozent
Study Title:	Comparison of 3D Endoscopy with 2D Endoscopy during Functional Endoscopic Sinus Surgery
Short Title / Study ID:	"Endoscopic 3D study", (ID 2018-00005)
Investigation Plan Version and Date:	Plan version 2, 21.1.2018.
Trial registration:	Registry applied at swissethics (21.1.2018)
Study category and Rationale	Clinical study with IMD Category A.
Background and Rationale:	Chronic rhinosinusitis is a common disease with a prevalence of 3-5% and may lead to a significant impairment of the quality of life in individuals suffering from the disorder. Medical therapy is the treatment of choice to reduce the symptoms. In severe disease, however, medical therapy may not be sufficient to control the disease activity and symptoms. In these cases, surgical therapy is indicated. The principle of surgical therapy is to open the narrow and blocked drainage pathways of the paranasal sinuses and therefore to restore mucociliary clearance and widening the access for topical medical treatment of the diseased mucosa in the paranasal sinuses. This procedure is known as "Functional Endoscopic Sinus Surgery" (FESS) and it is generally accepted and recommended by all mayor international guidelines as procedure of choice in chronic rhinosinusitis not responding sufficiently to medical treatment. Modern technology helps reduce the potential risks of FESS such as injury of the orbit, the optic nerve, the carotid artery, the skull base and the brain which are neighbouring the paranasal sinuses. A key component of this endoscopic surgery of the paranasal sinuses is the endoscope and camera which enables a good visualisation of the surgical field. The actual standard technique of endoscopic visualisation is using endoscopes combined with a high resolution (HD or 4k) camera, providing a 2-dimensional (2D) picture on a high resolution (HD or 4k) screen. A new development is recently commercially available providing a 3-dimensional picture, which gives additional information of "depth" in the surgical field. This "3D" - technology consists of special endoscopes combined with a 3D camera and a 3D-screen and the surgeon wears glasses to enable the 3D visualisation. The visualisation of a 3-dimensional surgical field has the theoretical advantage to provide the surgeon with more realistic information about the anatomy of the surgical field which may be a beneficial for surgical control and even reducing complications. Since the 3D-endoscopic technique is new, little scientific evidence is known, whether the new technique provides advantages compared to the 2D-endoscopic standard technique in FESS. The actual project compares the standard 2D-endoscopic surgical technique with the new commercially available 3D-endoscopic technique.

Objective(s):	The primary hypothesis is that both endoscopic techniques (2D and 3D) are identical regarding quality of visualization and therefore the average time for the procedure is the same with 2D- and 3D endoscopic technique. The secondary hypothesis is that the subjective rating of the technique by the performing surgeon is the same for both techniques
Outcome(s):	The primary endpoint is the average time for the procedure with the 2D endoscopic technique and the 3D endoscopic technique. Since one side of an individual patient is performed with 2D, the other with 3D on a randomized way, the bias of measuring the operation time in different patients which variable anatomy and amount of inflammatory disease is minimized. The size of the study including a total of 80 patients minimizes age and gender bias and the multicenter design with 4 surgeons minimizes the bias by an individual surgeon. The secondary endpoint is the subjective rating of the 2D- and 3D-technique by the surgeons using a standardized questionnaire which may give a description of clinically relevant experience.
Study design:	The study is designed as prospective randomized interventional study in an international multicentre setting. A total of 80 patients with chronic rhinosinusitis will be evaluated. A FESS procedure is performed, one side with the 2D-endoscopic technique, the other side with the 3D-endioscopic technique, the choice which side with which technique is randomized. There are four individual rhinosurgeons at four centers operating and evaluating 20 patients each. The centers are Graz (Prof. V. Tomazic), Austria, Munich (Prof. A. Leunig), Germany, Ulm (PD Dr. F. Sommer), Germany and Zurich (KD Dr. H.R. Briner), Switzerland.
Inclusion / Exclusion criteria:	Twenty patients with chronic rhinosinusitis which are candidates for endoscopic sinus surgery will be enrolled by each of the four study centers, resulting in a total of eighty patients. Exclusion criteria are age below 18 years, previous sinus operations, unilateral or asymmetric disease, severe comorbidities such as bleeding disorders and inability or unwillingness to give consent for the study.
Measurements and procedures:	During the FESS procedure on an individual patient, the time for the 2D- and 3D procedure is measured and at the end of the procedure the surgeon's questionnaire is completed. No further actions such as control visits or additional evaluations are needed after this evaluation.
Study Product / Intervention:	One side of the endoscopic surgery is performed with the standard 2D endoscopic camera whereas the other side is operated with the new 3D endoscopic camera devices (TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH)
Control Intervention (if applicable):	The use of the 3D camera is compared with the other side operated with the standard 2D camera in the same patient,
Number of Participants with Rationale:	Each of the four study centers enrolls 20 patients, resulting in a total number of 80 patients
Study Duration:	The estimation of the overall project duration is 6 months.
Study Schedule:	First patient planned January 2018. Last patient planned June 2018

Investigator(s):	Project Leader Zurich: KD Dr. med. Hans Rudolf Briner ORL-Zentrum Klinik Hirslanden Witellikerstrasse 40 CH-8032 Zürich Tel: +41 44 387 28 00 E-mail: briner@orl-Zentrum.com Project Leader HNO-Klinik der Universität Ulm: Priv.-Doz. Dr. med. Fabian Sommer HNO-Universitätsklinik Ulm Frauensteige 12 89075 Ulm, Germany Tel: +44 731 / 500 59526 Project Leader Rhinologie Zentrum Gärtnerklinik München: Prof. Dr. med. A. Leunig, HNO-Klinik München Bogenhausen Dr. Gaertner GmbH Possartstrasse 27-31 8169 München, Deutschland Tel: +44 89 9989 0220 Project Leader HNO-Klinik der Universität Graz: Prof. Dr. med. Valentin Tomazic, HNO-Universitätsklinik Graz Auenbruggerplatz 1 8036 Graz, Austria Tel: +43 31638581347
Study Centre(s):	International multicenter study with four centers: Klinik Hirslanden, Zurich, Switzerland Rhinologie Zentrum Gärtnerklinik Munich, Germany HNO-Klinik der Universität Ulm, Germany HNO-Klinik der Universität Graz, Austria
Statistical Considerations:	The zero hypothesis for the primary endpoint is that the time for the 2D and 3D procedure is equal. A paired t-test with a significance level of $\alpha = 0.05$ should be suitable to analyze the hypothesis within the planned number of 80 patients. Furthermore, descriptive analysis is planned for the subjective judgement of the surgeons.
Statement:	This study will be conducted in compliance with the investigation plan, the current version of the Declaration of Helsinki, the ISO 14155 as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
ClinO	Clinical Trials Ordinance
CRF	Case Report Form
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
H0	Null hypothesis
H1	Alternative hypothesis
IMD	Investigational Medical Device
ISF	Investigator Site File
ITT	Intention to Treat
LHR	Law on human research
PI	Principal Investigator
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trial Portal
SOP	Standard Operating Procedure
TMF	Trial Master File

STUDY SCHEDULE

The study schedule is simple and straight forward:

1) Information of the patient during clinical evaluation for functional endoscopic sinus surgery and enrollment to the study after signing of the informed consent.
2) Measuring the time of the procedure, one side with the conventional 2D camera, the other side with the new 3 D camera.
3) Evaluation of the surgeon's subjective experience with the two cameras via questionnaire immediately after the procedure
4) No further procedures or control visits are needed. Evaluation of the data.

1 STUDY ADMINISTRATIVE STRUCTURE

The study is planned and conducted by four rhinosurgeons at different organizations in Austria, Germany and Switzerland. The four rhinosurgeons are the official "sponsors" of the study at their local organization, there is no other external sponsor involved.

The four rhinosurgeons and organizations where the study is conducted are:

Project Leader Zurich:
KD Dr. med. Hans Rudolf Briner
ORL-Zentrum Klinik Hirslanden
Witellikerstrasse 40
CH-8032 Zürich
Tel: +41 44 387 28 00
E-mail: briner@orl-Zentrum.com

Project Leader HNO-Klinik der Universität Ulm:
Priv.-Doz. Dr. med. Fabian Sommer
HNO-Universitätsklinik Ulm
Frauensteige 12
89075 Ulm, Germany
Tel: +44 731 / 500 59526

Project Leader Rhinologie Zentrum Gärtnerklinik München:
Prof. Dr. med. A. Leunig,
HNO-Klinik München Bogenhausen
Dr. Gaertner GmbH
Possartstrasse 27-31
8169 München, Deutschland
Tel: +44 89 9989 0220

Project Leader HNO-Klinik der Universität Graz:
Prof. Dr. med. Valentin Tomazic,
HNO-Universitätsklinik Graz
Auenbruggerplatz 1

8036 Graz, Austria
Tel: +43 31638581347

The study is designed as international multicenter randomized interventional study. The involved rhinosurgeons are responsible for the conduction of the study at their local organization respecting all the local regulations and ethic committees.
The main coordination of the study will be performed by Priv.-Doz. Dr. med. Fabian Sommer, HNO-Universitätsklinik Ulm, in strong collaboration with Prof. Dr. med. Valentin Tomazic, HNO-Universitätsklinik Graz

1.1 Sponsor, Sponsor-Investigator

As mentioned above, the sponsors are the four rhinosurgeons listed above, they are also the local investigators

1.2 Principal Investigator(s)

The principal investigator is:
Priv.-Doz. Dr. med. Fabian Sommer
HNO-Universitätsklinik Ulm
Frauensteige 12
89075 Ulm, Germany
Tel: +44 731 / 500 59526

1.3 Coordinating Investigator

The principal investigator, Priv.-Doz. Dr. med. Fabian Sommer, is also the coordinating investigator

1.4 Statistician (“Biostatistician”)

The biostatistician will be designed by the principal and coordinating investigator, Priv.-Doz. Dr. med. Fabian Sommer. Due to the simple study design, the statistic evaluation is not complex and does not require extensive biostatistical involvement.

1.5 Laboratory (if applicable)

There is no laboratory involved in this study.

1.6 Monitoring Institution

Due to the simple design of the study, there is no monitoring institution involved.

1.7 Any other relevant Committee, Person, Organization, Institution

Not applicable.

2 ETHICAL AND REGULATORY ASPECTS

Before this study will be conducted, the investigation plan, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) in agreement with local legal requirements, for formal approval. Any amendment to the investigation plan must as well be approved.

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study Registration

The study will be registered in the Swiss Federal Complementary Database („Portal“) and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov).

2.2 Categorization of Study

The study is categorized as **Category A** according to ClinO Art. 20.

2.3 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for each study site in the clinical trial. The reporting duties and allowed time frame are respected. No substantial changes are made to the investigation plan without prior Sponsor, CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent authority (CA)

No approval from Swissmedic is necessary for this category A clinical trial.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority’s requirements. CEC will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.5.1 Compliance with the EN ISO 14155 standard

For clinical trials involving a particularly low risk, certain deviations are possible, particularly for post-market trials. However, the protection of the participants and data quality and security may not be affected by such deviations. All deviations must be disclosed in the clinical investigation plan (CIP) of the clinical trial. A separate, dedicated section in the CIP is recommended for deviations (e.g. "Compliance with the ISO 14155 standard"). The deviation must be described and the absence of effects of the deviation on the protection of the participants and data quality and security must be justified.

2.6 Declaration of Interest

There is no conflict of interest of the singing project leaders which interferes with this study

2.7 Patient Information and Informed Consent

The investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for this study will be provided a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study.

The participant information sheet and the consent form will be submitted with the investigation plan for review and approval for the study by the CEC. The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant Privacy and Confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant’s personal physician or to other appropriate medical personnel responsible for the participant’s welfare, if the patient has given his/her written consent to do so.

For data verification purposes, authorized representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants’ medical history.

2.9 Early Termination of the Study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.:

- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- early evidence of benefit or harm of the intervention
- ethical concerns,

2.10 Investigation Plan Amendments

Substantial amendments (significant changes) are only implemented after approval of the CEC and CA respectively.

Significant changes to be authorised by the CEC are the following:

- changes affecting the participants' safety and health, or their rights and obligations;
- changes to the protocol, and in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis;
- a change of trial site, or conducting the clinical trial at an additional site; or
- a change of sponsor, coordinating investigator or investigator responsible at a trial site.

Under emergency circumstances, deviations from the investigation plan to protect the rights, safety and well-being of human participants may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible. All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3 INTRODUCTION

Chronic rhinosinusitis is a common condition with a prevalence of 3-5%. Therapy of choice is topical or systemic medication and if medication is not sufficient to control the symptoms, functional endoscopic sinus surgery is recommended. Goal of the surgical procedure is the opening of the narrow and blocked drainage of the diseased sinuses to restore ventilation and drainage and to give better access for topical treatment. Endoscopic sinus surgery is performed with an endoscope in conjunction with a camera to allow a good visualization. The actual cameras are providing a "2D" picture on a screen. The latest technological developments are "3D" cameras which allow a "3D" visualization on special "3D" screens. This "3D" visualization may provide the surgeon with a more "realistic" image of the surgical site and may therefore have the potential to improve the safety of the surgical procedure. Since this "3D" cameras are new, few data are available about possible advantages of this new technology. The actual project is designed to compare the conventional "2D" endoscopic technique with the new "3D" endoscopic technique in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis

3.1 Background and Rationale

Chronic rhinosinusitis is a common disease with a prevalence of 3-5% and may lead to a significant impairment of the quality of life in individuals suffering from the disorder. The disease defining leading symptoms are a blocked nose, hyposmia, rhinorrhea and facial pressure or cough in children. Medical therapy is the treatment of choice to reduce the symptoms. In severe disease, however, medical therapy may not be sufficient to control the disease activity and symptoms. In these cases, surgical therapy is indicated. The principle of surgical therapy is to open the narrow and blocked drainage pathways of the paranasal sinuses and therefore to restore mucociliary

clearance and widening the access for topical medical treatment of the diseased mucosa in the paranasal sinuses. This procedure is known as “Functional Endoscopic Sinus Surgery” (FESS) and it is generally accepted and recommended by all mayor international guidelines as procedure of choice in chronic rhinosinusitis not responding sufficiently to medical treatment. Modern technology helps reduce the potential risks of FESS such as injury of the orbit, the optic nerve, the carotid artery, the skull base and the brain which are neighbouring the paranasal sinuses. A key component of this endoscopic surgery of the paranasal sinuses is the endoscope and camera which enables a good visualisation of the surgical field. The actual standard technique of endoscopic visualisation is using endoscopes combined with a high resolution (HD or 4k) camera, providing a 2-dimensional (2D) picture on a high resolution (HD or 4k) screen. A new development is recently commercially available providing a 3-dimensional picture, which gives additional information of “depth” in the surgical field. This “3D” - technology consists of special endoscopes combined with a 3D camera and a 3D-screen and the surgeon wears glasses to enable the 3D visualisation. The visualisation of a 3-dimensional surgical field has the theoretical advantage to provide the surgeon with more realistic information about the anatomy of the surgical field which may be a beneficial for surgical control and even reducing complications.

Since the 3D-endoscopic technique is new, little scientific evidence is known whether the new technique provides advantages compared to the 2D-endoscopic standard technique in FESS. The actual project compares the standard 2D-endoscopic surgical technique with the new commercially available 3D-endoscopic technique. The study is designed as prospective randomized interventional study in an international multicentre setting.

3.2 Investigational Medical Device and Indication

One side of the endoscopic surgery is performed with the standard 2D endoscopic camera whereas the other side is operated with the new 3D endoscopic camera devices (TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH). CE Certification of these devices is available and is provided to the Ethics Committee separately.

3.3 Preclinical Evidence

Not applicable.

3.4 Clinical Evidence to Date

Since the 3D-endoscopic technique is new, little scientific evidence is known whether the new technique provides advantages compared to the 2D-endoscopic standard technique in FESS. So far, there are two published papers looking at this question (Albrecht et al, 2016 (1), Rampinelli et al 2017(2)). Both papers conclude that the 3D-technique may be beneficial, however, Albrecht et al. does not provide an intraindividual randomisation and Rampinelli et al. compared the techniques on a model and not in real life surgery, which lowers the value of their conclusion.

3.5 Explanation for Choice of Comparator

The conventional “2D” cameras are the standard technique used for endoscopic sinus procedures. Therefore, the new “3D” camera technique should be compared with the standard technique.

3.6 Risk / Benefits

The study design provides no additional risks for the participating patients compared with the risks of a normal surgical treatment under non-study conditions. The conventional “2D” camera as well as the new “3D” camera technique are already commercially available and used in clinical routine.

The study may provide information on the new 3D-endoscopic technology which may be useful for the surgical treatment of future patients.

3.7 Justification of Choice of Study Population

Patients with chronic rhinosinusitis with an indication for endoscopic sinus surgery which are otherwise healthy and are giving informed consent are enrolled to this study. These patients may benefit from the findings provided by this study.

There is no need to enroll vulnerable patients to achieve the goal of the study.

4 STUDY OBJECTIVES

The purpose of this study is to evaluate if there are objective or subjective differences between the conventional “2D” camera technique and the new “3D” camera technique for endoscopic sinus surgery in patients with chronic rhinosinusitis

4.1 Primary Objective

The primary hypothesis is that both endoscopic techniques (2D and 3D) are identical regarding quality of visualization and therefore the average time for the procedure is the same with 2D- and 3D endoscopic technique.

4.2 Secondary Objectives

The secondary hypothesis is that the subjective rating of the technique by the performing surgeon is the same for both techniques

4.3 Safety Objectives

Not applicable for this study.

5 STUDY OUTCOMES

The primary endpoint is the average time for the procedure with the 2D endoscopic technique and the 3D endoscopic technique. This is the best possible measurable parameter to compare the two technologies.

The secondary endpoint is the subjective rating of the 2D- and 3D-technique by the surgeons using a standardized questionnaire which may give a description of clinically relevant experience. This allows an experience based overall subjective judgement of the comparison of the two technologies

5.1 Primary Outcome

The primary endpoint is the average time for the procedure with the 2D endoscopic technique and the 3D endoscopic technique. Since one side of an individual patient is performed with 2D and the other with 3D on a randomized way, the bias of measuring the operation time in different patients which variable anatomy and amount of inflammatory disease is minimized. The size of the study including a total of 80 patients minimizes age and gender bias and the multicenter design with 4 surgeons minimizes the bias by an individual surgeon.

5.2 Secondary Outcomes

The secondary endpoint is the subjective rating of the 2D- and 3D-technique by the surgeons using a standardized questionnaire which may give a description of clinically relevant experience.

5.3 Safety Outcomes

Not applicable for this study.

6 STUDY DESIGN AND COURSE OF STUDY

6.1 General Study Design and Justification of the Design

The study is designed as prospective randomized interventional study in an international multicenter setting.

A total of 80 patients with chronic rhinosinusitis will be evaluated. A FESS procedure is performed, one side with the 2D-endoscopic technique, the other side with the 3D-endoscopic technique. The choice which side with which technique is randomized. The time of the procedure using the 2D-endoscope and the 3D-endoscope is measured and at the end of the procedure a standardized questionnaire is completed by the surgeon judging the subjective impression. No further interventions or controls are needed.

There are four individual rhinosurgeons at four centers operating and evaluating 20 patients each. The centers are Graz (Prof. V. Tomazic), Austria, Munich (Prof. A. Leunig), Germany, Ulm (PD Dr. F. Sommer), Germany and Zurich (KD Dr. H.R. Briner), Switzerland.

The estimation of the overall project duration is 6 months.

6.2 Study Duration and Study Schedule

The estimation of the overall project duration is 6 months. Begin is planned in february and the end in july 2018. Data analysis and publication are planned to be completed by end of 2018.

6.3 Methods of Minimizing Bias

Since one side of an individual patient is performed with 2D and the other with 3D on a randomized way, the bias of measuring the operation time in different patients which variable anatomy and amount of inflammatory disease is minimized. The size of the study including a total of 80 patients minimizes age and gender bias and the multicenter design with 4 surgeons minimizes the bias by an individual surgeon.

6.3.1 Randomization

One side of the patient is operated with the 2D-endocope, the other side with the 3D-endocope. In the first of the 20 patients, the side which is operated by the 2D-endoscope is determined by hazard (Los). In the further patients, the side is alternated after each patient.

6.3.2 Blinding Procedures

There is no blinding used in this study.

6.3.3 Other Methods of Minimizing Bias

The subjective experience is judged by a standardized questionnaire by the surgeon at the end of the procedure.

6.4 Unblinding Procedures (Code break)

Since there is no blinding used in this study, there is no need for unblinding procedures

7 STUDY POPULATION

Twenty patients with chronic rhinosinusitis which are candidates for functional endoscopic sinus surgery and which are signing an informed consent after being informed about the objectives and design of the study will be enrolled by each of the four study centers, resulting in a total of eighty patients.

7.1 Eligibility Criteria

7.1.1 Inclusion Criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Candidates suffering from chronic rhinosinusitis not responding sufficiently to medical treatment and therefore candidates for endoscopic sinus surgery (FESS)
- Informed Consent as documented by signature (Informed Consent Form (Appendix 1))
- Male and Female patients with 18 years or older

7.1.2 Exclusion Criteria

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

Exclusion criteria:

- Patients with contraindications for elective surgical procedures
- Age below 18 years
- Previous sinus operations
- Unilateral or asymmetric disease
- Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.),
- Known or suspected non-compliance, drug or alcohol abuse,
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
- Participation in another study with investigational drug/device within the 30 days preceding and during the present study,
- Previous enrolment into the current study,
- Enrolment of the investigator, his/her family members, employees and other dependent persons,

7.2 Recruitment and Screening

The recruitment of the patients will be performed by the project leader of the individual center during daily clinical practice. The study will be explained by the project leader. After this information, the patients will be provided a time of at least 24 hours for adequate consideration. and If a patient decides to participate, the informed consent form has to be signed by the patient and the project leader.

There will be no compensation or payments for the participants.

7.3 Assignment to Study Groups

Not applicable for this study

7.4 Criteria for Withdrawal/ Discontinuation of Participants

Due to the study design of the evaluation of only one defined procedure, there is no significant rate of withdrawal or discontinuation to expect. However, if there is any unexpected safety issue occurring or a withdrawal of the consent, the study is discontinued. If there are no general safety concerns, new candidates are enrolled to reach the goal of 20 participants per study location.

8 STUDY INTERVENTION

8.1 Identity of Investigational Medical Device

The FESS procedure on an individual patient enrolled in the study is performed on one side with the standard 2D endoscopic camera whereas the other side is operated with the new 3D

endoscopic camera devices (TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH).

8.1.1 Experimental Intervention

As mentioned above, one side of the operation is performed with the 3D endoscopic camera devices (TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH).

8.1.2 Control Intervention

As mentioned above, the other side of the operation is performed with the standard 2D endoscopic camera (Image 1, Karl Storz GmbH).

8.1.3 Packaging, Labelling and Supply (Re-Supply)

Not applicable since the 2D camera as well as the 3D camera device are already routinely implemented in the operating theatre.

8.1.4 Storage Conditions

There are no separate study specific storage conditions needed since the devices are already implemented in the operating theatre

8.2 Administration of Experimental and Control Interventions

8.2.1 Experimental Intervention

The FESS procedure on an individual patient enrolled in the study is performed on one side with the standard 2D endoscopic camera whereas the other side is operated with the new 3D endoscopic camera devices (TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH).

8.2.2 Control Intervention

See above, the side which is operated with the 2D-endoscope is used as control intervention.

8.3 Modifications of Device Application

If there is a failure with the 3D-camera, for example a technical dysfunction, the study is discontinued.

8.4 Compliance with Study Intervention

Not applicable for this study.

8.5 Data Collection and Follow-up for Withdrawn Participants

~~Not applicable for this study~~Data from withdrawn participants will be analyzed and included in the study and finally coded like the data of the other participants.

8.6 Trial Specific Preventive Measures

Not applicable for this study.

8.7 Concomitant Intervention(s)

If there is an unexpected failure using the new 3D-camera, the operation is continued with the conventional 2D camera. This event would lead to discontinuation of the study and would be recorded in the CRF.

8.8 Medical Device Accountability

Not applicable for this study.

8.9 Return or Destruction of Medical Device

Not applicable for this study.

9 STUDY ASSESSMENTS

A FESS procedure is performed, one side with the 2D-endoscopic technique, the other side with the 3D-endoscopic technique. The choice which side with which technique is randomized. The time of the procedure using the 2D-endoscope and the 3D-endoscope is measured and at the end of the procedure a standardized questionnaire is completed by the surgeon judging the subjective impression. No further interventions or controls are needed.

9.1 Study Flow Chart(s)/Table of Study Procedures and Assessments

The study schedule is simple and straight forward:

1) Information of the patient during clinical evaluation for functional endoscopic sinus surgery and enrollment to the study after signing of the informed consent.
2) Measuring the time of the procedure, one side with the conventional 2D camera, the other side with the new 3 D camera (first endpoint).

3) Evaluation of the surgeon's subjective experience with the two cameras via questionnaire immediately after the procedure (second endpoint)
4) No further procedures or control visits are needed. Evaluation of the data.

9.2 Assessments of Outcomes

Assessment of the first endpoint consists in measuring the time of the procedure, one side with the conventional 2D camera, the other side with the new 3D camera.
Assessment of the second endpoint consists in evaluation of the surgeon's subjective experience with the two cameras via questionnaire immediately after the procedure

9.2.1 Assessment of Primary Outcome

Assessment of the primary outcome consists in measuring the time of the procedure, one side with the conventional 2D camera, the other side with the new 3 D camera.

9.2.2 Assessment of Secondary Outcomes

Assessment of the second outcome consists in evaluation of the surgeon's subjective experience with the two cameras via questionnaire immediately after the procedure

9.2.3 Assessment of Other Outcomes of Interest

Not applicable for this study.

9.2.4 Assessment of Safety Outcomes

9.2.4.1 Adverse Events

If there occurs an adverse event with the 3D camera, for example a technical failure, the procedure would be completed with the conventional 2D technique if appropriate. The time of onset and the nature of the adverse event as well as specific circumstances are recorded in the CRF.

9.2.4.2 Laboratory Parameters

Not applicable for this study.

9.2.4.3 Vital Signs

9.2.5 Assessments in Participants Who Prematurely Stop the Study

Not applicable for this study

9.3 Procedures at Each Visit

Not applicable for this study

10 SAFETY

The Sponsor's SOPs provide more detail on safety reporting.

During the entire duration of the study, all adverse events (AEs), serious adverse events (SAEs) and incidents are to be collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompasses the time from when the participant signs the informed consent until the last investigation plan-specific procedure has been completed.

If there is a safety relevant event, such as an unexpected failure using the new 3D-camera, the operation is continued with the conventional 2D camera. This event would lead to discontinuation of the study and would be recorded in the CRF and reported to the CEC and CA.

10.1 Definition of (Serious) Adverse Events and Other Safety Related Events

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].

Device deficiency
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Serious adverse device effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event ISO 14155: 3.36].

Serious Adverse Event (SAE)
Adverse event that:

- results in death, or
- led to a serious deterioration in health that either:
  - results in a life-threatening illness or injury, or
  - results in a permanent impairment of a body structure or a body function, or
  - required in-patient or prolonged hospitalization, or
  - results in medical or surgical intervention to prevent life threatening illness, or
- led to fetal distress, death or a congenital abnormality or birth defect. [ISO 14155: 3.37].

Incident
Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Health hazards that require measures
Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants.

10.2 Recording of Serious Adverse Events and Other Safety Related Events

The investigator is responsible for reporting all SAEs occurring during the course of the study.

All observed or volunteered SAEs or serious adverse device effects, regardless of treatment group or suspected causal relationship to the investigational device or study related procedure will be recorded in the patient file and subsequently in the CRF. For each SAE, the investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the investigational device or study related procedure.

SAEs or abnormal test findings felt to be associated with the investigational device or study procedures will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

10.3 Assessment of Serious Adverse Events and Other Safety Related Events

An unanticipated serious adverse device effect is any serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified, in the current version of the risk analysis report of the medical device.

The investigator will promptly review documented SAEs,
- if there is a reasonable possibility that the SAE was caused by the investigational device or study related procedures, and
- if the SAE qualifies for a reportable SAE/incident.

The assessment by the investigator with regard to the study device relation is done according to the following definitions (MEDDEV 2.7/3 rev. 3, 2015):

Not related:	Relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ not expected to be affected by the device or procedure;

	• the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely:	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible:	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable:	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal relationship:	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that – the investigational device or procedures are applied to; – the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable;

	In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Note:	Device deficiencies that might have led to an SAE are always related to the medical device.

10.4 Reporting of Serious Adverse Events and Other Safety Related Events

- All SAEs
- Health hazards that require measures
- Device deficiencies

Reporting to Authorities

- The local Investigator is responsible to report to the local CEC **health hazards** that require immediate safety and protective measures **within 2 days.** The investigator shall notify the CEC of these measures and of the circumstances necessitating them.
- The Sponsor-Investigator is responsible to notify the competent authority (Swissmedic) of reportable incidents, based on the national materiovigilance regulations Art. 42, Abs. 3 ClinO/ Art. 15 Abs. 1 Medizinprodukte-Verordnung (v. 17.10.2001).

Periodic safety reporting

A yearly safety update-report is submitted by the Investigator to the CEC.

10.5 Follow up of Serious Adverse Events

Participants terminating the study (either regularly or prematurely) with

- reported ongoing SAE, or
- any ongoing SAEs of laboratory values or of vital signs being beyond the alert limit

will return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective AE page in the CRF. All other information has to be documented in the source documents. Source data has to be available upon request.

In case of participants lost to follow-up, efforts should be made and documented to contact the participant to encourage him/her to continue study participation as scheduled. In case of minor AEs, a telephone call to the participants may be acceptable.

All new SAE that the investigators will be notified of within 30 days after discontinuation of study medication have to be reported in appropriate report forms and in the CRF if required.

Follow-up investigations may also be necessary according to the investigator's medical judgment even if the participant has no AE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be noted in the source documents.

11 STATISTICAL METHODS

11.1 Hypothesis

The zero hypothesis for the primary endpoint is that the time for the 2D and 3D procedure is equal. A paired t-test with a significance level of α = 0.05 should be suitable to analyze the hypothesis within the planned number of 80 patients. Furthermore, descriptive analysis is planned for the subjective judgement of the surgeons.

11.2 Determination of Sample Size

The planned number of 80 patients should be suitable to analyze the zero hypothesis with a paired t-test with a significance level of α = 0.05. This number is also sufficient for descriptive analysis of the subjective judgement of the surgeons.

11.3 Statistical Criteria of Termination of Trial

The planned termination of the study does not rely on statistic criteria

11.4 Planned Analyses

The statistics will be conducted be the biostatistician that will be designed by the coordinating investigator, PD Dr. F. Sommer, Ulm.

11.4.1 Datasets to be Analyzed, Analysis Populations

The primary analysis is the comparison of the time needed for the procedure with the 2D and the 3D procedure in the study population of 80 patients, so there will be an analysis of 80 paired variables. There will also be descriptive statistics of the subjective impressions of the surgeons. The statistics will be conducted be the biostatistician that will be designed by the coordinating investigator, PD Dr. F. Sommer, Ulm.

11.4.2 Primary Analysis

The primary analysis is the comparison of the time needed for the procedure with the 2D and the 3D procedure in the study population of 80 patients, so there will be an analysis of 80 paired variables. The statistics will be conducted be the biostatistician that will be designed by the coordinating investigator, PD Dr. F. Sommer, Ulm.

11.4.3 Secondary Analyses

The secondary analysis consists of descriptive statistics of the subjective impressions of the surgeons. The statistics will be conducted be the biostatistician that will be designed by the coordinating investigator, PD Dr. F. Sommer, Ulm.

11.4.4 Interim Analyses

There is no need for interim analysis.

11.4.5 Safety Analysis

Due to the simple study design, there is no obvious need for specific safety analysis.

11.4.6 Deviation(s) from the Original Statistical Plan

Due to the simple study design, there is no expected deviation of the statistical plan. However, in case of a deviation it will be reported at the CEC and CA if appropriate.

11.5 Handling of Missing Data and Drop-Outs

Due to the simple study design, there is no significant missing data or drop outs to expect.

12 ELIGIBILITY OF THE PROJECT SITE(S)

There are four study centers: ORL-Zentrum Klinik Hirslanden, Witellikerstrasse 40, CH-8032 Zurich, Switzerland; HNO-Universitätsklinik Ulm, Frauensteige 12, 89075 Ulm, Germany; HNO-Klinik München Bogenhausen, Dr. Gaertner GmbH, Possartstrasse 27-31, 8169 München, Germany and HNO-Universitätsklinik Graz, Auenbruggerplatz 1, 8036 Graz, Austria.
Each of the study centers is fully certified by the local CA for conducting the planned procedures and provide all the technical and personal infrastructure needed to guarantee safety for the study participants.

13 DATA QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, ISO 14155, and applicable regulatory requirement(s). The SOPs and WI are followed by all study sites.

Monitoring and Audits will be conducted during the course of the study for quality assurance purposes.

13.1 Data Handling and Record Keeping / Archiving

The study will strictly follow the investigation plan. If any changes become necessary, they must be laid down in an amendment to the investigation plan. All amendments of the investigation plan must be signed by the Sponsor-Investigator and submitted to CEC.

13.1.1 Case Report Forms

The investigators will use paper case report forms (CRF), one for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study. All participants who either entered the study or were considered not eligible or were eligible but not enrolled into the study additionally have to be documented on a screening log. The investigator will document the participation of each study participant on the Enrolment Log.

CRFs must be kept current to reflect participant status at each phase during the course of study. Participants must not to be identified in the CRF by name. Appropriate coded identification (e.g. Participant Number) must be used. ***Please note:*** *Initials must not be used in combination with the date of birth in the CRF for identification of the study participant (combination of initials and year of birth possible).*

It must be assured that any authorized person, who may perform data entries and changes in the CRF, can be identified. A list with signatures and initials of all authorized persons will be filed in the study site file and the trial master file, respectively.

Documented medical histories and narrative statements relative to the participant's progress during the study will be maintained. These records will also include the following: originals or copies of laboratory and other medical test results (e.g. ECGs, etc.) which must be kept on file with the individual participants CRF.

The investigators assure to perform a complete and accurate documentation of the participant data in the CRF. All data entered into the CRF must also be available in the individual participant file either as print-outs or as notes taken by either the investigator or another responsible person assigned by the investigator.

Essential documents must be retained for at least 10 years after the regular end or a premature termination of the respective study (KlinV Art. 45). Essential documents must be retained according to local law in case of international multicenter studies.

Any patient files and source data must be archived for the longest possible period of time according to the feasibility of the investigational site, e.g. hospital, institution or private practice.

13.1.2 Specification of Source Documents

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Nurse records, records of clinical coordinators, and
- Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if participant visited any during the study period and the post study period.

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) should be included in the source documents:

- Demographic data (age, sex)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data (as specified in the investigation plan)
- AEs and concomitant medication
- Results of relevant examinations
- Laboratory printouts

- Dispensing and return of study device (details)
- Reason for premature discontinuation
- Randomization number

13.1.3 Record Keeping / Archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. The location of storage is defined according to the regulations of the local study site in order to secure safety regarding loss and unauthorized use of data.

13.2 Data Management

All data used for the study is processed and stored by the local project leader according to the local study site regulations.

13.2.1 Data Management System

The data for the study is primarily processed in paper forms (CRF, Questionnaire, Informed Consent).

13.2.2 Data Security, Access and Back-up

The access to the data is limited to the individual project leaders and exceptions must be authorized and documented by them. The data for the study is backed up in the individual patient's medical records.

13.2.3 Analysis and Archiving

A copy of the relevant data is sent to the coordinating project leader for data analysis in ~~anonymized~~ coded form.

13.2.4 Electronic and Central Data Validation

A copy of the relevant data is sent to the coordinating project leader for data validation and analysis in ~~anonymized~~ an coded form.

13.3 Monitoring

~~*Regular monitoring visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study.*~~

~~*All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for monitoring. The monitor will review all or a part of the CRF and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.*~~

Due to the simple and "straight forward design" of the study, there is no official monitoring ~~plan established~~planned. However, the correctness of the informed consent, of the data acquisition in the CRF and of the reporting of possible SAE will be evaluated according to the four-eye-principle.

13.4 Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the competent authority or CEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

13.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections.

Otherwise, the access to the data is limited to the individual project leaders and exceptions must be authorized and documented by them.

13.6 Storage of Biological Material and Related Health Data

14 PUBLICATION AND DISSEMINATION POLICY

After the statistical analysis of this trial, the sponsor will make every endeavor to publish the data in a medical journal. Publication of the data of the study is planned by the four project leaders as authors.

15 FUNDING AND SUPPORT

15.1 Funding

There is no specific funding for the project.

15.2 Other Support

Since the 3D camera technique is not yet permanently implemented at all study sites (for example Munich), the 3D camera is provided by the manufacturer if needed for the time of the study period.

16 INSURANCE

In the event of project-related damage or injuries, the liability of the involved study center, for Switzerland the Klinik Hirslanden and/or the Haftpflichtversicherung of the performing surgeon, KD Dr. H. R. Briner (AXA Winterthur, Police Nr. 14.205.422), provides compensation, except for claims that arise from misconduct or gross negligence.

Any damage developed in relation to study participation is covered by this insurance.

The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

A copy of the insurance certificate will be placed in the Investigator's Site File.

17 REFERENCES

1. Albrecht T, Baumann I, Plinkert PK, Simon C, Sertel S. Three-dimensional endoscopic visualization in functional endoscopic sinus surgery. Eur Arch Oto-Rhino-Laryngology 2016; 273: 3753–8.
2. Rampinelli V, Doglietto F, Mattavelli D, et al. 2D-HD versus 3D endoscopy in endonasal skull base surgery: a comparative pre-clinical study. World Neurosurg 2017.

18 APPENDICES

1. Informed Consent

Patienteninformation

Vergleich der 3D-Endoskopie mit der 2D-Endoskopie im Rahmen von Eingriffen an den Nasennebenhöhlen

Dieses Projekt ist organisiert durch: KD Dr. Hans Rudolf Briner, ORL-Zentrum Klinik Hirslanden

Sehr geehrte Dame, sehr geehrter Herr,

Wir möchten Sie anfragen, ob Sie an einem Forschungsprojekt teilnehmen wollen. Im Folgenden wird Ihnen das geplante Forschungsprojekt dargestellt.

1. ZIEL DES PROJEKTS
Wir wollen mit diesem Projekt untersuchen, ob die herkömmliche zweidimensionale (2D) Bilddarstellung während einer Operation an den Nasennebenhöhlen sich von der neueren dreidimensionalen (3D) Darstellung unterscheidet.

2. AUSWAHL
Es können alle Personen über 18 Jahre teilnehmen, die an einer chronischen Nasennebenhöhlenentzündung leiden welche beide Seiten betrifft und mit einer Nasennebenhöhlen Operation behandelt werden müssen. Ausserdem müssen Sie keine Voroperationen an den Nasennebenhöhlen gehabt haben und auch an keinen schweren anderen Erkrankungen leiden wie zum Beispiel eine schwere Herzerkrankung mit notwendiger Blutverdünnung.

3. ALLGEMEINE INFORMATIONEN ZUM PROJEKT
Die immer besser werdende technische Entwicklung führte innerhalb der letzten Jahre zu der Entwicklung von 3D-Endoskopen, die bereits in der Bauchchirurgie standardmäßig eingesetzt werden. Der Vorteil dieser Technik liegt in einer besseren Darstellung der Entfernungen zwischen den anatomischen Strukturen. Dreidimensionale Endoskope sind seit kurzem auch mit einem Außendurchmesser von 4 mm verfügbar, was den Einsatz in der Nasennebenhöhlenchirurgie ermöglicht. Insgesamt ist diese Technik neu und wird u.a. wegen der hohen Kosten bislang nur an wenigen Zentren eingesetzt.
Ziel dieser Studie ist der Vergleich der zweidimensionalen endoskopischen Operationstechnik mit der dreidimensionalen Technik. Die zweidimensionale Darstellung ist der etablierte Standard, welcher seit vielen Jahren in der klinischen Routine eingesetzt wird. Die dreidimensionale Technik ist neuer und ebenfalls für den Einsatz in der Nasennebenhöhlenchirurgie zugelassen.
Um die 3D-Endoskopie mit der 2D-Endoskopie vergleichen zu können, sind möglichst symmetrische anatomische Bedingungen erforderlich, da sonst eine Verzerrung der Ergebnisse entstehen könnte. Deshalb ist die Anwendung beider Techniken während Ihrer Operation vorgesehen.

Vorgesehen ist die Operation einer Seite mit dreidimensionaler Endoskopie Technik und die Operation der anderen Seite mit zweidimensionaler Endoskopie-Technik. Die entsprechende Zuteilung erfolgt zufällig (per Los), um möglichst unbeeinflusste Ergebnisse zu erzielen. Die Zeit pro Seite für die Operation mit der 2D und der 3D Technik wird gemessen und nach der Operation füllt Ihr Chirurg einen Fragebogen aus, in welchem bestimmte Beurteilungen der zwei Techniken detailliert abgefragt werden. Das Ziel ist die Erfassung von möglichen Vorteilen der dreidimensionalen Operationstechnik wie z.B. eine bessere räumliche Darstellung oder die bessere Handhabung des Endoskops.
Die gleiche Studie wird parallel in Graz (Universitätsklinik), München (Gärtnerklinik) und Ulm (Universitätsklinik) durchgeführt, es handelt sich somit um eine internationale Multizenterstudie. Dieses Projekt wird so durchgeführt wie es die Gesetze in der Schweiz vorschreiben. Die zuständige Ethikkommission hat dieses Projekt geprüft und bewilligt.

4. ABLAUF

Im Rahmen der bei Ihnen vorgesehenen Nasennebenhöhlen-Operation wird die eine Seite mit dreidimensionaler (3D) und die andere Seite mit zweidimensionaler (2D) Endoskopie-Technik operiert. Die entsprechende Zuteilung, welche Seite mit welcher Technik, erfolgt zufällig, um möglichst unbeeinflusste Ergebnisse zu erzielen. Die Zeit pro Seite für die Operation mit der 2D und der 3D Technik wird gemessen und nach der Operation füllt Ihr Chirurg einen Fragebogen aus, in welchem bestimmte Beurteilungen der zwei Techniken detailliert abgefragt werden. Ein zusätzlicher Aufwand aus Sicht des Patienten entsteht nicht, insbesondere sind keine weiteren Massnahmen oder Kontrollen notwendig.

5. NUTZEN

Sie werden persönlich keinen Nutzen von der Teilnahme am Projekt haben. Wenn Sie bei diesem Projekt mitmachen, können die Resultate aber vielleicht helfen, einen möglichen Vorteil der neueren 3D Technik zu objektivieren. Dies könnte wichtig sein für andere Patienten, welche an einer chronischen Nasennebenhöhlen Entzündung leiden und eine Nasennebenhöhlen Operation benötigen.

6. RECHTE

Sie nehmen freiwillig teil. Wenn Sie nicht mitmachen oder später Ihre Teilnahme zurückziehen wollen, müssen Sie dies nicht begründen. Ihre medizinische Behandlung/Betreuung ist unabhängig von Ihrem Entscheid gewährleistet. Sie dürfen jederzeit Fragen zur Teilnahme und zum Projekt stellen. Wenden Sie sich dazu bitte an die Person, die am Ende dieser Information genannt ist.

7. PFLICHTEN

Als Teilnehmer ist es notwendig, dass Sie sich an die notwendigen Vorgaben und Anforderungen durch die Projektleitung halten und insbesondere Angaben über frühere allfällige Nasennebenhöhlen Operationen und begleitende schwere Erkrankungen sowie aktuell eingesetzte Medikamente machen.

-

8. RISIKEN

Durch das Projekt sind Sie nur geringfügigen Risiken ausgesetzt.
Denkbar ist beispielsweise eine geringgradig erhöhte Operationszeit beim Wechsel der endoskopischen Kamerasysteme.

9. ERGEBNISSE

Der Prüfarzt/die Projektleitung wird Sie während des Projekts über alle neuen Erkenntnisse informieren, die den Nutzen oder Ihre Sicherheit und somit Ihre Einwilligung zur Teilnahme beeinflussen können

10. VERTRAULICHKEIT VON DATEN UND PROBEN

Für dieses Projekt werden Ihre persönlichen und medizinischen Daten erfasst. Nur sehr wenige Fachpersonen werden Ihre unverschlüsselten Daten sehen, und zwar ausschliesslich, um Aufgaben im Rahmen des Projekts zu erfüllen. Bei der Datenerhebung zu Studienzwecken werden die Daten verschlüsselt. Verschlüsselung bedeutet, dass alle Bezugsdaten, die Sie identifizieren könnten (Name, Geburtsdatum), gelöscht und durch einen Schlüssel ersetzt werden. Die Schlüssel-Liste bleibt immer in der Institution, das heisst im ORL-Zentrum der Klinik Hirslanden. Diejenigen Personen, die den Schlüssel nicht kennen, können daher keine Rückschlüsse auf Ihre Person ziehen. Bei einer Publikation sind die zusammengefassten Daten daher auch nicht auf Sie als Einzelperson rückverfolgbar. Ihr Name taucht niemals im Internet oder einer Publikation auf. Manchmal gibt es die Vorgabe bei einer Zeitschrift zur Publikation, dass Einzel-Daten (sogenannte Roh-Daten) übermittelt werden müssen. Wenn Einzel-Daten übermittelt werden müssen, dann sind die Daten immer verschlüsselt und somit ebenfalls nicht zu Ihnen als Person rückverfolgbar. Alle Personen, die im Rahmen des Projekts Einsicht in Ihre Daten haben, unterliegen der Schweigepflicht. Die Vorgaben des Datenschutzes werden eingehalten und Sie als teilnehmende Person haben jederzeit das Recht auf Einsicht in Ihre Daten.

Die Daten werden verschlüsselt nach Ulm zum Koordinator der Studie, PD Dr. F. Sommer, Hals-Nasen-Ohren Universitätsklinik, versandt, dort für dieses Projekt analysiert und für mindestens 10 Jahre aufbewahrt. Zugriffsrecht auf diese Verschlüsselung haben nur der unterzeichnende Projektleiter, KD Dr. Hans Rudolf Briner, ORL-Zentrum Klinik Hirslanden, sowie berechtigte Institutionen wie zum Beispiel die beurteilende Ethikkommission. Die Datenbank im Ausland hat gleichwertige Standards wie die Datenbank in der Schweiz. Verantwortlich für die Einhaltung der nationalen und internationalen Richtlinien zum Datenschutz ist die Projektleitung, die im Ausland einen gleichwertigen Datenschutz gewährleistet.

Möglicherweise wird dieses Projekt durch die zuständige Ethikkommission überprüft. Der Projektleiter muss eventuell Ihre persönlichen und medizinischen Daten für solche Kontrollen offenlegen. Ebenso kann es sein, dass ausnahmsweise auch ein Vertreter der Versicherung Ihre Daten ansehen muss. Alle Personen müssen absolute Vertraulichkeit wahren. Wir halten alle Vorgaben des Datenschutzes ein und werden Ihren Namen weder in einer Publikation noch im Internet öffentlich machen.

11. RÜCKTRITT

Sie können jederzeit aufhören und von dem Projekt zurücktreten, wenn Sie das wünschen. Die bis dahin erhobenen Daten und Proben werden noch verschlüsselt auswertet, weil das ganze Projekt sonst seinen Wert verliert. Nach der Auswertung werden Ihre Daten vollständig anonymisiert, d.h. Ihre Schlüsselzuordnung wird vernichtet, so dass danach niemand mehr erfahren kann, dass die Daten und Proben ursprünglich von Ihnen stammten.

12. ENTSCHÄDIGUNG

Wenn Sie an diesem Projekt teilnehmen, bekommen Sie dafür keine Entschädigung. Es entstehen Ihnen oder Ihrer Krankenkasse keine Kosten durch die Teilnahme.

13. HAFTUNG

Während der Teilnahme an der Studie genießen Sie den üblichen, gesetzlich geregelten Versicherungsschutz. Der Studienarzt, KD Dr. Hans Rudolf Briner und die an der Studie mitwirkenden Mitarbeiter der Klinik Hirslanden sind haftpflichtversichert für den Fall, dass Sie durch deren Verschulden einen Schaden erleiden.
Gleichzeitig weisen wir darauf hin, dass Sie für die direkten Wege zum und vom Studienzentrum nicht unfallversichert sind.

Einen Schaden, der Ihrer Meinung nach auf dieses Forschungsprojekt zurückzuführen ist, melden Sie bitte unverzüglich dem unterzeichnenden Projektleiter.

14. FINANZIERUNG
Das Projekt wird vollständig von den jeweiligen lokalen Projektleitern bezahlt.

15. KONTAKTPERSON(EN)
Bei allen Unklarheiten, Befürchtungen oder Notfällen, die während des Projekts oder danach auftreten, können Sie sich jederzeit an den unterzeichnenden Projektleiter wenden:

KD Dr. med. Hans Rudolf Briner
ORL-Zentrum Klinik Hirslanden
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Tel. Praxis: +41 44 387 28 00
Tel Mobile: +41 79 68 55 888
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Einwilligungserklärung

Schriftliche Einwilligungserklärung zur Teilnahme an einem Studienprojekt
Bitte lesen Sie dieses Formular sorgfältig durch. Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten.

BASEC-Nummer (nach Einreichung):	**2018-00005**
Titel des Projekts (wissenschaftlich und Laiensprache):	**Vergleich der 3D-Endoskopie mit der 2D-Endoskopie im Rahmen von Eingriffen an den Nasennebenhöhlen**
verantwortliche Institution (Projektleitung mit Adresse):	**KD Dr. med. Hans Rudolf Briner ORL-Zentrum Klinik Hirslanden Witellikerstrasse 40 CH-8032 Zürich Tel. Praxis: +41 44 387 28 00 Tel Mobile: +41 79 68 55 888 E-mail: briner@orl-Zentrum.com**
Ort der Durchführung:	**ORL-Zentrum Klinik Hirslanden Zürich**
Leiter / Leiterin des Projekts am Studienort: Name und Vorname in Druckbuchstaben:	**KD Dr. med. Hans Rudolf Briner**
Teilnehmerin/Teilnehmer: Name und Vorname in Druckbuchstaben: Geburtsdatum:	☐ weiblich ☐ männlich

- Ich wurde vom unterzeichnenden Prüfarzt mündlich und schriftlich über den Zweck, den Ablauf des Projekts, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Ich nehme an diesem Projekt freiwillig teil und akzeptiere den Inhalt der zum oben genannten Projekt abgegebenen schriftlichen Information. Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Meine Fragen im Zusammenhang mit der Teilnahme an diesem Projekt sind mir beantwortet worden. Ich behalte die schriftliche Information und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung.
- Ich bin einverstanden, dass die zuständigen Fachleute der Projektleitung/ des Auftraggebers des Projekts und der für dieses Projekt zuständigen Ethikkommission zu Prüf- und Kontrollzwecken in meine unverschlüsselten Daten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Bei Studienergebnissen oder Zufallsbefunden, die direkt meine Gesundheit betreffen, werde ich informiert. Wenn ich das nicht wünsche, informiere ich meinen Prüfarzt.
- Ich weiss, dass meine gesundheitsbezogenen und persönlichen Daten nur in verschlüsselter Form zu Forschungszwecken **für dieses Projekt** weitergegeben werden können, auch ins Ausland.
- Ich kann jederzeit und ohne Angabe von Gründen von der Teilnahme zurücktreten, ohne dass ich deswegen Nachteile bei der weiteren medizinischen Behandlung/Betreuung habe. Die bis dahin erhobenen Daten und Proben werden für die Auswertung des Projekts noch verwendet.
- Die Haftpflichtversicherung des Projektleiters, KD Dr. Hans Rudolf Briner, respektive gegebenenfalls der Klinik Hirslanden, kommt für allfällige Schäden auf.
- Ich bin mir bewusst, dass die in der Teilnehmerinformation genannten Pflichten einzuhalten sind. Im Interesse meiner Gesundheit kann mich der Projektleiter jederzeit ausschliessen.

Ort, Datum	Unterschrift Teilnehmerin/Teilnehmer

Bestätigung des Prüfarztes/der Prüfperson: Hiermit bestätige ich, dass ich dieser Teilnehmerin/ diesem Teilnehmer Wesen, Bedeutung und Tragweite des Projekts erläutert habe. Ich versichere, alle im Zusammenhang mit diesem Projekt stehenden Verpflichtungen gemäss des geltenden Rechts zu erfüllen. Sollte ich zu irgendeinem Zeitpunkt während der Durchführung des Projekts von Aspekten erfahren, welche die Bereitschaft der Teilnehmerin/ des Teilnehmers zur Teilnahme an dem Projekt beeinflussen könnten, werde ich sie/ ihn umgehend darüber informieren.

Ort, Datum	KD Dr. Hans Rudolf Briner Unterschrift

~~**Vergleich der 3D-Endoskopie mit der 2D-Endoskopie im Rahmen von Eingriffen an den Nasennebenhöhlen**~~

Sehr geehrter Patient, sehr geehrte Patientin,

Um allen Patienten eine optimale Therapie anbieten zu können ist es von allgemeinem Interesse, bestehende Behandlungsmethoden zu verbessern und technische Neuerungen in den klinischen Alltag zu integrieren. Hierzu sind klinische Studien erforderlich, bei denen wir auf Ihre Unterstützung als Patient angewiesen sind.
Gerne möchten wir Sie einladen, an einer Studie teilzunehmen, welche die herkömmliche zweidimensionale Bilddarstellung während einer Operation an den Nasennebenhöhlen mit einer neueren dreidimensionalen Darstellung vergleicht.
Bei Ihnen ist eine Operation an den Nasennebenhöhlen geplant. Hierbei handelt es sich um eine „Standard-Operation" der Hals-Nasen-Ohrenheilkunde. Die Operation wird endoskopisch über die Nasenlöcher durchgeführt. Hierbei kommen spezielle Optiken und eine hochauflösende Kamera zu Einsatz, die das Bild aus der Nase auf einen großen Monitor übertragen und so eine sehr detaillierte Darstellung des Operationsfeldes ermöglichen.

Was ist der Hintergrund der Studie?
Die immer besser werdende technische Entwicklung führte innerhalb der letzten Jahre zu der Entwicklung von 3D-Endoskopen, die bereits in der Bauchchirurgie standardmäßig eingesetzt werden. Der Vorteil dieser Technik liegt in einer besseren Darstellung der Entfernungen zwischen den anatomischen Strukturen.

Dreidimensionale Endoskope sind seit kurzem auch mit einem Außendurchmesser von 4 mm verfügbar, was den Einsatz in der Nasennebenhöhlenchirurgie ermöglicht. Insgesamt ist diese Technik neu und wird u.a. wegen der hohen Kosten bislang nur an wenigen Zentren eingesetzt.

Ziel dieser Studie ist der Vergleich der zweidimensionalen endoskopischen Operationstechnik mit der dreidimensionalen Technik. Die zweidimensionale Darstellung ist der etablierte Standard, welcher seit einigen Jahren in der klinischen Routine eingesetzt wird. Die dreidimensionale Technik ist neuer und ebenfalls für den Einsatz in der Nasennebenhöhlenchirurgie zugelassen.

Wie läuft die Studie ab?
Um die 3D-Endoskopie mit der 2D-Endoskopie vergleichen zu können sind möglichst symmetrische anatomische Bedingungen erforderlich, da sonst eine Verzerrung der Ergebnisse entstehen könnte. Deshalb ist die Anwendung beider Techniken während Ihrer Operation vorgesehen.

Vorgesehen ist die Operation einer Seite mit dreidimensionaler und die Operation der anderen Seite mit zweidimensionaler Endoskopie-Technik. Die entsprechende Zuteilung erfolgt zufällig (per Los), um möglichst unbeeinflusste Ergebnisse zu erzielen.

Nach der Operation füllt Ihr Chirurg einen Fragebogen aus, in dem bestimmte Beurteilungen der zwei Techniken detailliert abgefragt werden. Das Ziel ist die Erfassung von Vorteilen der dreidimensionalen Operationstechnik wie z.B. eine bessere räumliche Darstellung oder die bessere Handhabung des Endoskops.
Die gleiche Studie wird parallel in Graz (Universitätsklinik), München (Gärtnerklinik) und Ulm (Universitätsklinik) durchgeführt, es handelt sich somit um eine internationale Mulitzenterstudie.

Warum sollten Sie an der Studie teilnehmen?

Operationen an den Nasennebenhöhlen zählen zu den am häufigsten durchgeführten Eingriffen in der Hals-Nasen-Ohrenheilkunde. Von jeder Erkenntnis, die in diesem Bereich erlangt wird, profitiert eine Vielzahl von Patienten.
Durch die Teilnahme an der Studie entsteht für Sie kein Risiko und es ergibt sich für Sie kein Nachteil. Beide Operationstechniken sind etablierte und offiziell zugelassene Verfahren, mit denen erwiesenermaßen sehr gute Resultate erzielt werden. Das Ziel ist, die feinen Unterschiede zu erfassen, um die Qualität unserer Arbeit noch weiter zu optimieren.

FREIWILLIGKEIT:

An diesem Forschungsprojekt nehmen Sie freiwillig teil. Ihr Einverständnis können Sie jederzeit und ohne Angabe von Gründen widerrufen. Alle bis dahin erhobenen Daten und Proben werden vernichtet.

ERREICHBARKEIT DES PROJEKTLEITERS:

Sollten während des Verlaufes des Forschungsprojektes Fragen auftauchen, so können Sie jederzeit den Studienleiter in Zürich, Klinischer Dozent Dr. med. Hans Rudolf Briner, unter der Telefonnummer erreichen: 044 387 28 00.

VERSICHERUNG:

Während der Teilnahme an der Studie genießen Sie den üblichen Versicherungsschutz. Der Studienarzt, KD Dr. Hans Rudolf Briner und die an der Studie mitwirkenden Mitarbeiter der Klinik Hirslanden sind haftpflichtversichert für den Fall, dass Sie durch deren Verschulden einen Schaden erleiden.
Gleichzeitig weisen wir darauf hin, dass Sie für die direkten Wege zum und vom Studienzentrum (nicht) unfallversichert sind.
Einen Schaden, der Ihrer Meinung nach auf dieses Forschungsprojekt zurückzuführen ist, melden Sie bitte unverzüglich dem Studienarzt.

SCHWEIGEPFLICHT/DATENSCHUTZ:

Alle Personen, welche Sie im Rahmen dieses Projektes betreuen, unterliegen der Schweigepflicht und sind auf das Datengeheimnis verpflichtet.

Die studienbezogenen Untersuchungsergebnisse sollen in anonymisierter Form in wissenschaftlichen Veröffentlichungen verwendet werden.

Soweit es zur Kontrolle der korrekten Datenerhebung erforderlich ist, dürfen autorisierte Personen Einsicht in die studienrelevanten Teile der Krankenakte nehmen.

Sofern zur Einsichtnahme autorisierte Personen nicht der obengenannten ärztlichen Schweigepflicht unterliegen, stellen personenbezogene Daten, von denen sie bei der Kontrolle Kenntnis erlangen, Betriebsgeheimnisse dar, die geheim zu halten sind.

....
Datum Name des/der aufklärenden Arztes/Ärztin

.....
Name des Patienten